Exemplary Tales of (Mostly) Nineteenth Century Medical and Epidemiological Discovery Through Abductive Reasoning

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Part I

Preamble

The motivating framework for the present book is the contention that many of the significant medical, epidemiological, and public health discoveries from the Nineteenth Century can be placed under a common reasoning system, called abduction, first articulated specifically by Charles Sanders Peirce in the late 1800s to the early 1900s. Obviously, medical advances made prior to Peirce's formal writing, or even after for that matter, were not explicitly guided by the reasoning structures he laid out. Nevertheless in hindsight, it is informative to note that the various instances of innovative medical research to be discussed seem to generally follow the same broad path set down by Peirce. Writing in 1903, Peirce himself forcefully stated as a general conclusion that "... every single item of scientific theory which stands established today has been due to abduction."

The initial chapter will introduce in a general way several maxims or principles of what might be referred to as everyday plausible reasoning, including the various syllogistic patterns that extend back to the ancient Greeks. Once some of this basic terminology has been presented, Peirce's notion of abductive reasoning and inference is reviewed. Abduction is then used as a way of characterizing the various Nineteenth Century tales of scientific (medical) discovery that make up the major portion of the present book. All of these narratives typically incorporate additional deductive verification stages that follow the first step of hypothesis generation, or, alternatively stated, that follow the initial formation of an abductive conjecture which then serves as a "working hypothesis" for generating additional implications that should obtain if the given abductive conjecture were true.

Because the first introductory chapter provides all the necessary background to place the various tales of medical advance within a

general framework of abductive reasoning, the reader may simply wish at that chapter's finish to proceed directly to the various discovery narratives provided. For those who might care to have a more nuanced understanding at the outset of what it might mean to become "more and more plausible," a short second introductory and optional chapter is provided as an Appendix that presents some basics of probability theory and develops in this context what is known as Bayes Theorem. This latter well-known result is used to characterize the idea of "plausibility" in a more formal way, and to show explicitly the validity of the three plausible reasoning schemes presented in the first introductory chapter. Also, Bayes Theorem can be applied sequentially so that multiple deductive verification stages having positive outcomes lead to an ever increasing plausibility for the original abductive conjecture. Peirce referred to the latter process of sequential multiple verification by the term "induction."

Part II

Preface

> The most exciting phrase to hear in science, the one that heralds new discoveries, is not "Eureka" (I found it), but [rather] "That's funny ..."
>
> – Isaac Asimov (1920–1992)

The aphorism just given and attributed to Isaac Asimov was contained within an auxiliary file for the UNIX operating system from the late 1980s. It was one of many such sayings that would be issued as a "fortune cookie" more or less at random when first logging into a UNIX server. The intended meaning of the aphorism was to note that most discoveries in science do not follow the legendary but probably apocryphal tale involving the ancient Greek scholar, Archimedes. Supposedly, Archimedes observed that the water level rose when he stepped into a bath according to the volume of the body part submerged. Realizing that the volume of an irregular object could thus be measured with precision by the amount of water displaced, he leapt out of his bath exclaiming, "Eureka" (from the ancient Greek word meaning, "I have found it"), and proceeded to run naked through the streets of Syracuse.

The adage ascribed to Asimov questions whether real scientific discovery ever occurs in an explosive manner that would justify a shout of "Eureka." Instead, many if not most scientific advances simply begin with a set of anomalous or surprising observations which could be explained by some (abductive) hypothesis or conjecture. Such a hypothesis once formulated would then be scrutinized further, perhaps through additional observation and/or explicit experimentation. This is the main contention developed in this book using a collection of seminal medical discoveries chosen mostly from the Nineteenth Century. All of these advances began with some collection of

"surprising" observations that could be tentatively understood by formulating a hypothesis which if true would make the supposedly surprising or anomalous observations "a matter of course."

One paradigmatic illustration for the Asimov aphorism is the Twentieth Century discovery of penicillin by Alexander Fleming (1881–1955).[1] Fleming was a Scottish physician and microbiologist working at St. Mary's Hospital in London; in addition he was a Professor of Bacteriology at the affiliated University of London. In the late 1920's, Fleming's research centered on the properties of bacteria from the ubiquitous genus of *Staphylococcus*. In the summer of 1928, Fleming went on his usual family vacation but before leaving he inoculated *Staphylococci* onto a number of culture plates and left them in a corner of his lab. Upon return in September he noted that one of the culture plates was contaminated with a fungus mold; moreover, the *Staphylococci* colonies around the fungus were destroyed but colonies further away were normal in their development. At this point Fleming supposedly uttered the critical phrase "that's funny," and showed the plate to his assistant, Merlin Pryce. Pryce remarked, "that's how you discovered lysozyme," referring to an earlier mild antimicrobial enzyme identified by Fleming in 1922 produced by animal secretions such as tears, saliva, mucus, and human milk.[2]

The *Staphylococci* destroying fungus seen by Fleming was from the genus *Penicillium*, and apparently came from another lab one floor below. Although Fleming himself was never able to obtain a pure form for the specific antibacterial substance present in the mold, he nevertheless gave it the name of "penicillin" in March of 1929, and for some twelve years thereafter continued to grow cultures of *Penicillium* mold and distribute them freely to whoever asked. Several

other individuals in the early 1940s, most notably Howard Florey and Ernst Chain, developed purification processes that allowed penicillin to be produced in the large quantities then necessary for the ongoing war effort. The 1945 Nobel Prize in Physiology or Medicine was shared by Fleming, Florey, and Chain.

The main part of the present book consists of the background stories for some dozen major medical discoveries from throughout the Nineteenth Century (with some small overlap with the beginnings of the Twentieth) that all could be seen as following the same type of discovery paradigm that led Fleming to identify the presence of penicillin. First, there is a "surprising observation" similar to that of bacterial growth being impeded in the vicinity of the *Penicillium* mold. Next, some tentative conjecture is made that would explain the surprising observation, such as that of the mold producing some substance that was effective in destroying bacteria. If this hypothesis were true, the surprising observation would then be "a matter of course," and thus there is reason to believe that the hypothesis may be true or that it remains at least plausible. A further verification process then undertaken would take the form of further experimentation and observation, all with a view of providing evidence either for or against a continued belief in the initial (abductive) conjecture now considered as a "working hypothesis," and provisionally accepted as a basis for continued investigation. A quote from Antoine Lavoisier (1743–1794) sums up well the view generally held at least implicitly by all of the various medical scientists introduced later:[3]

> We must trust nothing but facts: these are presented to us by nature and cannot deceive. We ought, in every instance, to submit our reasoning to the test of experiment, and never to search for

truth but by the natural road of experiment and observation.

So, to summarize, the process of scientific discovery illustrated through the stories of medical advance that form the main part of this book can be viewed as being characterized by the American philosopher, Charles Sanders Peirce (1839–1914). In Peirce's formalization of what he referred to as abductive reasoning, one proceeds from a set of "surprising" observations to an abductive conjecture or hypothesis that if true would explain these anomalous observations "as a matter of course." This abductive reasoning framework will be developed in more detail in the first chapter to follow. This discussion will then be used as a context for presenting and understanding the various Nineteenth Century medical and scientific advances documented in the remainder of the book.

Notes

[1]The story of Alexander Fleming and his discovery of penicillin is told in a number of sources. One of the best and most complete was written by a former Professor of Bacteriology at the University of London, Ronald Hare. Hare was present both for penicillin's initial discovery and its later development; he knew and later interviewed all of the relevant participants. Hare's book is entitled, *The Birth of Penicillin and the Disarming of Microbes* (1970; London: George Allen and Unwin).

[2]Writing much later in his career, Fleming remarked that "When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionize all medicine by discovering the world's first antibiotic, or bacteria killer. But I guess that's exactly what I did."

[3]Antoine Lavoisier was a French chemist and nobleman best known for his discovery of the role that oxygen plays in combustion. Unfortunately, he did not make it into the Nineteenth Century. Lavoisier was guillotined at the age of fifty in 1794 at the height of the French Revolution, accused of selling adulterated tobacco and tax fraud.

Chapter 1

Plausible, Deductive, and Abductive Reasoning

As noted in the Preface, the majority of the present book gives the background stories for some dozen or so mostly Nineteenth Century medical and epidemiological researchers and the major scientific advances they made. The basic reasoning processes documented in these narratives invariably include the formation of tentative explanatory conjectures or hypotheses along with their subsequent testing and evaluation. All of this can be put under a common reasoning framework of abductive inference developed by Charles Sanders Peirce in the late 1800s to the early 1900s. Although these crucial medical discoveries were obviously carried out without any explicit knowledge of Peirce's writing as such, it is of some historical interest to note that at least conceptually the Peircean pattern of abductive reasoning is very natural and can be adopted as a *post hoc* organizing principle behind all of these seminal advances. This contention also points to the universality of Peirce's notions of scientific discovery and abductive inference that proceeds systematically through the development of explanatory conjectures and their subsequent verification (or nonverification, as the case may be).[1]

This first chapter introduces some terminology that will prove useful in the later discussions of these Nineteenth Century medical breakthroughs. As noted, Peirce's characterization of abductive reasoning is presented as an organizing framework for these later narratives. As part of this, an intuitive idea of plausibility and plausible reasoning is helpful. As an example, one item becomes more plausible than a second when it is judged more likely to be true, or to occur, or to be the underlying causative agent leading to some observed phenomenon. Several of these notions of plausibility within a general framework of abductive reasoning can be formalized further but this would require a short excursion into the basics of probability theory, and specifically to a presentation of what is known as Bayes Theorem. Because this more technical development is secondary to a presentation of the Nineteenth Century medical narratives, it is reserved for an optional Appendix although some of the terminology could be used intuitively somewhat earlier for those who might already be familiar with these elements of probability theory.

1.1 Some Beginning Terminology, Useful for Scientific Reasoning and Discovery

> When you hear hoofbeats behind you, don't expect to see a zebra.
> When you hear hoofbeats, think horses, not zebras.
> – Theodore Woodward (1914–2005)

The epigrams just given were coined in the late 1940s by Theodore Woodward, a Professor from the University of Maryland School of Medicine. They were intended as cautionary notes to his medical interns — because horses are common in Maryland and zebras rare,

it is just "common sense" to infer that animals making hoofbeats are more likely to be horses than zebras. Or alternatively stated, a horse conjecture is more plausible than that of a zebra. To cast this into a medical context, a commonplace medical diagnosis is more likely to be true than a more exotic explanation. So, as one initial maxim of "plausible reasoning," we are more likely to be correct with a commonplace conjecture than one that is rarer or more esoteric. As an informal corollary to this first maxim, it is prudent to first seek verification (or non-verification, as the case may be) of a common or plausible hypothesis before proceeding to the more unusual.

Although it might seem sensible to operate as if an everyday hypothesis is more likely to be true than a conjecture that is more unusual, that isn't necessarily always the norm at the present time. For example, some years ago during the early part of the first Trump presidential term and continuing throughout, there were "alternative facts" and "fake news," along with a variety of old and new conspiracy theories being aired over a variety of media outlets. Alex Jones of Infowars touted the idea that the massacre of children at Sandy Hook elementary school was a "false-flag" scenario staged by Democrats to advance a gun control agenda; or that pharmaceutical companies were deliberately hiding the proven connection between vaccines and autism to increase their profits. In the quotes below taken from several articles in the *New York Times* in early February of 2017, there are a number of documented examples of implausible reasoning in news items about the President's Executive Order restricting travel from seven predominately Muslim countries and the temporary court order staying the ban:

> Late in the day, Mr. Trump took to Twitter to preemptively blame

> the judge and the judiciary for what the president suggested would be a future terrorist attack.
>
> "Just cannot believe a judge would put our country in such peril," Mr. Trump wrote, a day after referring to the "so-called judge" in the case. "If something happens blame him and [the] court system."
>
> The White House offered no evidence for Mr. Trump's suggestion that potential terrorists would now pour over the border because of the judge's order. Since September 11, 2001, no American has been killed in a terrorist attack on American soil by anyone who immigrated from any of the seven countries named in Mr. Trump's order.
>
> ...
>
> In a brief filed Saturday, the Trump administration argued that Judge Robart's order would cause irreparable harm to national security.
>
> In response, lawyers for Washington and Minnesota said that was not plausible, because it would mean the nation had long been suffering "some unspecified, ongoing irreparable harm."
>
> "That makes no sense," the brief said. "As this court has held, preserving the status quo against sudden disruption is often in the interest of all parties."

It appeared to many at the time that the United States was entering a troubled period that might be labeled the "Age of Implausible Reason(ing)." That particular fear became even more apparent later in the Trump presidential term. To indicate how bad it currently still is, there are masses of QAnon supporters who gather periodically in Dealey Plaza in Dallas keenly awaiting the reappearance of John F. Kennedy or his late son. Supposedly, Kennedy along with Donald Trump would then rule the United States from that date forward.

As a second plausible reasoning adage, and one that is generally more annoying because various irritating versions of it are heard so often, comes initially from the Hoosier poet James Whitcomb Riley (1849–1916):

> When I see a bird that walks like a duck and swims like a duck and quacks like a duck, I call that bird a duck.

Restating in different words, we have three pieces of evidence about a bird before us – walking, swimming, and quacking – and this is enough to put forward a reasonable (plausible) hypothesis that the bird is a duck. As is true for any instance of purely plausible reasoning, the "duckness" conjecture may be wrong, but that isn't very likely given the three strong bits of available evidence. Similarly, based on the initial epigrams for this section and given the rarity of zebras in Maryland, it is unlikely that zebras are being heard rather than horses, but it does remain a slight possibility (because of a nearby zoo, perhaps). Another example of "duckness" at work came again from the current news in 2017 when the Trump Executive Order on travel from the Mideast was defended because it was obviously not a "Muslim ban." The appropriate response here is the familiar double positive,"yeah, right!"

Although there is probably no end to the individual situations where plausible reasoning is absent, some categorization may be possible where several broad types of faulty reasoning can be identified. One such category includes the adoption of conspiracy theories defined as beliefs that some covert but influential entity is responsible for a specific circumstance or event. For instance, there is a "deep state" governmental group that thwarted the Trump presidency; or,

there exists a cabal of Satanic cannibalistic pedophiles operating a global sex trafficking enterprise that also conspired against Donald Trump, and finally, there is the "big lie" that somehow the 2020 Presidential election "was stolen" from Trump. A second form of faulty reasoning is magical thinking that may be religious in origin or involve various types of superstitions. Here, the basic idea is that you can influence the outcome of specific events by doing something that has no discernible bearing on the situation. Common examples include throwing salt over one's shoulder, knocking on wood, or carrying a rabbit's foot in one's pocket.

A substantial portion of the later discussion of Nineteenth Century medical breakthroughs involves replacing procedures based on magical medical thinking such as blood-letting, the use of leeches or other unproven medicinals, or the attribution of disease causation to the presence of miasma vapors and/or unhealthy smells, with an understanding of infectious disease transmission and prevention through the eventual development of a "germ theory" as a causative mechanism for explaining these maladies. The emphasis in the Nineteenth Century turned to various preventative public health measures such as the availability of clean drinking water, the control of various insect vectors responsible for disease propagation, a general improvement in methods of sanitation, and the use of quarantine methods whenever necessary to limit human contact.

In the short time period from 2020 to 2022 the general lack of everyday plausible reasoning or common sense was clearly on display in how some people dealt with the on-going Covid-19 pandemic. There is a pervasive trust in unproven cures such as hydroxychloroquine, injections of bleach, and ivermectin. Related beliefs were that wearing

a mask actually "activates" the virus, or that because of Bill Gates, the vaccines were being used to implant microchips in people. For most rational individuals such vaccine hesitancy was hard to fathom given the enormous data base available on effectiveness and the lack of serious side effects.

1.2 Modes of Reasoning

> Common sense is not so common.
> – Voltaire (*Dictionnaire philosophique*, 1764)

In contrast to plausible reasoning that might be incorrect, one can go back and revisit Aristotle from the Fourth Century B.C., and discuss deductive (or demonstrative) inference in terms of two syllogisms having the familiar forms given below. To give a common illustration for these syllogisms, a proposition P (the "antecedent") might be: "Socrates is a man," and a second proposition Q (the "consequent") might be: "Socrates is mortal":

First (Direct) Form:
If P is true, then Q is true
P is true
Therefore, Q is true

Second (Contrapositive) Form:
If P is true, then Q is true
Q is false
Therefore, P is false

Although we all might hope to rely solely on deductive reasoning in our daily lives because of its clarity and obvious validity, such

situations are relatively rare. Most of the time some form of plausible reasoning must be invoked, or to adopt a more colloquial phrase, there is a need to rely on one's "common sense."

Three generic plausible reasoning schemes having the syllogistic-type forms given below are developed in greater detail in an optional Appendix that first presents some prerequisite probability theory:

Affirming the Consequent:
If P is true, then Q is true
Q is true
Therefore, P becomes more plausible

If "P becomes more plausible" is replaced by the stricter "P is true," the classic "fallacy of affirming the consequent" results. For example, when we begin with the statement that "if Socrates is a man, then Socrates is mortal" and assert that "Socrates is mortal," it does not necessarily follow that Socrates is a man — "Socrates " could be, for instance, the name given to my pet dog. The weaker assertion about "Socrates is a man" becoming more plausible, however, will follow directly from arguments given in the aforementioned Appendix that were originally set forth by George Polya in the 1950s.

As a second plausible reasoning scheme, it can be shown that denying the antecedent renders a consequent less plausible or credible:

Denying the Antecedent:
If P is true, then Q is true
P is false
Therefore, Q becomes less plausible

If "Q becomes less plausible" is replaced by the stricter "Q is false," the classic "fallacy of denying the antecedent" is obtained. For ex-

ample, when we begin with the statement that "if Socrates is a man, then Socrates is mortal" and subsequently assert that "Socrates is not a man," it does not necessarily lead to "Socrates not being mortal"; again, my mortal pet dog Socrates provides a needed exception. The weaker statement about the mortality of Socrates becoming less plausible will again follow from later arguments, where it is shown that the negation of an antecedent makes the consequent less plausible.

A third and even weaker plausible reasoning scheme similar to "affirming the consequent" is given here without further discussion at this point. The reader may substitute in the statements about Socrates at the appropriate places:

If P is true, then Q becomes more plausible

Q is true

Therefore, P becomes more plausible

In summary, the classic fallacies of "affirming the consequent" and "denying the antecedent" are no longer strict fallacies in the context of these plausible reasoning schemes.

1.2.1 Charles Sanders Peirce and Abductive Reasoning

An alternative way of presenting the plausible reasoning scheme called "affirming the consequent" is through the notion of abductive reasoning or inference as developed in the late 1800s to the early 1900s by the American philosopher Charles Sanders Peirce (1839–1914). As typically framed, Peirce's form of abductive inference or reasoning can be phrased as follows:

The surprising fact, B, is observed

But if A were true, then B would be a matter of course
Therefore, there is reason to suspect that A is true

As an example, suppose we observe that the lawn is wet when going out for the paper in the morning. If it had rained last night, it would be unsurprising that the lawn is wet; therefore, by abductive reasoning, the possibility that it rained last night is reasonable or plausible. Obviously, abducing rain last night from the evidence of a wet lawn could lead to a false conclusion – even in the absence of rain, some other process such as dew or automatic lawn sprinklers may have resulted in the wet lawn.

The "duckness" adage of the introductory section provides another example of abductive reasoning. There is the surprising observation that this bird before us, swims, walks, and quacks like a duck. This observation would be a matter of course if the bird were a duck; therefore, there is reason to suspect that this bird is a duck.

Abduction is a form of logical inference that goes from an observation to a hypothesis that accounts for the observation and which explains the relevant evidence. Or, stated in a slightly different way, a cause is conjectured by observing its effect. Peirce first introduced the term "abduction" as "guessing" and said that to abduce a hypothetical explanation, say A: "it rained last night," from an observed circumstance, say B: "the lawn is wet," is to surmise that A may be true because then B would be a matter of course. Thus, to abduce A from B involves determining that A is sufficient (or nearly sufficient) for B to be true, but not necessary for B to be true.

There are several cautions that might be made at this point about abduction. The first goes back to the spirit of the zebra/horse di-

chotomy and suggests that the most-likely hypothesis A explaining B should typically be the first conjecture chosen to verify (or not). So, for example, if the hypothesis of rain last night is the most likely, it could be tested by first observing whether the street is also wet. When performing hypothesis assessment according to those that are the most plausible, the process is typically referred to as "inference to the best explanation." A second caution would prevent the classic Latin-phrased fallacies of *post hoc ergo propter hoc* ("after this, therefore because of this"), and *cum hoc ergo propter hoc* ("with this, therefore because of this"). So, just because there might be reason to suspect that A is the cause of B because of a (temporal) co-occurrence of A and B, that does not mean it has to be true. In a somewhat similar manner, a spatial co-occurrence of two events does not necessarily imply causality; for example, the observation, B, of a cluster of cancer cases in children from a specific area does not imply that the presence, A, of a nuclear reactor in the same area is necessarily the cause.

Besides introducing the notion of abduction, Peirce also provided a clever bean bag analogy to distinguish between the reasoning modes of induction, deduction, and abduction. A particularly accessible source for this illustration is C.S. Peirce, "Deduction, Induction, and Hypothesis" (*Popular Science Monthly*, *13*, 1878, 470–482). Note that the three reasoning modes are distinguished by the order of the three clauses labeled Rule, Case, and Result:

Deduction proceeds from the major (Rule) and minor (Case) premises to a conclusion (Result):

(Step 1) Rule: All the beans in this bag are white

(Step 2) Case: These beans are from this bag

Therefore,
(Step 3) Result: These beans are white

Induction is the inference of a major premise (Rule) from a minor premise (Case) and the conclusion (Result):
(Step 1) Case: These beans are from this bag
(Step 2) Result: These beans are white
Therefore,
(Step 3) Rule: All the beans in this bag are white
Because induction generally makes a conclusion based on a sample, a collection of beans being white from a specific bag suggests that *all* beans in the bag are white.

Abduction is the inference of the minor premise (Case) from the conclusion (Result) and the major premise (Rule):
(Step 1) Rule: All the beans in this bag are white
(Step 2) Result: These beans are white
Therefore,
(Step 3) Case: These beans are from this bag
To state this last abduction in the alternative Peirce form: "the surprising fact is observed that these beans are white"; "but if these beans were from this bag, then these beans being white would be a matter of course"; "therefore, there is reason to suspect that these beans are from this bag."

The information on Socrates being a mortal man provides another simple example of the three modes of reasoning. Deduction relies on the fact that Socrates is a member of the class of men who are all mortal:

Deduction

(Step 1) Rule: All men are mortal
(Step 2) Case: Socrates is a man
Therefore,
(Step 3) Result: Socrates is mortal

Induction infers the Rule or generalization that "all men are mortal" from the two bits of information that Socrates is both a man and is mortal:

Induction
(Step 1) Case: Socrates is a man
(Step 2) Result: Socrates is mortal
Therefore,
(Step 3) Rule: All men are mortal

Finally for abduction, it is first observed that Socrates is mortal; but if Socrates were a man, then Socrates being mortal would be a matter of course; so, there is reason to suspect that Socrates is a man, and that guess or hypothesis is made:

Abduction
(Step 1) Rule: All men are mortal
(Step 2) Result: Socrates is mortal
Therefore,
(Step 3) Case: Socrates is a man

The subsequent verification stages that may follow the identification of an abductive conjecture can also be phrased in syllogistic terms. Assuming A represents the explanatory conjecture for our original "surprising" observation, let B' now indicate some further observation(s) or experimental outcome(s) that should be obtained if A were true. If B' does occur, then the conjecture A becomes even

more plausible (and "stays in the running," so to speak). If, however, B' does not occur, the conjecture A does not then appear to be true. This situation possibly leads to the formation of an alternative explanatory hypothesis and/or to a rethinking that A being true should have led to B' being true. Stated another way, hypotheses are tested with (multiple) deductions, with a more final evaluation carried out by induction using these multiple verifications.[2]

1.2.2 Abduction as a General Model for How Science Progresses

The plausible reasoning scheme of "affirming the consequent" (or equivalently, Peirce's abduction), can serve as a model for how science typically progresses. One example has already been given in the Preface that involved Alexander Fleming's discovery of penicillin. As another and more current example, suppose the surprising fact is observed that the world appears to be warming. If there is an increase in the amount of greenhouse gases present in the atmosphere, then such warming would be a matter of course. Thus, there is reason to suspect that an increase in atmospheric greenhouse gases is occurring (and in turn, this increase is at least contributing to climate change). The continuing task of climate scientists is to make this particular hypothesis "stick" (or not, as the case may be), possibly by examining the historical record; the amount of increase in greenhouse gases and concomitant temperature rise; or by developing and testing the intermediate mechanisms (such as solar flares and warming, icecap melt, ocean level rise) by which the connection between greenhouse gas increase and climate change might operate.

For another recent example of how science proceeds first by ab-

duction and then with follow-up testing of the "guess" to bolster the plausibility of the hypothesis, there is the marvelous story of Barry Marshall and Robin Warren who jointly won the 2005 Nobel Prize for Physiology or Medicine. Through the initial surprising observation that the bacterium, *Helicobacter pylori*, was typically present when various stomach ailments were also occurring, Marshall and Warren made the case that the bacterium was the cause, and not the then assumed psychosomatic conjecture of "stress" and increased stomach acid. A few parts of an article are given below from the *New York Times* on October 4, 2005, announcing the Nobel Prize (Lawrence Altman, *Two Win Nobel Prize for Discovering Bacterium Tied to Stomach Ailments*). Notice, in particular, how the follow-up verifications proceeded, some through self-experimentation (by Barry Marshall), and the important role that antibiotics and other agents had in killing the bacterium and thereby relieving the various stomach ailments:

> Two Australian scientists who upset medical dogma by discovering a bacterium that causes stomach inflammation, ulcers and cancer won the 2005 Nobel Prize for Physiology or Medicine yesterday.
>
> The winners were Dr. Barry J. Marshall, 54, a gastroenterologist from the University of Western Australia in Nedlands, and Dr. J. Robin Warren, 68, a retired pathologist from the Royal Perth Hospital.
>
> ...
>
> A famous experiment Dr. Marshall conducted on himself was crucial in linking the bacterium to inflammation of the stomach, or gastritis, and showing that it resulted from an infection.
>
> ...
>
> After Dr. Marshall and Dr. Warren discovered the role of the

> spiral-shaped *H. pylori* bacterium, they and others conducted trials showing that antibiotics and drugs inhibiting the production of stomach acid could cure gastritis and most stomach and duodenal ulcers.
>
> ...
>
> In the early 1980's, Dr. Warren noted the bacterium in the lower part of the stomach in about half of the patients who had biopsies. *He made a crucial observation that signs of inflammation were always present in the surface lining of the stomach near where he observed the bacterium.* (italics added)
>
> ...

According to Peirce, the true source of scientific originality lies in abduction and in the formation of an explanatory hypothesis that accounts for some set of "surprising observations." As noted in the Preamble, Peirce went so far as to contend that "every single item of scientific theory which stands established today has been due to abduction." With this view in mind, abduction can be considered a general model for how science typically progresses as long as only those hypotheses are considered that can be put to experimental or (at least) observational test. Also, the "best" hypotheses that should be evaluated first would satisfy the three natural conditions of *coherence* (by accounting for all the "surprising" observations); *simplicity* (by being the least complex or contrived); and *generality* (by being able to explain the most pertinent observations, "surprising" or not).

Depending on the specific medical topic being studied, the verification paradigms for assessing the viability of a given explanatory conjecture can take on a variety of forms. For example, some might involve experimental manipulation of various kinds, such as the differential placement of livestock on contaminated/uncontaminated fields

(Theobald Smith); the institution of antiseptic procedures to prevent the propagation of infection (Ignaz Semmelweis; Joseph Lister); the inoculation of animals with a supposed cause of a specific disease obtained from other sources (Robert Koch; Charles Nicolle); the vaccination of humans and animals with various types of attenuated disease agents (Louis Pasteur; Edward Jenner).

Besides actually carrying out experimental manipulations, there are a variety of natural occurring experiments and subsequent observation that could prove useful in hypothesis verification and evaluation. These might include the presence of disinfecting mechanisms or various types of filtration systems to eliminate the putative cause of a particular disease (John Snow; William Budd; Patrick Manson); or, the identification of a vector for disease transmission by its ubiquitous presence whenever the disease occurs and its absence whenever the conjectured disease vector is missing (Paul-Louis Simond; Carlos Finlay; Patrick Manson; Charles Nicolle; Theobald Smith).

A set of repeated positive replications of various verification methods led Peirce to consider the original abductive conjecture to be more and more plausible. Peirce refers to this sequential procedure as *induction* (see endnote 2). Although one may never quite get to an absolute certainty as to the truth for an initial abductive conjecture, it would seem that one might be able to get close. How all of this could be formalized in greater detail is discussed in the Appendix that relies on Bayes Theorem and George Polya's view of (repeated) plausible reasoning. The central paradigm of plausible reasoning that can be replicated may be stated succinctly as follows: if A (the abductive conjecture) is true, then B (some set of circumstances) must be true; B is true and therefore, A is *more plausible* than before. As

noted above, a repeated series of these partial verification steps that trace the necessary consequences of the initial abductive hypothesis is what Peirce refers to as induction.

Notes

[1]The Latin word, *a posteriori*, provides another way of phrasing a Peircean pattern of abductive reasoning. *A posteriori* reasoning proceeds from observations and/or experiences to the formulation of probable causes. It moves from known facts or past events rather than just by making assumptions or predictions. To introduce another Latin word, Peircean abductive reasoning can be contrasted with *a priori* knowledge, which is somehow acquired independently of any particular experiences or observations.

[2]Peirce discussed abduction in a number of his writings. One convenient source is in the edited volume first published in 1940 by Justus Buchler, *Philosophical Writings of Peirce*. We give a short section below that was written in the early 1900s; it is from a chapter entitled, "Abduction and Induction" (pp. 151–152):

> Before we go further, let us get the points stated above quite clear. By a hypothesis, I mean, not merely a supposition about an observed object, as when I suppose that a man is a Catholic priest because that would explain his dress, expression of countenance, and bearing, but also any other supposed truth from which would result such facts as have been observed ... The first stating of a hypothesis and the entertaining of it, whether as a simple interrogation or with any degree of confidence, is an inferential step which I propose to call *abduction* [or *retroduction*]. This will include a preference for any one hypothesis over others which would equally explain the facts, so long as this preference is not based upon any previous knowledge bearing upon the truth of the hypotheses, nor on any testing of any of the hypotheses, after having admitted them on probation. I call all such inference by the peculiar name, *abduction*, because its legitimacy depends upon altogether different principles from those of other kinds of inference.
>
> Long before I first classed abduction as an inference it was recognized by logicians that the operation of adopting an explanatory hypothesis – which is just what abduction is – was subject to certain conditions. Namely, the hypothesis cannot be admitted, even

as a hypothesis, unless it be supposed that it would account for the facts or some of them. The form of inference, therefore, is this:

The surprising fact, C, is observed;
But if A were true, C would be a matter of course,
Hence, there is reason to suspect that A is true.

Thus, A cannot be abductively inferred, or if you prefer the expression, cannot be abductively conjectured until its entire content is already present in the premiss, "If A were true, C would be a matter of course."

...

The operation of testing a hypothesis by experiment, which consists in remarking that, if it is true, observations made under certain conditions ought to have certain results, and then causing those conditions to be fulfilled, and noting the results, and, if they are favourable, extending a certain confidence to the hypothesis, I call *induction*. For example, suppose that I have been led to surmise that among our coloured population there is a greater tendency toward female births than among our whites. I say, if that be so, the last census must show it. I examine the last census report and find that, sure enough, there was a somewhat greater proportion of female births among coloured births than among white births in that census year. To accord a certain faith to my hypothesis on that account is legitimate. It is a strong induction. I have taken all the births of that year as a sample of all the births of years in general, so long as general conditions remain as they were then. It is a very large sample, quite unnecessarily so, were it not that the excess of the one ratio over the other is quite small. ...

Part III

Four Early Nineteenth Century Medical Pioneers: Edward Jenner, Ignaz Semmelweis, John Snow, and William Budd

> The scientist takes off from the manifold observations of predecessors, and shows his intelligence, if any, by his ability to discriminate between the important and the negligible, by selecting here and there the significant steppingstones that will lead across the difficulties to new understanding. The one who places the last stone and steps across to the terra firma of accomplished discovery gets all the credit.
>
> – Hans Zinsser (1878–1940)

The first set of four narratives of medical discovery presented in this Part II all come from the earlier part of the Nineteenth Century and before a germ theory of disease causation had been firmly established in the latter part of that century by Louis Pasteur (1822–1895) and Robert Koch (1843–1910). The presentation begins with Edward Jenner (1749–1823), the "father of immunology," before moving on to a discussion of several infectious diseases other than smallpox, most notably typhoid fever and William Budd (1811–1880), cholera and John Snow (1813–1858), and puerperal (childbed) fever and Ignaz Semmelweis (1818–1865). In all four cases, substantial snippets and larger excerpts from the original writings of these investigators will be given, either incorporated directly into the chapter proper or in Appendices external to the book itself.

Edward Jenner (1749–1823): The first chapter in this Part II is reserved for the oldest of our medical researchers, Edward Jenner. This British physician developed the first vaccine, for smallpox, from the much milder malady of cowpox that regularly infected dairy maids and other farm workers exposed to infected cows. Prior to Jenner's cowpox-derived vaccine, the method used to protect against smallpox was to give a (hopefully) mild form of the disease itself through a process called variolation. Jenner's "surprising observation(s)" that

led to his abductive conjecture of cowpox being protective against smallpox was through his own inability to variolate individuals who previously had cowpox, and of the failure of dairy maids generally who had cowpox in their past to ever contract smallpox although they might be repeatedly exposed. Jenner performed a number of subsequent experimental verifications for his initial abductive conjecture. The most famous of these involved a dairy maid, Sarah Nelmes, infected with cowpox, and the inoculation of his gardener's son, James Phipps, with pus from Sarah Nelmes' hand. After Phipps came down with a mild case of cowpox and recovered, repeated variolations would "not take," thus showing an immunity to smallpox.

A second clever use of abductive reasoning by Jenner is from his study of the brood parasitism of the cuckoo. Jenner conjectured that the lone presence of a baby cuckoo left in a nest was due to the baby cuckoo itself expelling the others, contrary to all the current thinking at the time that it was the work of the adult cuckoos doing the expulsions. Jenner verified this hypothesis through repeated observation of baby cuckoos actually doing the expulsions themselves, including when additional eggs and/or nestlings were mechanically and repeatedly put back into the nest. Also, Jenner showed that baby cuckoos even had an adaptive groove in their backs for a short period after hatching which served as a spoon for the expulsions.

Ignaz Semmelweis (1818–1865): The second chapter in this Part II is devoted to Ignaz Semmelweis, a Hungarian obstetrician working at the large Vienna General Hospital in the late 1840s. The "surprising observation" that motivated all of Semmelweis' work was the dramatically high maternal mortality rate from puerperal (childbed) fever following births that were assisted by (male) doctors and medi-

cal students in one clinic as compared to a second clinic where births were carried out by (female) midwives. Semmelweis investigated a variety of conjectures, all to no avail, to explain the clinic differences. Some were evaluated experimentally (how priests gave last rites and differing birth positions), and others through general observation (crowding, diet, general care). After observing his close friend, Jacob Kolletschka, die of puerperal fever as a result of a scalpel wound during an autopsy, and noting that only the male physicians and students came directly from autopsies to examine the women in one clinic (but the midwives from the second clinic never performed autopsies), Semmelweis abductively hypothesized that puerperal fever was a contagious disease carried by cadaver material from the autopsies to the women who were examined soon thereafter. To test this conjecture experimentally, Semmelweis instituted chlorine handwashes before the examination of pregnant women, which resulted in a dramatic reduction in the maternal mortality rate and put the male doctor clinic "in line" with that staffed only by female midwives.

John Snow (1813–1858): The disease most closely associated with John Snow is cholera. His abductive hypothesis regarding cholera's mode of transmission was that it was carried by an oral-fecal route and primarily through drinking water, and was not the result of the then dominant miasma (or bad air) theory. The initial test of Snow's conjecture was done by the detailed study of cholera cases around the infamous Broad Street pump. Later, the study of different sources of city water in London and the differential prevalence of cholera cases provided yet another quasi-experimental test. Most of what John Snow did in evaluating his abductive conjecture would now be considered "shoe-leather" epidemiology, which still forms the basis

of that field as we know it today.

William Budd (1811–1880): The disease of most concern to William Budd was typhoid fever. In the sparsely populated rural area in which he practiced, Budd could clearly see the routes of transmission through water and an oral-fecal mechanism, much as Snow did for cholera. His primary abductive conjecture was that typhoid was a contagious disease caused by a living organism and disseminated by dejecta from the intestines of the sick. In terms of evidence for his hypothesis, Budd provided a variety of observational evidence as to typhoid's transmission – the instance of Richmond Terrace being one of the best examples. Also, Budd showed that the living agent, whatever it might be, could be killed by the use of disinfectants. Budd was also instrumental in disproving a miasma hypothesis for diseases such as cholera and typhoid by documenting the consistent presence of terrible smells without any attendant disease. In other words, one could have a great stink without disease, suggesting that a miasma theory for disease causation was misguided.

Budd also anticipated the possibility of an asymptomatic carrier state for typhoid that foreshadowed the saga of Typhoid Mary in the early 1900s. This chapter on William Budd includes the story of the sanitary engineer, George Soper, and his prescient abductive reasoning that eventually led to the identification of Typhoid Mary and her incarceration.

Chapter 2

Edward Jenner

> While the vaccine discovery was progressive, the joy I felt at the prospect before me of being the instrument destined to take away from the world one of its greatest calamities [smallpox], blended with the fond hope of enjoying independence and domestic peace and happiness, was often so excessive that, in pursuing my favourite subject among the meadows, I have sometimes found myself in a kind of reverie.
>
> – Edward Jenner (1749–1823)

> I hope that some day the practice of producing cowpox in human beings will spread over the world – when that day comes, there will be no more smallpox.
>
> – Edward Jenner (1749–1823)

The person of primary interest for this chapter, Edward Jenner (1749–1823), is known as the father of immunology for his development during the last part of the Eighteenth Century of a "safe" vaccine against smallpox. At the time of Jenner's discovery, smallpox was an extremely dreaded disease, with a mortality rate of some thirty percent and even higher among infants and children. Those who survived were commonly disfigured forever from the pockmarks that characterized the malady. It was also a leading cause of blind-

ness whenever it spread to the eyes as it frequently did. The only mitigating aspect of contracting smallpox, assuming that one survived, was of achieving a permanent immunity against ever having it again. What Jenner was able to develop was a means of obtaining such an immunity against smallpox through vaccination from the much milder and nonlethal cowpox.

President Thomas Jefferson wrote to Jenner in 1806 with the hope that his smallpox vaccine would soon rid the world of this terrible scourge:

> Future generations will know by history only that the loathsome smallpox has existed.

Jenner himself in reviewing the origins of smallpox vaccination in 1801, expressed a similar thought:

> The numbers who have partaken of its benefits [i.e., of vaccination] throughout Europe, and other parts of the globe, are incalculable; and it now becomes too manifest to admit of controversy, that the annihilation of the Small-pox, the most dreadful scourge of the human species, must be the final result of this practice.

It would take almost two-hundred more years, however, before these two sentiments would be realized. On May 8, 1980, the 33rd World Health Assembly officially declared the world free of smallpox, which represented the biggest achievement ever in international public health. Also, because smallpox was limited to humans only, with no animal reservoir for the virus, any future resurgence would have to be an explicit act of man-made bioterrorism.

During much of the Eighteenth Century, and prior to the introduction of Jenner's smallpox vaccine derived from the cowpox virus,

one mechanism for generating immunity to smallpox was called variolation (or inoculation). This involved a process of placing a small amount of active smallpox material, such as that obtained from a blister or pustule, under a person's skin, typically on the arm or leg. Presumably, the person so inoculated would get a very mild form of smallpox, but would then be forever immune. Unfortunately, there were several difficulties with variolation. First and foremost, such inoculations were not always safe — real active cases of smallpox developed that were in themselves contagious to others. Also, a non-trivial number of deaths occurred from variolation itself, and further serious infections were possible. It was also expensive and only the well-off could afford the procedure because it necessitated undergoing quarantine for a significant period of time. Those who needed smallpox immunity the most were probably paupers who were generally unemployable without it. Potential employers were reluctant to hire any person who might contract smallpox and then be a burden if only for their burial expenses.

The individual commonly credited with introducing variolation to England is Lady Mary Wortley Montegu (1689–1762), the wife of the British Ambassador to Turkey who took up his appointment in 1716 along with his accompanying wife. Lady Montegu was interested in any procedure that could protect against contracting smallpox, especially for her two children. Her brother had died of smallpox a few years earlier, and she herself had smallpox at age 26 in 1715 that left her without eyelashes and a severely disfigured face. As the following letter written in 1717 to her London friend, Sarah Chiswell, indicates, Lady Montegu became an advocate for variolation shortly after her arrival in Istanbul. She had her five-year-old son inoculated

in 1718 by the embassy surgeon, Charles Maitland. Upon her return to England in 1721, Maitland performed the first professional inoculation in England on her four-year-old daughter. It might be noted that the London friend, Sarah Chiswell, never did take Lady Montegu's recommendation to undergo variolation and died of smallpox in 1726:

> *Apropos* of distempers, I am going to tell you a thing, that will make you wish yourself here. The small-pox, so fatal, and so general amongst us, is here entirely harmless, by the invention of engrafting [variolation], which is the term they give it. There is a set of old women, who make it their business to perform the operation, every autumn, in the month of September, when the great heat is abated.
>
> People send to one another to know if any of their family has a mind to have the small-pox; they make parties for this purpose, and when they are met (commonly fifteen or sixteen together) the old woman comes with a nut-shell full of the matter of the best sort of small-pox, and asks what vein you please to have opened.
>
> She immediately rips open that you offer to her, with a large needle (which gives you no more pain than a common scratch) and puts into the vein as much matter as can lie upon the head of her needle, and after that, binds up the little wound with a hollow bit of shell, and in this manner opens four or five veins.
>
> The Grecians have commonly the superstition of opening one in the middle of the forehead, one in each arm, and one on the breast, to mark the sign of the Cross; but this has a very ill effect, all these wounds leaving little scars, and is not done by those that are not superstitious, who choose to have them in the legs, or that part of the arm that is concealed.
>
> The children or young patients play together all the rest of the day, and are in perfect health to the eighth. Then the fever begins to seize them, and they keep their beds two days, very seldom three. They have very rarely above twenty or thirty in their faces, which never mark, and in eight days time they are as well as before

> their illness. Where they are wounded, there remains running sores during the distemper, which I don't doubt is a great relief to it.
>
> Every year, thousands undergo this operation, and the French Ambassador says pleasantly that they take the small-pox here by way of diversion, as they take the waters in other countries. There is no example of any one that has died in it, and you may believe I am well satisfied of the safety of this experiment, since I intend to try it on my dear little son. I am patriot enough to take the pains to bring this useful invention into fashion in England, and I should not fail to write to some of our doctors very particularly about it, if I knew any one of them that I thought had virtue enough to destroy such a considerable branch of their revenue, for the good of mankind. But that distemper is too beneficial to them, not to expose to all their resentment, the hardy weight that should undertake to put an end to it. Perhaps if I live to return, I may, however, have courage to war with them. Upon this occasion, admire the heroism in the heart of your friend.

On her return to England, Lady Montegu lobbied the English royal family to support the practice of variolation. This was done primarily through Princess Caroline of Anspach, the wife of the then Prince of Wales. Charles Maitland was granted royal permission to conduct an experimental trial inoculation that would demonstrate its safety. Six condemned prisoners from Newgate Prison underwent variolation in 1721, as witnessed by the King's physicians and some several dozen medical representatives, mostly from the Royal Society of the College of Physicians. All survived and received their freedom. Finally, the Prince of Wales' two daughters were inoculated in 1722, as sanctioned by their grandfather, George I. From that point on in the Eighteenth Century, variolation developed into a somewhat routine practice, at least for those who could afford all the expenses involved. This included royalty outside of England; for example,

Catherine the Great of Russia and her son, the future Tsar Paul, were inoculated in 1768.

Variolation came to the United States through the unlikely person of Cotton Mather, the New England Puritan minister who figured so prominently in the Salem witch trials of 1692. In 1706, the congregation of Boston's Old North Church purchased a slave for Mather, who he named Onesimus after an escaped biblical slave converted to Christianity by the Apostle Paul. On questioning him as to whether he ever had smallpox, Onesimus said that he had been inoculated in Africa and was therefore immune; as proof, he showed Mather the scar on his arm. Given the periodic smallpox epidemics that plagued Boston, Mather was rightly intrigued by this immunity assertion from his slave and proceeded to verify the presence of variolation among other slaves in the Boston area who were also originally from Africa. The final proof of variolation effectiveness for Mather came from a Greek physician, Emmanuel Timoni, writing in the 1714 *Philosophical Transactions of the Royal Society* on his experiences with variolation in Turkey: *An Account, or History, of the Procuring the Small Pox by Incision, or Inoculation; as it Has for Some Time Been Practiced at Constantinople.*

A smallpox epidemic affecting Boston during 1721–1722 gave Mather an opportunity to demonstrate the effectiveness of variolation. Unfortunately, he was able to convince only one doctor, Zabdiel Boylston, to engage in the inoculation process for the Boston community. After Boylston introduced inoculation to North America by first variolating his own young son and two of his slaves, he went on to inoculate some 280 Bostonians, 6 of whom died (about 2.1 percent); of the 5,759 Bostonians contracting smallpox during this period, there were

some 844 deaths (about 14.7 percent). This may be one of the first community-wide empirical demonstrations for the mortality reduction possible through variolation (these data are given in Boylston's 1726 book: *An Historical Account of the Small-Pox Inoculated in New England Upon all Sorts of Persons, Whites, Blacks, and of all Ages and Constitutions*).

* * *

The main figure for this chapter, Edward Jenner, was born in May of 1749 in Berkeley, Gloucestershire. His father was the vicar of Berkeley, suggesting a relatively affluent family. After receiving an elementary education in the local area, Jenner was apprenticed for seven years, beginning when he was fourteen, to Daniel Ludlow, a surgeon of Chipping Sodbury in South Gloucestershire. It was during this apprenticeship period that Jenner first heard the folk wisdom about cowpox being protective against contracting smallpox. This latter information appeared in the form of individuals for whom variolation would "not take," or in the common legends about dairy maids forever having perfect skin because they could never get smallpox because of an earlier bout with cowpox.[1]

Upon completion of his first apprenticeship with Ludlow in 1770 when he was twenty-one, Jenner went on to study with one of the most famous surgeons and scientists of the day, John Hunter at St. George's Hospital in London. Hunter was an avid naturalist, and long

[1]The folk wisdom connection between having had cowpox and a subsequent immunity to cowpox dates backs to at least the early Seventeenth Century. As one often-repeated story goes, the notorious Barbara Palmer (1640–1709), the Duchess of Cleveland, and the favorite mistress of Charles II, was being teased by courtiers on the possible loss of her status as Lady of the Bedchamber should smallpox bring her disfigurement. She is said to have replied that she had nothing to fear, for she had had the cowpox.

after Jenner's formal education with him had ended, they remained in close correspondence on various topics in natural history until Hunter's death in 1793. As an early advocate of careful observation and the scientific method, Hunter was very influential in Jenner's career beginning with Jenner's study of the cuckoo. This latter work eventually earned him the distinction of being named a Fellow of the Royal Society in 1788. This election was a direct result of Jenner following Hunter's advice: "don't think; try (or experiment)." Before continuing to Jenner's work with cowpox vaccination, some of this earlier research with the cuckoo will be reviewed. This was all carried out after Jenner's return to his native Berkeley countryside in 1773, and during the time he was developing a career as a successful area family doctor.

As was known in Jenner's time, the English cuckoo is a brood parasite and does not build its own nest. Instead, female cuckoos deposit their eggs in the nests of other birds and have these foster parents raise their young. Also, any eggs or nestlings belonging to the foster parents are somehow destroyed, leaving only a single cuckoo to be cared for. It was assumed that either the cuckoo parent birds or the foster parents were somehow responsible for the destruction of the non-cuckoo eggs and nestlings — because how else could a solitary cuckoo remain in the nest to be raised by the foster-parent birds? It was this behavior of the cuckoo that Hunter encouraged Jenner to study in the countryside around his home in Berkeley. Hunter apparently hoped that Jenner might prepare a manuscript suitable for publication in the *Philosophical Transactions* that would also be sufficient for election to Fellow of the Royal Society.

After initially preparing a manuscript containing some more-or-

less superficial observations about the behavior of the cuckoo that accepted the common wisdom about the parent cuckoos and/or the foster parents themselves destroying the foster-parent eggs and nestlings, Jenner was given a "revise and resubmit" decision based on some new observational and experimental data that he had collected after the initial manuscript had been submitted. These revisions centered around what can be characterized as a specific abductive reasoning conjecture accounting for the eventual presence of a sole cuckoo remaining in the foster-parent nest. Explicitly, if the sole cuckoo left in the nest were itself responsible for removing all other eggs and nestlings, then the lone presence of the cuckoo would be a matter of course. In a series of astute observations and innumerable experimental manipulations involving additions and removals of eggs and nestlings to the foster-parent nests, Jenner made the case that it was the solitary cuckoo itself that emptied the nest of any competitors. To make the argument for this remarkable inference even stronger, Jenner demonstrated by dissection a clever evolutionary adaptive skeleton in a newly-born cuckoo. This was in the form of a depression in its back that enabled a newly-hatched cuckoo to cup eggs or other nestlings so that they might be expelled more easily from the nest. This skeletal depression disappeared some dozen days after the cuckoo had been hatched.

A large part of the *Philosophical Transactions* paper is included in an Appendix external to this chapter that earned Jenner the sought for initials after his name of F.R.S.; note, in particular, the exemplary experimental technique in how the Titlarks were identified in Example I.

Jenner's contention that the sole cuckoo remaining in the nest was

itself responsible for the emptiness of the nest, was considered preposterous by several well-known English naturalists in the early Nineteenth Century, such as Charles Waterton (1782–1865). It wasn't until the Victorian illustrator, Jemima Blackburn (1823–1909), published her *Birds from Nature* (1868) that Jenner's observations were generally accepted. Blackburn included an explicit drawing and description of the ejection of nestling meadow pipits by a blind and naked cuckoo hatchling. The interested reader might consult the more recent, *Blackburn's Birds*, edited by Rob Fairly (1993), which presents the complete story. For those who might wish to see a video of the removal process by a cuckoo nestling, we might suggest the one done by Artur Homan:

https://naturedocumentaries.org/4727/cuckoo-artur-homan/

Alternatively, Google "david attenborough cuckoo" to see a BBC wildlife video produced by David Attenborough.

* * *

Although the *Philosophical Transactions* paper on the cuckoo earned Jenner a coveted Fellow status in the Royal Society, it was his 1798 monograph on a cowpox vaccination against smallpox that initiated Jenner's reputation as the father of immunology: *An Inquiry Into the Causes and Effects of the Variole Vaccinae, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of The Cow Pox*. An earlier version of this monograph had been rejected by the Royal Society for what they considered was too little evidence for the extraordinary claims being made. Jenner proceeded to publish the monograph at his own expense, including two additional sections

added in 1799 and 1800 that contained some further discussion and observations about the cowpox vaccine.

In the initial 1798 monograph, a total of twenty-three cases were presented, all involving cowpox as somehow protective against contracting smallpox. Most of these cases were retrospective and provided non-experimental observational instances in which cowpox was present earlier in a person's life and who later did not contract smallpox when, for example, caring for others with active cases, or for whom variolation would "not take." In addition to the many retrospective cases, there were two sets of rightly-famous experimental demonstrations that gave the monograph its importance as convincing evidence for the protective effects of having had cowpox and the immunity it provided with respect to smallpox. These two sets of cases from the 1798 monograph are given below. The first set (Cases XVI and XVII) involve a dairymaid, Sarah Nelmes, with an active case of cowpox, and James Phipps, the son of Jenner's gardener, who was vaccinated from her cowpox pustule on May 14, 1796, a date that is still commemorated. After vaccination, Phipps showed no effects from repeated variolation. The second set of cases start with William Summers (Case XX) and end with J. Barge (Case XXIII). This sequence of cases showed the feasibility of sequential vaccination, passing from one human subject to another through many gradations without the vaccine material losing its potency:

> CASE XVI
>
> Sarah Nelmes, a dairymaid at a farmer's near this place, was infected with the Cow Pox from her master's cows in May, 1796. She received the infection on a part of the hand which had been previously in a slight degree injured by a scratch from a thorn. A large pustulous sore and the usual symptoms accompanying the disease

were produced in consequence. The pustule was so expressive of the true character of the Cow Pox, as it commonly appears upon the hand, that I have given a representation of it in the annexed plate. The two small pustules on the wrists arose also from the application of the virus to some minute abrasions of the cuticle, but the livid tint, if they ever had any, was not conspicuous at the time I saw the patient. The pustule on the forefinger shews [sic] the disease in an earlier stage. It did not actually appear on the hand of this young woman, but was taken from that of another, and is annexed for the purpose of representing the malady after it has newly appeared.

CASE XVII

The more accurately to observe the progress of the infection, I selected a healthy boy, about eight years old, for the purpose of inoculation for the Cow Pox. The matter was taken from a sore on the hand of a dairymaid [Sarah Nelmes] who was infected by her master's cows, and it was inserted, on the 14th of May, 1796, into the arm of the boy [James Phipps] by means of two superficial incisions, barely penetrating the cutis, each about half an inch long. On the seventh day he complained of uneasiness in the axilla, and on the ninth he became a little chilly, lost his appetite, and had a slight headache. During the whole of this day he was perceptibly indisposed, and spent the night with some degree of restlessness, but on the day following he was perfectly well.

The appearance of the incisions in their progress to a state of maturation were much the same as when produced in a similar manner by variolous matter. The only difference which I perceived was, in the state of the limpid fluid arising from the action of the virus, which assumed rather a darker hue, and in that of the efflorescence spreading round the incisions, which had more of an erysipelatous look than we commonly perceive when variolous matter has been made use of in the same manner; but the whole died away (leaving on the inoculated parts scabs and subsequent eschars) without giving me or my patient the least trouble.

In order to ascertain whether the boy, after feeling so slight an affection of the system from the Cow Pox virus, was secure from the contagion of the Small Pox, he was inoculated the 1st of July following with variolous matter, immediately taken from a pustule. Several slight punctures and incisions were made on both his arms, and the matter was carefully inserted, but no disease followed. The same appearances were observable on the arms as we commonly see when a patient has had variolous matter applied, after having either the Cow Pox or the Small Pox. Several months afterwards he was again inoculated with variolous matter, but no sensible effect was produced on the constitution.

...

CASE XIX

William Summers, a child of five years and a half old, was inoculated the same day with Baker, with matter taken from the nipples of one of the infected cows, at the farm alluded to ... He became indisposed on the sixth day, vomited once, and felt the usual slight symptoms till the eighth day, when he appeared perfectly well. The progress of the pustule, formed by the infection of the virus was similar to that noticed in Case XVII, with this exception, its being free from the livid tint observed in that instance.

CASE XX

From William Summers the disease was transferred to William Pead, a boy of eight years old, who was inoculated March 28th. On the sixth day he complained of pain in the axilla, and on the seventh was affected with the common symptoms of a patient sickening with the Small Pox from inoculation, which did not terminate till the third day after the seizure. So perfect was the similarity to the variolous fever that I was induced to examine the skin, conceiving there might have been some eruptions, but none appeared. The efflorescent blush, around the part punctured in the boy's arm was so truly characteristic of that which appears on variolous inoculation, that I have given a representation of it. The drawing was made

when the pustule was beginning to die away, and the areola retiring from the centre. ...

CASE XXI

April 5th: Several children and adults were inoculated from the arm of William Pead. The greater part of them sickened on the sixth day, and were well on the seventh, but in three of the number a secondary indisposition arose in consequence of an extensive erysipelatous inflammation which appeared on the inoculated arms. It seemed to arise from the state of the pustule, which spread out, accompanied with some degree of pain, to about half the diameter of a six-pence. One of these patients was an infant of half a year old. By the application of mercurial ointment to the inflamed parts (a treatment recommended under similar circumstances in the inoculated Small Pox) the complaint subsided without giving much trouble.

Hannah Excell, an [sic] healthy girl of seven years old, and one of the patients above mentioned received the infection from the insertion of the virus under the cuticle of the arm in three distinct points. The pustules which arose in consequence, so much resembled, on the ninth day, those appearing from the insertion of variolous matter, that an experienced inoculator would scarcely have discovered a shade of difference at that period. Experience now tells me that almost the only variation which follows consists in the pustulous fluids remaining limpid nearly to the time of its total disappearance; and not, as in the direct Small Pox, becoming purulent. ...

CASE XXII

From the arm of this girl matter was taken and inserted April 12th into the arms of John Marklove, one year and a half old, Robert F. Jenner, eleven months old, Mary Pead, five years old, and Mary James, six years old.

Among these Robert F. Jenner did not receive the infection. The arms of the other three inflamed properly, and began to affect the

system in the usual manner; but being under some apprehensions from the preceding cases that a troublesome erysipelas might arise, I determined on making an experiment with the view of cutting off its source. Accordingly after the patients had felt an indisposition of about twelve hours, I applied in two of these cases out of the three, on the vesicle formed by the virus, a little mild caustic, composed of equal parts of quick-lime and soap, and suffered it to remain on the part six hours. It seemed to give the children but little uneasiness, and effectually answered my intention in preventing the appearance of erysipelas. Indeed it seemed to do more, for in half an hour after its application, the indisposition of the children ceased. These precautions were perhaps unnecessary, as the arm of the third child, Mary Pead, which was suffered to take its common course, scabbed quickly, without any erysipelas.

CASE XXIII

From this child's arm matter was taken and transferred to that of J. Barge, a boy of seven years old. He sickened on the eighth day, went through the disease with the usual alight symptoms, and without any inflammation on the arm beyond the common efflorescence surrounding the pustule, an appearance so often seen in inoculated Small Pox.

After the many fruitless attempts to give the Small Pox to those who had the Cow Pox, it did not appear necessary nor was it convenient to me, to inoculate the whole of those who had been the subjects of these late trials; yet I thought it right to see the effects of variolous matter on some of them, particularly William Summers, the first of these patients who had been infected with matter taken from the cow. He was therefore inoculated with variolous matter from a fresh pustule; but, as in the preceding cases, the system did not feel the effects of it in the smallest degree. I had an opportunity also of having this boy (Barge) and William Pead inoculated by my nephew, Mr. Henry Jenner, whose report to me is as follows: "I have inoculated Pead and Barge, two of the boys whom you lately

> infected with the Cow Pox. On the second day the incisions were inflamed, and there was a pale inflammatory stain around them. On the third day these appearances were still increasing and their arms itched considerably. On the fourth day the inflammation was evidently subsiding, and on the sixth it was scarcely perceptible. No symptom of indisposition followed.
>
> To convince myself that the variolous matter made use of was in a perfect state, I at the same time inoculated a patient with some of it who never had gone through the Cow Pox, and it produced the Small Pox in the usual regular manner."
>
> These experiments afforded me much satisfaction, they proved that the matter in passing from one human subject to another, through five gradations, lost none of its original properties, J. Barge being the fifth who received the infection successively from William Summers, the boy to whom it was communicated from the cow.

The reactions to Jenner's monograph were somewhat mixed. Several critics were dismissive merely because of Jenner's earlier extraordinary claims about the cuckoo. But some criticism was more nuanced and required an effort on Jenner's part to respond and develop further explanatory context. One major class of counterexamples offered by some critics were instances in which a person supposedly had cowpox but still contracted smallpox either naturally or by variolation. Here, Jenner made a distinction between "spurious" and "true" cowpox, where the former was a disease that mimicked the look of having cowpox but really wasn't, and therefore, offered no future protection against smallpox. Another class of difficulties included those where someone may have been vaccinated with the cowpox but got smallpox either through variolation or naturally. For these cases, Jenner needed a notion of potency of the cowpox vaccine material being lost over time. In general, Jenner was mostly right in

these assertions about true and spurious cowpox and vaccine degradation, but at the time he had no way of showing it convincingly. To some, these refinements may have seemed like so much post-hoc rationalizations for failure.

There are several areas in which Jenner was not right initially, but over time most of these miscues faded in the face of the seminal contributions that the monograph actually made. One prominent example was a contention that cowpox originated from an inflammation of a horse's heels, called "grease." It is now known that the repository for cowpox was probably the rodent, and although there is such a thing as horsepox, "grease" was not the forerunner of cowpox. A second misstep by Jenner was a belief that immunity lasts forever once vaccinated with the true cowpox. As is now understood, vaccinations for many diseases require booster shots or re-vaccination to maintain immunity over time. Jenner's assertion of lifelong immunity was a serious mistake since when immunity appeared to fail, he had to attribute it to other causes without any real proof, such as vaccinator error, the use of spurious cowpox, or vaccine material that had lost its potency.

Another criticism of Jenner's monograph centered around the fact that he was not the first to consider the cowpox as a protective against smallpox, and therefore, he lacked priority. One instance pointed to was John Fewster, an inoculator in Gloucestershire who had failed repeatedly to variolate two brothers. Upon questioning, both brothers denied ever having smallpox but did acknowledge cases of cowpox in their past. This was in 1763, the same year that Jenner began his apprenticeship with Ludlow. In the local medical gathering that involved Fewster, Ludlow, and several others including possibly

Jenner, this failure to variolate was discussed extensively, possibly strengthening the connections Jenner was developing about cowpox providing an immunity to smallpox.

An instance of actual cowpox vaccination involved a dairy farmer, Benjamin Jesty. His two dairy maids routinely took care of smallpox patients and never contracted the malady themselves. Both asserted their immunity was due to earlier cowpox infections. On this informational basis and because of an approaching smallpox epidemic, Jesty vaccinated his wife and two young sons with material from a nearby farmer who had cows with active cowpox pustules. Neither Jesty and Fewster made any attempt to communicate their efforts to any larger body. And that was Jenner's unique contribution — he proved immunity was generated through vaccination with cowpox; and further showed that person-to-person vaccination was possible. As noted by Francis Darwin (1914): "In science, the credit goes to the man who convinces the world, not to the man to whom the idea first occurs."

* * *

As might have been expected, the publication of Jenner's *Inquiry* elicited substantial interest among the medical community, including in particular, George Pearson, who published his own observations within months of Jenner's monograph. Pearson's title was: *An Inquiry Concerning the History of the Cowpox* (1798). In early 1799, Pearson helped set up the Original Vaccine Pock Institute in London and started to distribute the cowpox vaccine. Unfortunately, some samples became contaminated with the actual smallpox virus causing several serious reactions when administered. Because this

was attributed incorrectly to the cowpox vaccine itself, it caused some major confrontations with Jenner who believed that his own work was being compromised. Partly because of this and to reassert credit for the cowpox vaccine, Jenner published the article on the origins of the cowpox vaccine that is given in an Appendix external to this chapter. Jenner's article includes a number of major points of clarification. First, Jenner reviews how he first came to the abductive conjecture about cowpox being protective against smallpox. He then goes on to make a distinction between "true" and "spurious" cowpox, and the need to maintain potency so the cowpox material can have its desired effect. Although Jenner attributed a failure to protect against the smallpox to an attenuation of the cowpox material itself, it may also be due to the need for re-vaccination after some period of time. As we have noted, Jenner always believed in life-long immunity, which, as we now know, is generally false. Finally, Jenner rightly reviews the two strongest experimental pieces of evidence in his monograph for the immunity that the cowpox vaccine provides: the Sarah Nelmes/James Phipps cases (XVI and XVII), and the successive vaccinations over several individuals (XIX through XXIII).

George Pearson was highly envious of Jenner's growing reputation, and went so far as to oppose Jenner's petition to Parliament for financial assistance for his extraordinary efforts to distribute the cowpox vaccine to all who wanted it. Jenner's own medical practice had suffered greatly because of the time he had devoted to the promotion of the cowpox vaccine; also, he had incurred substantial expenses in self-publishing his *Inquiry*. Pearson opposed Jenner's petition and offered an alternative narrative that detailed his own contributions. He also highlighted evidence that Jenner did not dis-

cover the cowpox vaccination and pointed to the farmer Benjamin Jesty and others, who Pearson argued had claims of priority although none of this had ever been communicated publicly. Eventually, Pearson just faded away. Jenner's reputation, on the other hand, only increased over the next several hundred years — he was the first person to show convincingly how the use of a harmless measure (cowpox vaccination) could protect against a deadly disease (of smallpox).

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Chapter 3

Ignaz Semmelweis

> When I look back upon the past, I can only dispel the sadness which falls upon me by gazing into that happy future when the infection [puerperal fever] will be banished. But if it is not vouchsafed for me to look upon that happy time with my own eyes ... the conviction that such a time must inevitably sooner or later arrive will cheer my dying hour.
>
> – Ignaz Semmelweis (1818–1865)

During the last years of her reign, Maria Theresa (1717–1780), the only female ruler ever for the vast Hapsburg Empire, laid the foundations for the large General Hospital of Vienna (*Allgemeines Krankenhaus der Stadt Wein*). Formally established four years after her death in 1784 by her Emperor son, Joseph II, the hospital included a lying-in unit for women giving birth. Typically, women admitted to the lying-in hospital were pregnant unwed charity patients receiving free medical care and support for some period of time before and after giving birth. This was all in exchange for participation in the ongoing medical instruction carried out in the unit for both the male obstetricians in training and female student midwives. Also, whenever a woman gave birth in a state hospital, the state itself would accept responsibility for the child. So once born, new infants

could be transferred directly to an adjoining foundling hospital, thus avoiding the infanticide and abortion common in the larger community. From its inception, this lying-in unit of the General Hospital was the largest facility of its kind in the world.[1]

Continuing the autocratic but somewhat enlightened policies of his mother, Joseph II sent Lucas Boër to the United Kingdom to learn English midwifery practice. Upon his return in 1788, Boër was appointed professor of midwifery and director of the new Viennese lying-in hospital. Boër's views on childbirth centered on patience and letting nature take both its course and time. This practice permitted only a limited and judicious use of forceps in delivery so as to avoid harm to the tissues of a mother that aggressive medical intervention often produced. Also, and contrary to hospital regulations requiring obstetrical students to practice on cadavers, Boër only permitted the use of fabricated leather mannequins. Given Boër's reluctance to force his students to perform autopsies and his general dislike of pathological anatomy, which emphasized the structural changes accompanying disease that were identifiable through such autopsies, he was forced to resign in 1822 after some thirty-odd years of directing the lying-in hospital. For future reference, the mortality rate due to puerperal (or childbed) fever in Boër's last year of 1822 was 0.8 percent (based on 26 deaths for 3,066 births). As we now know all too well, most cases of puerperal or childbed fever are due to an infection from Group A *Streptococcus pyogenes* obtained from some external

[1]Poignant stories could be told for many of the charity patients admitted anonymously to the lying-in hospital. Upon admission, the patient's name and address were written on a piece of paper and sealed, and then put on a shelf next to her bed. When a patient died, the paper was unsealed so that next-of-kin and/or neighbors could be notified. When the patient survived, the unopened piece of paper was returned upon discharge.

source during the time a birthing woman was present in a maternity unit. In the Nineteenth Century such an infection invariably led to a pyemia or septicemia (blood poisoning) that proved fatal.

Boër's replacement was Johannes Klein, one of his former students and an assistant who could charitably be called a sycophant (German: *Höfling*). Klein immediately resumed autopsies on female and fetal corpses, and required both the male students and female midwives to practice obstetrical manipulations on cadavers so their training would be as realistic as possible. Again, for future reference, during Klein's first year of 1823 as director of the Vienna maternity clinic, the mortality rate from puerperal fever was 7.5 percent (based on 217 deaths for 2,873 births), and about ten times the rate from Boër's last year of 1822.

Because of an increasing demand on the Vienna maternity clinic from the large number of unwed charity patients, two separate clinics were formed in the early 1830s (the First and Second Clinic for future reference) that initially carried out identical functions — one-half of the male obstetrical students and one-half of the female student midwives were assigned to each of the two clinics. This even distribution of personnel, however, was changed by governmental edict in 1840. After that date, all male students plus a number of female student midwives would be assigned to the First Clinic; all remaining female student midwives were assigned to the Second Clinic.

Admission to the two clinics was done on a rotating (and obviously less than random) basis. All women needing special medical care were assigned directly to the First Clinic where male obstetricians were being trained. The remaining patients were then allocated to the two clinics according to the day of the week based on the following

scheme: starting on Monday afternoon at four p.m., new admissions went to the First Clinic; twenty-four hours later at four p.m. on Tuesday, the Second Clinic received new admissions; and so on. For the forty-eight hour period from Friday to Sunday afternoon, all admissions went to the First Clinic. Thus, the First Clinic received patients for one more day than did the Second Clinic, and therefore had some four to five hundred more admissions per year.

* * *

Into this two clinic structure entered our protagonist, Ignaz Semmelweis (1818–1865), variously referred to after his death as the "father of infection control," the "saviour of mothers," and much less generously, the "fool of Pest." Born in what is now Budapest, Hungary, in 1818, Semmelweis received a doctor of medicine degree in 1844 from the University of Vienna. Failing to obtain a preferred clinical appointment in internal medicine, Semmelweis decided instead to specialize in obstetrics. After completing the practical obstetrics course offered in the First Clinic and obtaining a Master of Midwifery degree, he applied for and was appointed an assistant to Professor Klein in 1846, a position that would now be the equivalent to that of chief resident. Semmelweis was responsible for examining patients each morning in preparation for Professor Klein's rounds conducted later, supervising difficult deliveries, and generally for teaching the students in obstetrics. He was also the clerk of records, a position that required amassing and analyzing the mortality data meticulously kept for the First and Second Clinics, and since its founding in 1784, for the lying-in hospital more generally.

A first "surprising" observation that Semmelweis made and which

would serve as the initial step in an abductive reasoning scheme looking for the cause of puerperal fever, was in the major mortality differences present between the First and Second Clinics. The Second Clinic staffed only by female student midwives had by far the much lower rates. This difference was even anecdotally known to Vienna proper; women begged on their knees to be admitted to the Second Clinic in the event they mistakenly came on the wrong day when only First Clinic admissions were being done. But the most dramatic documentation for this mortality difference appeared as Table 1 in the Semmelweis *magnum opus* published in 1861: *The Etiology, the Concept and the Prophylaxis of Childbed Fever*. This table, provided below, gives puerperal fever mortality rates for the First and Second Clinics over the years from 1841 to 1846. As can be seen, the overall mortality rates differ by a factor of three: 3.38 for the Second Clinic versus 9.92 for the First Clinic.[2]

Table 3.1: Mortality Rates for the First and Second Clinics: 1841 to 1846

	First Clinic			Second Clinic		
Year	Births	Deaths	Rate	Births	Deaths	Rate
1841	3,036	237	7.8	2,442	86	3.5
1842	3,287	518	15.8	2,659	202	7.6
1843	3,060	274	9.0	2,739	164	6.0
1844	3,157	260	8.2	2,956	68	2.3
1845	3,492	241	6.9	3,241	66	2.0
1846	4,010	459	11.4	3,754	105	2.8
Totals	20,042	1,989	9.92	17,791	691	3.38

To phrase the abductive process more clearly that would eventually help identify a cause for puerperal fever, first, the surprising

[2]The translation and edited version of the Semmelweis treatise used throughout this chapter is from K. Codell Carter, published in 1983 by the University of Wisconsin Press.

fact was observed of a mortality discrepancy between the First and Second Clinics. If some difference in (medical) practice existed between the First and Second Clinics that had mortality implications, then the mortality difference would (or could) be a matter of course. Therefore, there is reason to hypothesize or suspect that some difference in medical practice exists. In a search for factors that might help distinguish the First from the Second Clinic and that might therefore be associated with and help explain the mortality discrepancy, Semmelweis first considered two broad categories of possible explanations. One of these included factors that could actually be manipulated experimentally with the results then observed. A second category included factors that could be dismissed more-or-less out-of-hand because of "common sense" reasoning. We first deal with two of the experimental manipulations that Semmelweis performed as quoted in *The Etiology, ...* The first involved a change in religious practice; the second imposed a constancy within clinics as to how women were positioned when births actually occurred:

> Even religious practices did not escape attention. The hospital chapel was so located that when the priest was summoned to administer last rites in the second clinic, he could go directly to the room set aside for ill patients. On the other hand, when he was summoned to the first clinic he had to pass through five other rooms because the room containing ill patients was sixth in line from the chapel. According to accepted Catholic practice when visiting the sick to administer last rites, the priest generally arrived in ornate vestments and was preceded by a sacristan who rang a bell. This was supposed to occur only once in twenty-four hours. Yet twenty-four hours is a long time for someone suffering from childbed fever. Many who appeared tolerably healthy at the time of the priest's visit, and who therefore did not require last rites, were so ill a

few hours later that the priest had to be summoned again. One can imagine the impression that was created on the other patients when the priest came several times a day, each time accompanied by the clearly audible bell. Even to me it was very demoralizing to hear the bell hurry past my door. I groaned within for the victim who had fallen to an unknown cause. The bell was a painful admonition to seek this unknown cause with all my powers. It had been proposed that even this difference in the two clinics explained the different morality rates. ... I appealed to the compassion of the servant of God and arranged for him to come by a less direct route, without bells, and without passing through the other clinic rooms. Thus, no one outside the room containing the ill patients knew of the priest's presence. The two clinics were made identical in this respect as well, but the mortality rate was unaffected. (pp. 71–73)

...

The reader can appreciate my perplexity ... when I, like a drowning person grasping at a straw, discontinued supine deliveries, which had been customary in the first clinic, in favor of deliveries from a lateral position. I did this for no other reason than that the latter were customary in the second clinic. I did not believe that the supine position was so detrimental that additional deaths could be attributed to its use. But in the second clinic deliveries were performed from a lateral position and the patients were healthier. Consequently, we also delivered from the lateral position, so that everything would be exactly as in the second clinic. (p. 87)

The deductive syllogistic paradigm in its contrapositive form (also called *modus tollens*) can serve as a model for how reasoning might proceed when experimental interventions are possible. For example, the supine/lateral position birthing conjecture can be phrased as follows: If (A: delivering from a supine position is more likely to lead to puerperal fever as compared to a lateral delivery), then (B: mortality will drop in the First Clinic when all deliveries are done

from a lateral position). But B is not true; therefore, A is not true. Or, in evaluating the change in religious practice: If (A: continually hearing bells and seeing priests constantly pass by for last rites makes puerperal fever more likely), then (B: mortality will drop in the First Clinic when the last rites bells are stopped and the priests no longer pass by all rooms). But, again, B is not true; therefore, A is not true.

Reasoning in a nonexperimental context but in a manner similar to the contrapositive syllogistic format could be phrased somewhat like this: if a cause for puerperal fever was proposed that led to other implications that were not true or contrary to established fact(s) and/or common sense, then that cause could be rejected as implausible. Although there are several of these mentioned later that can be extracted from Semmelweis's thinking, the most common explanation for puerperal fever was that it was due to some type of epidemic influence which at the time was synonymous with atmospheric-cosmic-telluric (terrestrial) changes (or a miasma) that spread over an area causing puerperal fever in women in confinement. In comments quoted below, Semmelweis raises the obvious question as to why the First and Second Clinics, situated so closely adjacent, were affected differently by these epidemic influences. Or for that matter, why wasn't Vienna proper affected by these same epidemic influences? For example, it was well-known that women who gave birth at home commonly had lower rates of puerperal fever than women giving birth in lying-in hospitals. Semmelweis went on to argue that the cause of puerperal fever must be endemic and limited to the boundaries of the hospital, and especially to the First Clinic:

> It has not been questioned and has been expressed thousands

of times that the horrible ravages of childbed fever are caused by epidemic influences. By epidemic influences one understands atmospheric-cosmic-terrestrial changes, as yet not precisely defined, that often extend over whole countrysides, and by which childbed fever is generated in persons predisposed by the puerperal state. But if the atmospheric-cosmic-terrestrial conditions of Vienna cause puerperal fever in predisposed persons, how is it that for many years these conditions have affected persons in the first clinic while sparing similarly predisposed persons in the second? To me there appears no doubt that if the ravages of childbed fever in the first clinic are caused by epidemic influences, the same conditions must operate with minimal variation in the second clinic. Otherwise, one is forced to the unreasonable assumption that lethal epidemic influences undergo twenty-four-hour remissions and exacerbations and that the remissions, through a series of years, have exactly coincided with admissions to the second clinic, while the exacerbations begin precisely at the time of admission to the first clinic.

However, even with such unreasonable assumptions, epidemic influences cannot explain the differences in mortality. The exacerbated influences must affect individuals either before they are admitted to the maternity hospital or during their stay. If they operate outside the hospital, certainly those who are admitted to the first clinic will be no more subject to them than those admitted to the second. No significant difference in mortality between the equally exposed patients admitted to the two clinics would then exist. On the other hand, if epidemic influences operate on individuals during their stay in the hospital, there could be no difference in the mortality rate, since two clinics so near one another that they share a common anteroom must necessarily be subject to the same atmospheric-cosmic-terrestrial influences. These considerations alone forced me to the unshakable conviction that epidemic influences were not responsible for the horrible devastations of the maternity patients in the first clinic.

Once I had come to this conviction, other supporting consid-

erations occurred to me. If the atmospheric influences of Vienna occasion an epidemic in the maternity hospital, then necessarily there must be an epidemic among maternity patients throughout Vienna because the entire population is subject to the same influences. But in fact, while the puerperal disease rages most furiously in the maternity hospital, it is only infrequently observed either in Vienna at large or in the surrounding countryside. During a cholera epidemic, people in general are affected, not just those in a particular hospital. A common and successful expedient for halting an epidemic of childbed fever is to close the maternity hospitals. Hospitals are closed not to force maternity patients to die somewhere else, but because of the belief that if patients deliver in the hospital they are subject to epidemic influences, whereas if they deliver elsewhere they will remain healthy. However, this proves one is not dealing with a disease dependent on atmospheric influences, because these influences extend beyond the hospital into every part of the city. This proves that the disease is endemic — a disease due to causes limited by the boundaries of the hospital. (pp. 65–67)

A number of other potential causes of puerperal fever were discussed by Semmelweis but discarded after some brief reasoning about the implications of such hypothesized causes. For example, one possible distinction between the First and Second Clinics was overcrowding. As noted by Semmelweis, however, the Second Clinic was typically the more crowded even though the First Clinic had more admission hours, was larger in size, and had a greater number of beds:

If overcrowding were the cause of death, mortality in the second clinic would have been larger, because the second clinic was more crowded than the first. Because of the bad reputation of the first clinic, everyone sought admission to the second clinic. For this reason, the second clinic was often unable to resume admissions at the specified time because it was impossible to accommodate new

> arrivals. Or if the second clinic began to admit, within a few hours it was necessary to resume admitting patients to the first clinic because the passageway was crowded with such a great number of persons awaiting admission to the second clinic. In a short time all the free places were taken. In the five years I was associated with the first clinic, not once did overcrowding make it necessary to reopen admission to the second clinic. This was true even though once each week the first clinic admitted continuously for a period of forty-eight hours. In spite of this overcrowding, the mortality rate in the second clinic was strikingly smaller.
>
> Each year, the first clinic recorded hundreds more births than the second. This, however, was because each week it had one more day of admissions and had, therefore, a larger assigned area. In spite of its smaller number of births with respect to its capacity, the second clinic was more crowded. This is verified by the fact that the second clinic was often unable to resume admissions or had to discontinue admissions early, which never happened at the first clinic. Had the second clinic been large enough to admit all who sought admission, it would have had significantly more births each year than the first clinic, even though it had fifty-two fewer days of admissions. If we disregard the comparative overcrowding within the two clinics, and consider only the degree of overcrowding within the first clinic as determined by the number of patients treated within a given month, it is apparent than the favorable or unfavorable health of the patients was not due to the degree of overcrowding. (pp. 69–70)

Several theories of what caused puerperal fever rested on the suppression of liquids related to the birth process. One was for lochia, the fluid that discharged from a uterus after a normal delivery. According to this idea, if the free flow of lochia could not purge the blood of impurities after childbirth, it would back up into the blood and cause puerperal fever and death. A second theory might be

called the milk-metastasis (or milk-fever) cause. Here, because the pus and infected fluid found in the abdomens of autopsied victims of puerperal fever looked similar to breast milk, it must be that milk was somehow rerouted away from its normal path and forced instead into general circulation throughout the body.

These female-related blockage theories of puerperal fever were also inconsistent with the autopsies performed on fetuses that showed exactly the same type of liquids as did the mother, whether or not the fetus was male or female. Also, an infant never died of puerperal fever when the mother remained healthy. Presumably, when an infant died it was because of some transfer through the placenta of whatever led to the death of the mother. And because this all occurred prior to an actual birth, it was quite a stretch to believe it could be either breast milk or lochia.

Several more fanciful causes of puerperal fever were proposed but quickly dismissed. One was modesty of the women in the First Clinic being examined by the male obstetricians; a second was the supposed rough examination by the male obstetricians in the First Clinic. Semmelweis comments:

> It had also been proposed that the high mortality rate in the first clinic resulted from the obstetricians examining the patients in a rougher manner than did the student midwives. If inserting the finger, however roughly, into the vagina and to the adjacent parts of the uterus — already widened and extended by pregnancy — was sufficient to cause damages leading to so horrible a condition, then surely the passage of the baby's body through the birth canal must cause damage so much worse that every birth would end in the death of the mother.
>
> It had also been suggested that the mortality rate in the first clinic resulted from the offense to modesty incurred through the

> presence of males at delivery. As those familiar with the Viennese maternity hospital realize, patients are troubled by fear but not by offended modesty. Moreover, it is not clear how this offended modesty would bring about the exudative mortal processes of the disease. (p. 73)

One major difference in the activities carried out within the First and Second Clinics would eventually allow Semmelweis to identify a probable cause of puerperal fever, and in turn, a reason for the greater mortality levels within the First Clinic. It was common practice to perform bare-handed autopsies early in the morning by the male obstetricians in training within the First Clinic, including by Semmelweis himself. But autopsies were never done by female student midwives from the Second Clinic. Coming immediately from the morgue with hands smelling of the cadavers being autopsied, the male obstetricians, including Semmelweis, would then carry out the examination of women present in the First Clinic. As we now know, a possible *Streptococcus* infection could be transmitted from the decaying cadaverous organic matter present and carried from the morgue to the women waiting to give birth in the First Clinic.

The realization by Semmelweis that puerperal fever could be induced in women by examination with unclean hands and a lingering cadaver smell, would require a particularly salient event that occurred while Semmelweis was away on a short Venetian vacation. A fellow doctor of forensic medicine and a friend, Jacob Kolletschka, was cut by a student performing an autopsy; Kolletschka subsequently died. This incident and the inferences Semmelweis drew from it are described in *The Etiology, ...*:

> On 20 March of the same year, a few hours after returning to Vienna, I resumed, with rejuvenated vigor, the position of assistant

in the first clinic. I was immediately overwhelmed by the sad news that Professor [Jacob] Kolletschka, whom I greatly admired, had died in the interim.

The case history went as follows: Kolletschka, Professor of Forensic Medicine, often conducted autopsies for legal purposes in the company of students. During one such exercise, his finger was pricked by a student with the same knife that was being used in the autopsy. I do not recall which finger was cut. Professor Kolletschka contracted lymphangitis and phlebitis [inflammation of the lymphatic vessels and of the veins respectively] in the upper extremity. Then, while I was still in Venice, he died of bilateral pleurisy, pericarditis, peritonitis, and meningitis [inflammation of the membranes of the lungs and thoracic cavity, of the fibroserous sac surrounding the heart, of the membranes of the abdomen and pelvic cavity, and of the membranes surrounding the brain, respectively]. A few days before he died, a metastasis also formed in one eye. I was still animated by the art treasures of Venice, but the news of Kolletschka's death agitated me still more. In this excited condition I could see clearly that the disease from which Kolletschka died was identical to that from which so many hundred maternity patients had also died. The maternity patients also had lymphangitis, peritonitis, pericarditis, pleurisy, and meningitis, and metastases also formed in many of them. Day and night I was haunted by the image of Kolletschka's disease and was forced to recognize, ever more decisively, that the disease from which Kolletschka died was identical to that from which so many maternity patients died.

Earlier, I pointed out that autopsies of the newborn disclosed results identical to those obtained in autopsies of patients dying from childbed fever. I concluded that the newborn died of childbed fever, or in other words, that they died from the same disease as the maternity patients. Since the identical results were found in Kolletschka's autopsy, the inference that Kolletschka died from the same disease was confirmed. The exciting cause of Professor Kolletschka's death was known; it was the wound by the autopsy knife that had been

> contaminated by cadaverous particles. Not the wound, but contamination of the wound by the cadaverous particles caused his death. Kolletschka was not the first to have died in this way. I was forced to admit that if his disease was identical with the disease that killed so many maternity patients, then it must have originated from the same cause that brought it on in Kolletschka. In Kolletschka, the specific causal factor was the cadaverous particles that were introduced into his vascular system. I was compelled to ask whether cadaverous particles had been introduced into the vascular systems of those patients whom I had seen die of this identical disease. I was forced to answer affirmatively. (pp. 87–88)

To frame the Semmelweis reasoning in an abductive form, there is the surprising fact that Kolletschka died of puerperal fever; if cadaveric particles can cause puerperal fever, then the death of Kolletschka is a matter of course. So, there is reason to hypothesize that cadaveric particles can cause puerperal fever. Semmelweis went on to then argue experimentally: if cadaveric particles can cause puerperal fever, one should be able to reduce puerperal fever incidence by removing cadaveric particles from hands carrying out examinations. The latter was to be done by the use of chlorine washings that removed the cadaveric smell, and presumably then, all cadaveric particles. Continuing with the discussion by Semmelweis in *The Etiology, ...* :

> Because of the anatomical orientation of the Viennese medical school, professors, assistants, and students have frequent opportunity to contact cadavers. Ordinary washing with soap is not sufficient to remove all adhering cadaverous particles. This is proven by the cadaverous smell that the hands retain for a longer or shorter time. In the examination of pregnant or delivering maternity patients, the hands, contaminated with cadaverous particles, are brought into contact with the genitals of these individuals, creating the possibility of resorption. With resorption, the cadaverous particles are

> introduced into the vascular system of the patient. In this way, maternity patients contract the same disease that was found in Kolletschka. Suppose cadaverous particles adhering to hands cause the same disease among maternity patients that cadaverous particles adhering to the knife caused in Kolletschka. Then if those particles are destroyed chemically, so that in examinations patients are touched by fingers but not by cadaverous particles, the disease must be reduced. This seemed all the more likely, since I knew that when decomposing organic material is brought into contact with living organisms it may bring on decomposition. To destroy cadaverous matter adhering to hands I used *chlorina liquida*. This practice began in the middle of May 1847; I no longer remember the specific day. Both the students and I were required to wash before examinations. After a time I ceased to use *chlorina liquida* because of its high price, and I adopted the less expensive chlorinated lime. In May 1847, during the second half of which chlorine washings were first introduced, 36 patients died — this was 12.24 percent of 294 deliveries. In the remaining seven months of 1847, the mortality rate was below that of the patients in the second clinic. (pp. 88–89)

Decades before the advent of the germ theory of disease, it was the genius of Semmelweis, relying purely on empirical observation, to first recognize the similarity between the accidentally acquired infection of Kolletschka and puerperal fever, and then to propose a new principle of prophylaxis along with a demonstration of its validity by experimentation. Semmelweis noted that the puerperal state was not necessary for "childbed fever" to occur, as witnessed both in the deaths of Kolletschka and the many newborns that died of the same cause as their mothers. In 1848, the first full year in which chlorine washing was assiduously followed, the mortality rate in the First Clinic (at 1.27%) was slightly below that of the Second (at 1.30%) — First Clinic: 45 deaths out of 3556 births; Second Clinic: 43 deaths

out of 3319 births.

Several other occurrences of puerperal fever forced Semmelweis to broaden its probable cause from cadaveric particles to decaying organic matter more generally — an example of which would be the watery pus or ichor discharging from a wound. Such ichor could be carried sequentially from patient to patient and bed to bed through contaminated hands, or possibly through the air of a contaminated enclosure (or, what may be more likely in the second example to follow, transmission through the hands of nurses dressing the knee wound). Two cases are given below from *The Etiology, ...* that led to this broadening of a putative cause for puerperal fever:

> In October 1847, a patient was admitted with discharging medullary carcinoma [cancer of the innermost part] of the uterus. She was assigned the bed at which the rounds were always initiated. After examining this patient, those conducting the examination washed their hands with soap only. The consequence was that of twelve patients then delivering, eleven died. The ichor from the discharging medullary carcinoma was not destroyed by soap and water. In the examinations, ichor was transferred to the remaining patients, and so childbed fever multiplied. Thus, childbed fever is caused not only by cadaverous particles adhering to hands but also by ichor from living organisms. It is necessary to clean the hands with chlorine water, not only when one has been handling cadavers but also after examinations in which the hands could become contaminated with ichor. This rule, originating from this tragic experience, was followed thereafter. Childbed fever was no longer spread by ichor carried on the hands of examiners from one patient to another.
>
> A new tragic experience persuaded me that air could also carry decaying organic matter. In November of the same year, an individual was admitted with a discharging carious left knee. In the genital region this person was completely healthy. Thus the exam-

> iners' hands presented no danger to the other patients. But the ichorous exhalations of the carious knee completely saturated the air of her ward. In this way the other patients were exposed and nearly all the patients in that room died. The reports of the first clinic indicate that eleven patients died in November and eight more in December. These deaths were largely due to ichorous exhalations from this individual. The ichorous particles that saturated the air of the maternity ward penetrated the uteruses already lacerated in the birth process. The particles were resorbed, and childbed fever resulted. Thereafter, such individuals were isolated to prevent similar tragedies. (p. 93)

The consistency between the cases of "puerperal fever" for Kolletschka and the two just summarized is based on three factors: a source of putrid material (such as a cadaver, a discharging cancer, or a carious knee); a means of transporting the putrid material to a victim (by a knife, or through hands that are contaminated, or less likely through air that is completely saturated with the putrid material); an injured surface that provides an entry point for the putrid matter (a lacerated finger or a denuded uterine lining). Using this type of characterization, Semmelweis was, in effect, conjecturing a single cause for all cases of "puerperal fever," and arguing that if two diseases were the same, then they must have the same cause. It would take some thirty more years, however, for the germ theory of disease to be developed and for Pasteur to identify the *Streptococcus pyogenes* to be the actual cause of "puerperal fever."

Once the probable cause of puerperal fever was identified as decaying organic matter, a number of unexplained but "surprising" observations of an increased or decreased mortality rate made more sense. Many of these involved situations that produced a change in

the total number of examinations done and how they were performed, which in turn served as a proxy for the number of instances in which contamination could occur. Thus, the observation that women in the First Clinic tended to sicken in rows could now be explained by the practice of carrying out examinations in (row) order by the male students, and also by Professor Klein and his assistant, Semmelweis.

Increased mortality due to a greater number of examinations was also present for long labors or periods of dilation, which was especially the case for first births. A reduced mortality rate was seen in premature births, and in "street" births that supposedly happened on the way to the maternity clinic, also presumably because of a fewer number of examinations. Mortality was also reduced when fewer exams were done more generally for other reasons such as during vacation periods or when there were a fewer number of male obstetrical students. But mortality somehow increased when there were many foreign students present in the First Clinic, a fact explained by Semmelweis in *The Etiology, ...* as follows:

> Foreigners come to Vienna to perfect medical training already begun in their own universities. They visit pathological and forensic autopsies in the general hospital. They take courses in pathological anatomy, in surgery, obstetrics, microscopic surgery of cadavers, they visit the medical and surgical wards of the hospital, etc. In a word, they utilize their time as efficiently and educationally as possible. They have, therefore, many opportunities for their hands to become contaminated with foul animal-organic matter. Thus, it is no wonder that foreigners, busy in the maternity hospital at the same time, are more dangerous for patients. Natives take the course in practical obstetrics after completing two difficult examinations ... to attain the degree of Doctor of Medicine. The law stipulates that the minimum preparation time for these examinations is six

> months. Thus the natives have already toiled excessively before they are admitted into the maternity hospital, and they regard the time there as a rest. While enrolled in practical obstetrics, natives do not concern themselves with other activities that would contaminate their hands. Indeed, while working at the maternity hospital, they concern themselves even less with other aspects of medicine because, after completing the course, they can perfect their knowledge of medicine to the highest possible degree. Since the foreigners are generally able to remain in Vienna only a few months, they are compelled to work simultaneously in more than one aspect of medicine. Even so, one cannot impute guilt to the foreigners any more than to me or to all the others who undertook examinations with contaminated hands. None of us knew that we were causing the numerous deaths. (pp. 104–105)

In a somewhat related vein, the jump in mortality rates when Klein took over from Boër in 1822/1823 can be attributed directly to the greater number of autopsies carried out, and thus, to a greater number of opportunities for infection from decaying cadaver material to be passed along to women giving birth. Also, there was always a generally lower mortality rate for home births, presumably because of a reduced number of examinations and therefore chances for infection as compared to a hospital setting.

An early biography of Semmelweis in English (or better, an early hagiography) was written by William Sinclair in 1909: *Semmelweis: His Life and his Doctrine*. The Doctrine (German: *Lehre*) referred to in the title is summarized by Sinclair as follows:

> Now, in the autumn of 1847, was the Discovery of Semmelweis complete, and the Doctrine firmly established in his own mind. It amounted to this: that puerperal fever was caused by a decomposed animal organic matter conveyed by contact to the pregnant, parturient [in labor], or puerperal [post-birth] woman without regard

> to its origin, whether from the cadaver or from a living person affected with a disease which produced a decomposed animal organic matter. (p. 61)

To this we might add the notion of removing the offending material through chlorine washing. In current terminology, Semmelweis introduced an antisepsis practice of using an explicit chlorine antiseptic to eliminate the microorganisms that caused puerperal fever. It would take until 1879, however, for Louis Pasteur to announce that the *Streptococcus* microorganism was the actual cause of puerperal fever, and to indicate what it looked like.

Although we have presented the now familiar story of how Semmelweis came to his *Lehre* through the unfortunate death of Kolletschka, any teacher of experimental design, such as we are, would fault Semmelweis for not first asking a more obvious question: were there differences between those patients generally present in the First and Second Clinics that could help explain the mortality discrepancy. As was known, the patients were not assigned randomly to the clinics as would be required by any modern-day randomized clinical trial. First of all, patients needing specialized medical attention were automatically assigned to the First Clinic where male obstetricians could oversee their care. (This is noted explicitly, for example, by K. Codell Carter and Barbara R. Carter in their biography of Semmelweis, *Childbed Fever* [2005, p. 23].). The obvious unanswered question is how more at risk of death were those patients who needed special medical care, and maybe more importantly, how many of them were there? Second, is there something that distinguished those patients who knew how the rotating admission system worked to get into the Second Clinic from those who didn't? And did this distinction have

any mortality implications?

A final question that might be asked about Semmelweis's methodology, is why he didn't avail himself of a microscope at the Vienna Hospital to see what "cadaver particles" and/or "decaying organic matter" might actually consist of. Semmelweis left his *Lehre* closer to "magical thinking" than necessary. As noted earlier, it would take several decades more before Pasteur identified microscopically the actual culprit of *Streptococcus pyogenes* that caused puerperal fever.

* * *

Semmelweis's term as an assistant in the First Clinic ended as of March, 1849, and because of Klein's opposition, he was denied a customary two-year extension. Semmelweis petitioned the Viennese authorities for a position as Privat-Dozent, which allowed the teaching of students as a private lecturer and some access to the university facilities. Again, because of Klein's opposition, Semmelweis' application was first denied. He reapplied, and after some eighteen months, Semmelweis was granted a Privat-Dozent position in October of 1850 but with the humiliating provision that he no longer had access to cadavers and could only teach using a leather mannequin.

Semmelweis was rightly offended at the restrictive offer, and returned abruptly to Budapest without any words of farewell to his friends, including his closest supportive colleague, Doctor Ferdinand von Hebra. Hebra, as editor of the *Transactions of the Medical Society of Vienna*, had published in 1847 and 1848 two short accounts of Semmelweis's work in his own journal. Semmelweis himself adamantly refused to publish any account of his *Lehre* until *The*

Etiology, ... was published much later in 1860.

Because only second-hand accounts of the *Lehre* and the recommended antiseptic chlorine washings were available, it was generally misunderstood or dismissed as implausible and just plain wrong, or at best, limited to the transmission of cadaveric particles. For example, the English (and Americans) believed that puerperal fever was a contagious disease, like smallpox, and concluded that was all the *Lehre* contended as well. In *The Etiology, ...* Semmelweis belatedly responded:

> Childbed fever is not a contagious disease. A contagious disease is one that produces the contagion by which the disease is spread. This contagion brings about only the same disease in other individuals. Smallpox is a contagious disease because smallpox generates the contagion that causes smallpox in other individuals. ... Smallpox causes only smallpox and no other disease. ... Childbed fever is different. This fever can be caused in healthy patients through other diseases. In the first clinic it was caused by a discharging medullary carcinoma of the uterus, by exhalations from a carious knee, and by cadaverous particles from heterogeneous corpses. ... However, childbed fever cannot be transmitted to a healthy maternity patient unless decaying animal-organic matter is conveyed. For example, suppose a patient is seriously ill with a form of childbed fever in which no decaying matter is produced. Then the disease cannot be transmitted to healthy patients. On the other hand, if the patient with childbed fever has septic endometritis or discharging metastases, then her disease can be conveyed to healthy patients.
>
> This explains why the conflict over whether childbed fever is or is not contagious could never be conclusively resolved. Those who believe in contagion cite cases in which childbed fever had undeniably spread from an ill patient to a healthy one. Their opponents cite cases in which the disease did not spread as it would have done if it had been contagious. Childbed fever is not a contagious disease,

> but it can be conveyed from diseased to healthy patients by decaying animal-organic matter. After death, the corpses of puerperae, like all corpses, are sources of the decaying matter that causes the disease.
>
> I assert that in the overwhelming majority of cases childbed fever is caused by external infection and that these cases can be prevented. (pp. 117–118)

Semmelweis eventually held two different medical appointments in Budapest. The first began in 1851 as an unpaid director of the obstetrical ward at St. Rokus Hospital. He stayed in this position for six years until 1857. As might have been expected, a chlorine hand washing regimen was imposed that produced a low number of puerperal fever deaths during this six-year period (8 out of 933 births for a mortality rate of 0.86%). A second appointment for Semmelweis began in 1855 when he was named Professor of Theoretical and Practical Obstetrics at the University of Pest. Here, a serious problem of increased puerperal fever occurred during the school year of 1856/57 that Semmelweis ultimately traced to the reuse of unclean laundry for mothers that had recently given birth. Semmelweis identified the source of organic matter infecting these new mothers by first noting the surprising fact that infants lived even though their mothers died of puerperal fever. The implication here was that the infecting agent reached mothers only after a child was born. Because the newly delivered mothers lay in sheets still soiled from other women who had given birth earlier, the decaying organic matter was transferred directly from the soiled sheets.

Despite an aversion to writing, Semmelweis began *The Etiology, ...* in the Fall of 1857. Up until that point, only colleagues such as Hebra and former students had published accounts in the medical

literature of the *Lehre* and the attendant antiseptic practice of chlorine washings. In parts of the Preface to *The Etiology, ...* that are given below, one can see the early signs of a self-destructive messianic complex that would ultimately lead to Semmelweis's untimely death:

> The object of this essay is this: to present historically to the medical instructor observations that I made at this clinic in this period, to demonstrate how I began to doubt existing teachings concerning the origin and the concept of childbed fever, and how I was irresistibly forced to my present conviction, in order that he also, for the welfare of mankind, may derive the same convictions.
>
> By nature I am averse to all polemics. This is proven by my having left numerous attacks unanswered. I believed that I could leave it to time to break a path for the truth. However, for thirteen years my expectations have not been fulfilled to the degree that is essential for the well-being of mankind. An additional misfortune was that in the school years of 1856–57 and 1857–58, maternity patients died in such numbers at my own obstetrical clinic in Pest that my opponents could use these deaths as evidence against me. It must be shown that these two unfortunate years provide tragic and unintentional yet direct confirmation of my views.
>
> To my aversion to all polemics must be added my innate aversion to every form of writing. Fate has chosen me as the representative of those truths that are laid down in this essay. It is my inescapable obligation to support them. I have given up the hope that the importance and the truth of the matter would make all controversy unnecessary. Rather than my inclinations, people's lives must be considered, people who do not even participate in the conflict over whether my opponents or I have the truth. Since silence has proven futile, I must forcibly restrain my inclinations and step once more before the public as though uncautioned by the many bitter hours I have endured. I have made the best of these hours; for those yet to come I find consolation in knowing that I advocate only that which is firmly grounded in my own convictions.

Pest, 30 August 1860 (pp. 61–62)

The reviews in the medical literature for *The Etiology, ...* were highly negative, as might have been expected for a long, poorly written and rambling document. The main reason that we have a reasonable sense of what *The Etiology, ...* had to offer is the clear editing and translation by K. Codell Carter, used for the various excerpts given throughout this chapter. For his part, Semmelweis lashed out against his critics in a series of open letters addressed to prominent obstetricians throughout Europe. These were full of arrogance, anger, and bitterness; he denounced his critics as irresponsible murderers and ignoramuses.

A good example of Semmelweis's vitriol toward his critics is the letter written to William Scanzoni, the director of the obstetrical clinic in Prague. Sinclair's translation of parts of this letter as given in his 1909 biography of Semmelweis follows:

> ... and in this matter, Herr Hofrath, you have sent all over Germany a considerable contingent of practitioners who will, in their ignorance, engage in homicidal practices. ... Your teaching, Herr Hofrath, is based upon the dead bodies of lying-in women slaughtered through ignorance; and ... I have formed the unshakeable resolution to put an end to this murderous work as far as [it] lies in my power to do so. ... If, however, Herr Hofrath, without having discussed my Doctrine as an opponent, you go on to write ... in support of the doctrine of epidemic puerperal fever, to teach your students the doctrine of epidemic puerperal fever, I denounce you before God and the world as a murderer, and the History of Puerperal Fever will not do you an injustice when, for the service of having been the first to oppose my life-saving *Lehre* [,] it perpetuates your name as a medical Nero.

From at least the date of publication for *The Etiology, ...* in 1860, Semmelweis showed various signs of mental deterioration. He became severely depressed, absent-minded to the extreme, and psychotically obsessed with puerperal fever. Some current authors, such as Nuland and Carter, hypothesize an onset of Alzheimer's disease or another dementia, or possibly late stage tertiary syphilis, an apparently common disease among obstetricians who treated women in charity lying-in hospitals before rubber examination gloves were introduced in the very late 1800s.

In 1865, Semmelweis's wife in a plan enacted with an old colleague, Hebra, lured Semmelweis to Vienna on a pretext of seeing Hebra's new facilities. Instead, Semmelweis was led to a public insane asylum and committed. Two weeks later on August 13, 1865, Semmelweis died from a septicemia obtained through a gangrenous wound on his right hand, and in much the same way as Kolletschka died. A possible secondary contributing cause may have been from a beating he endured by the guards at the asylum when he tried to escape right after his initial commitment.

* * *

The final chapter of the Semmelweis biography by Frank Slaughter, *Immortal Maygar* (1950), included mention of two important events in medicine that could be considered immediate consequences of the *Lehre* and the notion of prophylaxis. One is Pasteur's identification of the *Streptococcus* bacteria as the cause of puerperal fever; the second is Lister's use of antisepsis in the setting of a compound fracture, notably at about the same time as Semmelweis' death. The excerpt follows:

The justification of the work of Semmelweis came with the discovery by Louis Pasteur of the identity of bacteria as the real culprit in the causation of puerperal fever.

Dr. Emile Roux [Pasteur's assistant] described the occasion on March 11, 1879, when Pasteur proclaimed his discovery of the real cause of puerperal fever:

> One day, in a discussion on puerperal fever at the Academy, one of his (Pasteur's) most weighty opponents was eloquently enlarging upon the causes of epidemics in lying-in hospitals; Pasteur interrupted him: "None of those things cause the epidemic; it is the nursing and medical staff who carry the microbe from an infected woman to a healthy one." And as the orator replied that he feared that microbe would never be found, Pasteur went to the blackboard and drew a diagram of the chain-like organism, saying, 'There, that is what it is like.'

Pasteur had found the Streptococcus in the lochia of dying patients and also in the bloodstream, bringing forth the final evidence in support of the Semmelweis theory of a concrete infecting agent.
...

... Even before Pasteur hit upon the precise agent of puerperal fever, however, Semmelweis's work had been carried to its fulfillment by yet another worker. On August 12, 1865, the day before the death of Semmelweis, Joseph Lister of Glasgow, acting on conclusions he had reached on reading certain memoirs by Louis Pasteur, used carbolic acid as an antiseptic in treating a case of compound fracture. The wound healed rapidly, without suppuration [the production of pus]. Lister continued his experiments with complete success and published in 1867 his report, "A New Method of Treating Compound Fractures, Abscesses, Etc." Shortly thereafter he addressed the British Medical Association "On the Antiseptic Principle in the Practice of Surgery," giving a full account of his development of the first rational treatment of wounds in the history of surgery, a treatment based on a sound knowledge of the etiology and pathogenesis of suppuration.

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Chapter 4

John Snow

> All that would be required to prevent the disease [cholera] would be ... a close attention to cleanliness in cooking and eating, and to drainage and water supply, as is desirable at all times.
>
> – John Snow (1813-1858)

The dominant framework used to explain certain infectious diseases up until the late 1800s was miasma theory. Although diseases such as smallpox, syphilis, and measles were generally understood to be contagious and transmittable person-to-person through physical contact, it was unclear what to think about the epidemic diseases such as cholera, typhoid, and typhus. The cantankerous founding editor of the *Lancet*, Thomas Wakley, for example, wrote an 1853 editorial that asked the question, "What is cholera?":

> All is darkness and confusion, vague theory, and a vain speculation. Is it a fungus, an insect, a miasma, an electrical disturbance, a deficiency of ozone, a morbid off-scouring from the intestinal canal? We know nothing; we are at sea in a whirlpool of conjecture.

Miasma theory held that certain diseases, such as cholera, were caused by a noxious form of "bad air" (a miasma), filled with particles from decomposed organic matter (called miasmata). It could

be identified by its foul smell. A leading Victorian sanitary reformer, Edwin Chadwick, famously asserted that "all smell is disease," implying that if odors could be eliminated, then so could any underlying disease as a result. Although obviously faulty as a causal theory of disease, a belief in the existence of miasmas and in the necessary sanitary reforms required to eliminate noxious odors did have a salutary effect in reducing the overall prevalence of disease in such highly urbanized and crowded areas as Victorian London.

The miasma theory of disease became an appealing and dominant causal explanation in the middle 1800s for English public health reformers who could now focus on environmental problems as opposed to those tied only to infection, poverty, and personal health. For example, miasmas were commonly used to explain the quick spread of cholera in London and Paris in the 1850s, and partly justified Haussmann's massive renovation of the French capital which then served as a model for other European and North American cities. Two influential Nineteenth Century English statisticians were fervent and important supporters of miasma theory: William Farr, the assistant commissioner for the 1851 London Census (among other high-level data gathering positions in the government), and Florence Nightingale, the famous Crimean War nurse (and, we might add, the first woman inducted into the Royal Statistical Society in 1858).

William Farr believed that cholera in London was transmitted by noxious air specifically emanating from the deadly concentration of miasmata near the banks of the Thames River. In fact, Farr had a well-developed theory about the influence of elevation on the prevalence of cholera based on coincidentally consistent data — the greater the elevation above the Thames and the miasmata it held, the

less cholera was present during the various outbreaks that occurred in the Nineteenth Century. Eventually, Farr came to accept the theory of cholera transmission brought forth by John Snow that it was spread primarily through water and ingestion. Florence Nightingale, however, never did accept this mode of cholera transmission, even after the germ theory breakthroughs of Louis Pasteur in the late 1800s and the identification of the specific cholera bacterium, *Vibrio cholerae*, by Robert Koch in 1883. Nightingale stuck fast to the miasma theory of cholera transmission, most likely because it fit so well with her emphasis on sanitary reform and hygiene. We provide a relevant Nightingale quote below given by Sandra Hempel in her account of John Snow's search for the mode of cholera transmission (*The Medical Detective*, 2006, p. 278):

> What does contagion mean? It implies communication of disease from person to person contact. It presupposes the existence of certain germs like the sporules of fungi, which can be bottled up and conveyed any distance attached to clothing, to merchandise ... There is no end to the absurdities connected with this doctrine. Suffice it to say that in the ordinary sense of the word, there is no proof such as would be admitted in any scientific enquiry that there is any such thing as contagion.

As is now well-known, cholera is an infectious disease that can quickly lead to dehydration and death when left untreated. It can be caused by ingesting food or drinking water contaminated with a comma-shaped bacterium (*Vibrio cholerae*), identified as the infecting agent by Robert Koch in 1883, and much earlier by the Italian, Filippo Pacini, in 1854. Pacini's extensive microscopic work in identifying the vibrions in a cholera patient's bowel dejections was discussed extensively in William Farr's seminal *Report on the*

Cholera Epidemic of 1866 in England (1868). Because of our current understanding that cholera is commonly waterborne and can be prevented by the use of clean drinking water and avoiding contamination through a fecal-oral mode of transmission, cholera is now generally nonexistent in developed countries. It still appears in sporadic outbreaks, however, such as in 2010 after the massive earthquake in Haiti. The source of contamination in this last instance was traced to a group of UN peace keepers from Nepal.

There have been seven cholera pandemics in the last two hundred years, with the seventh, and thus far the last, originating in Indonesia in 1961 with a new bacterium strain called *El Tor*. The very first pandemic (1817–1824) began in the Bengal area of India near Calcutta, and although it never reached Europe or North America, it decimated the British Army stationed in the area. The second pandemic (1826–1837) did reach both North America and Europe, including the United Kingdom (UK) in 1831–1833. Two other outbreaks in the UK of interest here were in 1848–1849 and 1853–1854, during which times our protagonist John Snow was active. The last cholera outbreak in the UK occurred in 1866, right before the massive new London sewer system designed by Joseph Bazalgette was completed so that sewage was no longer just being dumped into the Thames. Although this massive infrastructure project was undertaken primarily to eliminate the incredible periodic stench from untreated human waste present in the Thames, it also had the unintended effect of removing the major source of cholera reinfection for London and the surrounding area.

* * *

John Snow (1813–1858) was born in York, England, in March of 1813. When he was 14, Snow obtained a surgeon-apothecary apprenticeship with William Hardcastle in the general area of Newcastle-upon-Tyne. As noted later, Snow's initial experience with cholera was during the first UK outbreak in 1831–1833 when he was sent as a surrogate for Hardcastle to the coal mining village of Killingworth, just north of Newcastle-upon-Tyne. Upon completing his various apprenticeships, Snow enrolled in the Hunterian School of Medicine in London. He graduated with a medical degree from the University of London in 1844, and promptly set up practice as a physician in the Soho region of London.

John Snow is known for work in two major scientific areas, one is purely medical and the second is epidemiological. In medicine, Snow did seminal work on the use of anesthetics that had just been introduced from the United States, particularly as to dosage for chloroform and methods of controlled administration. Snow did much of his extensive chloroform experimentation on himself, which may have been a contributory factor to his early death from a stroke when he was just 45 years old. During the middle 1800s Snow was the best known anesthetist in London, and, for example, administered chloroform to Queen Victoria during the births of her last two children.

For the purposes of this chapter on John Snow, however, our interests center just on his work as a founder (and father) of contemporary epidemiology, and particularly, for his view that cholera was essentially an infectious waterborne disease passed by ingestion, rather than being a disease caused by a miasma operating primarily through the lungs. A substantial part of this chapter deals with Snow's seminal work on cholera transmission, *On the Mode of Communica-*

tion of Cholera (hereafter, denoted simply as MCC), published in 1855, and specifically with the shrewd (abductive) reasoning that it documents. It is a record of a Victorian success story for scientific reasoning based on non-experimental observational data.

Snow's 1855 MCC monograph was actually a revision of a much shorter thirty-one page pamphlet having the same title but published earlier in 1849. Although this earlier pamphlet had all of Snow's views that cholera was essentially a waterborne disease and not miasmatic, it did not provide the totality of evidence given in the 1855 revision. The final summary paragraph of the 1849 MCC pamphlet is provided below, which shows that Snow's views on cholera transmission were firmly established by the late 1840s, including the observation that well-intentioned sanitary reforms, such as hooking up and flushing all sewers directly into the Thames, most likely had the unintended consequence of making the 1849 cholera outbreak much worse than it otherwise would have been:

> The belief in the communication of cholera is a much less dreary one than the reverse; for what is so dismal as the idea of some invisible agent pervading the atmosphere, and spreading over the world? If the writer's opinions be correct, cholera might be checked and kept at bay by simple measures that would not interfere with social or commercial intercourse; and the enemy would be shorn of his chief terrors. It would only be necessary for all persons attending or waiting on the patient to wash their hands carefully and frequently, never omitting to do so before touching food, and for everybody to avoid drinking, or using for culinary purposes, water into which drains and sewers empty themselves; or, if that cannot be accomplished, to have the water filtered and well boiled before it is used. The sanitary measure most required in the metropolis is a supply of water ... from some source quite removed from the sewers.

Snow's 1855 MCC monograph begins by relating a variety of circumstances all involving cholera that Snow either witnessed personally or were made known to him from reliable sources. From this collection, Snow developed his basic ideas about cholera's mode of transmission that might be summarized in a few short statements: First, cholera can be communicated from the sick to the healthy by means of some (germ-like) material that can increase and multiply in the systems of the persons attacked; secondly, this morbid matter can be transmitted at a distance, such as on soiled linen or clothes; thus, a proximity to a patient's "emanations," whatever they may be, is not essential; and finally, cholera invariably begins with an affection of the alimentary canal, and therefore, the morbid matter must be ingested; it does not enter by another mechanism such as through the lungs.

Two examples of such events from many more reported in MCC are given below. The first is a summary of the initial case of Asiatic cholera appearing in London in 1848; the second discusses the coal mining pits of Great Britain that Snow witnessed during his apprenticeship with Hardcastle:

> The first case of decided Asiatic cholera in London, in the autumn of 1848, was that of a seaman named John Harnold, who had newly arrived by the *Elbe* steamer from Hamburgh [sic], where the disease was prevailing. He left the vessel, and went to live at No. 8, New Lane, Gainsford Street, Horsleydown. He was seized with cholera on the 22nd of September, and died in a few hours. Dr. Parkes, who made an inquiry into the early cases of cholera, on behalf of the then Board of Health, considered this as the first undoubted case of cholera.
>
> Now the next case of cholera, in London, occurred in the very room in which the above patient died. A man named Blenkinsopp

came to lodge in the same [presumably, uncleaned] room. He was attacked with cholera on the 30th September, and was attended by Mr. Russell of Thornton Street, Horsleydown, who had attended John Harnold. Mr. Russell informed me that, in the case of Blenkinsopp, there were rice-water evacuations; and, amongst other decided symptoms of cholera, complete suppression of urine from Saturday till Tuesday morning; and after this the patient had consecutive [lasting three or more days] fever. Mr. Russell had seen a great deal of cholera in 1832, and considered this a genuine case of the disease; and the history of it leaves no room for doubt. (p. 3)

...

The mining population of Great Britain have [sic] suffered more from cholera than persons in any other occupation — a circumstance which I believe can only be explained by the mode of communication of the malady above pointed out. Pitmen are differently situated from every other class of workmen in many important particulars. There are no privies in the coal-pits, or, as I believe, in other mines. The workmen stay so long in the mines that they are obliged to take a supply of food with them, which they eat invariably with unwashed hands, and without knife and fork. The following is a reply which I received from a relative of mine connected with a colliery [coal mine] near Leeds, in answer to an inquiry I made: — "Our colliers descend at five o'clock in the morning, to be ready for work at six, and leave the pit from one to half-past three. The average time spent in the pit is eight to nine hours. The pitmen all take down with them a supply of food, which consists of cake, with the addition, in some cases, of meat; and all have a bottle, containing about a quart of 'drink.' I fear that our colliers are no better than others as regards cleanliness. The pit is one huge privy, and of course the men always take their victuals with unwashed hands."

It is very evident that, when a pitman is attacked with cholera whilst at work, the disease has facilities for spreading among his fellow-labourers such as occur in no other occupation. That the men are occasionally attacked whilst at work I know, from having seen

> them brought up from some of the coal-pits in Northumberland, in the winter of 1831-2, after having had profuse discharges from the stomach and bowels, and when fast approaching to a state of collapse. (pp. 19–20)

From various situations reported in MCC, such as the two just given, Snow made a number of explanatory abductions that were particularly germane to individuals as opposed to larger geographical regions. One of the first was that cholera was carried by humans and followed the paths of human intercourse, implying that it was not contracted merely by going into some type of miasmal area:

> There are certain circumstances, however, connected with the progress of cholera, which may be stated in a general way. It travels along the great tracks of human intercourse, never going faster than people travel, and generally much more slowly. In extending to a fresh island or continent, it always appears first at a sea-port. It never attacks the crews of ships going from a country free from cholera, to one where the disease is prevailing, till they have entered a port, or had intercourse with the shore. Its exact progress from town to town cannot always be traced; but it has never appeared except where there has been ample opportunity for it to be conveyed by human intercourse. (p. 2)

Related to this general conjecture that humans themselves are the carriers for cholera, Snow further hypothesized it to be generally infectious and transmitted by means of an oral-fecal route from the sick to the healthy through the actual ingestion of contaminated matter. Cholera invariably begins with an affection of the alimentary canal, with the resulting copious diarrhea containing the much reproduced morbid material and the source of contamination for further transmission. It was not spread from any effluvia given off by a specific

patient into the surrounding air and then inhaled by others through their lungs. Thus, it was possible to be in the same room attending to a patient without any intake of the morbid poison.

In commenting on those environments most suitable for cholera transmission, Snow gives rather modern COVID-19 admonitions about cleanliness and the washing of one's hands:

> The instances in which minute quantities of the ejections and defections of cholera patients must be swallowed are sufficiently numerous to account for the spread of the disease; and on examination it is found to spread most where the facilities for this mode of communication are greatest. Nothing has been found to favor the extension of cholera more than want of personal cleanliness, whether arising from habit or scarcity of water, although the circumstance till lately remained unexplained. The bed linen nearly always becomes wetted by the cholera evacuations, and as these are devoid of the usual color and odor, the hands of persons waiting on the patient become soiled without their knowing it; and unless these persons are scrupulously cleanly in their habits, and wash their hands before taking food, they must accidentally swallow some of the excretion, and leave some on the food they handle or prepare, which has to be eaten by the rest of the family, who, amongst the working classes, often have to take their meals in the sick room: hence the thousands of instances in which, amongst this class of the population, a case of cholera in one member of the family is followed by other cases; whilst medical men and others, who merely visit the patients, generally escape. The *post mortem* inspection of the bodies of cholera patients has hardly ever been followed by the disease that I am aware, this being a duty that is necessarily followed by careful washing of the hands; and it is not the habit of medical men to be taking food on such an occasion. On the other hand, the duties performed about the body, such as laying it out, when done by women of the working class, who make the occasion one of eating and drinking, are often followed by an attack

> of cholera; and persons who merely attend the funeral, and have no connection with the body, frequently contract the disease, in consequence, apparently, of partaking of food which has been prepared or handled by those having duties about the cholera patient, or his linen and bedding. (pp. 16–17)

In addition to presenting instances of cholera contracted by individuals on a one-by-one basis, Snow also provided several examples where cholera was transmitted to whole neighborhoods or housing complexes *en bloc* through the contamination of a communal water supply, and, just as telling, where cholera was not transmitted to similarly situated adjacent units or areas not sharing in that common water supply. Two of the best known occurrences discussed in MCC (in both the 1849 and 1855 versions), which have been diagrammed and repeated in more modern subsequent texts, are the outbreaks that happened in 1849 in Horsleydown on Thomas Street and in Albion Terrace on Wandsworth Road. Snow introduced these two illustrations as follows:

> If the cholera had no other means of communication than those which we have been considering, it would be constrained to confine itself chiefly to the crowded dwellings of the poor, and would be continually liable to die out accidentally in a place, for want of the opportunity to reach fresh victims; but there is often a way open for it to extend itself more widely, and to reach the well-to-do classes of the community; I allude to the mixture of the cholera evacuations with the water used for drinking and culinary purposes, either by permeating the ground, and getting into wells, or by running along channels and sewers into the rivers from which entire towns are sometimes supplied with water. (p. 22)

Although the examples given by Snow of Albion Terrace and Hosleydown, among others, are rather definitive in showing the place

that a communal water source can have on the transmission of cholera, the most well-known example of cholera emanating from a common water supply is the justifiably famous case of the Broad Street pump. This particular instance has become the formative example for all of modern epidemiology; it remains to this day as the most prominent example of successful public health reasoning and intervention. A lengthy summary of the Broad Street episode from MCC is given in an Appendix external to this chapter.

Snow's investigation of the Broad Street outbreak represents a clear example of abductive reasoning. There is the surprising observation of cholera deaths clustered around the Broad Street pump; if the Broad Street pump was a cholera source, then the cluster of cholera deaths around the Broad Street pump would be a matter of course. Thus, there is reason to hypothesize that the Broad Street pump was indeed the cholera source. At this point, Snow proceeded to investigate whether the evidence upheld the conjecture by detailing the water pump drinking behavior of those in the area who died of cholera as well as those who died out of the area, and for those situations where there was an unexpected paucity of deaths if the conjecture were true.

Snow's hypothesis that the Broad Street pump was the culprit in the cholera outbreak had three characteristics that any good hypothesis should have: it had coherence in the sense that all the evidence "fits"; it was simple, and had a generality in its ability to explain a wide range of observations. A miasmal area centered around the pump, on the other hand, would have had a difficult time explaining all the observations that Snow amassed: the absence of cases in the Workhouse and Brewery, and the presence of cases much further

away (for example, for dining-room, coffee-shop, and public-house patrons; the woman and her niece from the West End; children going to school near the pump; the percussion-cap factory workers; and so on).

There are several other aspects to the Broad Street pump story that are still germane to how modern epidemiology is conducted. Besides the narrative provided in MCC, what has remained central to the Broad Street pump saga are the maps that Snow produced showing the spatial clustering of cholera cases around the Broad Street pump, and the general lack of such concentrations around the many other pumps in the area that would be closer to use for their respective residents. It should be remembered, however, that although Snow thought geographically, his maps were produced "after the fact" and were intended for illustration and explanation rather than for use in Snow's initial investigation.

A second aspect of epidemiology's current COVID-19 emphasis on testing and contact tracing, relates to Snow's familiarity with the outbreak area given that he lived close by, and his ability to actually visit those residences where cholera deaths had occurred. On observing the beginnings of the outbreak directly and the apparent spatial clustering of cases around the pump, he (abductively) reasoned as to the probable source of contaminated water being the pump. After obtaining the list of cholera deaths and addresses from the Register-General (who happened to be William Farr, by the way), Snow then engaged in what has become known as "shoe-leather" epidemiology. As best he could, Snow visited the residences of those who had died, and when possible, determined the source of drinking water used by that person. Also, in the area around the pump where there seemed

to be an odd paucity of deaths, such as in the Workhouse and the Brewery, Snow found out that alternative water sources were generally relied on. In addition, for many cases of cholera deaths beyond the pump area, Snow could still ascertain that indeed Broad Street pump water had been consumed.

The epidemiological search for an initial cause in any epidemic typically centers around the identification of what is called "patient zero" or the "index patient." In the case of the Broad Street pump, the first individual that fell ill a day prior to and most likely started the Broad Street outbreak was an infant who died of cholera at 40 Broad Street, just adjacent to the pump. The child's soiled diapers were washed in pails of water which were then discarded in a cesspool with direct communication with the Broad Street well. This index case was identified by a local prelate, Henry Whitehead, who along with Snow had been investigating the cholera outbreak in the area around the pump. Part of Whitehead's testimony is given below for the "Report on the cholera outbreak of St. James, Westminister, during the autumn of 1854" [called the Vestry report]:

> One day last week, however, I happened to be studying the Registrar's Returns for a purpose unconnected with this matter, when my eye suddenly fell upon the following entry, in page 340:
>
> "At 40, Broad Street, 2nd September, a daughter, aged five months, exhaustion, after an attack of Diarrhoea [sic] four days previous to death."
>
> I knew the case, and had recorded the date of death, but somehow had neglected to inquire about the date of attack, having passed it by lightly, I suppose, because it was the case of an infant. Neither had it occurred to me that the child might have been ill all the week. I immediately went to the house and ascertained from the mother, who occupied the back parlour, that the child was at-

tacked on Monday, 28th August, and that the dejections at first were abundant, but ceased on Wednesday, 30th August. In answer to further questions, she told me that the dejections were collected in napkins, which, on being removed, were immediately steeped in pails, the water from which was poured partly into a sink in the backyard, and partly into a cesspool in the front area.

Being struck with the dangerous proximity of the cesspool to the pump well, I lost no time in communicating the facts to the Committee, who ordered an investigation to be made forthwith. This investigation, carried out by our Secretary and Surveyor, is described elsewhere. It clearly established the general fact of percolation of fluid from the cesspool into the well. I do not pretend to any practical knowledge of such matters, but, having been down the well and examined the places where the steining [a lining of stone or brick] was removed for the purpose of inspection, I can at least say that I saw enough to convince me on this point. The importance of this investigation, even apart from any consideration of Cholera, cannot be overrated. The sooner all shallow pump wells are filled up, and all house drains rigorously examined, the better. (pp. 159–160)

Besides identifying the likely index patient that precipitated the Broad Street outbreak, Whitehead also provided in the same (Vestry) report a crucial bit of data that Snow didn't have. Snow assessed the pump drinking behavior for those who actually died of cholera (which was high), but did not have explicit information on those residents who avoided cholera. Whitehead, however, did:

"I have thus inquired, or at least attempted to inquire, concerning 497 of 896 persons resident in Broad Street at the time of the pestilence." (p. 131)

For 444 of the individuals he contacted (out of the 497), Whitehead could unambiguously assign a label of "drinking: Yes" or "drinking:

Table 4.1: Drinking from the pump versus contracting cholera.

	Ill:No	Ill:Yes	Row Totals
Drink:No	279 [226.3]	20 [72.7]	299
Drink:Yes	57 [109.7]	88 [35.3]	145
Column Totals	336	108	444

No"; for these 444 he also had a "ill: Yes" or "ill: No" assessment.

A cross-classification of the 444 individuals is given above as a 2×2 contingency table. In parentheses next to each count in the table is an expected value obtained under a conjecture of independence for the "drinking" and "illness" classifications. As is obvious, there is a clear positive relation between the two variables: if you drink from the pump, you tend to get sick; if you don't drink from the pump, you tend to stay well.

* * *

In the middle 1800s, a number of different companies supplied water to the residences of London. The two that are of concern here are the Lambeth and the combined Southwark/Vauxhall. During the first London cholera outbreak in 1848-1849, both of these companies pumped water from the Thames at the same heavily polluted part of the river. However, by the time of the second London cholera outbreak in 1854-1855, the Lambeth company had moved its water intake out of reach of the main sewage discharge points, but Southwark/Vauxhall had not.

In certain parts of London, both the Lambeth and Southwark/Vauxhall companies provided water in the same areas with their respective water pipes intermixed and running down the same streets. Thus, this

Table 4.2: Cholera mortality rates during the outbreak in 1854.

	Number of Houses	Deaths from Cholera	Deaths per 10,000 Houses
Southwark/Vauxhall	40,046	1,263	315
Lambeth	26,107	98	38
Rest of London	256,423	1,422	59

was the structure of Snow's (ecological) Grand Experiment (or as he called it, an *experimentum crucis*), where the effect of contaminated water from the Thames could be assessed. During the cholera outbreak of 1854-1855, Snow visited those residences in the study area where cholera had appeared and determined which of the two water companies had supplied the house. The results of this evaluation appear in MCC as Table IX (given above). The "number of houses" variable was obtained from parliamentary records. The effect of contaminated water on cholera can be seen quite clearly: the rate of cholera in the Southwark/Vauxhall supplied residences is over eight times that for the Lambeth residences.

Part of the extensive narrative from MCC for Snow's Grand Experiment is given in an external Appendix.

* * *

Throughout much of the early part of the Victorian Era, the miasma theory of disease, particularly for cholera, was the dominant view as to why such epidemics occurred. In 1846, for example, Parliament passed the Nuisances Removal and Diseases Prevention Act, commonly called the Cholera Bill, in an attempt to eliminate the source of foul smells from decomposing material, such as from cesspools and other accumulations of manure and similar waste, or

from filth generated by the keeping of animals close to human residences, and so on. A few years later in 1855, an amendment to the Act was proposed to regulate the many so-called "offensive" trades, such as bone-boiling, soap making, and leather tanning, all of which released noxious fumes into the atmosphere as part of the normal manufacturing process. Supporters of miasma theory wanted various sanitary reforms implemented to eliminate the effluvia from these offensive industries, and therefore, to eliminate an obvious source of disease.

John Snow was asked by several of the manufacturers from the offensive trades to testify on the proposed amendment, which he did on March 5, 1855 to a committee of Parliament chaired by Sir Benjamin Hall (of "Big Ben" fame). Hall was a confirmed miasmatist convinced of the public health need to eliminate all sources of foul vapors. Parts of Snow's testimony are given in an Appendix external to this chapter. The questions asked by Hall or the other committee members are indicated by the letter "Q"; Snow's answers are identified by the letter "A". One gets the sense that if Benjamin Hall could have had Snow sent to the Tower of London and flogged, he would have done so gladly.

The testimony of Snow that foul smells by themselves were incapable of producing acute fever or actual disease in an individual, incensed confirmed miasmatists such as the *Lancet* editor, Thomas Wakely, who believed that such testimony would lead to the blockage of crucial public health sanitary reform. Several months after Snow's testimony to Parliament, a scathing editorial appeared in the *Lancet* commenting on Snow's views about cholera transmission. Parts of this editorial follow:

...

But Mr. Kintrea [a soap-boiler] and his colleagues do not rely upon these acts alone. They have "scientific" evidence! They bring before the Committee a doctor and a barrister. They have formed an Association. They have a Secretary, a bone merchant, who has read the writings of Dr. Snow. Now, the theory of Dr. Snow tallies wonderfully with the views of the "Offensive Trades Association" — we beg pardon if that is not the right appellation — and so the Secretary puts himself in communication with Dr. Snow. And they could not possibly get a witness more to their purpose. Dr. Snow tells the Committee that the effluvia from bone-boiling are not in any way prejudicial to the health of the inhabitants of the district; that "ordinary decomposing matter will not produce disease in the 'human subject.' " He is asked by Mr. Adderley (of the Committee), "Have you never known the blood poisoned by inhaling putrid matter?" (Snow's response) "No; but by dissection-wounds the blood may be poisoned." (Adderley asked) "Never by inhaling putrid gases?" (Snow responded) "No; gases produced by decomposition, when very concentrated, will produce sudden death; but when the person is not killed, if he recovers, he has no fever or illness."

Dr. Snow next admits that gases from the decay of animal matter may produce vomiting but says this would not be injurious unless frequently repeated.

Is this scientific evidence? Is it consistent with itself? It is in accordance with the experience of men who have studied the question without being blinded by theories?

Let it first be observed that Dr. Snow admits that the gases from decomposing matter may kill outright — a pretty convincing proof of their potency. He also admits that in a less concentrated form they may cause vomiting. And here he stops, assuring us, that if the don't kill us, or cause repeated vomiting, they do us no harm. Now, as a matter of mere reasoning, we think the conclusion inevitable, that agents capable, when in a certain degree of concentration, of killing or causing vomiting, will in a lesser degree of concentration,

also act on the animal economy; albeit in a less sudden and perceptible manner. It will be very difficult to persuade us that the long-continued action of gases known to have such lethal powers, if concentrated, is not injurious to health, when in a state of dilution. We shall not easily be reconciled, on the assurance of Dr. Snow, to endure a leakage in our house drains.

...

We have a strong conviction, that as soon as our noses give us intimation of a communication between those conduits of decomposing animal and vegetable matter and our dwellings, it is time to call in bricklayer and plumber. We decline to wait until repeat vomiting, or a sudden death amongst our children, satisfy us that the gases evolved [sic] are in a highly concentrated state. Our professional avocations have, indeed, frequently given us the opportunity of tracing failing strength, flabby muscles, pallid cheeks, lassitude of body and torpidity of mind to this cause. We have felt it our duty to urge removal from the houses so affected, when the drains could not be repaired effectively, and we have commonly been gratified by observing a restoration to bodily and mental vigor. And we presume that there is hardly a practitioner of experience and average powers of observation who does not daily observe the same thing.

Why is it then, that Dr. Snow is singular in his opinion? Has he any fact to show in proof? No! But he has a theory, to the effect that animal matters are only injurious when swallowed! The lungs are proof against animal poisons; but the alimentary canal affords a ready inlet. Dr. Snow is satisfied that every case of cholera for instance, depends upon a previous case of cholera, and is caused by swallowing the excrementitious matter voided by cholera patients. Very good! But if we admit this, how does it follow that the gases from decomposing animal matter are innocuous? We cannot tell. But Dr. Snow claims to have discovered that the law of propagation of cholera is the drinking of sewage water. His theory, of course, displaces all other theories. Other theories attribute great efficacy

in the spread of cholera to bad drainage and atmospheric impurities. Therefore, says Dr. Snow, gases from animal and vegetable decompositions are innocuous! If this logic does not satisfy reason, it satisfies a theory; and we all know that theory is often more despotic than reason. The fact is, that the well whence Dr. Snow draws all sanitary truth is the main sewer. His specus [pit], or den, is a drain. In riding his hobby very hard, he has fallen down through a gully-hole and has never since been able to get out again. And to Dr. Snow an impossible one: so there we leave him.

In that dismal Acherontic [dark] stream is contained the one and only true cholera germ, and if you take care not to swallow that you are safe from harm. Smell it if you may, breathe it fearlessly, but don't eat it.

Now we do not think it necessary to prove, by adducing evidence in opposition to Dr. Snow, that decomposing animal and vegetable matters are injurious to health. They ought not to be suffered to be stored in inhabited localities. We are not acquainted with a single medical practitioner of established reputation who would not consider that the removal of deposits of decomposing animal and vegetable matters was an essential condition for the improvement of the health of towns. We have adverted [referred] to the evidence of Dr. Snow, for the purpose of repudiating it as the expression of the teaching of medical science. ... The Committee seems to have contented itself with listening to the statements and objections of those who are interested in opposing the Bills. Those objections it was of coarse bound to hear. If it did not for any scientific evidence in reply, we hope it was because the statements of the dirt-and-effluvium-interest contained their own refutation.

A year after the condemning editorial in the *Lancet*, Snow published what amounted to a rebuttal, and in the *Lancet*, no less. Its title was, "On the supposed influence of offensive trades on mortality." It was based on mortality data for males working in the offensive trades or elsewhere for the last eighteen months prior to the publica-

tion date of the article (July, 1856); these data were obtained from the Weekly Returns of the Registar-General (who was William Farr, it might be remembered). The questions that Snow asked were the familiar ones that miasma theory had difficulty answering:

If miasma theory were true, why are sewer workers no more prone to get cholera?

Because gases decline rapidly over distance, how could a miasma from one source pollute an entire neighborhood?

Why are workers who are close to stench unaffected while those further away might be?

Because cholera affects the alimentary canal and not the respiratory tract, why is cholera due to the air and not from something that must be ingested?

Snow's short *Lancet* article is given in an external Appendix, including his table of mortality data.

Besides attacking the miasmatists directly in his testimony to Parliament, Snow also took on William Farr's well-developed contention that cholera prevalence depended on elevation. Presumably, the higher one was above the miasmata produced by the Thames, the cleaner the air, and therefore, the less chance that cholera would be present in the elevated area. In the 1855 MCC monograph, Snow effectively demolished the elevation-cholera connection in a few short paragraphs and from several well-chosen counterexamples:

> RELATION BETWEEN THE GREATER OR LESS MORTALITY FROM CHOLERA IN LONDON AND THE LESS OR GREATER ELEVATION OF THE GROUND
>
> Dr. Farr discovered a remarkable coincidence between the mortality from cholera in the different districts of London in 1849, and

the elevation of the ground; the connection being of an inverse kind, the higher districts suffering least, and the lowest suffering most from this malady. Dr. Farr was inclined to think that the level of the soil had some direct influence over the prevalence of cholera, but the fact of the most elevated towns in this kingdom, as Wolverhampton, Dolais, Merthyr Tydfil, and Newcastle-upon-Tyne, having suffered excessively from this disease on several occasions, is opposed to this view, as is also the circumstance of Bethlehem Hospital, the Queen's Prison, Horsemonger Lane Gaol, and several other large buildings, which are supplied with water from deep wells on the premises, having nearly or altogether escaped cholera, though situated on a very low level, and surrounded by the disease. The fact of Brixton, at an elevation fifty-six feet above Trinity high-water mark, having suffered a mortality of 55 in 10,000, whilst many districts on the north of the Thames, at less than half the elevation, did not suffer one-third as much, also points to the same conclusion.

THIS RELATION SHOWN TO DEPEND ON THE DIFFERENCE OF WATER SUPPLY AT DIFFERENT ELEVATIONS

I expressed the opinion in 1849, that the increased prevalence of cholera in the low-lying districts of London depended entirely on the greater contamination of the water in these districts, and the comparative immunity from this disease of the population receiving the improved water from Thames Ditton during the epidemics of last year and the present, as shown in the previous pages, entirely confirms this view of the subject; for the great bulk of this population live in the lowest districts of the metropolis. (pp. 97–98)

* * *

John Snow died in 1858 before his theories about the transmission of cholera were finally accepted a few years later, and then by none other than William Farr, one of the staunchest supporters of a miasma theory of disease transmission. This would prove to be

quite a turnaround for Farr given his steadfast miasmatic views up to that time. Earlier, in 1854, Farr was appointed a leading member of the Committee for Scientific Inquires in Relation to the Cholera-Epidemic of 1854. The report of this committee was presented in 1855 to both Houses of Parliament by command of Her Majesty Queen Victoria. In essence, the report's main conclusions repudiated all of Snow's views as to how cholera was transmitted, or when acknowledging any possible influence that water might have, it was only because miasmata must have contaminated the water, which then served soley as a secondary means of cholera transmission.

Several parts of this Parliamentary report are given below, including what can only be termed tortuous arguments for maintaining a miasma account of cholera:

> On hearing of the late fearful outburst of Cholera, the question which we heard asked on all sides, and which naturally suggests itself to every inquiring mind, is, What was the cause? The very importance of the question makes us diffident in replying to it, nor could we receive any satisfactory answer to it from the medical practitioners, or from the more intelligent of the inhabitants in the district; the sewers, the air, the water, [et]c., were each assigned as the cause, more particularly the sewers. For ourselves, we have no new theory to offer. We are inclined to believe that there existed a peculiar condition of the atmosphere, which has been called choleraic, wherein the exhalations from sewers, impure water, bad house drainage, overcrowding, intemperance, fear, may operate on individuals, so as to produce the disease; nor can we call to mind an instance in which the sufferer had not been exposed to the action of some of these circumstances which, during the prevalence of epidemics, act as fuel on a fire.
>
> Allowing, indeed, more than their utmost effect — to the miasmata diffused by the construction of the new sewer, to the unhealthy

condition of the water from the Broad Street pump, we cannot help thinking that the outbreak mainly arose from the multitude of untrapped and imperfectly trapped gullies and ventilating shafts constantly emitting an immense amount of noxious, health destroying, life-destroying exhalations, the intensity of which must have been greatly increased by the structural peculiarity of the streets, and by the stagnant condition of the atmosphere at the time of, and preceding the attack. Thus, as the poisonous emanations rose from the sewers, they remained suspended in the immediately surrounding atmosphere, which was remarked at the time to have little or no horizontal movement. The benefit of what little movement did exist, would be mostly experienced at the corner of the streets; and it is a remarkable fact that houses thus situated experienced a decided immunity, "except in the case of those corner houses where abundant *materia morbi*" existed in, or adjoining the premises, as, for instance, at the corner of Little Windmill Street and Brewer Street, where several most offensive gullies at the side, and a choked up necessary behind, belonging to the next house, sent up their pestiferous vapours. As a proof of the immunity of several corner houses, we may mention the six corner houses on the north side of Broad Street, although the street itself was the most heavily visited in the district. (p. 36; in an Appendix to the main report that dealt only with the Broad Street outbreak)

...

In explanation of the remarkable intensity of this outbreak within very definite limits, it has been suggested by Dr. Snow that the real cause of whatever was peculiar in the case lay in the general use of one particular well, situate [sic] at Broad Street in the middle of the district and having (it was imagined) its waters contaminated by the rice-water evacuations of cholera patients.

After careful enquiry we see no reason to adopt this belief. We do not find it established that the water was contaminated in the manner alleged; nor is there before us any sufficient evidence to show, whether inhabitants of the district, drinking from that well,

> suffered in proportion more than other inhabitants of the district who drank from other sources.
>
> There is mentioned, however, a remarkable instance in which it seems probable that the water of this well did really act as a vehicle of choleraic infection; but (assuming the absence of fallacy in the case) this probability might easily be admitted, without its therefrom resulting that infection depended on the specific material alleged. The water was undeniably impure with organic contamination; and we have already argued that, if, at the times of epidemic invasion there be operating in the air some influence which concerts putrefiable impurities into a specific poison, the water of the locality, in proportion as it contains such impurities, would probably be liable to similar poisonous conversions. Thus, if the Broad Street pump did actually become a source of disease to persons dwelling at a distance, we believe that this may have depended on other organic impurities than those exclusively referred to, and may have arisen, not in its containing choleraic excrements, but simply in the fact of its impure waters having participated in the atmospheric infection of the district ... (p. 52)
>
> ...
>
> ... on the whole evidence, it seems impossible to doubt that the influences, which determine in mass the geographical distribution of cholera in London, belong less to the water than to the air. (p. 48)

The final cholera pandemic to reach London occurred in 1866 with the major outbreak limited to the East End, and primarily, as it turned out, to those residences supplied by the East London Water Company. The Metropolis Water Companies Act of 1852 introduced for the first time, minimum standards of water quality for all water supply companies operating in London. It became unlawful for any company to extract water for domestic use from the tidal reaches of the Thames after August 31, 1855; also, from December 31, 1855

onward, all such water had to be "effectually filtered." In addition to mandating adequate filtration, all uncovered reservoirs were outlawed.

The East London Water Company drew its supply from the heavily polluted Lea River. Also, as of 1866, the East End of London was not yet hooked up to the massive Bazalgette sewer system being constructed for all of London; it was to be the last area connected. When the East End cholera outbreak occurred, the pattern of deaths reported to the Registrar-General's office, alerted Farr to the possibility that contaminated drinking water could be the cause. Upon further investigation, Farr uncovered what was probably for its time the greatest case of public health malfeasance for any company operating under the public trust.

In summary, William Farr finally engaged in an appropriate abductive reasoning scheme: a "surprising" pattern of cholera death was present in the East End of London where water was generally supplied by the East London Water Company. Conjecturing that this observation would be a "matter of course" if the East London Water Company were the source of the cholera contamination, Farr had reason to believe this conjecture to be true and investigated it further. Farr obtained the type of substantiating evidence that would verify the guilt of the East London Water Company "beyond any reasonable doubt," and in the process uncovered corporate misdeeds having the most severe consequences.

Parts of Farr's report to both Houses of Parliament (*Report of the Cholera Epidemic of 1866 in England*) are given in an external Appendix that discuss the reasons for the East End Cholera outbreak and the nefarious role played by the East London Water Company.

This report represents a belated acknowledgement of the views of John Snow as to how cholera could be transmitted through the water supply and the contamination that it might contain. Most notedly, the report was written by one of the best known statisticians and sanitary reformers of the Nineteenth Century, who up until the earlier 1860s was a confirmed miasmatist. Note that index cases for the outbreak were identified as a couple named Hedges who lived on the Lea River near where the East London Water Company drew its supply. The "shoe-leather" work to identify these initial cases was done by none other than Henry Whitehead, the prelate involved in investigating the Broad Street outbreak; he was aided in this instance by a doctor, John Netten Radcliffe.

The *Lancet* in August of 1868 finally gave an endorsement of John Snow's views on cholera transmission albeit through the report authored by William Farr:

> ... the elaborate array of facts which Dr. Farr has set forth with so much skill, as the result of great labor and research, will render irresistible the conclusions at which he has arrived in regard to the influence of the water supply in the causation of the epidemic.

* * *

This chapter on John Snow will end by reproducing the last several pages from his 1855 monograph, *On the Mode of Communication of Cholera*. These provide Snow's considered recommendations as to how cholera and similar epidemic diseases (such as typhus, which he explicitly mentioned) might be prevented. To my own reading and even though written over a hundred and sixty years ago, these seem so current that they could just as well have been issued by the Center

for Disease Control and Prevention. We note that Snow's comments on the importance of finding the mode of transmission for typhus come some fifty years before the 1928 Nobel Prize winner, Charles Nicolle, finally discovered that human body lice were the mechanism for person-to-person transmittal:

> MEASURES REQUIRED FOR THE PREVENTION OF CHOLERA AND OTHER DISEASES WHICH ARE COMMUNICATED IN THE SAME WAY
>
> The measures which are required for the prevention of cholera, and all diseases which are communicated in the same way as cholera, are of a very simple kind. They may be divided into those which may be carried out in the presence of an epidemic, and those which, as they require time, should be taken beforehand.
>
> The measures which should be adopted during the presence of cholera may be enumerated as follows:
>
> 1st. The strictest cleanliness should be observed by those about the sick. There should be a hand-basin, water, and towel, in every room where there is a cholera patient, and care should be taken that they are frequently used by the nurse and other attendants, more particularly before touching any food.
>
> 2nd. The soiled bed linen and body linen of the patient should be immersed in water as soon as they are removed, until such time as they can be washed, lest the evacuations should become dry, and be wafted about as a fine dust. Articles of bedding and clothing which cannot be washed, should be exposed for some time to a temperature of 212 degrees or upwards.
>
> 3rd. Care should be taken that the water employed for drinking and preparing food (whether it come from a pump-well, or be conveyed in pipes) is not contaminated with the contents of cesspools, house-drains, or sewers; or, in the event that water free from suspicion cannot be obtained, is should be well boiled, and, if possible, also filtered.

Works are in progress for supplying a great part of London with water from the Thames, obtained, like that of the Lambeth Company, above Teddington Lock. Although this is not the best possible source for supplying a large town, it is a great improvement on the practice of many of the water companies; and the water, owing to filtration, and especially to its detention in large reservoirs, will probably be quite salubrious [healthy]: at all events it will be much safer than that of the shallow pump-wells of London, which are fed from very polluted sources. It is very desirable that the handles of nearly all the street-pumps of London and other large towns should be fastened up, and the water used only for such purposes as watering the streets. A proper supply of water for the shipping in the Thames is much wanted. Water acquires a flat taste by being boiled; but if it is filtered after it becomes cold, it gets re-aerated, and the flat or vapid taste is entirely removed.

4th. When cholera prevails very much in the neighborhood, all the provisions which are brought into the house should be well washed with clean water, and exposed to a temperature of 212 degrees Fahrenheit; or at least they should undergo one of these processes, and be purified either by water or by fire. By being careful to wash the hands, and taking due precautions with regard to food, I consider that a person may spend his time amongst cholera patients without exposing himself to any danger.

5th. When a case of cholera or other communicable disease appears among persons living in a crowded room, the healthy should be removed to another apartment, where it is practicable, leaving only those who are useful to wait on the sick.

6th. As it would be impossible to clean out coal-pits, and establish privies and lavatories in them, or even to provide the means of eating a meal with anything like common decency, the time of working should be divided into periods of four hours instead of eight, so that the pit-men might go home to their meals, and be prevented from taking food into the mines.

7th. The communicability of cholera ought not to be disguised

from the people, under the idea that the knowledge of it would cause a panic, or occasion the sick to be deserted.

British people would not desert their friends or relatives in illness, though they should incur danger by attending to them; but the truth is, that to look on cholera as a "catching" disease, which one may avoid by a few simple precautions, is a much less discouraging doctrine than that which supposes it to depend on some mysterious state of the atmosphere in which we are all of us immersed and obliged to breathe.

The measures which can be taken beforehand to provide against cholera and other epidemic diseases, which are communicated in a similar way, are —

8th. To effect good and perfect drainage.

9th. To provide an ample supply of water quite free from contamination with the contents of sewers, cesspools, and house-drains, or the refuse of people who navigate the rivers.

10th. To provide model lodging-houses for the vagrant class, and sufficient house room for the poor generally.

The great benefit of the model lodging-houses arises from the circumstance that the apartments for cooking, eating, and sleeping, are distinct, and that all the proper offices which cleanliness and decency require are provided. The very poor who choose to avail themselves of these institutions, suffer a rate of mortality as low as that of the most opulent classes. The public wash-houses, which enable poor persons to wash the soiled linen of the sick or the healthy, without doing it in the midst of the plates and dishes and provisions of the family, are well calculated to prevent the spread of disease.

11th. To inculcate habits of personal and domestic cleanliness among the people everywhere.

12th. Some attention should undoubtedly be directed to persons, and especially ships, arriving from infected places, in order to segregate the sick from the healthy. In the instance of cholera, the supervision would generally not require to be of long duration.

In the autumn of 1853, certain German emigrants, on their way to America, who had crossed the sea from Hamburgh [sic] and Rotterdam, where cholera was prevailing, to the port of Hull, and had gone thence, by rail, to Liverpool, were seized with cholera (some of them fatally) in the latter town; and it is most likely to the well-regulated Emigrant's Home, in which these cases occurred, that the town of Liverpool owed its freedom from the epidemic at that time. And a little medical supervision, and the detention of some of the emigrants for a short time in Liverpool, before their embarkation, would probably have prevented the great mortality which occurred in some of the emigrant ships during their passage to America.

The measures which are intended to prevent disease should be founded on a correct knowledge of its causes. For want of this knowledge, the efforts which have been made to oppose cholera have often had a contrary effect. In 1849, for instance, the sewers of London were frequently flushed with water — a measure which was calculated to increase the disease in two ways: first, by driving the cholera evacuations into the river before there was time for the poison to be rendered inert by decomposition; and second, by making increased calls on the various companies for water to flush the sewers with — so that the water which they sent to their customers remained for a shorter time in the reservoirs before being distributed. It should be remarked, also, that the contents of the sewers were driven into the Thames by the flushing, at low water, and remained flowing up the stream for four or five hours afterwards. Flushing the sewers was not repeated during the recent epidemic, but increased quantities of water were distributed by some of the Companies, and at more frequent intervals, causing the water-butts to overflow for hours together into the drains, and producing nearly the same effect as flushing the sewers; in addition to which, the water in the butts of the Southwark and Vauxhall Company's customers was prevented from settling, as it might have done if less frequently disturbed.

I feel confident, however, that by attending to the above-mentioned precautions, which I consider to be based on a correct knowledge of

the cause of cholera, this disease may be rendered extremely rare, if indeed it may not be altogether banished from civilized countries. And the diminution of mortality ought not to stop with cholera. The deaths registered under the name of typhus consist chiefly of the typhoid fever mentioned above. Its victims are composed chiefly of persons of adult age, who are taken away from their families and connections. In 1847 upwards of 20,000 deaths were registered in England from typhus, and in 1848 upwards of 30,000 deaths. It is probable that seven times as many deaths have taken place from typhus as from cholera, since the latter disease first visited England in 1831; and there is great reason to hope that this mortality may in future be prevented by proper precautions, resulting from a correct knowledge of the mode of communication of the malady.

Major References for John Snow

Two websites are devoted to John Snow: the John Snow archive and research companion at Michigan State University (maintained by Peter Vinten-Johansen):

https://johnsnow.matrix.msu.edu

and the site maintained by Ralph Frerichs at UCLA:

https://www.ph.ucla.edu/epi/snow.html

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Chapter 5

William Budd

> [On Typhoid Fever] How often have I seen in past days, in the single narrow chamber of the day-labourer's cottage, the father in the coffin, the mother in the sick-bed in muttering delirium, and nothing to relieve the desolation of the children but the devotion of some poor neighbour, who in too many cases paid the penalty of her kindness in becoming herself the victim of the same disorder.
>
> – William Budd (1811–1880)

William Budd (1811–1880) and John Snow (1813–1858) were Victorian era contemporaries. Both were practicing English doctors and can be considered among the earliest English epidemiologists. Snow resided in urban London and Budd lived as a country doctor in South-West England around Bristol. What Snow determined about cholera and its typical mode of transmission through water and by an oral-fecal route, Budd did the same for typhoid. Although Budd was concerned with the contagiousness of infectious diseases more generally, including cholera, he readily acknowledged Snow's priority "in print" as to how cholera was generally transmitted. The main emphasis in this chapter will be on Budd's observations and conclusions regarding the contagiousness of typhoid fever and how that disease is transmitted, which again is primarily through an oral-fecal route.

Budd believed that the agent of contagion was a living organism — a *contagium vivum*: a substance by which a contagious disease could be transmitted. Some later discussion is also provided about contagious but asymptomatic carriers of typhoid and their importance to public health practice, particularly in the early Twentieth Century; this includes the famous case of "Typhoid Mary." Here, some timely abductive reasoning by Dr. George Soper, a sanitary engineer for the New York City Department of Health, led to Mary's identification and eventual detention for life.

Typhoid is an infectious disease that just like cholera primarily affects the intestines (and thus, is referred to as "enteric"). As Snow noted for cholera, Budd argued that typhoid could be caused by ingesting food or drinking water contaminated with the typhoid producing poison. A bacterium, *Salmonella typhi*, was explicitly identified as the infecting agent for typhoid in 1880 by Carl Eberth (1835–1926), the same year that Budd died. Again, as for cholera, and because of the understanding that cholera is commonly waterborne and can be prevented by the use of clean drinking water and avoiding transmission through some fecal-oral mechanism, very few deaths now appear in developed countries with improved sanitation and the general availability of antibiotics. Worldwide, however, some 150,000 typhoid deaths still occur annually.

The outward signs of a typhoid infection of a high fever, abdominal pain, and a skin rash with rose-colored spots, may not be clinically sufficient to distinguish typhoid from other maladies such as typhus. There is one definitive tell-tale sign of typhoid but it can only be determined *post mortem*. As an enteric disease, typhoid affects what are called Peyer patches in the small intestine. These areas are masses

of lymphatic tissue where typhoid bacilli multiply; they become inflamed and necrotic and slough off leaving ulcers on the intestinal walls. Although cholera is also an enteric disease where bacilli multiply profusely in the intestines, the Peyer patches are not involved as they are for typhoid. In reference works that concern typhoid, it is routine to provide illustrations of the *post mortem* results from the small intestine as definitive evidence of a prior typhoid infection.

Charles-Edward Amory Winslow (1877–1957) was a prominent American bacteriologist during the first half of the Twentieth Century. Among other achievements, he was the founder of the Yale School of Public Health. Winslow published an epic text in 1943, *The Conquest of Epidemic Disease*, that included the following summary paragraph regarding the contributions of our two Victorian epidemiologists, John Snow and William Budd. Given the emphasis of the current monograph, we have taken the liberty of suggesting the phrase "abductive reasoning" in place of Winslow's possibly less apt "logical deduction," at least for us:

> Between them, these two great English epidemiologists — working in the sixth decade of the Nineteenth Century and with no knowledge of the work of Pasteur — demonstrated the basic facts with regard to the causation of cholera and typhoid fever; they showed beyond peradventure [doubt] that these diseases were specific entities; that they were transmitted only by direct transfer of material from an infected human body to a susceptible victim; that the contagious elements were contained in the dejecta from the alimentary canal; that these elements were particulate and not miasmatic in nature; that they enjoyed the biological properties of survival in the environment and continuing reproduction when reintroduced into the human body; and that the passage of these contagious entities from one human being to another was accom-

> plished chiefly by direct contact or fomites [materials likely to carry infection] and by drinking water. They thus laid the basis for a theoretically sound and practically effective epidemiology of the intestinal infections; and they accomplished this brilliant result by keen observation and sound logical deduction [or better, sound abductive reasoning] from field experience, with little or no assistance from the germ-theory of disease as that theory was to be elaborated by the bacteriologists. Their accomplishment was perhaps the greatest triumph of pure epidemiology in the history of that science. (p. 290)

* * *

William Budd was born in September of 1811 in North Tawton, County Devon, England. He began his medical training as an apprentice to his father, himself a doctor with a practice in North Tawton and vicinity. Budd furthered his training first with four years in Paris, partly under the contagionist French clinician, Pierre Louis. Subsequently, he attended the University of Edinburgh, receiving a medical degree in 1838. Immediately after graduation, Budd contracted a severe case of typhoid, possibly sensitizing him to the malady when he began his own practice as a doctor in North Tawton. A few years later in 1842 he went to work at St. Peter's Hospital in Bristol, England, and thereafter, as a physician in the Bristol Royal Infirmary.

Budd had a deep interest in the diseases he encountered in his various medical practices, starting in North Tawton. As we will see, Budd's ideas on how typhoid originated and was spread began in earnest in the late 1830s from this initial practice in North Tawton. As noted by the earlier quote from Charles Winslow, Budd had

keen observational skills and the ability to reason abductively from what he saw. He also had two additional attributes of a successful researcher/practitioner: the ability to seek out and replicate what he observed and inferred, and the necessary skills to write both coherently and extensively about his conclusions regarding contagious diseases generally and typhoid in particular.

Budd wrote widely about contagious diseases over the course of his career, but our emphasis will be on his comprehensive monograph published in 1873, *Typhoid Fever: Its Nature, Mode of Spreading, and Prevention* (hereafter, referred to as *TF*; page numbers given for *TF* will refer to the edition reissued in 1931). This summary text includes most of Budd's previous writing on typhoid, especially that which appeared serially in the *Lancet* during the late 1850s. The *TF* monograph consists of nine chapters:

Chapter I: Introductory

Chapter II: Typhoid fever: a contagious or self-propagating fever

Chapter III: Nature of the intestinal affection

Chapter IV: Nature of the relation of typhoid fever to defective sewerage

Chapter V: Conditions attaching to the contagious agent as it exists in media external to the body

Chapter VI: Prevention — disinfectants and disinfection

Chapter VII: The pythogenic theory [i.e., produced by decomposition or filth]

Chapter VIII: Spontaneous origin

Chapter IX: Summary

We proceed sequentially and, whenever appropriate, provide some comments on each chapter as well as a few clarifying excerpts.

The introductory Chapter I presents Budd's basic thesis: typhoid is a self-propagating (or contagious) disease disseminated by the specific discharges from the intestines of the sick. He goes on to comment on his anti-contagionist colleagues who live in crowded urban areas that obscure the contagion that is so obvious in a more rural setting where "the lines of intercourse are few and always easily traced":

> ... medical writers, and especially those among them who exercise the widest influence, pass the greater part of their lives in great metropolitan cities — amid conditions, that is to say, under which, for reasons that will abundantly appear in the following pages, the operation of contagion in this particular fever is not only masked and obscured, but issues in a mode of distribution of the disease, which to the superficial observer would appear to exclude the idea of contagion altogether. (p. 7)
>
> ...
>
> It is obvious that the formation of just opinions on the question how diseases spread may depend less on personal ability than on the opportunities for its determination which may fall to the lot of the observer. It is equally obvious that where the question at issue is that of the propagation of disease by human intercourse, rural districts, where the population is thin, and the lines of intercourse are few and always easily traced, offer opportunities for its settlement which are not to be met with in the crowded haunts of large towns.
>
> This is one of the cases in which medical men practi[c]ing in the country have for the acquirement of medical truths of the highest order advantages which are denied to their metropolitan brethren, and which constitute, on the whole, no mean set-off against the greater privileges of other kinds which the latter enjoy.
>
> In the early part of my professional life, while engaged in country

practice in Devonshire, outbreaks of typhoid fever continually fell under my eye, amid conditions singularly favourable to the study of its origin and mode of dissemination.

Of these outbreaks the most memorable occurred in the village of North Tawton, where I then lived.

In addition to the advantages enjoyed by country practitioners, generally, in the observation of such events, there were others peculiar to the position I then occupied.

Having been born and brought up in the village, I was personally acquainted with every inhabitant of it; and being, as a medical practitioner, in almost exclusive possession of the field, nearly every one who fell ill, not only in the village itself, but over a large area around it, came immediately under my care.

For tracing the part of personal intercourse in the propagation of disease, better outlook could not possibly be had. (pp. 8–9)

The miasmatists' view that disease resulted from repellent odors produced by decaying organic matter is countered by Budd by observing that terrible smells were present for many years in areas where no disease existed, and that more was needed to produce disease than just odor:

... In the cottages of the men who earned their bread with their hands, and who formed the great bulk of the inhabitants, there was nothing to separate from the open air the offensive matters which collect around human habitations. Each cottage, or group of three or four cottages, had its common privy, to which a simple excavation in the ground served as cesspool. Besides this, it was a part of the economy of all who worked in the fields, as indeed of many more, to keep a pig, one of whose functions was to furnish manure for the little plot of potatoes which fed man and pig alike. Thus, often, hard by the cottage door there was not only an open privy, but a dungheap also.

Nevertheless, these conditions existed for many years without leading to any of the results which it is the fashion to ascribe to them.

Much there was, as I can myself testify, offensive to the nose, but fever there was none. It could not be said that the atmospheric conditions necessary to fever were wanting, because while this village remained exempt, many neighbouring villages suffered severely from the pest. It could not be said that there were no subjects, for these, as the sequel proved, but too much abounded.

Meanwhile privies, pigstyes and dungheaps continued, year after year, to exhale ill odours, without any specific effect on the public health.

Many generations of swine innocently yielded up their lives, but no fever of this or any other sort could be laid to their charge. I ascertained by an inquiry conducted with the most scrupulous care that for fifteen years there had been no severe outbreak of the disorder, and that for nearly ten there had been but a single case.

For the development of this fever a more specific element was needed than either the swine, the dungheaps, or the privies were, in the common course of things, able to furnish.

In the course of time, as was indeed pretty sure to happen, this element was added, and it was then found that the conditions which had been without power to generate fever, had but too great power in promoting its spread when once the germ of fever had been introduced.

On the 11th July, 1839, a first case of typhoid fever occurred in a poor and crowded dwelling. Before the beginning of November, in the same year, more than eighty of the inhabitants had suffered from it under my care.

I kept an accurate record of all the principal events which marked this terrible outbreak; and it is to certain of these events, in their bearing on the mode in which this fatal disorder spreads, that I now wish to draw attention. (pp. 10–11)

The typhoid outbreak alluded to in the excerpt just given occurred in North Tawton where Budd first practiced before moving to Bristol. It was obviously a formative part of Budd's views reported in Chapter II (Typhoid fever: a contagious or self-propagating fever). Although it is only the first such episode given in the chapter among many other similar ones that Budd provided, it will be the sole one excerpted extensively here:

> The first thing to arrest attention after the disorder had become rife in North Tawton was the strong tendency it showed, when once introduced into a family, to spread through the household. Thus, in the family of Ann N —, a young woman who was taken ill in the second week in July, and who was the subject of the first case, the mother, a brother, and a sister — making four in all — were one after another laid up with the same fever; the father, who had already had the disease in former years, and the young infant, being the only inmates spared. In another house, four out of six persons were successively attacked; in another three, and so on. Without going into further details of these cases (of all of which I possess accurate notes), it will be sufficient to say that, before the disease finally died away, there were few houses in which, having once appeared, it did not further extend itself to one or more members of the family. This, which was throughout its most striking character, was, in itself, sufficient to lead to a strong presumption of the contagious nature of the disorder.
>
> But while these events were occurring in the village itself, there were others happening at a distance, which converted this presumption into a certainty. During the prevalence of the fever in North Tawton, it so happened that three persons left the place after they had become infected. By a fatality which is but too common under such circumstances, all three communicated the disease to one or more of the persons by whom they were surrounded in the new neighbourhood in which they fell ill. Two of these three persons

were sawyers by trade, who had hired themselves for a few weeks to a timber merchant living in the village. While these men remained in North Tawton, they lodged in a court with a single and a common privy, and next door to a house in which the fever was. In the course of time both these men sickened for the disorder, and on the occurrence of the first decided symptoms, both returned to their own homes, in the parish of Morchard, about seven miles off.

The first was a married man, with two children. He left North Tawton on August 9, being already too ill to work. Two days after reaching Morchard he took to his bed, and at the end of five weeks he died. Ten days after his death his two children were laid up with the same fever, and had it severely; the widow escaped. The other sawyer, was a single man, and an aged couple who lived with him were the only other inmates of the house. Like his comrade, he was driven from North Tawton by indisposition, which rendered him unable to follow his employment, and cut off his means of support. He began to droop on July 26, but did not leave for Morchard until August 2. On the 3rd he finally took to his bed. His attack was severe, but, after a long struggle, he recovered. When this man was at his worst, a friend who came to see him was called upon to assist in raising him in bed. While thus employed, the friend was quite overpowered by the smell from the sick man's body. He felt very unwell from that time, and continued to be harassed for days afterwards by a sense of the same pestilent smell, and by a fixed impression, which under the circumstances was natural enough, that he had caught the fever. On the tenth day from the date of this event, he was seized with a violent shiver, which was immediately followed by an attack of typhoid fever of long duration. Before he became convalescent, two of his children got the same fever, as well as a brother, who lived at some distance, but who had repeatedly visited him during his illness.

The houses occupied by these four men lay some way apart, and, unless underneath their roofs, there was no fever at the time in that part of the country. (pp. 12–14)

Continuing with Chapter II, Budd argued for the contagious nature of typhoid by emphasizing the mode of transmission and its ability "to propagate itself and no other." Also, as in other contagious diseases, there was a latent or incubation period for typhoid to appear, and once an individual had the malady, an immunity against ever having it again was produced:

> Now I need scarcely add, that of the various properties that can be shown to belong to any given malady, this one, of all others, is incomparably the most important. In the first place, it is clear that, in a far higher sense than can possibly attach to any other conceivable property, this mode of propagation sets upon a disease the stamp of a specific nature. In order to appreciate its full significance in this respect, we must not forget that, like the other contagious fevers, this fever, in particular, not only propagates itself, but, if common observation can be trusted in such a matter, propagates no other kind. In the numerous cases in which I have seen the disease palpably spreading by contagion, the offspring has always borne the same specific marks which distinguished the parent; and one case has followed another with the same constancy of specific type with which small-pox follows small-pox, or measles succeed to measles. It is well known, in fact, that there are many countries in which continued fever is not only common, but rife, and in which this particular kind is the only kind that occurs. But *to propagate itself and no other*, and that in a series of indefinite progression, constitutes the very essence of the relation on which the idea of species is founded. How much this implies in the animal and in the plant we all know. It is strange that what it implies in the case of disease should be so seldom recognised.
>
> ...
>
> The existence here, *as in the other contagious fevers*, of a latent period after the occurrence of infection; the exemption conferred by one attack against any future attack; and, lastly, the immunity of large numbers of persons, who, though freely exposed to the fever

> poison, yet remain proof against it, are characteristics of which the significance cannot be doubtful. (pp. 26–27)

Chapter III discusses the "nature of the intestinal affection," and illustrates the unique changes in Peyer patches from *post mortem* examination. The overriding abductive conjecture proposed by Budd is that the whole contagious process (for typhoid) is driven by the intestinal discharges that contain "the most virulent part of the poison by which the contagion takes effect." In turn, this "working hypothesis" led Budd to state nine deductions that should be true given the correctness of the abductive conjecture. These nine are given below, including Budd's summary argument (highlighted in italics) that his overarching abductive hypothesis is correct:

> Assuming the intestinal discharges to have the principal hand in the dissemination of the fever, we come at once, then, to the following deductions: —
>
> 1st. That, as a rule, this fever will spread the more, the less perfect the provisions for preventing the discharges from the human intestine from contaminating the soil and air of the inhabited area.
>
> 2nd. That where these provisions fulfill this end, the disease will show little or no contagious power.
>
> 3rd. That its tendency to run through families will oftenest take effect where there is only a common privy; least often where there is a well-appointed watercloset. That this tendency will be observed very commonly, therefore, in country places, and comparatively rarely amongst the wealthy inhabitants of large towns.
>
> 4th. That, generally speaking, the distribution of the disease will be different in country and in town; that in the country, where there are few or no sewers, and where, consequently, the intestinal discharges accumulate around the infected dwelling, the disease will occur in a thickly clustered manner; that in the town, where these discharges are conveyed, often for long distances, by sewers, the

ramifications of which extend through large communities, it will appear in a more scattered form.

5th. That, as what the sewer receives from the fever patient is incomparably more virulent than anything else thrown off by him, the infection (until the true interpretation of the events be known) will appear, for the most part, as if it had its source in the sewer, and not in the already infected man.

6th. That in the country, the contagious nature of the fever will be obvious and unmistakable; but that in the town, it will most commonly be masked and obscure.

7th. That in the former, the fever will be epidemic and thickly clustered; in the latter, as a rule, endemic and scattered.

8th. That separation of the healthy from the infected will be of no avail to prevent the spread of the fever, unless it include separation from the intestinal discharges also.

9th. That, for this reason, the severest outbreaks will be seen in schools, barracks, and other large establishments, where a single common privy is often, alike, the receptacle of the discharges from the sick, and the daily resort of large numbers of healthy persons.

To appreciate the full strength of the case, we must bear in mind that, with the exception of what relates to season and place, *all that is here enunciated is elicited, not from observation of the events as they really occur, but as the result of pure deduction from the twofold assumption — that intestinal fever is contagious, and that the intestinal discharges contain the most virulent part of the poison by which the contagion takes effect.* (italics added)

These nine propositions embody, not the results of experience, but the anticipations of theory. If experience and theory happen in this case to offer an exact coincidence, is it not because the one is in reality the true expression of the other? (italics added) (pp. 51–53)

Chapter IV discusses the relation of typhoid fever to defective sewerage, which generally implies the infection of a group of individuals through a common water supply contaminated from the intestinal

dejecta from typhoid patient(s). Budd gives a number of illustrations where this had occurred; we will be content to provide Budd's description of just one outbreak at Richmond Terrace in Clifton, a suburb of Bristol, where much as in the saga of Snow and the Broadstreet pump, a tainted well was the source of the disease:

> In the present chapter I shall endeavour to show, *as a matter of fact*, that, whether we accept this theory of the intestinal affection or not — that, whatever the view we take of its nature — the intestinal discharges constitute the material by which the fever is mainly propagated — and that this, and this alone, gives the key to the relation which the spread of this particular species of fever bears to sewerage.
>
> That typhoid fever is actually caused by a poison which sewers and other cloacae often contain or carry, is a proposition which no English physician will dispute.
>
> Were there no other evidence, the history of the Windsor Fever referred to in the last chapter, would, of itself, be sufficient to establish the fact.
>
> As this fact, however, is quite fundamental to the present inquiry, it must not be allowed to stand on the footing of a mere article of popular belief, but must be made the subject of scientific demonstration. At the risk of being redundant, therefore, I will venture to cite another outbreak in illustration of it, in which the events, regarded in the light of scientific data, leave absolutely nothing to desire.
>
> In the autumn of 1847 an outbreak of fever occurred in Richmond Terrace, Clifton, which acquired great notoriety, at the time, on account of the suddenness, extent, and severity of the visitation.
>
> The terrace in question is built somewhat in the form of a horseshoe, and consists of thirty-four houses of a good class, occupied by persons in a genteel rank of life. At the end of the terrace there is a pump, from which, at that date, the inhabitants of thirteen houses drew their drinking water. In the latter end of September

it became evident that this water was tainted with sewage. The fact first made itself known by a characteristic taste and smell in the water, and was afterwards further verified by an examination of the well and discovery of the actual leakage. Early in October, typhoid fever broke out nearly at once in all the thirteen houses in which the tainted water had been drunk. In almost every house of the thirteen, two or three persons were laid up, and in some a much larger number. Amongst others, the case of a school for young ladies was very striking. The first to suffer in the school was the lady of the house. She was taken ill on the first Monday in the month. Four of her pupils were seized on the following day; and before the end of the week, the mistress, six school-girls, and two maid-servants, were all in bed with the same fever. In the beginning of the week following, two more were added to the list. Three children who were sent home on the first outbreak of the disorder, and three others who remained at the school, were the only persons who escaped.

The houses in which the same specific fever thus simultaneously broke out on so large a scale were many of them far apart in the length of the terrace, and their inmates were, for the most part, not in the habit of personal intercourse. The other families on the terrace, living side by side with these, continued all the while to be perfectly free from fever. The only important circumstance in which those who suffered so severely differed from those who did not suffer at all, was that the former had drunk of the tainted well, and the latter had not.

Only a few doors from the school already mentioned there was another girls' school, with about the same number of pupils. In all that related to their internal economy the two schools were exactly alike; but while, in the one, eleven persons out of seventeen were struck down with fever, in the other there was not a single case. The one was supplied with drinking water from the poisoned well, and the other from an entirely different source. The circumstances gave to the contrast, here, all the force of an experiment. In complex questions it is not often, indeed, that even experiment yields results

so clear and precise.

Amongst the sufferers at Richmond Terrace were nine servants, who were removed to the Bristol Infirmary soon after being attacked. To make the case complete, I have only to add, that all nine presented, in full development, the diagnostic marks of this species of fever. Two of the number, who were my own patients, offered perfectly typical specimens of the disorder. In two others, who died, the small intestine was crowded with the ulcerations which are characteristic of the disease. (pp. 64–66)

Chapter V presents several topics about the contagious agent responsible for typhoid and how it may be carried by material external to a person's body, or still be present after a patient has ceased to show any outward signs of the disease. For example, fomites such as clothes, bedding, or other linen were common sources for transmitting the typhoid agent to new victims. There is a prescient discussion of the period of contagion for a patient including the possibility of being an asymptomatic carrier after all outward signs of the disease have disappeared: "I am quite sure that patients, so far recovered, cannot always be safely allowed to mix with others without precaution." The notion of being a carrier is discussed in a later section when the famous case of "Typhoid Mary" is reviewed —

MEDIA OF TRANSMISSION — TAINTED HANDS — TAINTED LINEN, BEDDING, AND CLOTHES

In the cases related in previous chapters in illustration of the contagious nature of typhoid fever various modes of communication have already, incidentally, come into view.

The part they severally play in the dissemination of the disease must now be examined more closely.

One mode of communication has attracted little attention, which it is important, nevertheless, not to overlook; I speak of the tainted

hands of those who wait on the sick. Among the poor, and in ways that will suggest themselves, and need not be more particularly described, there is reason to believe that this mode often has a large share in spreading the disease through the family circle. Passing from the hand to other things under contingencies that are not only very conceivable, but are sure now and then to occur, the contagion thus arising may sometimes have a much wider scope. I possess evidence which renders it in the highest degree probable, that milk and butter, especially, may become infected in this way.

Linen, wearing apparel, bedding, and other porous fabrics, tainted with fever, constitute another important form of vehicle.

In 1867 there was a very severe epidemic of typhoid fever in one or two small villages in the neighbourhood of Berkeley, and, among others, several members of a clergy man's family were laid up with it.

A young woman who lived in a hamlet more than two miles away, but who washed the tainted linen of these patients, caught the fever, which afterwards attacked two other sisters living under the same roof with her.

Examples of infection by tainted linen or clothing are not very common now, for the obvious reason that people generally have learnt the vital importance of disinfecting such things before sending them to the wash. But before this precaution had come into vogue, nothing was more common than to see washerwomen and their families stricken with typhoid fever in consequence of having washed the bed and body linen of patients suffering from it. Some of the most painful tragedies I have ever seen have originated thus. (pp. 96–97)

TYPHOID FEVER — AT WHAT PERIOD BEGINNING, AND AT WHAT PERIOD CEASING, TO BE CONTAGIOUS

One or two supplementary questions yet remain to be examined before we can obtain a complete view of the modes in which typhoid fever is disseminated.

At what precise period does the fever first become contagious, and when does it cease to be so?

To the first question a tolerably precise answer may be given.

Putting pathological probability aside, facts have repeatedly come before me which appear to show, by evidence free from all ambiguity, that the contagion begins with the diarrhoea. Or rather it would be more exact to say — for the evidence does not go beyond that — that, when diarrhoea is present, the disease is, certainly, already contagious. As this symptom often begins a considerable time before the patient takes to his bed, and while he is still up and about, it is easy to see what an important influence the fact may have in spreading the disorder. Persons in this stage, going about from place to place, may obviously lay a train of wide-spread infection.

But it is in schools, workhouses, and other large establishments, where a common latrine often serves for a large number of persons, that this contingency tells most. Since I came to Bristol, I have seen three very considerable epidemics of typhoid, originating in the infection of the latrine of a particular day-school, by one of the scholars, who, having contracted fever and already affected with diarrhoea, still continued to attend the school for some time longer.

In my various writings on infection, I have repeatedly had occasion to draw attention to these relations in their bearing on the part which large establishments play in the spread of epidemics. This mode of spreading constitutes one of the greatest of all the difficulties in the way of prevention, and forms the ground of my proposal to make it compulsory to provide all such establishments with self-disinfecting latrines. Obviously, it is a difficulty that can only be completely met by what I have ventured, elsewhere, to call disinfection by anticipation.

The precise date at which the fever patient ceases to give fever to others is not so easy to define. But I have seen so many instances in which fever has broken out in a family living in a previously healthy neighbourhood, soon after the arrival of a convalescent, that I am

quite sure that patients, so far recovered, cannot always be safely allowed to mix with others without precaution.

In the cases referred to, all traces of actual fever had disappeared, and diarrhoea had long ceased.

In what form the infection still lurked — whether in articles of wearing apparel that had become tainted in an earlier stage of the fever, or whether in the form of specific exuviae from which the diseased intestine may not have entirely cleared itself, I confess myself unable to say.

The facts suggest two important precautions. The first is, always to provide the convalescent with clothes perfectly free from specific taint; the other, to charge the cistern of the closet belonging to the house, in which he may be staying, with a powerful disinfectant.

For many years past, I have been in the habit of enforcing both, and, since I began to do so, I have never seen a convalescent give fever to a healthy person. (pp. 111–112)

Chapters VI through VIII develop several topics of importance to a thorough understanding of typhoid and how it can be controlled and prevented. Chapter VI advocates for the use of disinfectants to kill the morbid material responsible for the transmission of typhoid wherever it may be. Chapter VII discusses and discounts a pythogenic (miasmatic) theory of typhoid causation; this chapter's long subtitle is a good representation of its contents: "The pythogenic theory of typhoid fever irreconcilable with the prolonged absence of this fever frequently in places where putrescent effluvia are habitually rife. Also with the low rate of prevalence of this fever on the banks of the Thames in the summer of 1858, when that river stank so badly." The excerpt below provides Budd's observations about the "Great Stink," as it was known, and the surprising lack of disease produced by it, contrary to the expectations derived from pythogenic theory:

The occasion, indeed, as already hinted, was no common one. An extreme case, a gigantic scale in the phenomena, and perfect accuracy in the registration of the results — three of the best of all the guarantees against fallacy — were all combined to make the induction sure. For the first time in the history of man, the sewage of nearly three millions of people had been brought to seethe and ferment under a burning sun, in one vast open *cloaca* [sewer] lying in their midst.

The result we all know. Stench so foul, we may well believe, had never before ascended to pollute this lower air. Never before, at least, had a stink risen to the height of an historic event. Even ancient fable failed to furnish figures adequate to convey a conception of its thrice Augean foulness. For many weeks, the atmosphere of Parliamentary Committee-rooms was only rendered barely tolerable by the suspension before every window, of blinds saturated with chloride of lime, and by the lavish use of this and other disinfectants. More than once, in spite of similar precautions, the law-courts were suddenly broken up by an insupportable invasion of the noxious vapour. The river steamers lost their accustomed traffic, and travellers, pressed for time, often made a circuit of many miles rather than cross one of the city bridges.

For months together, the topic almost monopolised the public prints. Day after day, week after week, the 'Times' teemed with letters, filled with complaint, prophetic of calamity, or suggesting remedies. Here and there, a more than commonly passionate appeal showed how intensely the evil was felt by those who were condemned to dwell on the Stygian banks. At home and abroad, the state of the chief river was felt to be a national reproach. 'India is in revolt, and the Thames stinks,' were the two great facts coupled together by a distinguished foreign writer, to mark the climax of a national humiliation. But more significant still of the magnitude of the nuisance was the fact that five millions of money were cheerfully voted by a heavily taxed community to provide the means for its abatement. With the popular views as to the connection between

epidemic disease and putrescent gases, this state of things naturally gave rise to the worst forebodings.

Members of Parliament and noble lords, dabblers in sanitary science, vied with professional sanitarians in predicting pestilence. If London should happily be spared the cholera, decimation by fever was, at least, a certainty. The occurrence of a case of malignant cholera in the person of a Thames waterman early in the summer, was more than once cited to give point to these warnings, and as foreshadowing what was to come. Meanwhile, the hot weather passed away; the returns of sickness and mortality were made up, and, strange to relate, the result showed, not only a death-rate below the average, but, as the leading peculiarity of the season, a remarkable diminution in the prevalence of fever, diarrhoea, and the other forms of disease commonly ascribed to putrid emanations.

After describing in scientific and forcible terms the unprecedented state of the river, Dr. Letheby adds: 'With all this condition of the Thames, however, the health of the metropolis has been remarkably good. In the corresponding period of last year (i.e., of the year 1857), the cases of fever, diarrhoea, and dysentery, attended in the city by the medical officers of the unions, amounted to 293 of the former and 181 of the latter; but during the past quarter (i.e., the quarter of intolerable stench), they were only 202 of the former, and 93 of the latter!'

So that, while pythogenic compounds were poisoning the air with what may be called a forty thousand fever power, the so-called pythogenic fever, so far from rising in proportion, fell much below its average. (pp. 141–143)

Chapter VIII raises and then dismisses the notion that typhoid could arise spontaneously: "The position taken in the foregoing pages, broadly stated, amounts to this: — that typhoid fever is not only self-propagating, but that it originated in no other way." The final Chapter IX in *TF* is an eleven point summary of the various

assertions made up to this last chapter. These items are provided below along with Budd's own general conclusions regarding what he had presented:

> The conclusions arrived at in the foregoing pages may be summed up in the following propositions: —
>
> 1. That typhoid fever is, in its essence, a contagious, or self-propagating fever, and is a member of the great natural family of contagious fevers, of which small-pox may be taken to be the type.
>
> 2. That the living body of the infected man is the soil in which the specific poison, which is the cause of the fever, breeds and multiplies.
>
> 3. That the reproduction of this poison in the infected body, and the disturbance attaching to it constitute the fever.
>
> 4. That this reproduction is the same in kind as that of which we have, in small-pox, ocular demonstration.
>
> 5. That the disease of the intestine, which is its distinctive anatomical mark, is the specific eruption of the fever, and bears the same pathological relation to it which the small-pox eruption bears to small-pox.
>
> 6. That, as might have been anticipated from this view, the contagious matter by which the fever is propagated is cast off, chiefly, in the discharges from the diseased intestine.
>
> 7. That as a necessary result, sewers and the cloacae which, under existing sanitary arrangements, are the common receptacles of these discharges are, also, the principal instruments in the transmission of the contagion; and, consequently, that, in many instances, the infected sewer, and not the infected man, appears as if it were the primary source of the specific poison.
>
> 8. That once cast off by the intestine this poison may communicate the fever to other persons in two principal ways — either by contaminating the drinking water, or by infecting the air.
>
> 9. That, as an inevitable consequence of the impalpable minuteness of the contagious unit, and the many invisible and untraceable

ways in which it is transmitted, cases must be constantly occurring, exactly as in the other contagious fevers, whose linear descent cannot be followed, and which spring up, therefore, under the semblance of spontaneous origin.

10. That the occurrence of such cases obviously constitutes no proof, whatever, that this fever ever does arise spontaneously.

11. That the exceeding speciality of the conditions attaching to the reproduction of the specific poison in the living body itself, as well as the facts relating to the geographical distribution, past and present, of this and the other contagious fevers, constitute evidence as strong as such evidence can ever be, that none of these fevers originate spontaneously, but are propagated solely by the law of continuous succession.

And, lastly — to crown the whole induction, by a practical test — That by destroying the infective power of the intestinal discharges, by strong chemicals, or otherwise, the spread of the fever may be entirely prevented, and that by repeating this process in every fresh case as it arises, the disease may in time be finally extinguished. In arriving at these conclusions, I would observe: —

That the principal data on which they rest are, to the best of my belief, sure. Where these data consist in events observed by myself, I can vouch for their accuracy; where in events reported by others, I have taken, whenever this was possible, the most conscientious pains to verify them. In addition to this, all the great cardinal facts are distinguished in a peculiar degree by that precision and exactness which fit them alike for scientific statement and severe scientific deduction.

Whether the inferences drawn from the facts be logical, or whether, consistently with the laws of logic, any other inferences can be substituted for them, it is for others than myself to determine.

The whole induction is gradual. There are no great leaps, but the argument is conducted step by step; and I have striven to the utmost throughout to make one step sure before attempting the next.

> The theory, in its entirety, is not only simple and harmonious, but it is in strict accordance with what we already know, of a certainty, of other members of the same family group.
>
> Above all, its truth may be tested every day by a practical test, the employment of which can do no harm, and may do incalculable good. (pp. 171–173)

* * *

George Soper (1870–1948) was an American sanitation engineer for the New York City Department of Health during the first several decades of the Twentieth Century. The more notable aspects of Soper's career are all tied to typhoid prevention and suppression, such as in his taking control over the major epidemic that began in Ithaca, New York, during the winter of 1903. Soper is most well known, however, for his identification of Mary Mallon (also known as "Typhoid Mary"), the first asymptomatic carrier of typhoid bacilli in America. Although there are a number of major studies of Mary Mallon herself (see the comprehensive presentation by Judith Walzer Leavitt, *Typhoid Mary: Captive to the Public Health* (1996); or the cook-to-cook biography, *Typhoid Mary*, by Anthony Bourdain (2005)), our interests center on the perceptive abductive reasoning and "shoe-leather" epidemiology engaged in by Soper that resulted in the identification of Mary Mallon.

In tracking down Mary Mallon as a chronic carrier of typhoid, George Soper had the advantage of knowing the work of the German bacteriologist, Robert Koch (1843–1910). In 1902, Koch published an influential paper, read by Soper, that documented the concept of an asymptomatic typhoid carrier. The paper was partially based on

extensive data collected around the German city of Trier. Because typhoid only resides in humans and has no animal reservoir, it is natural to look for an asymptotic carrier coming into an area whenever a typhoid outbreak has newly occurred. We should point out, however, that it is only natural once one knows about asymptomatic carriers, as George Soper did from the work of Robert Koch.

To present the story of Mary Mallon, a slightly redacted version is given in an external Appendix of a paper written by Soper for *The Military Surgeon* (July, 1919). This was originally delivered as an address to the Surgeons of the Sixth Division in 1913 when Soper was attached as an epidemiologist to the Army a few years before the United States entered World War I. What is central to the story for our purposes is, first, the abductive reasoning conjecture of a possible typhoid carrier coming into the household when the outbreak occurred in Oyster Bay, Long Island, during the summer of 1906. Second, there is the classic "shoe-leather" epidemiological follow-up search and subsequent amassing of data to verify the initial conjecture.

The retelling of the saga of Typhoid Mary as given by Soper is less sensational than most of those available in the first half of the Twentieth Century — a good example of the later would be Stanley Walker's profile of Mary Mallon that appeared in the *New Yorker* in January of 1935: *Typhoid Carrier No. 36*. Soper refers to this article as "flippant" in comments, given below, provided to the *British Medical Journal* (January 7, 1939) right after Mallon's death. We might also note that this is just one story among many others that appeared in the newspapers of the time; for example, a simple search on "Typhoid Mary" brings up a whole collection of stories about

Mary Mallon's life from the archives of the *New York Times*, including an extensive piece about her "recapture" on April 4, 1915 that extended over four full-page columns ("TYPHOID MARY" HAS REAPPEARED: Human Culture Tube, Herself Immune, Spreads Disease Wherever She Goes). Soper's comments from the *BMJ* follow:

> The Discovery of Typhoid Mary
>
> SIR, – The death of Miss Mary Mallon, widely known as "Typhoid Mary," on November 11, 1938, has brought forth such a flood of misstatement in which my name as her discoverer has been associated that I feel compelled to do something to defend my reputation. In the misstatements referred to I regret to say that the lay press is not alone at fault. Medical periodicals, bulletins of public health departments, and even official epidemiologists, who certainly have no excuse to offer for ignorance in this matter, are equally to blame.
>
> On tracking the statements down, I have found that a flippant article, without pretense of accuracy, written by a free-lance journalist for an allegedly smart periodical has been the source of much of the misinformation. Instead of taking the trouble to look up my professional papers in the *Journal of the American Medical Association* (1907) or the *Military Surgeon* (July, 1919), in which I described my investigation, the writers have turned to the popular periodical and recommended it to the medical profession as substantially correct. The misstatements substitute a wholly imaginary account not only of the investigation itself but of the circumstances which led up to it, and rob me of whatever credit belongs to the discovery of the first typhoid carrier to be found in America and (to the time of her death) the most famous carrier anywhere.
>
> This is not the place for me to describe again the investigation which led me to find "Typhoid Mary" and to recommend the New York City Department of Health to take her into custody. Suffice it to say that I did not stumble upon her in the course of routine

duties as an employee of the Health Department or as a blind disciple of Robert Koch. I was at the time a thoroughly trained and experienced epidemic fighter who had seen service in the laboratory and the field. I was acquainted with the German work and the English views as to the danger of urinary carriers of typhoid germs. The discovery of "Typhoid Mary" is rather to be regarded as an outcome of my work for the control of the epidemic of over 1,300 cases of typhoid at Ithaca, N.Y., in 1903, where I had seen typhoid spread from person to person and initiated energetic measures to prevent it.

Just as I had been called from private practice by the New York State Department of Health to go to Ithaca and use every effort, in the name of the State, to put a stop to the epidemic, I was later called on by the owner of a private estate at Oyster Bay, N.Y., to investigate and if possible remove the cloud of mystery which hung over this property as a result of an outbreak of typhoid which had occurred there in the summer of 1906. It was a difficult investigation, partly because I was not called for more than six months after the outbreak and the people had become separated and the house vacated. The cook (Miss Mallon) could not be found for some months, and then proved most refractory.

It may be of interest for me to state that the Oyster Bay epidemic, like most of the other outbreaks which I eventually traced to this woman, had, before I entered upon the case, been carefully studied by other investigators and ascribed with more or less plausibility to other causes. I am, etc.,

GEORGE A. SOPER, Ph.D.,
Honorary Fellow, Royal Sanitary Institute
Great Neck, N.Y., Dec. 16, 1938

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Part IV

Three Central Germ Theorists of the Nineteenth Century: Louis Pasteur, Robert Koch, and Joseph Lister

> Jesus said unto them, "A prophet is not without honor except in his own town, among his relatives, and in his own home."
> – Mark 6:4

The two most famous medical scientists of the Nineteenth Century were arguably Louis Pasteur (1822–1895) and Robert Koch (1843–1910). These two individuals firmly established a germ theory of disease causation and ushered in a golden age of microbiology. We begin with a chapter on Pasteur, the older of the two men, before the work of Koch is presented. Koch effectively made germ theory the central tenet and concern of medicine during the last several decades of the Nineteenth Century. Again, substantial excerpts from the original writings of both men will be presented in the course of discussing their respective careers. A third individual, Joseph Lister (1827–1912), is also given a chapter in this section devoted to germ theory. Based on the Antiseptic Principle of preventing germs from entering wounds done surgically or through accidents, Lister effectively solved the problem of the often fatal wound infections that accompanied major surgical procedures.

Louis Pasteur (1822–1895): The chapter on Pasteur that immediately follows discusses many of his major contributions to science. Among these are the concept of molecular asymmetry and its connection with living organisms; the central idea that fermentation and putrefaction processes along with extensions to include infectious diseases are all the result of living organisms; the development of the field of immunology through the use of attenuated disease agents, most notably for anthrax and rabies; the refutation of a theory of spontaneous generation for various life forms; and through the eponymous process of pasteurization, his work with wine, beer, milk

and other liquids that might be contaminated with various offending microorganisms.

One of the connections between Pasteur and an emphasis on identifying exemplars of Peirce's notion of abductive reasoning is that Pasteur informally developed ideas seemingly parallel to those of Peirce. Pasteur called the hypotheses generated from the various sets of "surprising observations" he encountered, his "preconceived ideas." Based on these conjectures, Pasteur then emphasized the need to develop decisive experiments for verification. René Dubos in his masterful biography, *Louis Pasteur, Free Lance of Science* (1950, p. 376), quotes Pasteur as follows:

> Preconceived ideas are like searchlights which illumine the path of the experimenter and serve him as a guide to interrogate nature. They become a danger only if he transforms them into fixed ideas — this is why I should like to see these profound words inscribed on the threshold of all the temples of science: "The greatest derangement of the mind is to believe in something because one wished it to be so." ...
>
> The great art consists in devising decisive experiments, leaving no place to the imagination of the observer. Imagination is needed to give wings to thought at the beginning of experimental investigations on any given subject. When, however, the time has come to conclude, and to interpret the facts derived from observations, imagination must submit to the factual results of the experiments.

Robert Koch (1843–1910): While working as a practicing German physician, Koch was the first to document the connection between a specific living microbe (for anthrax) and the disease that it caused. Because of this work, he carried the dual nicknames of "father of microbiology" and "father of medical bacteriology." In addition to

isolating the causative agents for several infectious diseases (anthrax, cholera, and tuberculosis), Koch is known not only for his innovative methods in microbiology utilizing the most advanced microscope and microphotography techniques then being developed, but also for his invention of methods for bacterial culture using solid nutrients such as agar (along with his assistant's introduction of glass "Petri" dishes). This allowed him to be the first to grow pure bacterial cultures in the laboratory. The "surprising observation" that led Koch to his abductive conjecture that a solid medium would be necessary to consistently grow pure cultures, was from a sliced potato that became contaminated through the air; the separate bacterial colonies grew by themselves for awhile, isolated and apart from the others. The various liquid media used up to that time did not allow pure cultures to develop separately from the other bacterial colonies.

Another remarkable abductive conjecture made by Koch involved a staining technique by which he was able to identify consistently the tubercle bacillus responsible for tuberculosis. Using a newly prepared methylene blue solution that was counterstained with vesuvin, Koch was unable to see the blue-staining rods characteristic of tuberculosis that he had seen earlier with an older such preparation. Koch conjectured that the older solution had been in the laboratory long enough to absorb ambient ammonia to make the staining solution work. By merely adding an appropriate amount of any alkali to a newly prepared staining solution, Koch was able to optimize his staining procedure for clearly identifying the tubercle baccillus.

In discovering the causal agents for anthrax and tuberculosis, Koch implicitly relied on what have become known as his four postulates, which are still familiar to all beginning microbiology students. These

four criteria were meant to help establish a causal connection between a specific disease and a specific microbe. In short, Koch's postulates were a way to proceed to the verification stage for an abductive conjecture that a particular agent caused a particular disease. As noted in the chapter on Koch, in addition to needing a nonhuman animal model for a particular disease, the Koch staining and pure culture techniques were generally central to any attempt to satisfy the four postulates.

In contrast to Pasteur whose main concern was directed toward individuals and immunology, particularly for rabies, Koch had a broad interest in public hygiene partly as a result of the various named research positions he held. One such public health example was Koch's "surprising observation" of a cholera epidemic being present in Hamburg but not in the adjoining city of Altona even though both took their water from the polluted Elbe River. Koch's abductive hypothesis to explain the difference was due to Altona having a sand filtration system whereas Hamburg had none. Thus, for Koch, the control of epidemic diseases such as cholera and typhoid partially rested with the need to provide adequate public resources for clean water.

Another important concept developed by Koch was that of an asymptomatic disease carrier. Here, the "surprising observation" was that infectious diseases can occur in individuals who have had no apparent contact with other infected individuals. Koch's abductive conjecture to explain this phenomenon was one of a carrier state and related acquired immunity in some individuals who were asymptomatic but could still transmit a disease without themselves showing any sickness. Koch demonstrated that such individuals exist for typhoid, cholera, and yellow fever.

Joseph Lister (1827–1912): The third individual tied closely to the development of germ theory is Joseph Lister, considered to be a father of modern surgery for his introduction of antiseptic surgical practice in the last third of the Nineteenth Century. Major surgeries in the first half of the century were characterized by its two main features of first incredible pain from the surgery itself followed by the development of an often fatal infection. The 1840s witnessed the introduction of anesthesia in the form of ether and chloroform so the issue of pain was effectively solved. The problem of post-surgical infection remained, however, and took much longer to be understood and prevented.

Joseph Lister was a Professor of Surgery at the University of Glasgow in the 1860s when a colleague mentioned the recent work done by Pasteur on fermentation and putrefaction. Lister quickly recognized the importance of the germ theory being developed by Pasteur to the problem he was facing of wound infection caused surgically or by accident. The main abductive conjecture developed by Lister was that infection was caused by "germs" present in the surrounding environment that were somehow able to enter a wound and produce pus and infection. Thus, to prevent infection subsequent to a surgical procedure or an accident such as that of a compound fracture, it was necessary to first cleanse a wound of any existing "germs" and then to prevent any more from re-entering thereafter.

The Antiseptic Principle developed by Lister relied on the chemical antiseptic of carbolic acid for any initial cleaning of the wound that might be necessary as well as for subsequent dressings to prevent additional germs from entering the yet unhealed wound. Gradually there was a move away from a formal use of chemical antiseptics to

one of a more general aseptic practice where the environment and material surrounding an individual undergoing surgery was made sterile, often through the use of heat rather than by chemicals.

Chapter 6

Louis Pasteur

> In the field of observation, chance favors only the prepared mind.
> – Louis Pasteur (1822–1895)

The principal figure for this chapter is the Nineteenth Century scientist, Louis Pasteur (1822–1895), whose tomb in the crypt beneath the Pasteur Institute in Paris is arguably the most impressive shrine to science in the whole world. The arches of Pasteur's tomb list nine areas that encompass his great discoveries, all arranged in the chronological order of when they were publicly announced:

molecular asymmetry (1848)
fermentation (1857)
spontaneous generation (1862)
diseases of wine (1863)
diseases of silkworms (1865)
microorganisms in beer (1871)
virulent diseases (1877)
preventive vaccinations (1880)
rabies prophylactics (1885)

This chapter discusses several of these nine areas more or less in chronological order, highlighting as best as we can the implicit ab-

ductive reasoning specific to the problem being considered. Emphasis will be placed on whatever subsequent experimental verification Pasteur then carried out to evaluate his initial intuitions and conjectures, or as Pasteur liked to call them, his "preconceived ideas."

Louis Pasteur was born in December of 1822 in the small town of Dôle located in the eastern part of France. He was raised in the nearby commune of Arbois where his father had a tannery in the same house in which he grew up. Throughout his career Pasteur returned regularly to Arbois during the summers; it was here, for example, that he carried out much of his research into the maladies affecting wine. His childhood home is now preserved close to its original state as the Louis Pasteur House, and contains many of the historically relevant objects from his life. After finishing secondary school in Arbois, Pasteur enrolled at the Collège Royal at Besançon and received a Bachelor of Letters degree in 1840. Pasteur eventually enrolled in the École Normale Supérieure, submitting two doctoral theses in 1847, one in chemistry and the second in physics. Here, Pasteur also started a longer-term research program in crystallography inspired by his first major scientific discovery involving molecular asymmetry; this is the chronologically first item on the archway of his tomb.

Throughout this chapter on Pasteur and the many scientific discoveries he made throughout his life, the presentation will adhere to the usual historical retellings that have been passed down over the years, starting with the "biography" written by his son-in-law, René Vallery-Radot, entitled *Louis Pasteur, His Life and Labours*, published some number of years before Pasteur died. A more recent 1995 biography by Gerald Geison, *The Private Science of Louis*

Pasteur, is based on Pasteur's many unpublished laboratory notebooks that were not made publicly available until the 1970s. Geison suggests that some of the recounting of incidents in Pasteur's career may not be as clean and direct as the many retellings have suggested, such as his work on optical isomers and why he became interested in fermentation in the first place. The reader interested in these types of deconstructions should consult Geison's biography. Here, the review will be one of the main milestones in Pasteur's life as they are most commonly understood.

* * *

The French chemist, Jean-Baptiste Biot (1774–1862), showed in 1832 that tartaric acid even in solution could rotate polarized light to the right. Because of this property, tartaric acid, which occurs naturally in many fruits notably grapes, is said to be optically active. A salt of tartaric acid, potassium bitartrate (cream of tartar) develops naturally in the fermentation of grapes, a fact of importance to some of Pasteur's later research. A few years after Biot's discovery of optical activity in tartaric acid, the German chemist, Eilhardt Mitscherlich (1794–1863), noted that another form of tartaric acid could also be found in the fermentation of wine, called paratartaric or racemic acid (*racemus* is the Latin word for grape). Although these two forms of tartaric acid supposedly have the same chemical composition, the paratartaric solution is not optically active in contrast to the tartaric solution. Pasteur learned of Mitscherlich's aberrant observations during the doctoral work he was pursuing in the then scientifically fashionable field of crystallography.

In the context of a Peircean abductive reasoning scheme, the "surprising

observation" is about the different optical properties of two supposedly identical tartaric substances. Pasteur conjectured that this difference in optical activity might be due to differing crystalline shapes for the two acids. Under a microscope, Pasteur was able to physically separate the paratartrate crystals into two types (called isomers) that were right- and left-handed mirror images of each other. Moreover, Pasteur could show that even in solution the two types were optically active but in opposite directions – one to the right, as in the original tartaric acid, and one to the left. An equal mixture of the two optically active substances resulted in an optically inactive solution, presumably because of a cancelling effect produced by the mixture.

Legend has it that at this point of discovery Pasteur became so overcome with emotion that he ran from the laboratory, and upon encountering a lab assistant in the hall, embraced him, saying (in French): "I have made a great discovery ... I am so happy that I am shaking all over and am unable to set my eyes again to the polarimeter [the instrument that measures the degree of rotation for polarized light]." What is characteristic about this incident is that even at Pasteur's young age of twenty-five, he was first able to recognize the important problem of explaining different optical activities for two supposedly otherwise identical substances, and then to formulate it in a manner amenable to experimentation.

Pasteur never tired of telling the story of his first major scientific discovery and its subsequent verification by the chemist Biot himself. In 1863, for example, before the Chemical Society of Paris, Pasteur recounted the complete discovery narrative as given below. This excerpt and a few others in this chapter are taken from the masterful 1950 biography, *Louis Pasteur: Free Lance of Science* by René

Dubos:

I was a student at the École Normale Superiéure, from 1843 to 1846. Chance made me read in the school library a note of the learned crystallographer, Mitscherlich, related to two salts: the tartrate and the paratartrate of sodium and ammonium. I meditated for a long time upon this note; it disturbed my schoolboy thoughts. I could not understand that two substances could be as similar as claimed by Mitscherlich, without being completely identical. To know how to wonder and question is the first step of the mind toward discovery.

Hardly graduated from the École Normale, I planned to prepare a long series of crystals, with the purpose of studying their shapes. I selected tartaric acid and its salts, as well as paratartaric acid, for the following reasons. The crystals of all these substances are as beautiful as they are easy to prepare. On the other hand, I could constantly control the accuracy of my determinations by referring to the memoir of an able and very precise physicist, M. de la Provostaye, who had published an extensive crystallographic study of tartaric and paratartaric acid and of their salts.

I soon recognized that ... tartaric acid and all its combinations exhibit asymmetric forms. Individually, each of these forms of tartaric acid gave a mirror image which was not superposable upon the substance itself. On the contrary, I could not find anything of the sort in paratartaric acid or its salts.

Suddenly, I was seized by a great emotion. I had always kept in mind the profound surprise caused in me by Mitscherlich's note on the tartrate and paratartrate of sodium and ammonium. Despite the extreme thoroughness of their study, I thought, Mitscherlich, as well as M. de la Provostaye, will have failed to notice that the tartrate is asymmetric, as it must be; nor will they have seen that the paratartrate is not asymmetric, which is also very likely. Immediately, and with a feverish ardor, I prepared the double tartrate of sodium and ammonium, as well as the corresponding paratartrate, and proceeded to compare their crystalline forms, with the

preconceived notion that I would find asymmetry in the tartrate and not in the paratartrate. Thus, I thought, everything will become clear; the mystery of Mitscherlich's note will be solved, the asymmetry in the form of the tartrate crystal will correspond to its optical asymmetry, and the absence of asymmetry in the form of the paratartrate will correspond to the inability of this salt to deviate the plane of polarized light. ... And indeed, I saw that the crystals of the tartrates of sodium and ammonium exhibited the small facets revealing asymmetry; but when I turned to examine the shape of the crystals of paratartrate, for an instant my heart stopped beating: all the crystals exhibited the facets of asymmetry!

The fortunate idea came to me to orient my crystals with reference to a plane perpendicular to the observer, and then I noticed that the confused mass of crystals of paratartrate could be divided into two groups according to the orientation of their facets of asymmetry. In one group, the facet of asymmetry nearer my body was inclined to my right with reference to the plane of orientation which I just mentioned, whereas the facet of asymmetry was inclined to my left in the other. The paratartrate appeared as a mixture of two kinds of crystals, some asymmetric to the right, some asymmetric to the left.

A new and obvious idea soon occurred to me. These crystals asymmetric to the right, which I could separate manually from the others, exhibited an absolute identity of shape with those of the classical right tartrate. Pursuing my preconceived idea, in the logic of its deductions, I separated these right crystals from the crystallized paratartrate; I made the lead salt and isolated the acid; this acid appeared absolutely identical with the tartaric acid of grape, identical also in its action on polarized light. My happiness was even greater the day when, separating now from the paratartrate the crystals with asymmetry at their left, and making their acid, I obtained a tartaric acid absolutely similar to the tartaric acid of grape, but with an opposite asymmetry, and also with an opposite action on light. Its shape was identical to that of the mirror image

of the right tartaric acid and, other things being equal, it rotated light to the left as much in absolute amount as the other acid did it to the right.

Finally, when I mixed solutions containing equal weights of these two acids, the mixture gave rise to a crystalline mass of paratartaric acid identical with the known paratartaric acid.

...

He [M. Biot] sent for me to repeat before his eyes the several experiments and gave me a sample of racemic acid which he had himself previously examined and found to be quite inactive toward polarized light. I prepared from it, in his presence, the sodium ammonium double salt, for which he also desired himself to provide the soda and ammonia. The liquid was set aside for slow evaporation in one of the rooms of his own laboratory, and when thirty to forty grams of crystals had separated, he again summoned me to the Collège de France, so that I might collect the dextro and levorotatory crystals [crystals deviating the plane of polarized light to the right or to the left] before his eyes, and separate them according to their crystallographic character asking me to repeat the statement that the crystals which I should place on his right hand would cause deviation to the right, and the others to the left. This done, he said that he himself would do the rest. He prepared the carefully weighed solutions, and at the moment when he was about to examine them in the polarimeter, he again called me into his laboratory. He first put into the apparatus the more interesting solution, the one which was to cause rotation to the left. Without making a reading, but already at the first sight of the color tints presented by the two halves of the field in the "Soleil" polarimeter, he recognized that there was a strong levorotation. Then the illustrious old man, who was visibly moved, seized me by the hand, and said, "My dear son, I have loved science so deeply that this stirs my heart."

In his discovery of the mirror-image crystalline forms present in

paratartaric acid, Pasteur was predisposed to see the small facets on the tartrate crystals that characterized asymmetry in the original tartaric acid. Pasteur's predecessors had all failed to notice these small facets, presumably because they were not interested in them. Pasteur, on the other hand, had the "working hypothesis" or abductive conjecture that optical activity was somehow associated with crystalline shape, and therefore crystalline shape should be the key to the optical inactivity of paratartaric acid. Also, because the optical activity for the right- and left-handed versions of tartaric acid was still present when in solution, the optical activity most likely reflected a more basic molecular asymmetry as well as a crystalline asymmetry. In contrast, quartz is only optically active at the crystalline level because that activity disappears when quartz is melted.

There is an oft-quoted comment from Pasteur, given at the beginning of this chapter, that reflected his ability to see what others could not: "In the field of observation, chance favors only the prepared mind." Or even more pointedly from the Nineteenth Century American scientist, Joseph Henry (1797–1878): "The seeds of great discoveries are constantly floating around us, but they only take root in minds well-prepared to receive them." In any case, after receiving his doctoral degree and his discovery of crystalline (and ultimately, molecular) asymmetry in a racemic mixture, Pasteur spent the next decade studying the optical activity of organic substances, thus helping to provide a basis for the new science of stereochemistry. Because of this work on tartrate crystals and among many such similar titles that would eventually be used, Pasteur could be known as the father of stereochemistry.

Throughout his career, Pasteur maintained a belief (or conjecture)

that optical activity was an indication of life itself, such as in the wine fermentation that produced the tartaric acids he first studied. Pasteur was led to characterize fermentation as a living process, and ultimately to formulate a "germ theory" for both fermentation and disease. This latter "germ theory" might be considered Pasteur's grand abduction; it helped unify and explain all the living processes that he studied. As a corollary, these causative microorganisms or germs differed according to the specific fermentation process or disease being considered. Or stated differently, these germs were not generic and were produced by parent organisms having exactly the same form – they never arose by "spontaneous generation."

* * *

Pasteur accepted a position in 1854 as Professor of Chemistry and Dean of the newly formed Faculty of Sciences in the northern French town of Lille. Attached to this particular position was an expectation that Pasteur would conduct research relevant to local industry. Therefore it was no surprise that when M. Bigo, a local wine manufacturer whose son was one of Pasteur's students, sought help in making alcohol from beet sugar (also called ethanol) that Pasteur obliged although he had no previous experience with the processes of fermentation.

In producing ethyl alcohol or ethanol from the fermentation of beet juice, M. Bigo was having difficulty with undesirable substances contaminating the finished product. In looking at the fermenting beet juice microscopically, Pasteur could see the small globules of yeast that others had seen as well, but in addition there were smaller structures that did not look like yeast. Pasteur also noticed that

the fermenting mixture was optically active, which immediately suggested to him that fermentation was not merely a chemical process but was more basically the result of living organisms or "living ferments." The common theory at the time was that yeast was just a complex chemical substance acting as a catalyst in converting sugars to alcohol. But because of Pasteur's prior belief that optical activity is a distinctive characteristic of living organisms, and is only produced by living organisms, fermentation in turn must be the result of some type of living process. As we now know, Pasteur's belief in the connection between living organisms and molecular asymmetry has a solid evidentiary base. For example, all the proteins of higher animals are made up of amino acids in a left-handed configuration. Also, our cells burn only the right-handed forms of sugar.

The intimate connection between optical activity and the presence of living organisms became a central tenet in Pasteur's research into fermentation, including his first published work in 1857 on the production of lactic acid, which occurs most notably when milk "sours." To phrase all of this in an abductive reasoning framework, we begin with the "surprising observation" of optical activity in the products of fermentation. Then, because optical activity is produced only by living processes, if fermentation is the product of living organisms, then optical activity would be "a matter of course." Therefore, there is reason to believe that fermentation is the product of living "ferments," or in Pasteur's words: "fermentation is a phenomenon correlative of life."

The connections between optical activity and living processes were continually reinforced for Pasteur through his observational skills and "prepared mind." One such example goes back to the optically in-

active paratartaric acid. In warm weather, a fungus quickly grows and clouds solutions of paratartaric acid that had been prepared for study. Most researchers merely threw such fungus contaminated samples away. Pasteur, on the other hand, wondered whether the two isomeric components would be affected differentially by the presence of mold. As it turned out, the solution became more optically active over time, and moreover, only the right-rotating isomers were consumed leaving a greater and greater concentration of the left-rotating isomer. As compared to the mechanical way of separating the isomers of the paratartaric mixture, the use of the fungal mold was much easier, at least in generating the left-rotating component.

Besides the contention that fermentation was the result of a living process, Pasteur also concluded that different fermentations resulted from different microbes. Thus, a lactic acid ferment that produces sour milk differs from the yeast microorganism responsible for alcoholic fermentation in wine. Also, the type of contamination that M. Bigo was seeing in his ethanol production was most likely due to extraneous organisms producing unwanted byproducts. It is not too far of a reach from these observations to the process of "pasteurization," where some substances such as milk, beer, or wine are heated sufficiently to destroy whatever unwanted microbes might be present and which would lead to some type of spoilage or disease if not destroyed. It would not be until 1865, however, that Pasteur actually patented this process of "partial sterilization" or what is now universally called "pasteurization."

A short paper that Pasteur published in 1857 on lactic acid fermentation is considered by many to be the beginnings of the science of microbiology, and, in turn, the initial justification for Pasteur be-

ing considered a father of microbiology. In it, Pasteur argues that the lactic acid ferment is alive and made up of a large number of small living beings that resemble each other, and these bodies could grow in number if given the proper food. In other words, fermentation is the act of reproduction for the living germs that make up yeast. Once grown in a pure state, the lactic ferment could be transferred to a new sugar solution which would then be quickly transformed into lactic acid. Thomas Brock in his text, *Milestones in Microbiology (1546 to 1940)* provides a translation of Pasteur's abstract for this first "Report on the Lactic Acid Fermentation"; part of this translated abstract is given in an external Appendix.

The last paragraph of Pasteur's short lactic acid paper gives a particularly succinct summary of Pasteur's stance on fermentation as a living process. A translation of this last section follows, taken from James Bryant Conant's *Pasteur's Study of Fermentation* (1952); the two comments in brackets are from Conant:

> All through this memoir, I have reasoned on the basis of the hypothesis that the new yeast is organized, that it is a living organism, and that its chemical action on sugar corresponds to its development and organization. [This is an explicit statement of Pasteur's working hypothesis.] If someone were to tell me that in these conclusions I am going beyond that which the facts prove, I would answer that this is quite true, in the sense that the stand I am taking is in a framework of ideas that in rigorous terms cannot be irrefutably demonstrated. Here is the way I see it: whenever a chemist makes a study of these mysterious phenomena and has the good fortune to bring about an important development, he will instinctively be inclined to assign its primary cause to a type of reaction consistent with the general results of his own research. It is the logical course of the human mind in all controversial questions.

> And it is my opinion, at this point in the development of my knowledge of the subject, that whoever judges impartially the results of this work and that which I shall shortly publish will recognize with me that fermentation appears to be correlative to life and to the organization of globules, and not to their death or putrefaction. [This sentence summarizes the significance of what might seem on first reading a trivial study of a special case. Pasteur presents his hypothesis and evidence for it in one case — lactic acid formation.] Any contention that fermentation is a phenomenon due to contact in which the transformation of sugar takes place in the presence of the ferment without giving up anything to it or taking anything from it, is contradicted by experiment as will be soon seen. In a work that will follow shortly, I shall take up the chemical action of the new yeast on sweetened substances.

Even in this first paper on lactic acid fermentation, Pasteur made several significant observations (or discoveries). First, fermentation is a consequence of life without air (that is, without oxygen), or what is called an anaerobic process. When yeast is exposed to air, the rate of fermentation drops. This inhibiting effect of oxygen on the fermentation process and, concomitantly, facilitating an increase in yeast cell growth, is a change from an anaerobic to an aerobic process; this is called the "Pasteur effect." In the phrases that Pasteur himself used, particularly in the context of wine production, "fermentation is respiration in the absence of air," or alternatively, "fermentation is life without oxygen."

* * *

Pasteur accepted a position in 1857 at his old Alma Mater, the École Normale Supérieure, as Assistant Director in charge of scientific studies and general administration. A series of curricular reforms and

the related competitive examination process that Pasteur instituted generally improved the standard of scientific work done at the school. However, the general administration part of Pasteur's Assistant Director position that involved the non-academic life of the students did not go as well. The following short passage from the 1998 biography by Patrice Debré, *Louis Pasteur*, illustrates Pasteur's general authoritarian style and rigidity in nonscientific matters:

> One of the episodes in the permanent conflict between Pasteur and the students became known by the name of "the bean revolt." One day, two tables in the dining hall refused to eat an allegedly wretched mutton stew. Pasteur was furious, did not listen to any of the complaints, and announced that the same stew would be served the following Monday. A week later almost all of the tables refused to eat the stew. Pasteur, beside himself with anger, came to the dining room and announced that this dish would stay on the menu for every Monday. Only those students who had shown a spirit of order and submission would go unpunished. The mutton stew divided the classes and separated the reactionaries from the revolutionaries. Resistance seemed to have gained the upper hand when, a few days later, Pasteur gave another speech in the dining hall after he had caught some students smoking. He warned the students that anyone caught smoking or returning from a smoke would be instantly dismissed from the school: "There is no point asking whether the punishment is proportionate to the offense. That decision is up to me. And the offense will not be the smoking but the failure to obey the injunction you are receiving at this moment." Seventy-three of the eighty students resigned from the school as a result of this decree. It took the skill of Nisard [the school Director] and the intervention of the minister [of education] to make them change their minds.

It was during the early years of Pasteur's return to the École Normale that his attention turned to the problem of spontaneous gen-

eration, a theory which held that living organisms could arise from nonliving substances. Pasteur's abductive contention to the contrary was that such living entities were the result of other living creatures that resided in the atmosphere or on other material that could serve as a contaminating source. Pasteur proceeded to amass a variety of evidence, both experimental and observational, that spontaneous generation when it appeared to be present, was actually the result of contamination from the atmosphere or from other substances that contained the parent organisms.

To show that microorganisms exist in the atmosphere, Pasteur used an apparatus with a hydraulic mechanism that could bring in air from the outside that was then filtered through a wad of nitrocellulose (guncotton) or asbestos. Once the wad was washed in a concave watch glass, the particles could be examined under a microscope. Pasteur also showed that these dust particles would proliferate in liquids that served as a nutrient medium, except when these particles were heated sufficiently to be destroyed. Presumably, the absence of such particles in a wad that was not used as a filter demonstrated that the particles were in the atmosphere and not inherent in the guncotton or asbestos.

In another set of experiments done somewhat later with grapes and fermentation, Pasteur showed that juice removed with a fine needle from grapes with undamaged skin and kept away from contact with the air or other objects, would not ferment until yeast had been added. Also, in a field experiment that Pasteur conducted in his small Arbois vineyard in the Jura Mountains, he could show that when yeast was prevented from attaching to the grape skins, fermentation could be prevented. We give a short English translation

from the René Dubos biography that presents Pasteur's discussion of this particular field experiment:

> Without too much care for expense, I ordered in all haste several hothouses with the intention of transporting them to the Jura, where I possess a vineyard some dozens of square meters in size. There was not a moment to lose. And this is why.
>
> I have shown, in a chapter of my *Studies on Beer*, that the germs of yeast are not yet present on the grape berry in the state of verjuice, which, in the Jura, is at the end of July. We are, I said to myself, at a time of the year when, thanks to a delay in growth due to a cold rainy season, the grapes are just in this state in the Arbois country. By taking this moment to cover some vine with hothouses almost hermetically closed, I would have, in October at grape harvest time, vines bearing ripe grapes without any yeasts on the surface. These grapes, being crushed with the precautions necessary to exclude yeast, will be able neither to ferment nor to make wine. I shall give myself the pleasure of taking them to Paris, of presenting them to the Academy, and of offering some clusters to those of my confreres [colleagues] who still believe in the spontaneous generation of yeast.
>
> The fourth of August, 1878, my hothouses were finished and ready to be installed. ... During and after their installation, I searched with care to see if yeasts were really absent from the clusters in the state of verjuice, as I had found hitherto to be the case. The result was what I expected; in a great number of experiments I determined that the verjuice of the vines around Arbois, and notably that of the vines covered by the hothouses, bore no trace of yeast at the beginning of the month of August, 1878.
>
> For fear that an inadequate sealing of the hothouses would allow the yeasts to reach the clusters, I decided to cover a certain number on each vine with cotton wrappings previously heated to a temperature of about 150 C. ...
>
> Toward the tenth of October, the grapes in the hothouses were

ripe; one could clearly distinguish the seeds through their skin and they were as sweet in taste as the majority of the grapes grown outside; the only difference was that the grapes under the cotton, normally black, were scarcely colored, rather violaceous [of a violet color] than black, and that the white grapes had not the golden yellow tint of white grapes exposed to the sun. Nevertheless, I repeat, the maturity of both left nothing to be desired.

On the tenth of October, I made my first experiment on the grapes of the uncovered clusters and on those covered with the cotton, comparing them with some which had grown outside. The result, I may say, surpassed my expectation. ... Today, after a multitude of trials, I am just where I started, that is to say, it has been impossible for me to obtain one single time the alcoholic yeast fermentation from clusters covered with cotton.

A comparative experiment naturally suggested itself. The hothouses had been set up in the period during which the germs are absent from the stems and clusters, whereas the experiments which I have just described took place from the tenth to the thirty-first of October during the period when the germs were present on the plant. It was then to be expected that if I exposed hothouse clusters from which the cotton had been removed on the branches of vines in the open, these clusters ... would now ferment under the influence of the yeasts which they could not fail to receive in their new location. This was precisely the result that I obtained.

Some of Pasteur's most convincing demonstrations about spontaneous generation involved a glass flask with a swan-like curved appendage (in French, a *col de cygne*). In fact, one might even label these demonstrations as crucial experiments (*experimentia crucis*). When a nutrient liquid was boiled in the flask expelling the air that was present and then either sealed or set aside so the dust in the air could not traverse the curve to reach the liquid, the material in the flask remained free of growth. On the other hand, if the glass neck

was removed so air could enter and reach the liquid, or if the flask were tilted to allow the liquid to touch the particles trapped in the curved neck, growth in the liquid quickly appeared. Thus, it was the dust in the air and not just the air by itself that caused the growth to occur.

In addition to the use of swan-like flasks, Pasteur experimented repeatedly with glass containers having a straight vertical neck. The nutrient liquid could first be boiled thus expelling the air in the container, and the neck then sealed. Upon reopening the flasks in different areas and then immediately resealing, Pasteur could show various germ and contaminant gradients present in the air. For example, the air appeared less contaminated at high mountain elevations, or in places where the air had remained stagnant for many years, such as in the Paris Observatory. The number of opened and resealed flasks that remained free of growth was taken as an indication of the germ and contaminant density at that specific location.

Pasteur gave a series of five lectures in 1881 to the French Academy of Sciences concerning his work on spontaneous generation. These presentations were published in 1882 under the title, *Mémoire Sur les corpuscules organisés qui existent dans l'atmosphére: Examen de la doctrine des générations spontanées* (Account of Organized Corpuscles Existing in the Atmosphere: Examining the Doctrine of Spontaneous Generation). Pasteur stated his forceful conclusion regarding spontaneous generation succinctly as follows:

> Never will the doctrine of spontaneous generation recover from the mortal blow of this simple experiment. There is no known circumstance in which it can be affirmed that microscopic beings came into the world without germs, without parents similar to themselves. ... Those who affirm it have been duped by illusions, by ill-conducted

> experiments, by errors that they either did not perceive, or did not know how to avoid.

To date, and over one-hundred years after they were prepared, several of Pasteur's swan-like flasks remain in a sterile condition at the Pasteur Institute in Paris.

* * *

From the time Pasteur was at Lille observing unwanted objects in the ferment that turned beet juice into ethanol, his work on the processes of fermentation and the possibility of spontaneous generation was all guided by an overall and comprehensive abductive conjecture of a "(living) germ theory" appropriate for fermentation, putrefaction, and decomposition generally. The causative living germs (microorganisms or microbes) came from the surroundings whether it was the yeast for wine production or the growth in flasks open to the air that originally contained a sterile solution generated by boiling. Pasteur became very good at identifying the offending organisms that were causing difficulty in the production of wine, beer, and vinegar. For example, at his summer home in Arbois and given the well-stocked wine cellars of his friends in the area, Pasteur became adept at predicting the flavor of a wine from examination of its sediments. In "healthy" wines, foreign bodies were absent and only the necessary yeast cells remained.

As noted earlier, for all the various products of fermentation and later for milk and other foodstuffs, Pasteur developed methods of partial sterilization known to this day as pasteurization, by heating the particular substance to destroy whatever offending microbes were present while leaving the other residual material intact. Pasteur

concerned himself particularly with the wine industry and invented several practical technological devices to effect his method of pasteurization on a large-scale basis. Two of the topics listed on the arches of his tomb refer to Pasteur's interests in the contaminating microbes that might be present in the production of wine and beer.

In addition to the processes of pasteurization, Pasteur and his research partner Charles Chamberland, invented several other devices that used heat for the purpose of sterilization. One was the Pasteur oven that was based on hot air; the second was the Chamberland autoclave developed in 1879 using pressurized saturated steam.

* * *

Pasteur's first studies of infectious disease were done on the unlikely subject of silkworms. In the middle of the Nineteenth Century, a mysterious malady, called pébrine (or "pepper disease") was causing devastation throughout the French silkworm industry. It generally manifested in the form of small black spots on the skin of the silkworm. Silkworms with pébrine typically showed an arrested development and died before completing a full life-cycle (thus depriving the farmers of their silk-generating cocoons). To give a sense of what a normal life-cycle of the silkworm should be when commercially raised on the leaves of a mulberry tree, an account is given below from the Émile Duclaux biography, *Pasteur: The History of a Mind* (1920):

> Everybody knows, at least in a general way, the principal phenomena of the life of the silkworm: its birth from an egg, whose resemblance to certain plant seeds has led to its being given the name of "seed," its four "molts," or changes of skin during which

the worm ceases to eat, remains motionless, seems to sleep upon its litter, and clothes itself, under its old skin, with a new skin, which allows it to undergo further development The fourth of these molts is followed after two or three days by a period of extreme voracity during which the worm rapidly increases in volume and acquires its maximum size: this is called the "grande gorge." This period ended, the worm eats no more, moves about uneasily, and if sprigs of heather on which it can ascend are present, it finds thereon a suitable place to spin its cocoon, a kind of silky prison which permits it to undergo in peace its transformation first into a chrysalis, and then into a moth. In this cocoon, the body of the worm, emptied of all the silky matter, contracts and covers itself with a resistant tunic in the interior of which all the tissues seem to fuse into a pulp of homogeneous appearance. It is in the midst of this magma that, little by little, the tissues of the moth are formed and become differentiated.

The moth has only a rudimentary digestive canal, for it no longer has any need of eating: the worm has eaten for it. It has wings, but, in our domestic races, it makes no use of them. It is destined only for the reproduction of the species, and the sex union takes place as soon as the moth comes out of the cocoon. The female then lays a considerable number of eggs, which may reach six hundred to eight hundred. In the races that we call annual, which are the most sought after, this "seed" does not hatch until the following year and is delayed until the reawakening of vegetation, the spring of the following year.

It is only when the grower wishes to induce the laying of eggs that he awaits this coming-forth from the cocoon, in which case the transformation of the worm into a moth requires about fifteen days. By adding thereto the thirty-five or forty days required for the culture of the worm, and the time necessary for the laying of the eggs, we see that the complete evolution of the silkworm, from the egg to the egg, is about two months. The period of industrial life is sensibly shorter. When the grower wishes to use only the cocoons,

> he must not wait until the moth, in coming forth, has opened them and thereby rendered them unfit for spinning. They are smothered five or six days after they have climbed the twigs of heather. That is to say, the cocoons are put into a steam bath, to kill the chrysalids by heat. In this case, scarcely six weeks separate the time of egg-hatching from the time when the cocoons are carried to market, from the time the silk grower sows to the time when he reaps. As, in former times, the harvest was almost certain and quite lucrative, the *Time of the Silkworm* was a time of festival and of joy, in spite of the fatigues which it imposed, and, in gratitude, the mulberry tree had received the name of *arbre d'or* [tree of gold], from the populations who derived their livelihood from it.

One of Pasteur's most revered teachers, the chemist Jean-Baptiste Dumas, came from one of the silk-producing areas most affected by pébrine. Given his formidable reputation, Dumas was able to induce the Minister of Agriculture to appoint a special commission to study the disease(s) then devastating the French silkworm industry. In turn, Dumas prophetically asked Pasteur to head the effort, even though Pasteur had no prior experience with either the biological or pathological processes inherent to man or other animals. Nevertheless, Pasteur accepted the appointment and spent the six years from 1865 to 1871 in the birthplace of Dumas, the southern French commune of Alès. Here, he set up a laboratory facility for the detailed study of silkworm production and the various maladies that then plagued the industry.

As we now know, pébrine is a disease caused by unicellular parasites that may come from contaminated food eaten by silkworms and/or that are passed to a next generation through infected eggs produced by infected mothers. When silkworms acquire the parasite in their larval stages, there are no visible signs; nevertheless, the fe-

male moths can pass the parasite to its eggs resulting in the death of the worms that subsequently hatch. As Pasteur recognized fairly quickly, it is necessary to cull all eggs from infected moths that are identified microscopically from the corpuscles present in their bodies.

Pasteur initially believed that the corpuscles to be seen in a moth's body were just a sign of some disease rather than the actual cause, as would become apparent later. Irrespective, the sorting of eggs based on corpuscle presence still provided a technological means of combating the disease in future silkworm generations. As given in the Dubos biography, *Free Lance of Science*, Pasteur described the culling process as follows:

> The technique consists in isolating each couple, male and female, at the moment of egg-laying. After the mating, the female, set apart, will be allowed to lay her eggs; she should then be opened as well as the male, in order to search for the corpuscles. If they are absent both from male and female, this laying should be preserved, as it will give eggs absolutely pure which should be bred the following year with particular care. ... As soon as the moths have left their cocoons and mated, they should be separated and each female placed on a little square of linen where she will lay her eggs. The moth is afterwards pinned up in a corner of the same square of linen, where it gradually dries up; later on, in autumn or even in winter, the withered moth is moistened in a little water, pounded in a mortar, and the paste examined with a microscope. If the least trace of corpuscles appears, the linen is burnt, together with the seed which would have perpetuated the disease.

In June of 1866, Pasteur sent the Minister of Agriculture, who had initially appointed the silkworm commission, a statement regarding how pébrine could now be controlled practically:

> In the past, the evil had been sought in the worm and even in the seeds, but my observations prove that it develops chiefly in the chrysalis, especially in the mature chrysalis, at the moment of the moth's formation, on the eve of the function of reproduction. The microscope then detects its presence with certainty, even when the seed and the worm seem very healthy. The practical result is this: You have a full nursery; it has been successful or it has not; you wish to know whether to smother the cocoons or whether to keep them for reproduction. Nothing is simpler. You hasten the development of about one hundred moths by raising the temperature, and you examine these moths through the microscope.
>
> The evidence of the disease is then so easy to detect that a woman or a child can do it. If the producer is a peasant, unable to carry out this study, he can do this: instead of throwing away the moths after they have laid their eggs, he can bottle them in brandy and send them to a testing office or to some experienced person who will determine the value of the seed for the following year.

Some of the egg selections carried out during the 1866 season performed admirably for Pasteur and for the many breeders who were given batches to evaluate under practical conditions. Several of the batches, however, although free of corpuscles, were giving disastrous results, with the worms hatched from the selected eggs turning brown and then dying. To the dismay of Pasteur, these worms, even though corpuscle-free, were infected with a second type of silkworm disease called flacherie (literally, "flaccidness"). This later disease manifests as a type of silkworm intestinal diarrhea with various attendant bacterial pathogens contributing to its severity.

Pasteur made what turned out to be a crucial abduction that eventually lead to a way of screening eggs for flacherie and how an environment could be provided that would inhibit its development. Whenever Pasteur entered a silkworm nursery infected with flacherie,

he noticed a very unpleasant smell that was particularly pungent near the beds of diseased worms. To Pasteur this odor was strongly reminiscent of that produced during the various fermentations he had studied, and conjectured that here too he was in the presence of some type of putrefaction process.

To evaluate whether some type of fermentation activity was actually operative in a silkworm affected by flacherie, Pasteur opened a number of infected silkworms and noted that little bubbles of gas, similar to that seen in fermentation, struck the intestinal walls as they arose. Pasteur was able to identify the possible sources for contagious flacherie: the wet mulberry leaves ground up and beginning to ferment; or mulberry leaves dipped in the excreta of ground-up intestines of worms that were infected with flacherie. So, again, one means of flacherie control was to select the eggs from silkworms that did not exhibit any languishment. In addition, careful hygienic control of the whole silkworm environment was necessary in terms of temperature and humidity and the careful management of the silkworms' food, including the careful picking and conservation of mulberry leaves.

It took some unexpectedly long period of time before Pasteur was able to accept that the corpuscles he could see microscopically were the actual agents of infection rather than just the symptoms. One incident, in particular, was a deciding event in Pasteur coming to terms with the corpuscles being the mechanism for the contagious transmission of pébrine. Not far from where Pasteur was carrying out his silkworm experimentation, a family of silkworm breeders had obtained two batches of healthy Japanese eggs, which to their surprise, produced corpuscular silkworms. Pasteur observed that a breeding

chamber full of diseased silkworms had been placed on a shelf above where the Japanese eggs were stored. The droppings from the diseased silkworms had fallen into the lower beds producing pébrine in the heretofore healthy silkworm batches. Thus, the surprising observation of diseased Japanese silkworms could be abductively explained by the contagiousness of the corpuscles in the droppings failing into the containers that held them.

In the spring of 1869, Pasteur sought to conclusively demonstrate the validity of his egg selection methods and to convince those breeders who still had doubts that the problem of disease in the silkworm industry could be effectively controlled. Also, this control could be carried out without an exact knowledge of what might be the actual cause of a particular disease. Pasteur offered the hesitant Silk Industry of Lyon different egg batches that he had sorted according to those that would succeed and those that would come down with pébrine, flacherie, or some combination of the two. Pasteur's designations were all correct, and every container of eggs had one or the other of the diseases, or none at all. By 1870 Pasteur had published a complete summary of his work on the diseases of silkworms in his *Etudes sur les Maladies des Vers à soie* (Studies on Silkworm Disease).

* * *

Pasteur began a study of chicken (or fowl) cholera in the spring of 1879, a disease that was then causing havoc throughout France, and which could devastate entire barnyards in just a few days. Pasteur was able to identify and culture the bacterial causative agent rather easily. Moreover, he could show how a few drops of the pure

culture injected into a normal chicken would invariably cause death, sometimes in less than twenty-four hours. Similarly, the feeding of contaminated food or excreta was typically sufficient to produce an equally fatal outcome. Rabbits were a similarly susceptible animal.

After the summer vacation of 1879, the bacterial cultures of chicken cholera that had been kept in the laboratory over the summer interlude failed to produce any disease when inoculated into chickens during the early fall. A new virulent culture was then started from a natural outbreak and used to inoculate a newly obtained set of chickens as well as those animals that had failed to contract any disease when the older cultures from the summer were used. At this point an extraordinary outcome occurred — all the newly bought chickens promptly died but almost all of those survived that had also been inoculated with the older culture from the summer.

In the shortened biography by René Dubos, *Pasteur and Modern Science*, one of Pasteur's collaborators is quoted to the effect that Pasteur gave a prescient abductive conjecture to the astonishing observation provided by the surviving chickens: "Don't you see that these animals have been *vaccinated*!" At a basic level this episode could be seen as the birth of medical (or protective) immunology, and the first among many other reasons to give Pasteur a title of "father of immunology." Although Jenner had produced a means of smallpox vaccination many years earlier through the use of the related cowpox disease, the degraded chicken cholera culture could be seen as the first time that an attenuated disease entity was used to generate a more general immunity to the disease itself.

As discussed elsewhere, the German physician and microbiologist, Robert Koch (1843–1910), is known for his work with anthrax, a dis-

ease that was devastating to the sheep and cattle industries throughout all of Europe. Koch discovered the anthrax causative agent to be a bacillus (*Bacillus anthracis*) that he was able to culture outside of an animal host. He also discovered that spores could be formed in anthrax bacteria, which could remain dormant for a period but then activated under optimal conditions to transmit the disease anew. Koch's work with anthrax supported the emerging germ theory of disease by clearly linking a specific microorganism to a specific disease. Koch published his work with anthrax in 1876 under the title (English translation): *The Etiology of Anthrax Disease, Based on the Developmental History of Bacillus Anthracis.*

At about the same time that Pasteur was studying the transmission of chicken cholera and had the serendipitous discovery of attenuated disease agents as a possible vaccine to protect against the disease itself, he also began an investigation into anthrax as informed by the earlier work of Koch. First, Pasteur gave definitive proof that it was the bacillus itself and not something carried along in the culture medium that caused the disease when injected into an animal. Pasteur placed one drop of blood from an anthrax-infected sheep into a fifty milliliter sterile culture and grew the bacillus. This process was replicated one-hundred times thus diluting the original culture so that no single molecule of it remained in the final culture. The last culture was as active in producing anthrax as the first. Because only the bacillus could evade dilution by being grown anew in each successive culture, it was thus established that the anthrax bacillus alone was responsible for the disease.

Besides these experiments based on dilution, Pasteur used several other mechanisms to show that the actual anthrax bacillus was re-

sponsible for producing the disease. One involved a filter patented by his colleague Charles Chamberland that captured bacteria and prevented it from passing through the filter. The clear filtrate from the anthrax bacillus culture that could pass through the filter did not produce anthrax in rabbits. In a similar manner, when flasks containing the anthrax bacteria were allowed to stand and the bacteria settled to the bottom, the clear top liquid could not produce anthrax although a few drops of the settled material could. All of these demonstrations further supported the germ theory of disease causation.

Pasteur identified a possible mechanism for how anthrax could spread, and how some fields seemed "cursed" and deadly to sheep while others did not. Farmers routinely buried sheep that had died of anthrax in the same fields where initially healthy animals were allowed to graze. During one of Pasteur's excursions to a field where anthrax was affecting the sheep, he noticed that parts of the field were differently colored, and this different coloration was due to earthworm casts corresponding to where the diseased sheep had been buried. This surprising observation lead Pasteur to the abductive conjecture that the earthworms were feeding off the diseased carcasses and bringing the anthrax spores to the surface where other sheep were grazing. Evidence for Pasteur's hypothesis was obtained by first explicitly observing the anthrax spores in the earthworm casts; then, animals remained healthy when restricted to uncontaminated areas where diseased sheep had not been previously buried.

The most famous and enduring work that Pasteur conducted with anthrax was his field demonstration in the spring of 1881 as to the effectiveness of an anthrax vaccine. A translation is provided in an

external Appendix of Pasteur's summary report on these experiments that appeared recently in the *Yale Journal of Biology and Medicine* (2002) as part of their series on Classics of Biology and Medicine. Given the international exposure and acclaim that this particular field experiment produced, it may also represent the height of scientific chutzpah on Pasteur's part. It is now known (as of the 1990s) that he used a competitor's method for attenuating the anthrax vaccine and not his own strategy based on oxygen. This fact was never disclosed by Pasteur during his lifetime; in fact, Pasteur asserted the opposite by saying that his own method of oxygen attenuation had been used.

* * *

The final item on the archway of Pasteur's tomb is "rabies prophylactics," and is the topic commonly cited as Pasteur's last great success that rightly justifies a claim for immortality. As a disease, rabies is caused by a virus, and therefore it cannot be cultured and attenuated in the same manner as anthrax. Nor can it be captured by the Chamberland filter as can any cultivable bacteria. Thus, rabies is known as a "filterable virus," and is invisible under any of the microscopes that were available in the Nineteenth Century. Nevertheless, using rabbits as the model for propagating rabies, Pasteur showed how the spinal cords of rabbits that had died of the disease could be differentially attenuated by keeping them in sterile dried air for varying periods of time. Stated in a different way, although rabies is a filterable virus, it can be handled almost as easily as cultivable bacteria — this was a great technical feat at the time.

Although not exactly like the serendipitous event that led to the

attenuated but still alive chicken cholera vaccine, a somewhat similar occurrence also happened with rabies. A dog bitten by another rabid dog came down with rabies but miraculously recovered. The dog remained free of rabies when injected with fresh brain material from a rabid dog. What this "surprising observation" suggested as an abductive conjecture was that an immunity even to rabies was possible. This led directly to the use of a successive sequence of (dead) viral material obtained from the spinal cord of rabbits as a way of providing the necessary prophylactic regime against the disease itself.

Rabies has a very long latency period before its symptoms appear, which allows an animal (or human) bitten by a rabid animal to be vaccinated after a bite has occurred. Pasteur showed how this was possible experimentally by inoculating dogs with progressively less attenuated spinal cord. At the end of the series, the dog was protected against inoculation with the most virulent and unattenuated viral agent.

The first instance of a human trial for Pasteur's rabies prophylactic regime came in the form of a young boy from Alsace, Joseph Meister, who had been bitten over much of his extremities by a rabid dog. After consulting with physicians, Pasteur was convinced that the boy would die a horrible death without his intervention. He began treatment on July 7, 1885, sixty hours after the initial rabid dog bites, with rabbit spinal cord that had been attenuated for fourteen days. A series of twelve successively less attenuated inoculations followed, ending with the most virulent on July 16. Joseph Meister recovered fully and returned in good health to Alsace soon thereafter.

The second human case treated by Pasteur was that of a fifteen year-old shepherd, Jean Baptiste Jupille, who was severely bitten by

a rabid dog as he protected with his whip several young children from being bitten. Again, the boy survived. These two instances of prophylactic success against rabies led in a short time to many patients seeking treatment from Pasteur for bites from animals assumed to be rabid. It was this initial success against rabies and the continuing need to provide treatment for those arriving in Paris with animal bites that eventually led to the founding of the Pasteur Institute.

An English translation of parts of the paper Pasteur read to the French Academy of Sciences in 1885 is given in an external Appendix. This translation is housed at a web site originally constructed by the late D.V. Cohn:[1]

* * *

Each of Pasteur's discoveries throughout his career seemed to lead naturally to others. Pasteur himself commented that he was "enchained" by the inescapable logic of his discoveries. Thus, the idea of optical activity being consistent with living organisms went from the study of tartrate crystals to the view that fermentation was the result of living entities. The latter "germ theory" of processes such as fermentation and putrefaction was then extended to human and animal diseases, first in silkworms and then to chicken cholera, anthrax, and rabies. Through several "surprising" observations in Pasteur's studies of chicken cholera and rabies, there are the beginnings of medical immunology more generally. In this section an emphasis will be placed on several other discoveries that could be considered offshoots of the more direct trajectory from tartrates to rabies.

In Pasteur's study of chicken cholera, it was noted that both guinea

[1] http://pyramid.spd.louisville.edu/~eri/fos/Rabies.html

pigs and chickens could be infective for the disease through abscesses, and for some extended period of time. This was at about the same moment that Robert Koch delineated the notion of a chronic disease carrier state and the related concept of an animal reservoir for typhoid. Thus, Pasteur did the same for chicken cholera. The concept of an asymptomatic carrier appears throughout several of our chapters but is given the most prominence in the sections devoted to Mary Mallon (Typhoid Mary) in the chapter on William Budd.

The 1936 highly fictionalized movie, *The Story of Louis Pasteur*, won several Academy Awards for Best Screenplay and Best Story plus a Best Actor Award to Paul Muni who portrayed Pasteur. The story begins in 1860 when a distraught husband shoots and kills his wife's doctor. At the time, Pasteur was touting the germ theory of disease and the need to prevent doctors from spreading various diseases by not washing their hands or sterilizing their instruments. The doctor attending the murderer's wife did not do so, resulting in her death due to childbed fever. Pasteur is blamed for the murder because his obviously wrong germ theories of cleanliness incited the husband to kill his wife's doctor. At that point in the film Pasteur retired to Arbois where his anthrax field trials were carried out shortly thereafter.

Although the movie is partly fictionalized both in content and time-frame, it was noted in the chapter on Ignaz Semmelweis that Pasteur first identified *Streptococcus* bacteria as a cause of childbed (puerperal) fever. In the 1879 excerpt reported in that chapter by his assistant, Émile Roux, Pasteur drew the diagram of the chain-like organism causing childbed fever during another doctor's lecture when he denied the possibility of ever identifying its real cause. The

Paul Muni figure of Pasteur explicitly mentions Semmelweis in the movie. There is also a fictionalized incident where Pasteur convinced his arch-rival, Doctor Charbonnet, to wash his hands and sterilize his instruments before attending to the birth of one of Pasteur's grandchildren.

One somewhat amusing episode in Pasteur's many arguments with other scientists, particularly with those from the French Academy of Medicine, is the story of Pasteur's interest in the influence that body temperature and other environmental factors can have on disease progression and microbe growth. One Academy member, M. Colin, a Professor of Veterinary Science at Alfort, had the annoying habit of always questioning in public Pasteur's evidence regarding spontaneous generation, or the role of microbes in fermentation and/or in diseases such as anthrax. One specific incident concerned Pasteur's contention that chickens could not contract anthrax, and Colin's retort that nothing could be easier. This interchange occurred in July of 1877 when Pasteur had just passed along to Colin a culture of the anthrax bacillus and requested that Colin return with a sick hen suffering from the disease. René Dubos relates the ensuing story as told to the Academy in March of 1878; this is reproduced below along with some of Dubos' clarifying narration:

> At the end of the week, I saw M. Colin coming to my laboratory, and even before I shook hands with him, I said, "Why, you have not brought me that diseased hen!" ... "Trust me" answered M. Colin, "you shall have it next week." ... I left for vacation; on my return, and at the first meeting of the Academy which I attended, I went to M. Colin and said, "Well, where is my dying hen?" "I have only just begun experimenting again," said M. Colin; "in a few days I shall bring you a hen suffering from anthrax." ... Days and weeks

went by, with fresh insistence on my part and new promises from M. Colin. One day, about two months ago, M. Colin acknowledged that he had been mistaken, and that it was impossible to give anthrax to a hen. "Well, my dear colleague," I told him, "I will show you that it is possible to give anthrax to hens; I shall myself, one day, bring to you at Alfort a hen which shall die of the disease."

I have told the Academy this story of the hen which M. Colin had promised in order to show that our colleague's contradiction of our findings on anthrax had never been very serious.

In reply, Colin stated before the Academy: "I regret that I have not been able as yet to hand to M. Pasteur a hen dying or dead of anthrax. The two that I had bought for that purpose were inoculated several times with very active blood, but neither of them fell ill. Perhaps the experiment might have succeeded later, but, one fine day, a greedy dog prevented that by eating up the two birds, whose cage had probably been badly closed."

On the Tuesday following this incident, Pasteur emerged from the École Normale, carrying a cage containing three hens, one of which was dead, and drove to the Academy of Medicine. After having deposited his unexpected load on the desk, he announced that the dead hen had been inoculated with anthrax two days before at twelve o'clock on Sunday, with five drops of culture of the anthrax bacillus and had died on Monday at five o'clock, twenty-nine hours after the inoculation. This result was the outcome of an original experiment. Puzzled by the fact that the hens were refractory to anthrax, he had wondered whether this resistance might not be due to the body temperature of the birds, known to be higher than that of animals susceptible to the disease. To test this idea, hens were inoculated with anthrax and then placed in a cold bath in order to lower their temperature. Animals so treated died the next day with their blood, spleen, lungs, and liver filled with bacilli. The white hen which lay dead on the floor of the cage was evidence to the success of the experiment. To show that it was not the prolonged bath which had killed it, a speckled hen had been placed in the same

bath, at the same temperature and for the same time, but without infection; this bird was in the cage on the desk, extremely lively. The third hen, a black one, had been inoculated at the same time as the white hen, with the same culture, using ten drops of culture instead of five, to make the experiment more convincing; but it had not been subjected to the bath treatment and had remained in perfect health.

A fourth experiment was carried out later to establish whether a hen, infected with anthrax and allowed to contract the disease by being placed in a cold bath, would recover if allowed to re-establish its ordinary body temperature by being removed from the bath early enough. A hen was taken, inoculated and cooled in a bath, until it was obvious that the disease was in full progress. It was then taken out of the water, dried, wrapped in cotton wool and placed at a temperature sufficient to allow rapid restoration of normal body temperature. To Pasteur's great satisfaction, the hen made a complete recovery. Thus, the mere fall of temperature from 42 C. (the normal temperature of hens) to 38 C. was sufficient to render birds almost as receptive to infection as rabbits or guinea pigs.

Unconvinced by this experiment, or moved by his antagonism to Pasteur, Colin suggested on July 9, 1878, that the dead hen which had been laid on the desk of the Academy in the preceding March meeting might not, after all, have died of anthrax. As had Liebig and Pouchet in earlier years, Colin thus opened himself to the riposte. Pasteur immediately extended to him the challenge of submitting their differences to a commission of the Academy, with the understanding that Colin himself would perform the post-mortem and microscopic examination of the dead bird. Pasteur's experiments were repeated on July 20, and naturally yielded the results that he had forecast. Colin ungraciously signed the commissioner's statement that hens inoculated with a culture of anthrax, then cooled in a water bath, died with a large number of anthrax bacilli in their blood and tissues.

> Despite the apparent simplicity of the experiment, the effect of temperature on the susceptibility of chickens to anthrax is certainly a more complex phenomenon than Pasteur assumed it to be. True enough, the cooling of chickens by immersion in cold water brought their body temperature down to a level compatible with the growth of the anthrax bacillus, but at the same time it probably interfered with the performance of normal physiological mechanisms, thus increasing the susceptibility of the animals to infection. The results, nevertheless, were of interest as being the first experimental demonstration that environmental factors influence the course of infection, and that the presence in the body of a pathogenic agent is not necessarily synonymous with disease.

In the selection just presented about hens and anthrax, note the classic example of abductive reasoning along with subsequent experimental verification. First, the surprising observation was made that hens are refractory to anthrax. Second, the explanatory conjecture was made that the resistance of a hen to anthrax is due to its body temperature which is higher for a hen than for other susceptible animals. By experimentally reducing a hen's body temperature from 42 C. to 38 C., Pasteur was able to induce anthrax by inoculation. Also, he showed several other facts experimentally: 1) It was not just the bath that produced a hen's death – Pasteur placed a hen in the bath for the same length of time but with no anthrax inoculation and no resulting death. 2) A hen was inoculated with a massive ten drops of the anthrax culture but still failed to get the disease. 3) Pasteur showed that a hen could make a full recovery if it were first cooled and infected with anthrax that was observed "to take," but then taken quickly out of the bath and warmed to regain normal body temperature.

* * *

Joseph Lister (1827–1912) was a British physician, commonly known as the father of modern surgery for his introduction of antiseptic/aseptic practice that kept patients, doctors, and operating theaters free of contamination from harmful microorganisms and pathogens. Lister championed the use of antiseptic substances in his practice, such as carbolic acid, and used these directly on the wounds suffered by surgical patients. Lister suspected that carbolic acid would be a safe antiseptic: it was commonly applied to stem the stench from fields irrigated with sewage water; moreover, livestock that later grazed on these fields showed no apparent ill-effects.

Throughout his life, Lister credited Pasteur with motivating and being the main precursor to his development of antiseptic surgical practices. Pasteur emphasized the need to prevent microorganisms from entering the human body either through wounds done surgically or those that occurred naturally, or through bad medical practice such as in childbed fever. At the Pasteur Jubilee at the Sorbonne in 1892, it was Lister representing the Royal Societies of London and Edinburgh who gave one of the key laudatory addresses. In part, Lister said to Pasteur:

> It is my great privilege to convey to you, tributes, thanks and respect from all involved in medicine and surgery; it is true to say that, of all people in the world today, medical sciences owe you the most ... For centuries, infectious diseases have been shrouded, as it were under a dark curtain. In discovering the microbial origin of disease you have raised that dark curtain!

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Chapter 7

Robert Koch

> If my efforts have led to greater success than usual, this is due, I believe, to the fact that during my wanderings in the field of medicine, I have strayed onto paths where the gold was still lying by the wayside. It takes a little luck to be able to distinguish gold from dross, but that is all.
>
> – Robert Koch (1843–1910)

> The pure culture is the foundation for all research on infectious disease.
>
> – Robert Koch (1843–1910)

The germ theory of disease asserts that many infectious maladies are caused by tiny microorganisms, known as pathogens or microbes, or more familiarly as "germs." Although these organisms are too small to see with a naked eye, they nevertheless may be able to invade the human body or that of other animals. The resulting growth and reproduction of these germs within a living host is considered the cause of a specific disease. Pathogens that incite disease come in a variety of forms from one-cell entities such as bacteria or protozoa, to multi-cell fungi and non-living viruses that are just snippets of genetic material. In short, and although the germ theory of disease can be viewed as the overall motivating abductive conjecture for disease

causation, there remains the problem of actually identifying the specific germ responsible for a specific disease, and then proving it to be the causative agent. This is what Robert Koch (1843–1910) did for anthrax; he "proved" for the first time that a specific microorganism caused a specific disease.

Although versions of germ theory have been around since at least the Middle Ages, it wasn't until the late 1850s and the work of Louis Pasteur (1822–1895) that a germ theory of disease and several related putrefaction processes such as fermentation began to eclipse other explanatory theories for infectious maladies, such as that of a miasma as discussed more fully in the chapter on John Snow. This initial work of Pasteur was extended by Robert Koch, beginning in the middle 1870s. Koch is the individual of primary interest to this chapter. He is considered the founder of bacteriology and medical microbiology, and for ushering in a "golden era" for these two fields. Among other seminal contributions to the research and instrumentation methods of bacteriology, many of which are still in use to this day, Koch explicitly identified the causal agents for anthrax, tuberculosis, and cholera. From very early on he also studied the various agents responsible for wound infections, such as the *Staphylococcus* bacillus that can produce blood septicemia. Although Koch had several major scientific fiascos later in his career, he eventually received the 1905 Nobel Prize in Physiology or Medicine for his work in identifying the tuberculosis bacillus.

* * *

Robert Koch (1843–1910) was born in December of 1843 in the small silver mining town of Claustal, located in northern Germany.

Koch's father was a mining engineer and eventually the overall head of the Claustal mining operation centered in the area's Harz Mountains. Koch was a rather precocious youngster and entered the gymnasium when he was just eight years old. In 1862, Koch began study at the University of Göttingen, passing his medical examination to become a physician in 1866. After several years spent as a peripatetic doctor, Koch volunteered service as a Prussian army surgeon during the Franco-Prussian War of 1870. After the war ended, Koch passed an exam to become the district physician for the town of Wöllstein (now, Wolsztyn in Poland). It was here that Koch would begin his solitary search for the causative agent of anthrax, a devastating disease then affecting both humans and the entire livestock industry in Germany and throughout Europe.

Besides being the official district physician for Wöllstein, Koch set up a private medical practice to supplement his income. The space that Koch used to see patients included an area partitioned off where he could pursue his solitary studies of anthrax. At the time Koch began his Wöllstein practice, anthrax was particularly rampant among the sheep herds in the surrounding area. As was true generally, there was no known means for preventing sheep from becoming infected when grazing on what were viewed as the area's "tainted" or "cursed" fields. The immediate impetus for Koch to begin work on anthrax when he did in 1873 was the birthday present of a new microscope from his wife, Emmy Fraatz, who he had married right after passing his medical exams at Göttingen.

There were several important precursors to Koch's own work on anthrax that should be mentioned. First, in 1849 the German physician Aloys Pollender (1799–1879) observed the rod-shaped structures

of bacterial size in the blood of cows that had died of anthrax. Somewhat later in 1863, the French physician Casimir Davaine (1812–1882) demonstrated that these rod-shaped structures and the disease itself could be directly transmitted through blood inoculation from a diseased animal to one that was healthy. Because anthrax could also be acquired from contaminated soil, it was unclear that anthrax should be considered "contagious" in the usual sense of the word as a direct transmission from one animal to another. Because of this, a third prior fact of utmost importance to Koch was the demonstration by the German biologist Ferdinand Cohn (1828–1898) that some bacteria can change into a tough dormant endospore state. As noted below, Cohn would be the first person to whom Koch would show his work on the life history of *Bacillus anthracis*, the fundamental cause of anthrax.

Although the overriding abductive conjecture of a germ theory of disease may have provided a guiding framework for Koch's study of anthrax, it was the surprising observation that anthrax was infectious through the soil that lead Koch to a more immediate explanatory hypothesis. Specifically, if the life cycle of the *Bacillus anthracis* ultimately led to the formation of hardy dormant spores, then the transmission of anthrax could be explained through spores present in the soil. Also, respiratory anthrax in humans, commonly called woolsorter's disease, could be explained by people who sorted wool as an occupation, and accidentally inhaled anthrax spores from contaminated wool or hair.

Through a combination of careful microscopic study and culturing methods, such as through the use of the aqueous humor from cows' eyes and "hanging drops" in a concave microscope slide, Koch

was able to document the complete life cycle for *Bacillus anthracis*. From the rod-shaped structures first observed by Aloys Pollender in the blood of cows that had died of anthrax, to the same type of endospores seen by Ferdinand Cohn for another bacillus species, Koch could explain the various anomalies associated with anthrax. He was also the first to show that a specific microorganism could cause a specific disease in an animal; also, the disease transmission itself was the result of spores that regenerated into the disease.

Koch, wishing to publicize his work and have it confirmed by a knowledgeable biologist, wrote a letter to Ferdinand Cohn at the University of Breslau and offered to demonstrate what he had found. The humble letter that Koch wrote to Cohn is reproduced below (as given in the Thomas Brock biography of Robert Koch):

> Wöllstein (Province of Posen)
> 22 April 1876
>
> Honored Professor!
>
> I have found your work on bacteria, published in the *Beiträge zur Biologie der Pflanzen*, very exciting. I have been working for some time on the contagion of anthrax. After many futile attempts I have finally succeeded in discovering the complete life cycle of *Bacillus anthracis*. I am certain now, as a result of a large number of experiments, that my conclusions are correct. However, before I publish my work, I would like to request, honored professor, that you, as the best expert on bacteria, examine my results and give me your judgement on their validity. Unfortunately, I am not able to send you preparations which would show the various developmental stages, as I have not succeeded in conserving the bacteria in appropriate fluids. Therefore, I earnestly request that you permit me to visit you in your Institute of Plant Physiology for several days, so that I might show you the essential experiments. If this request is

> agreeable to you, perhaps you might inform me of a suitable time that I could come to Breslau.

Upon receiving Koch's letter, Cohn immediately agreed to his request for a visit, and set it for that very next Sunday. Koch loaded all the equipment, animals, and apparatus he would need for his demonstrations, and took an overnight train to Breslau. As an understatement, Koch's demonstrations were a spectacular success. For example, the director of the Institute, the well-known pathologist Julius Cohnheim (1839–1884), in relaying to his assistants what he had just seen in Koch's demonstrations, spoke excitedly as follows (as quoted by Thomas Brock):

> Now leave everything as it is, and go to Koch. This man has made a magnificent discovery, which, for simplicity and the precision of the methods employed, is all the more deserving of admiration, as Koch has been shut off completely from all scientific associations. He has done everything himself and with absolute completeness. There is nothing more to be done. I regard this as the greatest discovery in the field of pathology, and believe that Koch will again surprise us and put us all to shame by further discoveries.

After seeing Koch's various demonstrations, Cohn suggested that he publish a paper in Cohn's own journal, *Beiträge zur Biologie der Pflanzen*. Koch's famous anthrax contribution was completed within a month after his visit to Breslau. A redaction of this paper appears in an external Appendix as translated and shortened by Thomas Brock for his book, *Milestones in Microbiology (1546 to 1940)* (1961). What is not given are the magnificent drawings of the various stages in the life cycle of *Bacillus anthracis*.

* * *

On the basis of his work with anthrax, Koch was offered and took a position in 1880 as a staff member at the Imperial Health Office in Berlin. Very soon after his arrival, Koch began his first work on tuberculosis on August 18, 1881. Less than a year later on March 24 of 1882, Koch communicated his discovery of the tubercle bacillus in a lecture to the Berlin Physiological Society. This date of March 24 is still celebrated as World Tuberculosis Day; it is an annual commemoration intended to build public awareness about the global tuberculosis epidemic and the ongoing efforts to eliminate the disease.

One of the hallmarks of Koch's career and the reason he was singularly successful in identifying the causative agents for diseases such as tuberculosis, anthrax, and cholera, was his concomitant development of innovative research techniques and methods, ranging from those based on the most recent advances in microscope technology to various enhancements for the preparation and staining of bacteria so that observation of their cultures could proceed. Koch had a symbiotic relationship with the Carl Zeiss Microscope Company and was among the first to use the variety of advances that the company developed: an oil immersion lens, the Abbe light condenser, and various compound microscopes using more than a single lens. Koch also pioneered the development of photomicrographs taken through a microscope which allowed the individualistic drawings of bacteria to be replaced by actual photographic images.

The most significant technical advance pursued by Koch was the development of methods for growing pure bacterial cultures through the use of a solid medium. Previous to Koch's insight about need-

ing solid nutrient material, the liquids relied on to cultivate bacteria made it impossible to develop separate pure bacterial colonies – the different bacteria would merely grow into each other making it impossible to separate out individual bacterial species. The "surprising observation" that Koch made which led to his abductive conjecture that a solid medium was necessary to grow pure cultures was a chance observation that pure cultures could grow on sliced potatoes contaminated from the air. Separate and pure bacterial cultures would typically grow on the potato surface; moreover, each separate bacteria colony would typically have a distinct color making it easy to identify. The cultures would remain distinct until they eventually grew into each other and the whole potato simply rotted away.

Thomas Brock in his text, *Milestones in Microbiology*, gives a translation and redaction of the 1881 Koch paper that introduced his solid culture method (also called Koch's plate technique). This translation will be given in an external Appendix but it will be first introduced below by Brock's summary comments pertinent to this entry:

> Brock's summary comments on Koch 1881 paper on using a solid culture medium:
>
> If I had to choose one paper as most significant for the rise of microbiology, this would be it. Koch presented a method for isolating pure cultures that is so simple, reproducible and understandable that it could be performed by anyone. The development of this method led to the isolation and characterization, during the 20 years after 1881, of the causal organisms of all of the major bacterial diseases which affected mankind. So far as I know, it is not recorded how Koch happened to make his original observations of colonies developing on potato slices. But it could have easily happened that

> he observed them accidentally while performing other experiments. He already knew the importance of pure cultures ... and knew that methods for developing them must be worked out. Watching the colonies develop on potatoes, suddenly everything become clear. He had his method, so, as he says " ... the principle had been found, and it was only necessary to devise conditions which could be used in all cases." He had only to take his known liquid media and devise ways of making them firm and rigid. Koch saw the advantages that the use of solid media would have for research on infectious disease. These advantages are well outlined in the present paper. But in addition, he saw the implications of his technique for basic bacteriology, for the concept of speciation. It was obvious that different colonial forms developed on the solid media. These colonial forms bred true and could be distinguished from one another by their colony characteristics. They also differed microscopically and in temperature and nutrient requirements. Although Koch was trained as a physician, he realized that these forms met all the requirements that botanists and zoologists set up for the delineation of species. It seemed quite reasonable to him that each form was a separate species, or variety, or other suitable designation. This idea had met with resistance in the past, before it had been possible to culture bacteria on solid media and observe their colonial forms. After the present paper was published, such resistance disappeared quickly, because it was possible for all workers to observe the distinctiveness of various bacterial forms on solid media and convince themselves that they were really separate species. When only observations in liquid media were possible, it was not possible to shed light on the controversy. So Koch's method for solid media cultivation had a tremendous impact on the young science of bacteriology, as well as on the whole field of medicine.

One of the major advantages of having reliable solid culture media available was the possibility of then developing a standardized methodology to use in the study of disinfection and sterilization.

With the plate technique it was possible to "count germs" and place the whole endeavor on a quantitative basis. Koch made the needed distinction between sterilization, where there is a complete killing of both spores and vegetative cells, and disinfection where only the vegetative cells need removal. He studied sterilization with heat, steam, and hot air, and disinfection using a variety of chemicals including the carbolic acid favored by Lister. Koch found carbolic acid to not be very good, and identified several chemical alternatives that performed much better in eliminating the germs incurred during surgery as well as in wound infections more generally.

There are two advances to Koch's plate technique that should be noted. Both of these were carried out by assistants to Koch right after the solid media paper was published in 1881; they still represent current scientific bacteriology practice. This first advance was the use of the solid nutrient medium of agar as suggested by Koch's assistant, Walther Hesse (1846–1911), whose wife Frannie Hesse had been incorporating this material derived from red algae in her canning gels for jams and jellies. To this day, agar is a standard medium for cultures because of its higher melting temperature as compared to gelatin. The use of agar allowed microbes to be grown at higher temperatures without melting the containing nutrient medium. The second advance was from another of Koch's assistants, Julius Petri (1852–1921), who developed the eponymous Petri dish to hold the growth medium where cells could be cultured. It was typically a shallow cylindrical glass dish with a glass lid that contained the nutrient agar. It might be remembered here that the first antibiotic, penicillin, was discovered in 1929 when Alexander Fleming made the "surprising observation" and the ensuing abductive conjecture that

something in the mold contaminating a bacterial culture in a Petri dish had unexpectedly killed all the bacteria that were around it. The rest, as they say, is history.

* * *

Koch's clearly most famous bacterial identification was for the bacillus that produces tuberculosis. When Koch began his quest to identify its causative agent, tuberculosis was the reason behind one-seventh of all European deaths, a truly terrifying malady. It was definitely not a romantic disease as depicted in several well-known operas, such as for the character of Mimi in Puccini's La Bohème, but rather it was a disease that kills through individuals just wasting away. The actual causative agent for tuberculosis was incredibly difficult to isolate. It was very small, and much smaller than the anthrax pathogen Koch had worked with successfully. It also grew extremely slowly, and was difficult to stain so that it would be microscopically visible. It was Koch's unwavering faith in his abductive hypothesis of a parasitic cause for tuberculosis that allowed him to succeed where others had not.

Although Jean Villemin (1827–1892) had shown that tuberculosis was transmittable through direct inoculation in animals, the actual causative agent had not been seen even microscopically. The key to Koch being able to stain the tubercle bacilli a beautiful blue and make it visible was due to the usual dye of methylene blue absorbing ammonia from the laboratory environment. The abductive reasoning followed here by Koch is remarkable: first, Koch noticed the "surprising failure" of a new solution of methylene blue to stain the tubercle bacillus even though an older solution had. He then hypothesized

that this was due to a lack of absorbed ambient ammonia in the newly prepared methylene blue.

The story of this crucial staining discovery is reported by Koch's assistant, Friedrich Loeffler (1852–1915), in remembrances published in 1907. A translated version of this relevant section from Brock's biography of Koch is given in an external Appendix.

* * *

As all beginning microbiology students learn, Koch's postulates refer to four criteria for establishing a causal relationship between a specific microbe and a specific disease. Although Koch's name is now typically the only one attached to these conditions, several other individuals did significant work in their initial formalization including Koch's assistant, Friedrick Loeffler (1852–1915), and especially Koch's old pathology teacher at Göttingen, Jacob Henle (1809–1885). Koch's publication of these postulates appeared in 1884 in the context of identifying the causal agents for anthrax and tuberculosis (parts of this paper are given in an external Appendix).

Koch's four postulates were used implicitly in his first paper in 1882 on the etiology of tuberculosis. These can be succinctly stated as follows:

1) The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms.

2) The microorganism must be isolated from a diseased organism and grown in a pure culture.

3) The cultured microorganism should cause the disease when introduced into a healthy organism.

4) The microorganism must be reisolated from the inoculated and diseased experimental host and identified as being the same as the original causative agent.

Koch's staining technique for observing the actual tubercle bacillus is particularly crucial for the satisfaction of postulates 1 and 4; his pure culture methods are central for postulate 2; and the availability of an animal model such as the guinea pig is needed for postulates 3 and 4. Using the guinea pig as an animal model, the induction of tuberculosis can be done through direct inoculation, or alternatively through the air. In considering postulates 3 and 4, Koch gave this additional proof of respiratory contagion by pumping tubercle bacilli mist into boxes that contained various animals, including the preferred guinea pigs.

Some three weeks after giving a famous lecture to the Berlin Physiological Society, Koch published his first paper on the etiology of tuberculosis. A translated and redacted version is given in an external Appendix as provided by Thomas Brock in his text, *Milestones in Microbiology*. Note that Koch attached great importance to his innovative staining strategy and to the use of solid coagulated blood serum to grow pure cultures of the tubercle bacillus. The test tubes that held the blood serum were creatively tilted to provide the largest possible solid surface area for the very slow growing pure cultures to develop.

* * *

Although Koch's postulates worked as a set of sufficient conditions for identifying the causal bacterial agents for tuberculosis and anthrax, they do not provide a universal set of necessary conditions

that are applicable for showing the definitive causal mechanisms for all infectious diseases. For example, considering postulate 1, the disease agent might be a virus and too small to be seen in abundance under standard microscopic conditions. Also, there are certain diseases that may be carried by asymptomatic individuals; for example, see the discussion of Typhoid Mary in the chapter on William Budd. For postulate 2, it may be impossible to grow a causative agent such as a virus in a pure culture. And finally, for postulates 3 and 4, there may not be an animal model for the disease, and human experimentation is generally considered unethical. Some discussion of this last point is given in the chapter on Carlos Finlay and the background story of yellow fever transmission in the work of Walter Reed in Cuba.

* * *

Robert Koch is typically given credit for the discovery of the bacillus causing cholera, *Vibrio cholerae*, when he directed a German commission formed in 1883 to investigate a cholera outbreak then occurring in Egypt. Although never referenced in Koch's writing, both the epidemiological writings of John Snow on the mode of cholera transmission and Filippo Pacini's microscopic identification in 1854 of the comma-shaped bacterium responsible for cholera are obvious precedents to Koch's work; they probably should have been acknowledged more directly.

Koch's commission set up a research operation at the Greek Hospital in Alexandria, Egypt. As Pacini had seen many years earlier, the comma-shaped bacillus was clearly visible in the intestinal tissues of patients suffering from the usual clinical signs of cholera. Unfor-

tunately, and despite carrying out many different animal inoculation studies, no animal model for the disease could be found. Also, at this time all attempts to develop pure cultures of the microorganism failed. Given the implicit emphasis on proving disease causality through the use of Koch's postulates, the commission was unable to do so in Alexandria.

The cholera epidemic waned in Egypt soon after the German commission arrived, depriving Koch's research team of readily available cholera patients for study. Koch received permission to continue on to Calcutta, India, the presumed ancestral home for cholera in the Ganges Delta. Arriving in December of 1883, and given the ready availability of fresh material, Koch and his assistants had produced pure cultures of cholera within several days of arrival. Nevertheless, because no animal model could be developed, the usual route to showing disease causality for cholera through Koch's postulates was cut off. So, just as Snow had done many years before the Koch commission came to work in India, an epidemiological approach had to be taken to reinforce the possible causal connections between the identified comma-shaped bacillus and cholera itself. Much of this work involved Indian water "tanks." We quote from a particularly telling paragraph in Brock's biography of Koch as it related to these Indian water storage devices:

> Pasteur was also skeptical that Koch had isolated the cholera pathogen ... However, this skepticism was mild compared to that of others. Consider the title of the following book, published [ten] years after Koch's work: *Robert Koch's comma bacillus is not the cause of cholera. Judgement of an East Indian doctor on the etiology of cholera*
>
> Such skeptics, however, were in the minority, and Koch's work

> became widely accepted, despite the failure of all animal inoculation studies. Koch turned to epidemiological analysis, which not only gave strong evidence that the comma bacillus was the cause of cholera, but cast important insight into the vehicle by which the pathogen was carried to humans — drinking water. Observations of the connection between cholera and the use of drinking water were made from studies of the so-called Indian "tanks." ... These tanks served as water storage in many parts of India. They were large square basins which the inhabitants used not only as sources of drinking water, but for bathing and washing clothes. Even the soiled clothes of cholera victims (ripe with fresh bacteria) were washed in these tanks. In one particular tank, [seventeen] cholera deaths were attributed by the Commission to the introduction into the tank of cholera bacteria derived from the clothes of a single cholera patient. The comma bacillus could be cultured from this tank, and the relationship of this tank to the particular cholera epidemic was thus clarified. This study is reminiscent of John Snow's famous study of the cholera epidemic associated with the Broad Street Pump in London. Interestingly, in none of Koch's or Gaffky's [Koch's assistant] writings on cholera is John Snow or his work (published in the 1850s) mentioned, despite the important parallels.

Robert Koch published in 1893 an epidemiological study of a cholera outbreak in 1892–3 that was centered in the bordering cities of Hamburg, Altona, and Wandsbeck. A particularly "surprising observation" made by Koch was that although Hamburg and Altona both received their water from the polluted Elbe, the cholera outbreak was restricted to Hamburg, with no cases appearing in Altona. The resulting abductive hypothesis that Koch evaluated concerned the differing water filtration systems each city had or didn't have. As a fully sovereign city-state until the unification of Germany in 1871,

Hamburg had no filtration of water taken from the Elbe as of the 1892 cholera epidemic. On the other hand, Altona as part of the Kingdom of Prussia had an excellent sand filtration system installed in 1859. The first part of Koch's extensive paper on *Water-filtration and Cholera* is given in an external Appendix as translated by George Duncan and published in 1895. This epidemiological gem reinforces both the causative role that the comma-shaped cholera bacillus plays in producing cholera and the important role that filtration can have in removing the contaminating bacteria from the water.

* * *

One of the more "surprising" observations about infectious diseases are the not infrequent occurrences of new cases of a disease in individuals known to have had no direct contact with previous instances. Or, relatedly, the complete absence of new cases among individuals who have undergone such exposure. Abductive explanations for these two phenomena can be given using the interrelated concepts of acquired immunity and that of an asymptomatic disease carrier. In the chapter on Carlos Finlay and yellow fever, there is a discussion of African slaves in Haiti revolting against the occupying French. The Haitian natives were immune to yellow fever ever since childhood whereas the French forces sent to subdue the rebellion were not. The devastation incurred by the French led directly to Haiti's independence from France, and indirectly to the Louisiana Purchase which allowed the French to escape any further conflict in the Western Hemisphere. In the chapter on William Budd there is the story of Typhoid Mary who besides having an acquired immunity to typhoid was also able to transmit the disease — a classic case of

an asymptomatic disease carrier.

As just noted, an earlier chapter on William Budd included a side story about Mary Mallon (Typhoid Mary) who was the first asymptomatic carrier of typhoid bacilli identified in America. Mary Mallon was finally tracked down and caught by the American sanitation engineer, George Soper. Soper had just read a 1902 paper published by Koch using data on asymptomatic typhoid carriers around the German city of Trier. Because there is no animal reservoir for typhoid, Soper used this fact and Koch's notion of an asymptomatic carrier to abductively conjecture that it was the now missing cook, Mary Mallon, who was the cause of the typhoid outbreak he was investigating on Long Island.

Besides asymptomatic typhoid carriers having an acquired immunity to the disease, Koch showed that such carriers also existed for both malaria and cholera. In December of 1900, Koch arrived in German New Guinea as part of an expedition to this protectorate of the German Reich. Koch, in examining the indigenous Papuan people, noticed that their blood contained *Plasmodium* parasites, the cause of malaria, although any manifestations of the disease itself were absent. In other words, the Papuan population were asymptomatic carriers of malaria and served as reservoirs for the disease. When German settlers and the Chinese workers arrived in New Guinea, they immediately fell sick having no such acquired immunity.

Koch's earliest development of a carrier state concept for asymptomatic individuals occurred for cholera during the epidemic that raged in Hamburg in 1892 to 1893. His monograph, *The Cholera in Germany During the Winter of 1892–93*, was translated by George Duncan and published 1895 along with Koch's paper on

Water-Filtration and Cholera, discussed earlier. Several parts of this monograph are given in an external Appendix that develop this concept of a carrier state for cholera. Again, because there is no animal reservoir for the disease, asymptomatic carriers are generally the source of new cholera outbreaks.

One of the noteworthy differences between the work of Pasteur and Koch was the emphasis on matters of public hygiene for Koch. Thus, for Koch the control of outbreaks of cholera and typhoid were of utmost concern, along with the public availability of clean drinking water. He emphasized the importance of asymptomatic disease carriers, the sterilization of items such as clothes and bed sheets for individuals sick with the various infectious maladies he studied, and preventing the spread of the tuberculosis bacillus by curtailing public spitting. Koch generally held positions that explicitly involved public hygiene whereas Pasteur's research institute was funded through vaccine production for individuals, particularly for rabies.

* * *

Koch was appointed Professor of Hygiene and Director of the Hygiene Institute at the University of Berlin in 1885. Given his new administrative and lecturing responsibilities, Koch put his own research program on hold until late in 1889. At that time, Koch turned his research efforts to finding an actual cure for tuberculosis in an extract of a pure culture of the tubercle bacillus that he called tuberculin. When injected subcutaneously this substance brought about a remarkable immune response in guinea pigs infected with tuberculosis. Unfortunately, Koch misinterpreted this delayed type of hypersensitivity as a "cure" for the disease itself.

The Tenth International Congress of Medicine was held in Berlin in August of 1890. Because of high-level governmental pressure to announce something spectacular, Koch unfortunately implied in his lecture that he had found a "cure" for tuberculosis. What he had actually identified was later called the Koch phenomenon — a hypersensitive reaction or immune response in an organism that had a previous tuberculosis infection. Although this reaction was useless as a cure, it would later have some diagnostic value in detecting tuberculosis in individuals.[1]

In his biography of Koch, Thomas Brock gives the following words (in translation) that Koch actually said to the Congress:

> [after long study of many chemicals] I have at last found substances which both in the test-tube and in the living body prevent the growth of the tubercle bacilli. All such investigations ... are very exhausting and slow, and my experiments with these substances, though lasting more than a year, are not yet concluded, so that all I can say at present is that if guinea pigs are treated they cannot be inoculated with tuberculosis, and guinea pigs which already are in the late stages of the disease are completely cured, although the body suffers no ill effects from the treatment. From these experiments I will draw no other conclusion at present than that it is possible to render pathogenic bacteria within the body harmless without ill effect on the body itself.

This announcement caused a massive invasion of Berlin by thousands of tuberculosis patients and physicians, all seeking a small amount of tuberculin for use in curing active cases of tuberculosis,

[1]The current author can personally attest to this sensitivity because he reacts positively to a tine test that uses a relative of tuberculin. The author's mother had tuberculosis in the early 1900s; and because of this, the author has what is called latent tuberculosis and will test positive without having an active case of the disease itself.

either in themselves or for their patients. Unfortunately, a large-scale clinical trial carried out by the German government resulted in a damning report issued in late 1881 that tuberculosis was not cured with tuberculin. This report led to a precipitous decline in Koch's scientific reputation and stature.

After the release of the negative report on the curative effects of tuberculin, Koch's scientific research program was in shambles. He left for an extended Egyptian vacation, and refused to return until the Prussian government had appropriated an operating budget for a new institute. Eventually, an agreement was reached for a new Institute of Infectious Diseases, which opened in 1900 with Koch as its director. After his death, it was renamed the Robert Koch Institute. It might be noted that during the Third Reich the Institute took part in several atrocities committed in the name of national socialism, including some disastrous experiments into typhus vaccines at the Buchenwald Concentration Camp in 1941.

Besides being hampered with a floundering research effort in the early 1890s, Koch's personal life was also in disarray. He divorced his first wife, Emmy, in 1893 and married a twenty-year-old art student, Hedwig Freiberg, who was thirty years his junior. In the years just before the turn of the century, Koch along with his second wife made numerous trips to Africa to study cattle diseases for both the British and German governments. Koch also traveled to India to study the plague, and to Italy for malaria.

Koch retired from government service in 1904 but was to be involved in one last controversy, discussed in the next section, concerning the identity/nonidentity of bovine and human tuberculosis, and of their differential importance to human health.

* * *

Theobald Smith (1859–1934), who is highlighted in a separate chapter for his work on the transmission of Texas cattle fever through ticks, published an extensive comparative study of the bovine and human tuberculosis bacillus in 1898. He concluded that (1) the two bacilli were different, (2) the human bacillus cannot infect cattle, but (3) the cattle bacillus may infect humans because it is highly pathogenic. In the early 1900s, Koch conceded that the two bacilli were different but argued that the bovine bacillus was not dangerous and of no health concern — and therefore there was no need to pay any special medical attention to it. To the contrary, and through the work of Smith and others at the time, there was evidence that bovine tuberculosis could be transmitted through infected meat and milk and was especially dangerous to children. All of the various milk pasteurization efforts and meat inspection laws from the early 1900s are a direct contradiction to Koch's contention that bovine tuberculosis wasn't dangerous. He obstinately restated this misguided view as late as 1908 at the Washington Congress on Tuberculosis.

In assessing Koch the scientist and his work, his biographer, Thomas Brock, provides some summary comments that are pertinent to this last controversy about the importance of bovine tuberculosis and public health:

> In the early years, many people had trouble repeating Koch's work. He was vilified and castigated; his veracity was doubted. In certain circles he was attacked with a passion. This is the lot of the true pioneer. His unruffled exterior belied the fact that Koch took these criticisms hard. It was not Koch's fault, or course, that his work could not be repeated, but the fault of his critics. Koch's cer-

tain knowledge that his critics were wrong led him to become combative and hostile. He was exceedingly opinionated and unyielding when his own ideas were attacked. Although in his youth he had been generally correct, in later years he was sometimes wrong, although unable or unwilling to admit it. During the tuberculin work, he was so beleaguered that he left Germany to avoid criticism. And his erroneous ideas about bovine tuberculosis were not only pigheaded, they were dangerous, being responsible for a serious delay in the introduction of appropriate control methods for tuberculosis in cattle, a bad breach of the public health.

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Chapter 8

Joseph Lister

> I like to think of Lister, with his courtly manners and indomitable courage, as one of the knights of older times sallying out single-handed to find and destroy a formidable enemy, armed with a great but imperfect generalization, or rather, working hypothesis, and a bottle of crude carbolic acid so impure that he tells us in his first paper that carbolic acid was insoluble in water. He had never seen his enemy but he saw his ravages on every hand; he did not know how he acted in producing diseases; he did not know where he lived or how he lived. ... All that he cared for or needed to know was that he had a terrible enemy who, however, probably had his vulnerable point, and that the gain was so great, if the battle were won, that it was well worth while to devote his whole mind and his whole energies and his whole life to the solution of the problem.
>
> – Sir William Watson Cheyne (*Lister and His Achievement* (1925))

> Success depends upon attention to detail.
>
> – Joseph Lister (1827–1912)

Medical surgery as practiced throughout the first half of the Nineteenth Century was a dismal undertaking due to its main attributes of immediate and incredible pain commonly followed by life-threatening infection. The introduction of ether and chloroform anesthetics in the middle of the Nineteenth Century alleviated the pain of surgery but

the threat of serious and often fatal infection remained. These so-called septic diseases were of several types: blood poisoning (pyaemia or septicemia); hospital gangrene that formed in dead tissue resulting from blood flow stoppage; and various skin infections caused by Streptococcal bacteria (erysipelas or St. Anthony's Fire). It was through the work of the individual to whom this chapter is devoted, Joseph Lister (1827–1912), that the infection issue was finally solved during the latter half of the Nineteenth Century through what can be called the Antiseptic Principle. After Lister, no longer would the often heard expression, "the operation was a success but the patient died," be so universally applicable.

As Professor of Clinical Surgery at University College Hospital in London, Robert Liston (1794–1847) performed on December 21, 1846, the first public operation in Europe that utilized the modern anesthetic of ether. As it so happened, Joseph Lister was a student at University College London at the time and was in the audience witnessing this first public surgical operation under anesthesia. Until then the skill of a surgeon was measured primarily in terms of speed, and Liston was a champion registering completed amputations in under two and a half minutes. Several possibly apocryphal stories have come down about Liston's legendary skill. Once he mistakenly cut off a patient's testicles along with a leg that was to be amputated. Another tale involving Liston was that because he was moving so quickly during a surgical procedure he took off a surgical assistant's fingers as he cut through a leg, and then during an instrument switch, slashed a spectator's coat. Legend has it that both the patient and surgical assistant died of ensuing wound infections and the spectator was so frightened that he had been stabbed, he instead died of shock.

This medical disaster is said to be the only known surgical procedure in history to have had a three hundred percent mortality rate.

* * *

As noted above, the main figure for this chapter is Joseph Lister (1827–1912), considered to be a father of modern surgery for his development of the Antiseptic Principle, designed to avoid the fatal complications from infection commonly attendant to major surgeries. The well-known mid-twentieth century historian of medicine, Douglas Guthrie, has gone so far as to call Lister, "the greatest surgeon of history." The Antiseptic Principle itself involved constructing some type of antiseptic barrier that prevented germs responsible for an infection from entering a wound. Anesthesia eliminated the issue of pain in the performance of a surgery; the Antiseptic Principle was intended to prevent infections from occurring after completion of a major surgical procedure.

Joseph Lister was born in April of 1827 into a prosperous and educated Quaker family in the village of Upton, Essex, now part of London proper. Lister's father, Joseph Jackson Lister, was a successful wine merchant and gentleman scientist. He was, for example, the designer of an innovative achromatic lens for use in compound microscopes; for this work Joseph Jackson Lister was elected to the Royal Society in 1832. Clearly, Lister's father was to be a continuing influence on his son's interests in natural science and microscopy, as well as on his eventual pursuit of a career in medicine as a surgeon.

Lister attended private primary and secondary Quaker schools before enrolling in the non-sectarian University College London in 1844. Because Lister was a Quaker, he was barred from enrolling at either

Oxford or Cambridge, which were both restricted at the time to individuals belonging to the Church of England. Before beginning his actual medical studies, Lister obtained a mandatory Bachelor of Arts degree in 1847. As noted earlier, it was during this period in 1846 that Lister witnessed the first operation of a limb amputation done by Robert Liston under the anesthetic of ether. Lister began his formal medical studies in 1848, and as part of his required clinical study, became a house surgeon (that is, a "dresser") to the well-known surgeon, John Erichsen (1818–1896). It was during the period Lister worked for Erichsen that his interests developed as to why infections occurred and how wounds healed.

After graduating with a Bachelor of Medicine degree in 1852, and on the advice of his professor of physiology, William Shapley (1802–1880), Lister went north to Edinburgh for a supposedly short visit with Shapley's close friend, James Syme (1799–1870), who at that time was considered one of the best surgeons in the United Kingdom. As it turned out, Lister spent some seven years in Edinburgh, working first as an assistant to Syme and later as Assistant Surgeon in the Edinburgh Royal Infirmary. During this same period, Lister married Syme's oldest daughter, Agnes; she would become Lister's close research assistant (and amanuensis) for the rest of her life.

In 1860, Lister was appointed to the Regius Professorship of Systematic Surgery at the University of Glasgow; in addition, a few years later in 1862 he became a practicing surgeon to the Glasgow Royal Infirmary. It was in Glasgow during the short two-year period from 1865 to 1866 that antiseptic methods were first developed and used by Lister in treating patients. As noted in detail later, Lister's first publications on the Antiseptic Principle appeared in 1867 based on

patient cases from the Glasgow Infirmary.

In his formulation of the Antiseptic Principle, several sets of "surprising" observations were available to Lister that led indirectly to the central abductive conjecture that "germs" present in the surrounding atmosphere and environment were somehow able to enter a wound causing infection and suppuration [pus formation]. One such general observation concerned wound infections that seemed almost inevitable and prevalent on hospital wards having patient beds close together, or where one patient would also become infected when bedded next to another with an existing infected wound. Something morbid seemed to be present in these wards that was capable of transmittal from one patient to another.

Another set of more specific but still "surprising" observations were the drastically different infection outcomes present in simple versus compound fractures. In a compound fracture where broken bones were openly exposed to the surrounding air and environment, serious infection was common and often required limb amputation. In contrast, a simple fracture with no breaking of the skin typically led to healing with no further complications from infection.

An additional set of observations suggested that it was not just the air responsible for infection. When a puncture of the lung occurred from a fractured rib, atmospheric air was introduced in abundance but no inflammation typically ensued. An external wound, however, that actually penetrated the chest and remained open to the air, generally did lead to dangerous suppuration.

In a related manner there were very different and lower rates of infection when surgeries were performed in a home as compared to a hospital. Even though open wounds in both homes and hospitals

were subject to the same general type of surrounding air, hospitals were generally places of greater filth and uncleanliness, and as we now know, places rife with a greater number and type of dangerous germs able to contaminant open wounds done surgically or through an injury such as a compound fracture. The situation was so bad that the term "hospitalism" was coined for the infections and diseases that appeared to result from merely being present and treated in a hospital. Contemporary suggestions were even made that all hospitals should be temporary and periodically destroyed and rebuilt.

Lister also noted that survival chances seemed to be better when wounds were cauterized, suggesting that there was something in the wound itself that could be destroyed through the burning of the skin and flesh present in and around an open wound. This is similar to the treatment of wounds by using maggots to remove damaged tissue and contaminating bacteria. Wound debridement carried out in this way supposedly helped the growth of healthy tissue and reduced complications resulting from infection.

It was a Glasgow colleague's suggestion that eventually led to Lister's abductive conjecture of germs being present in the surrounding environment and somehow entering an open wound that was the cause of serious infection. In the spring of 1865 during a walk with Lister, a professor of chemistry at Glasgow, Thomas Anderson, suggested that Lister consult some of the recent work of the French chemist Louis Pasteur. Lister proceeded to read (in the original French, by the way) Pasteur's work on fermentation and putrefaction, spontaneous generation, and food spoilage that could occur in the absence of oxygen (anaerobically) as long as micro-organisms were present. As might be said in a biblical sense, the scales quickly

fell from Lister's eyes.

After reading Pasteur's published research papers up to the middle 1860s, Lister replicated for himself much of Pasteur's research on fermentation and spontaneous generation using many of the same flask techniques Pasteur pioneered. At the same time, Lister experimented at the Glasgow infirmary with the antiseptic of carbolic acid and how he could keep serious infection under control through a careful regimen of initial wound cleansing followed by antiseptic dressings that would prevent any additional germs from entering. As can be seen in some of Lister's first publications on his successes in infection control at the Glasgow infirmary, Lister almost single-handedly provided the pillar of antisepsis, which alongside the use of anesthesia led to the successful development of modern surgery.

Lister's first publications on the Antiseptic Principle appeared in 1867 in the *Lancet*. Part of the beginning of this series is given below. Note, in particular, the comments about simple versus compound fractures; the work of Pasteur on fermentation and putrefaction; the distinction between a rib penetrating the chest or not; the use of carbolic acid to first kill germs that may already be present in an open wound and then as part of later dressings to prevent any additional germs from entering the wound. Most of this first *Lancet* article is devoted to some dozen applications of the Antiseptic Principle to compound fractures. Only the first of these cases is actually reported below — the famous instance of an eleven year-old boy, James Greenlees, in August of 1865:

> ON A NEW METHOD OF TREATING COMPOUND FRACTURE, ABSCESS, ETC.
>
> WITH OBSERVATIONS ON THE CONDITIONS OF SUPPURA-

TION

BY JOSEPH LISTER, PROFESSOR OF SURGERY IN THE UNIVERSITY OF GLASGOW

ON COMPOUND FRACTURE

The frequency of disastrous consequences in compound fracture, contrasted with the complete immunity from danger to life or limb in simple fracture, is one of the most striking as well as melancholy facts in surgical practice.

If we inquire how it is that an external wound communicating with the seat of fracture leads to such grave results, we cannot but conclude that it is by inducing, through access of the atmosphere, decomposition of the blood which is effused in greater or less amount around the fragments and among the interstices of the tissues, and, losing by putrefaction its natural bland character, and assuming the properties of an acrid irritant, occasions both local and general disturbance.

...

Turning now to the question how the atmosphere produces decomposition of organic substances, we find that a flood of light has been thrown upon this most important subject by the philosophic researches of M. Pasteur, who has demonstrated by thoroughly convincing evidence that it is not to its oxygen or to any of its gaseous constituents that the air owes this property, but to minute particles suspended in it, which are the germs of various low forms of life, long since revealed by the microscope, and regarded as merely accidental concomitants of putrescence, but now shown by Pasteur to be its essential cause, resolving the complex organic compounds into substances of simpler chemical constitution, just as the yeast plant converts sugar into alcohol and carbonic acid.

A beautiful illustration of this doctrine seems to me to be presented in surgery by pneumothorax with emphysema, resulting from puncture of the lung by a fractured rib. Here, though atmospheric

air is perpetually introduced into the pleura in great abundance, no inflammatory disturbance supervenes; whereas an external wound penetrating the chest, if it remains open, infallibly causes dangerous suppurative pleurisy. In the latter case the blood and serum poured out in the pleural cavity, as an immediate consequence of the injury, are decomposed by the germs that enter with the air, and then operate as a powerful irritant upon the serous membrane. But in case of puncture of the lung without external wound, the atmospheric gases are filtered of the causes of decomposition before they enter the pleura, by passing through the bronchial tubes, which, by their small size, their tortuous course, their mucous secretion, and ciliated epithelial lining, seem to be specially designed to arrest all solid particles in the air inhaled. Consequently the effused fluids retain their original characters unimpaired and are speedily absorbed by the unirritated pleura.

Applying these principles to the treatment of compound fracture, bearing in mind that it is from the vitality of the atmospheric particles that all the mischief arises, it appears that all that is requisite is to dress the wound with some material capable of killing these septic germs, provided that any substance can be found reliable for this purpose, yet not too potent as a caustic.

In the course of the year 1864 I was much struck with an account of the remarkable effects produced by carbolic acid upon the sewage of the town of Carlisle, the admixture of a very small proportion not only preventing all odour from the lands irrigated with the refuse material, but, as it was stated, destroying the entozoa which usually infest cattle fed upon such pastures.

My attention having for several years been much directed to the subject of suppuration, more especially in its relation to decomposition, saw that such a powerful antiseptic was peculiarly adapted for experiments with a view to elucidating that subject, and while I was engaged in the investigation the applicability of carbolic acid for the treatment of compound fracture naturally occurred to me.

...

Carbolic acid proved in various ways well adapted for the purpose. It exercises a local sedative influence upon the sensory nerves; and hence is not only almost painless in its immediate action on a raw surface, but speedily renders a wound previously painful entirely free from uneasiness. When employed in compound fracture its caustic properties are mitigated so as to be unobjectionable by admixture with the blood, with which it forms a tenacious mass that hardens into a dense crust, which long retains its antiseptic virtue, and has also other advantages, as will appear from the following cases, which I will relate in the order of their occurrence, premising that, as the treatment has been gradually improved, the earlier ones are not to be taken as patterns.

Case I. — James G, aged eleven years, was admitted into the Glasgow Royal Infirmary on August 12th, 1865, with compound fracture of the left leg, caused by the wheel of an empty cart passing over the limb a little below its middle. The wound, which was about an inch and a half long, and three-quarters of an inch broad, was close to, but not exactly over, the line of fracture of the tibia. A probe, however, could be passed beneath the integument [outer protective layer] over the seat of fracture and for some inches beyond it. Very little blood had been extravasated [forced out] into the tissues.

My house-surgeon, Dr. Macfee, acting under my instructions, laid a piece of lint dipped in liquid carbolic acid upon the wound, and applied lateral pasteboard splints padded with cotton wool, the limb resting on its outer side, with the knee bent. It was left undisturbed for four days, when, the boy complaining of some uneasiness, I removed the inner splint and examined the wound. It showed no signs of suppuration, but the skin in its immediate vicinity had a slight blush of redness. I now dressed the sore with lint soaked with water having a small proportion of carbolic acid diffused through it; and this was continued for five days, during which the uneasiness and the redness of the skin disappeared, the sore meanwhile furnishing no pus, although some superficial sloughs caused by the

acid were separating. But the epidermis being excoriated by this dressing, I substituted for it a solution of one part of carbolic acid in from ten to twenty parts of olive oil, which was used for four days, during which a small amount of imperfect pus was produced from the surface of the sore, but not a drop appeared from beneath the skin. It was now clear that there was no longer any danger of deep-seated suppuration, and simple water-dressing was employed. Cicatrisation [scarring] proceeded just as in an ordinary granulating sore. At the expiration of six weeks I examined the condition of the bones, and, finding them firmly united, discarded the splints; and two days later the sore was entirely healed, so that the cure could not be said to have been at all retarded by the circumstance of the fracture being compound.

This, no doubt, was a favourable case, and might have done well under ordinary treatment. But the remarkable retardation of suppuration, and the immediate conversion of the compound fracture into a simple fracture with a superficial sore, were most encouraging facts.

...

Parts of two other early publications from Lister are given in an Appendix external to this chapter. One is a paper read at a British Medical Association meeting in Dublin (August 6, 1867) on the Antiseptic Principle in the practice of surgery. The second is a *Lancet* article that appeared in 1870 on the effects of the antiseptic system on the health of a whole surgical hospital (the Royal Infirmary in Glasgow).

* * *

William Ford (1871–1941) was a well-known Professor of Bacteriology at Johns Hopkins University in the early part of the Twentieth Century. Writing in *The Scientific Monthly* in 1928 (a precursor

publication to *Science*), Ford provided a cogent review of Lister's contributions in his article, *The Bacteriological Work of Joseph Lister*. A few parts of this article are given below that pertain to Lister's development of the Antiseptic Principle. The first point is about Lister's (abductive) conjecture that germs are the cause of suppuration and putrefaction in the human and animal body:

> His merit lies in his vision. He saw that if Pasteur was right about the causation of fermentation and putrefaction in flasks of nutrient material a similar principle might hold for the putrefaction of the tissues. In just the same way as dust laden with bacteria dropped upon the surface of the fluids, so might bacteria drop on the surface of wounds. Furthermore, if this were the explanation of the putrefaction of wounds, two things were necessary to prevent it. First, the bacteria already in the wound must be killed, and second, a dressing must be applied which was free from organisms and impregnated with substances which would destroy any bacteria which might further be deposited. *We have here, it seems to me, one of the most beautiful examples of reasoning by analogy and a striking incident in which a pure hypothesis led to fundamental changes in our entire conceptions.* (italics added) For it must be remembered that at the time Lister studied and confirmed Pasteur's work and applied it to surgery not a particle of convincing evidence had been brought that bacteria are the cause of suppuration and putrefaction in the animal body, and one might even go further and say that no convincing evidence had thus far been presented that bacteria are the cause of disease. For this period in Lister's work may be roughly placed before 1870, six years before Koch proved that the anthrax bacillus is the cause of splenic fever.

A second point emphasized by Ford is that Lister did not confine his conjecture to germs being present only in the atmosphere. He believed that germs could gain entrance from other sources around

a patient — for example, from the patient's skin or that of the operating surgeon, or from the surgical instruments used or dressings applied. In fact, Lister's development toward aseptic (that is, sterile) surgical practice as opposed to relying just on chemical antiseptics led to his abolishing the use of a carbolic acid spray in the air around a patient. Lister came to view the air itself as a relatively unimportant source of germs that might lead to infection:

> A word or two should now be said about a much debated point. Impressed by Pasteur's work on fermentation and putrefaction, Lister regarded the atmosphere as the source of danger to open wounds, believing that bacteria were carried to them with particles of atmospheric dust. It should be noted, however, that from the very first Lister believed that bacteria might gain entrance to wounds from several other sources, chiefly from the skin of the patient, the hand of the operating surgeon, his instruments and the dressing applied. So we find him rapidly developing a technique for the disinfection of the skin, the cleansing of the hands, the sterilization of instruments and the preparation of bacteria-free dressings impregnated with substances capable of destroying micro-organisms. As was to be expected, he placed chief reliance on carbolic acid for this purpose. Later Lister's ideas changed as to the source of the bacteria which brought about putrefaction. He was eventually convinced that the bacteria of the air are harmless, calling definite attention to this at the London Medical Congress in 1881 and confirming it at the Berlin Congress in 1890. He therefore abandoned his complicated apparatus for spraying the atmosphere with carbolic acid. The main thesis that bacteria are the cause of the suppuration and putrefaction of tissues Lister never doubted, despite the opposition of many of his colleagues and despite the fact that as surgical technique improved and surgical bacteriology developed, successful results were obtained by other methods. It must be admitted that carbolic acid, used in such quantities as made necessary by

> Lister's original methods, was a dangerous agent and attacks of haemoglobinurea were not uncommon in a surgeon, after a long operation in which his hands were frequently immersed in strong solutions, or after a day spent in the atmosphere of carbolic acid produced by Lister's spray. On one occasion indeed Lister was invited to examine the work of one of his colleagues who had gotten brilliant results without employing carbolic acid. His comment is interesting. He admitted that the results of the other surgeon were as good as his own but he said that while "I do not understand the matter thoroughly, I will never abandon the thesis that bacteria are the cause of putrefaction in wounds and that their entrance must be prevented."

Finally, Ford comments on Lister's experimental tests of the germ theory hypothesis for infection. Here, the explicit experimental work of Robert Koch in 1878 is reviewed on first growing in pure culture the offending bacteria taken from suppurating wounds and then inoculating an animal with the septic material. The infections resulting in the animals based on this procedure provided the type of definitive experimental proof needed for verification of Lister's initial abductive conjecture:

> During the course of Lister's observations on the disinfection of wounds and the perfection of his technique he controlled his work constantly with his microscope, studying his tissues and looking for micro-organisms. One might ask at this point why Lister did not attempt to bring satisfactory experimental proof of his thesis by the inoculation of animals with septic material. Koch did. As soon as Koch learned to handle bacteria and was satisfied that he could obtain them in pure culture, he took material from suppurating wounds, inoculated animals and produced infections. Koch's paper on Wundinfectionskrankheiten [wound infection diseases], published in 1878, brought final proof of the relationship of bacteria to surgical infections and is one of our great classics in bacteriology. The

> answer to the question I have just raised is found in Lister's own words. As he said, the daily observation, carried out over long years, that micro-organisms are always present in suppurating wounds and are not to be found in wounds healing without suppuration, was far more convincing to him than any amount of experimental work on animals. Lister did, however, carry out several procedures which in the main established his thesis experimentally. Thus he obtained blood from animals under antiseptic precautions and succeeded in keeping it free from putrefaction indefinitely. Portions of this sterile blood he now exposed to the atmosphere, noting the decomposition which followed. Bits of this septic material were now transferred to his sterile blood and characteristic putrefaction promptly ensued. Lister also produced suppuration in animals. In his attempts to devise methods for the suturing of blood vessels, he cut down on the larger arteries, tied off short segments and introduced small glass canulas [tubes] containing putrefactive products. The subsequent spread of the suppuration Lister noted with care and interest.

In a short final summary Ford provided three main conclusions that could be made about Lister's bacteriological work:

> So much for the bacteriological aspects of Lister's work on wounds from which we may draw three main conclusions. Lister was the first to establish the thesis that bacteria are the cause of suppuration and putrefaction in the animal body; the first to attempt the disinfection of infected tissues; and the first to devise methods to prevent suppuration and putrefaction by preventing the entrance of micro-organisms.

* * *

Lister's father-in-law, James Syme, retired in 1869 because of illness, and Lister returned to Edinburgh as his successor and Regius

Professor of Surgery. As Lister continued to develop improved procedures of antisepsis/asepsis, his fame increased particularly in Scotland and on the continent in Germany and France. The situation was very different in London, however, where Lister's ideas were routinely mocked and ridiculed. Irrespective of these London attitudes, or possibly because of them, Lister left Edinburgh in 1877 and took a position as Chair of Clinical Surgery at King's College Hospital, hoping to spread his doctrine of antisepsis/asepsis within the larger venue of London.

The early part of Lister's move to London was marked by several contentious episodes. One of these with major importance to modern surgical practice involved committing what was then viewed as a "surgical sin" by turning a simple fracture into one that was compound so as to effect a better outcome. The patient in question, Francis Smith, fell from his cart on the Strand and fractured his kneecap. On October 26, 1877, Lister carried out on Smith at King's College Hospital the first successful operation to mend a surgically opened knee cap under antiseptic conditions. Three months later, Smith walked out of the hospital under his own power.

The operation on Francis Smith and its historical importance is reviewed in an article by F. F. Cartwright on antiseptic surgery that appeared in a 1968 volume entitled, *Medicine and Science in the 1860s*; this short except follows:

> The case of Francis Smith, Lister's first wiring of the fractured patella, is probably the most important single operation in the history of surgery. Lister proposed to infringe the most sacred rule of the pre-Listerian surgeon, to break the protecting skin over the site of a fracture. A simple fracture carried no risk to life; a compound fracture could often prove fatal; Lister was deliberately planning

> to convert a simple into a compound fracture. The fierce criticism aroused by his proposal centered attention upon his operation; when, in January 1878, Francis Smith walked out of King's College Hospital on both legs, the usefulness of antisepsis had been proved.

In concluding his article, Cartwright comments on the general move from antisepsis to asepsis and where Lister fit into that evolution:

> ... though we speak of modern asepsis and look upon antisepsis as obsolete, there is only one basic difference between the two methods and none in the principle underlying them. The sole difference is that Lister achieved an aseptic operation site by means of an antiseptic drug. His principle demanded and demands that no micro-organism shall ever come in contact with the wound.
>
> Presumably this principle will remain unchallenged so long a surgical operations are performed or wounds are dressed. Herein lies Joseph Lister's unique and lasting contribution to surgery.

A second unpleasant episode occurred in the fall of 1877 when Lister gave his inaugural lecture as Chair of Surgery at King's College. It is an understatement to say that it did not go well. A short summary of the reception Lister received is given below as reported by Peggy J. Parks in her biography, *Joseph Lister: Father of Antiseptics* (2005; pp. 51-52):

> An Uncomfortable Start
>
> On September 11, 1877, Lister and his wife moved to London. Three weeks later he gave his introductory lecture at King's College, which he called "On the Nature of Fermentation." His intention was to convince people that he was right about bacteria and antiseptics. The lecture theater was filled with scientists, surgeons, and students, all of whom were curious about this person they considered a bit strange. Lister started by showing drawings and diagrams of

germs. Then he showed test tubes and beakers that contained milk and other fluids in various stages of fermentation, and he discussed the experiments he had performed.

The audience's reception was nothing like those Lister had experienced in Edinburgh. Whereas his previous lectures had been met with eagerness and enthusiasm, he now gazed out at a sea of confused expressions. The surgeons were respectful, but they did not seem to understand the points Lister was making. Watson Cheyne, a surgeon who traveled to London to be one of Lister's assistants, describes the reaction (in his biography, *Lister and His Achievement* (1925, p. 33)):

> Perhaps not unnaturally they expected to be told about the revolution in surgery which Lister had inaugurated, and instead they had to sit for an hour listening to details of a series of experiments which proved that the lactic fermentation of milk was due to a particular bacterium! The expression on the faces of the audience was very interesting and rather amusing; the majority of the surgeons present could not understand what the lactic fermentation of milk had to do with surgery. Those were the days of the "practical surgeon" as opposed to the scientific surgeon — the latter being supposed (why I can't imagine) to have no practical skill or knowledge. It took a considerable time before the "practical surgeon" realized that his day was pa.

What Lister found most disturbing was the reaction of the students. He had always gotten along so well with young people, and his students in Edinburgh were fiercely loyal to him. These students, however, were disrespectful, and some even heckled him. They scuffed their feet loudly on the floor, and when he talked about milk, they made mooing sounds. Lister did his best to ignore them so he could finish his speech.

> His subsequent lectures were equally disappointing. Few students bothered to attend, and those who did typically straggled in long after the lecture had begun. Again, this was in stark contrast to Edinburgh, where hundreds of students were eager to hear whatever Lister had to say. In London he felt fortunate if twenty students showed up. It was obvious that aspiring surgeons in England did not care to learn about antiseptics.

Although Lister's early years at King's College Hospital may have been contentious, sheer persistence on Lister's part eventually convinced the London medical community of how antiseptic/aseptic practice could reduce infection and mortality from major surgical procedures. When Lister arrived in London in 1877, mortality at King's College Hospital was about 40%; it had dropped to around 3% by 1910. Although asepsis and sterile technique through sterilization using heat generally replaced antisepsis with chemicals as the primary strategy in combating infection, it was still Lister's application of germ theory to the care of surgical patients that first laid the foundation for what surgeons do to this day. He directed the minds of physicians and surgeons to the vital necessity of keeping wounds clean and free of microbial contamination.

* * *

In addition to Lister's central role in the general adoption of the Antiseptic Principle by the medical community, he also carried out a program of basic microscopic physiological research and contributed several technical advances in surgical practice more generally. Early in his career, for example, Lister published some fifteen papers regarding the action of muscles in the skin and eyes; the coagulation of blood; lymph flow; and blood vessel changes that occurred with

infection and inflammation. For surgical practice, Lister introduced rubber drainage tubes for abscesses (with a most notable use on an armpit abscess for Queen Victoria in 1871 at Balmoral Castle in Scotland); catgut sutures that were merely absorbed by the body rather than needing physical and often dangerous removal; and a variety of surgical instruments designed for very specific tasks. More broadly, Lister initiated a movement to aseptic surgical practice through heat sterilization rather than just relying on chemical antisepsis.

Lister also debunked one of the major faulty concepts from early Nineteenth Century medicine – that of "laudable pus," or alternatively, "kindly suppuration." Instead of pus being a sign of healthy healing, it is rather a mark of infection (typically Staphylococcal). A lack of pus was therefore not a cause for concern but exactly the opposite.

In the chapter on Pasteur it was noted that Lister gave one of the key laudatory addresses (in fluent French, no less) at Pasteur's 70th Birthday Jubilee in 1882 held at the Sorbonne. As was typical of Lister, he gave Pasteur the major credit for his own development of the Antiseptic Principle. Later, some of the deserved awards did accrue to Lister – he was made a baronet by Queen Victoria in 1883, and was elevated to a peerage in 1897 with the title of Lord Lister of Lyme Regis. Lister was the first medical doctor to be so honored.

Lister was made Sergeant Surgeon (that is, the chief medical officer for the Royal Family) by Queen Victoria in 1900. Soon after Victoria's death in 1901, Lister operated on her successor, Edward VII, for an appendicular abscess. (For those familiar with the PBS series, *Victoria*, Edward had the nickname of "Bertie.") At his coronation in August of 1902, Edward shook Lister's hand and said, "Lord Lis-

ter, I know well that if it had not been for you and your work, I would not have been here today."

* * *

Lister's wife Agnes died of pneumonia in 1893 while they were on holiday in Italy. Lister himself retired from King's College soon thereafter, and lived a somewhat solitary existence until he died in February of 1912. A funeral was held at Westminster Abbey with a burial next to Agnes in Hamstead Cemetery in London.

Hector Charles Cameron (1878–1958), the son of Sir Hector Clare Cameron, one of Lister's house surgeons at Glasgow, provides a good final summary of Lister's achievements in his biography, *Joseph Lister, The Friend of Man* (1948; pp. 170-171), particularly as it relates to Lister's initial (abductive) conjecture as to germs being the cause of wound infection, and to Lister's follow-up experimental verifications:

> There have been very different estimates of Lister's genius and achievement. Some have seen no more in him than the power to exploit to the full a fortunate and almost accidental discovery. Others have conceded to him a mind so trained and so receptive that he alone among the surgeons of his day could grasp the implication of Pasteur's work, that, in Clifford-Allbutt's often quoted words, "He was watching upon the heights and he was watching there alone." That was not the opinion of the distinguished men of science, who were his friends and who elected him to preside over them in the Royal Society, nor of their colleagues elsewhere in Europe. All these placed him on a far higher plane, regarding him as a master in experimental science of the rarest quality whose achievements had only been limited by his absorption in its details and routine.
>
> It is true that Lister was never to show the amazing versatility in research which was Pasteur's alone, a versatility which could

solve unerringly each new problem as it was brought to him, however unrelated to and different from its predecessors. Yet Lister's mind in many ways was of the same texture as Pasteur's. He had the same dissatisfaction with ills which had always been regarded as inevitable and in the course of nature. There was the same indefatigable patience which in the end could achieve all things. Above all there was the same power of seeing clearly, and of constructing, the particular experiment which could establish truth. As Sir Charles Sherrington has put it: "Like Pasteur, he had the supreme faculty of seeing by instinct the exact experiment required to eliminate some element of doubt."

At a time when all apparatus for scientific work was primitive, Lister, like Pasteur, could improvise what was necessary out of the most ordinary material with unfailing dexterity and resource. His little laboratory which led out of his consulting-room contained only the simplest of apparatus — test tubes and flasks with a good weighing machine and microscope. But, unlike Pasteur, Lister had to expend much of his time and energy upon relatively unprofitable labour, such as that entailed by the long trail which led him in the end to make the muslin of the bookbinders and the lining of the hatters serve new and nobler purposes. Often it was only when other people were betaking themselves to rest and bed that Lister, with Agnes at his side, was able to slip away to the delights of research in the laboratory. Pasteur spoke for all science when he expressed his appreciation of Lister's "perfect comprehension of the experimental method." It was the men of science who understood and acclaimed him, and the surgeons who for long failed to understand, and rejected him. His pupils in surgery knew his worth. Perhaps of these, Lucas Championnière has best summed up his achievement:

"Lister gave a scientific basis to surgery. He made it rest on established truths. He swept away the uncertainty in which the greatest surgeons up to that time had left it. Inspired by the ideas of Pasteur, he conceived the idea that the infinitely little, and its germs of all kinds, scattered everywhere in the outside world, strove

against the natural efforts of the organism towards healing. His genius showed itself in this, that starting from a fundamental observation, verified scientifically, he succeeded in determining the general laws of repair."

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[1]There are a substantial number of Lister biographies available that provide the chronological details of his career. Many of these were written by authors with a personal relationship with Lister and access to some of his more personal correspondence. (Sir) Rickman John Godlee, for example, was Lister's nephew and assistant in London; Hector Charles Cameron was the son of Sir Hector Cameron who was a house surgeon for Lister in Glasgow; William Watson Cheyne was a Lister house surgeon in Edinburgh, and later a prominent London surgeon on his own; John Leeson worked with Lister also at Edinburgh.

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Part V

Nineteenth Century Pioneers in Identifying Insects as a Mechanism (Vector) for Disease Transmission: Patrick Manson (Ronald Ross), Paul-Louis Simond (Alexandre Yersin), Carlos Finlay (Walter Reed), Theobald Smith, Charles Nicolle

> Throughout the early Christian period, every great calamity – famine, earthquake, and plague – led to mass conversions, another indirect influence by which epidemic diseases contributed to the destruction of classical civilization. Christianity owes a formidable debt to bubonic plague and to smallpox, no less than to earthquake and volcanic eruptions.
>
> – Hans Zinsser (1878–1940)

During the last several decades of the Nineteenth Century with some small overlap into the early Twentieth, various mechanisms involving insects were discovered as to how some diseases were transmitted in humans and animals. One of the earliest such discoveries was in the 1870s from Patrick Manson (1814–1922) who identified the mosquito as the means of conveying filariasis in humans. Filariasis is an infectious tropical disease generally acquired in childhood and caused by thread-like parasitic roundworms which typically leads to the disfiguring condition of elephantiasis. Manson's discovery is considered the foundation of tropical medicine, and Manson himself is given the sobriquet of "the father of tropical medicine."

In the early 1890s, Manson conjectured that in addition to filariasis, malaria was also transmitted by the mosquito. This was generally known as Manson's mosquito-malaria theory. A younger collaborator of Manson, Ronald Ross (1857–1932), was the first to describe the full life cycle of the malarial parasite, albeit for birds and not for humans. Human transmission was shown by the Italian researcher, Giovanni Grassi (1854–1925), who in one of the most controversial episodes in the history of the Nobel Prize, was denied in 1902 a deserved co-award along with Ross.

Insects, or more generally, arthropods of sundry kinds play a central role in the spread of various disease entities in humans and ani-

mals more broadly. In addition to the mosquito being the vector for filariasis and malaria, the chapters that make up this Part IV will discuss the mosquito as the means for yellow fever dissemination (Carlos Finlay (1833–1915) and Walter Reed (1851–1902)); the cattle tick as the way of spreading Southern cattle fever (Theobald Smith (1859–1939)); the rat flea and rats in general as to how bubonic plague is propagated (Paul-Louis Simond (1858–1947) and Alexandre Yersin (1863–1943)); and finally, the body louse as the mechanism for typhus transmission (Charles Nicolle (1866–1936)).

In identifying the various insect vectors for disease conveyance, the medical researchers in this Part IV relied on a variety of "surprising observations" that led to the specific abductive conjecture of insect transmission for the particular disease they studied. In all cases these initial hypotheses were then put to further experimental test and observation, some using highly creative procedures. We will note in summary a few of these conjecture/experimentation stories immediately below and before the actual chapters are given in their entirety.

Paul-Louis Simond (1858–1947): Simond is known for conjecturing and proving experimentally that the rat flea is the mechanism for transmitting bubonic plague from rats to humans and from rats to rats. Prior to Simond's demonstrations, Alexandre Yersin (1863–1943) working in Hong Kong in 1894 had discovered the bacillus responsible for bubonic plague in both humans and rodents. Yersin had been sent on behalf of the Pasteur Institute in Paris to study the origins of the plague epidemic then occurring in that part of Asia. Although Yersin did note the "surprising observation" of many dead rats appearing immediately before a plague outbreak among humans,

he did not make any further connections as to the flea being a possible intermediary for passing the plague to humans.

In 1897, Simond took Yersin's position in Bombay when Yersin was transferred to a post in Vietnam. The next year, Simond was in Karachi where he did his seminal work on plague transmission by way of the flea. Just as Yersin had noticed earlier, Simond observed that there were lots of dead rats present before humans were infected. But he also noted several other "surprising observations" that led him to finally postulate the flea mechanism for plague conveyance. Among these, Simond recognized that plague transmission could operate at a distance without any obvious person-to-person contact; the native Chinese would run away as soon as dead rats appeared; people were infected with the plague if they approached still warm dead rats but not if they were already cold; and finally, healthy rats had few fleas or none at all.

After conjecturing that the flea was the means of plague transference, Simond developed an ingenious "hanging rat in a cage" experiment described in a following chapter that was definitive as to the role that the flea had in plague propagation. Because of this work, Simond became the first individual to demonstrate experimentally the transmission of a bacterial disease by an insect. This was published in 1898 in the Annals of the Pasteur Institute under the title "La propagation de la peste."

Carlos Finlay (1833–1915): Although Carlos Finlay is the name used to caption a chapter that follows, it could have just as well been labeled with the name of Walter Reed (1851–1902). Both men were involved with the study of the viral blood disease of yellow fever in Cuba at the turn of the Twentieth Century. Carlos Finlay had

conjectured ever since the early 1880s that yellow fever was transmitted by the mosquito, basing this conjecture on the strong correlation between mosquito presence and the prevalence of yellow fever. For example, although common during the summer, yellow fever and mosquitos both disappeared with the first frost; higher altitudes were less prone to yellow fever presumably because mosquitos had more difficulty in flying, particularly when engorged with blood; and generally, conditions that were conducive to the presence of mosquitos were also conducive to the presence of yellow fever.

Although Finlay clearly conjectured the mosquito as the means of yellow fever conveyance, he could not produce convincing experimental evidence to that effect. The one crucial fact that prevented Finlay from demonstrating the truth of his hypothesis was the concept of an "extrinsic incubation" period, where after bitting an infected individual, the mosquito still needed a significant period of time before it was able to infect another individual. In contrast, Walter Reed went into the study of yellow fever knowing the work of Henry Rose Carter (1852–1925) on the concept of "extrinsic incubation," published in 1898.

Along with several other military doctors, Walter Reed formed the Army Yellow Fever Commission deployed to Cuba in 1900 with the express purpose of finding out how yellow fever was propagated. Based on the Finlay mosquito conjecture and several other pertinent observations, for example, that yellow fever was not being passed person-to-person since non-immune individuals could care for yellow fever victims without contracting the disease, and yellow fever was not a disease of filth because extensive sanitary clean-ups were of no help in preventing its spread, Reed and his team proceeded to

study yellow fever transmission using human subjects since no animal model was available.

The experimentation with human subjects was able to document yellow fever conveyance by infected mosquitos as long as an extrinsic incubation period was observed. Because yellow fever is caused by a virus that could not be seen with the microscopes then available, other experiments with infected bedding and clothing (that is, with fomites) in specially constructed houses, all showed that yellow fever could not be transmitted in this way, although these manipulations were all done somewhat "blindly" as to the actual infecting agent.

Theobald Smith (1859–1934): Theobald Smith is considered by many to be America's first internationally significant medical research scientist. While working at the U.S. Department of Agriculture and its Bureau of Animal Industry in the 1880s, Smith unraveled the mystery of Texas cattle fever, which is caused by a tick-borne single-cell protozoan parasite. This discovery marked the first time that an arthropod had been definitively tied to the transmission of an infectious disease, foreshadowing other discoveries of insects as vectors for several additional maladies such as yellow fever and malaria.

The extensive report on Texas cattle fever published by Smith in 1893 is one of the best examples of the complete abductive reasoning process that moves from hypothesis generation through experimental verification with a detailed elucidation of the transmission mechanism. First, there were numerous "surprising observations" about southern cattle coming north and infecting the native herds with something that they "carried along" with them. This led directly to the hypothesis of disease conveyance through the ubiquitous tick, followed up by extensive field experimentation carried out over

several years. In addition there was an extensive laboratory study of the tick's complete life-cycle which delineated just how the disease was actually conveyed – the disease was passed through the eggs of female ticks and then to non-immune cattle by the hatched larvae.

Charles Nicolle (1866-1936): Nicolle was a French bacteriologist working in the Pasteur Institute in Tunis, Algeria, in the early 1900s. It was here that he was able to identify human body lice as the means for transmitting epidemic typhus. Nicolle observed that typhus patients were able to infect other individuals inside and outside the hospital and were able to do so just through their clothes. However, once shaven and given a hot bath and a change of clothes, they were no longer infective. Nicolle's abductive hypothesis of the body louse as the medium of typhus transmission was then evaluated experimentally with chimpanzees and duly infected lice.

Chapter 9

Patrick Manson (Ronald Ross)

> Infectious disease is one of the few genuine adventures left in the world. The dragons are all dead and the lance grows rusty in the chimney corner. ... About the only sporting proposition that remains unimpaired by the relentless domestication of a once free-living human species is the war against those ferocious little fellow creatures, which lurk in dark corners and stalk us in the bodies of rats, mice and all kinds of domestic animals; which fly and crawl with the insects, and waylay us in our food and drink and even in our love.
>
> – Hans Zinsser (1878–1940)

The central individual for this chapter, Patrick Manson (1844–1922), made a number of pioneering discoveries in the field of human parasitology. Among the first and in many ways the most important was developed through his study of the infectious tropical disease of filariasis, caused by several species of thread-like parasitic roundworms (filaria). The primary manifestation of filariasis is elephantiasis (also called lymphatic filariasis) – the often grotesque enlargement of a victim's body tissue through the obstruction of lymphatic vessels, particularly in the legs, and for males, in the scrotum. Manson demonstrated how the mosquito might transmit filariasis through the incubation of filaria embryos. He thereby became the first individ-

ual to show that insects could possibility transmit disease. For this discovery and others within tropical medicine, Manson is commonly considered to be the father of tropical medicine.

Patrick Manson was born in October of 1844 near Aberdeen, Scotland. After receiving an M.D. degree from Aberdeen University in 1866, Manson became a medical officer for the island of Formosa (now, Taiwan), within the Chinese Imperial Maritime Customs. In the Formosan port where he was stationed, Manson was responsible for the inspection of ships entering and leaving the port, and for the general medical treatment of the various ship crew members. Under advisement to leave Formosa because of a continuing Japanese interest in taking over the island, Manson went to the mainland port of Amoy in 1870, where he was affiliated at various times with the Baptist Missionary Hospital. It was during this period that Manson became particularly interested in elephantiasis, given its widespread occurrence among his patients.

As might be expected, there was little literature available in Amoy on diseases such as elephantiasis that Manson could consult. It was during a furlough back to the United Kingdom in 1875 and to the British Library in London that Manson came across a published 1872 item from Timothy Lewis then serving in the Army Medical Service in Calcutta. Lewis reported on seeing a minute nematode worm that he named *Filaria sanguinis hominis* in the blood of an elephantiasis patient. Although Lewis had no idea as to how such a worm might be transmitted to humans, the observation itself gave Manson a key to clarifying the mystery of filariasis and a possible mosquito method of transmission.

Manson returned to Amoy in early 1876, armed with a new mi-

croscope as well as with a newly married wife. Very soon after his return, Manson was able to see the active filarial embryonic worms in the blood of his Chinese patients. The actual adult worms generally remained hidden and embedded in areas such as the lungs, the heart, and arterial tissue; this later fact was verified by Manson through an autopsy of a filaria-infested individual who had died by suicide. The active filariae were in the form of embryos encased in a transparent sheath that remained viable even when placed on a microscope slide. Moreover, Manson could show that the embryos "came out" of their sheaths upon cooling. This was to be one bit of evidence leading to the abductive conjecture that the mosquito might be a means of transmission for the filaria embryos. The internal organs of the cold-blooded mosquito, which bite their human victims at night, were cooler than the blood that the embryos came with, thus allowing their further development into forms that could then presumably reinfect humans.

Manson made a second surprising observation almost by accident. He had hired two assistants to look for the filaria parasites in the blood of patients present in the hospital. One helper worked only during the day and the other only during the night. The day helper rarely found the filaria parasites in the blood compared to the other helper who drew specimens at night. To check on the consistency of this observation, both assistants examined just one patient for a week — and again, a day/night discrepancy appeared in the abundance of filaria embryos.

To solidify the evidence for what was to be called the Law of Nocturnal Periodicity, Manson relied on his filaria-infected gardener, Hin Lo, and a second volunteer, Li Kha. These two individuals were

sequestered in a room in Manson's house where blood samples were taken every three hours, day and night, for fourteen days. With great clarity, the resulting graph showed the regularity of nocturnal appearance of filariae in the blood. The graph itself can still be seen at the London School of Hygiene and Tropical Medicine which Manson was instrumental in forming some years later.

Based on these several observations just described that filariae are embryonic worms needing development outside of the human blood stream, possibly in a cold-blooded creature that would allow its escape from an encasing sheath, plus the increased nocturnal presence of the filariae embryos, suggested to Manson that the ubiquitous brown mosquito, which fed only at night, might be the intermediate vehicle. What Manson got wrong in his initial abductive theorizing was the exact means of further human reinfection. He believed that the filariae would somehow be transmitted through water that was consumed by humans and which contained the remnants of dead mosquitos and the newly animated filariae. Initially, there was no understanding that mosquitos could feed more than once before they died and laid their eggs, and therefore, that they could transmit filariae directly through their bite.

As a test of the mosquito connection for filariae transmission, Manson once again called upon his gardener, Hin Lo, to provide sufficient infected mosquitos for study by having him inhabit a special "mosquito house" constructed for that purpose. This procedure was described in some detail in Manson's first major publication on filaria that is reproduced in an external Appendix: On the Development of *Filaria sanguinis hominis* and on the Mosquito considered as a Nurse. It was communicated by Manson's colleague back in the UK,

Dr. Spencer Cobbold, and appeared in the Linnean Society's Journal in Zoology in 1878.

Besides being the first known published communication that actually showed how an insect could be an intermediate mechanism for transmitting disease in humans, there are several other more subtle points made in the paper that deserve highlighting. First, to ensure species continuation, there is the need for filaria embryo development to be outside of the human host harboring the parent parasitic worm. Second, there is the observation that the proboscis of the female mosquito has been adapted to sift for embryos in the human blood stream – in other words, there are more embryos per unit in the blood retained by the mosquito than are present in the original human blood stream. A final point to note in the reproduced article is how Manson was led astray as to how the matured embryos escape the mosquito. Given the boring-like apparatus he saw developing, Manson assumed this was the means of first departing the mosquito, and when the matured embryos were ingested by a human, the apparatus was also the mechanism for entering the blood stream by boring through the walls of the human intestine.

Patrick Manson spent the years from 1883 to 1889 working in Hong Kong, primarily in medical education and in building a thriving private practice. He was the founder in 1887 of the Hong Kong College of Medicine for Chinese which later became the University of Hong Kong (1911). As an aside that we will come back to later, it might be noted that one of Manson's first students at the College of Medicine was Sun Yat-Sen who later became the first President of the Republic of China. Partially because of a severe and recurring case of gout, Manson returned to London in 1889. Besides setting

up a private practice, Manson became a physician at the Albert Dock Seaman's Hospital (1892), and later, Chief Medical Officer in the Colonial Office (1897) until he retired in 1912. As noted before, Manson was the primary force behind the formation of the famous London School of Hygiene and Tropical Medicine (1899).

* * *

The protozoan parasite (*Plasmodium*) responsible for human malaria was first identified in 1880 by a French military surgeon, Alphonse Laveran (1845–1922), while working in Constantine, Algeria. Using what were remarkable observational skills for the primitive microscope equipment and techniques available at the time, Laveran clearly saw the parasite in a blood smear from a patient who had just died of malaria. Eventually, Laveran was able to find the same parasite in 148 out of 192 malaria patients examined but never in those without malaria. He also showed that the parasite disappeared in the presence of quinine, confirming that he had truly identified a cause of malaria.

This was the first time that protozoans were identified as the cause of any disease. For this work and other identifications of protozoan induced disease, such as African sleeping sickness, Laveran received the Nobel Prize in Physiology or Medicine in 1907. The citation for the award reads as follows:

> In the tropics malaria is a common disease that causes high fever and other symptoms. By the middle of the 19th century, it was clear that many diseases are caused by microorganisms, and a great many people suspected that malaria was caused by a bacterium. After examining blood from people infected with malaria, Alphonse Laveran in 188[0] was able to definitively show that malaria is caused

by another type of single-celled organism, a protozoan of the Plasmodium family, which attacks red blood cells. He also identified other single-celled parasites that cause other diseases.

In the early 1890s, Manson became interested in malaria and how it was transmitted, partly because of his earlier work on the human filaria parasite and from earlier suggestions in the literature made by others that the mosquito was a likely means of malaria propagation. Manson published a short paper in 1894 in the *British Medical Journal* entitled: On the nature and significance of the crescentic and flagellated bodies in malarial blood. This paper, reproduced in an external Appendix, discusses the bodies that appear at various developmental stages in malarial blood. Manson argues that these bodies must be the agents that cause malaria because they reproduce malaria in humans when injected intravenously. Manson also speculated on the means of "nursing" these entities outside of a human body by suctorial insects such as the mosquito, with the faulty view [again] of an eventual transmission back into a human body through ingestion of contaminated water. This could be called the (Manson) mosquito-malaria (abductive) theory or conjecture:

* * *

Ronald Ross (1857–1932) is the individual many consider responsible for finally unraveling the mystery of malaria transmission, albeit using an animal model defined through birds. Ross showed that the bite of a mosquito can be used to acquire the malarial entities, but then and more importantly, that a second bite could pass them along in a matured form to an uninfected animal. For this discovery, Ross received the Nobel Prize in 1902 with the following citation:

> The Nobel Prize in Physiology or Medicine 1902 was awarded to Ronald Ross for his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it.

But the real story behind Ronald Ross is not so straightforward. It involves the crucial mentorship of Ross by Patrick Manson, and the proof of human as opposed to avian transmission of malaria by means of the mosquito given by the Italian researcher, Giovanni Grassi (1854–1925). These conflicting perspectives about priority and recognition evolved into one of the nastiest disputes in the medical sciences for the first part of the Twentieth Century.

Ronald Ross was appointed a surgeon in the Indian Medical Service in 1881, and was stationed in various parts of India where malaria was prevalent. Although Ross had heard of Laveran's discovery of the malarial parasites by 1892, he was unable to identify them for himself even though he spent many hours looking at blood smears from malaria patients through his microscope. When Ross took a furlough to England in 1894, and mentioned to his colleagues that he could not verify Laveran's observations, they suggested he visit Patrick Manson.

Ross meet Manson for the first time in April of 1894, and from that point on, Manson became Ross' mentor. He first showed Ross the proper microscope techniques to see the malarial parasite in blood smears and explained his mosquito-malaria theory of transmission that paralleled what Manson thought was also true for filaria. Ross continually referred to the mosquito-malaria theory as "Manson's Grand Induction," although we might change this phrase slightly to read "Manson's Grand Abduction." In any case, an energized Ross

returned to India in 1895 and began an intensive research program on malaria. The extensive mentor-mentee correspondence that ensued between Ross and Manson over the next five or so years has been preserved in a volume entitled: *The Beast in the Mosquito: The Correspondence of Ronald Ross and Patrick Manson* (Edited by W. F. Bynum and Caroline Overy, 1998).

After several years of failure because of the use of an inappropriate mosquito genus, Ross was finally able to infect mosquitos from a patient named Hasein Kahn who was monetarily compensated per allowed bite. The key to Ross' success in seeing the malarial parasites in his blood smears was in the eventual choice of mosquito to study – those from the genus *Anopheles* that we now know are able to transmit human malaria. It was on August 20, 1897, that Ross could finally identify the malarial parasite in a mosquito that had fed on Hasein Kahn. This date in August is still celebrated as World Mosquito Day – when Ross discovered that *Anopheles* mosquitos could be infected with the human malaria parasite.

It was just at this point in time that Ross was first sent to a malaria-free rural area and then to Calcutta which was also malaria-free. Given the absence of human malaria patients, Manson persuaded Ross to work with an animal model of malaria in the form of birds. By July of 1898, Ross established that the mosquito from the genus *Culex* was the intermediate host for avian malaria. Moreover, using birds that were malaria-free and allowing infected mosquitos to bite them, Ross showed that avian malaria was passed in the mosquito's saliva and not by ingesting water contaminated with infected dead mosquitos. These results on avian malaria transmission obtained by Ross were presented by Patrick Manson at a 1898

meeting of the British Medical Association in Edinburgh and published that same year in *The Lancet* under the title, The Role of the Mosquito in the Evolution of the Malarial Parasite: The Recent Researches of Surgeon-Major Ronald Ross, I.M.S.

* * *

Although Ronald Ross may have been the first to show the transmission of bird malaria by the mosquito, it was the Italian Giovanni Grassi, working at the University of Rome, who first described the life cycle of the human malarial parasite, and discovered that only female anopheline mosquitos were capable of transmitting the disease. The awarding of the Nobel Prize solely to Ross without being shared with Grassi remains to this day one of the lasting controversies in the history of the Nobel Prizes. It also engendered one of the nastiest disputes ever within the medical sciences over priority of discovery between Ross and Grassi.

When Giovanni Grassi began his studies of malaria and its transmission, he had, in effect, accepted the malaria-mosquito theory. But as someone with specific expertise in entomology, he also noted something surprising about the distribution of malaria and mosquitos — specifically, mosquitos could be numerous where malaria was rare, and conversely, malaria could be common where mosquitos were scarce. For Grassi the (abductive) conjecture that came to mind was that only one or a few types of mosquito could be the actual carrier of malaria.

In the summer of 1898, Grassi carried out a comprehensive search and capture for mosquitos, and noted the incidence of malaria where each specimen was found. By this process, Grassi was able to ex-

onerate all species from the genus *Culex* – the common grey house mosquito. This was also the genus on which Ross had wasted two whole years. The particular genus of mosquito identified by Grassi as most likely responsible for human malarial transmission was called "zanzarone" by the natives. It was Ross's "brown mosquito," now known to be from the genus *Anopheles*.

As of September, 1898, Grassi reported that *Anopheles claviger* was the human malarial transmitter. This was shown experimentally through a volunteer named Abele Sola in December, 1898. This individual contracted malaria after being shut up with infected *Anopheles* mosquitos every night for ten nights. Earlier attempts with Sola using mosquitos from the genus *Culex* had failed to induce malaria. Other successful human malaria inductions followed with other volunteers using the same procedure that had been used for Sola.

What became known as "Grassi's Law" was the observation that "there is no (human) malaria without *Anopheles*." Although this implication may be true in this direction, there can also be members of *Anopheles* present without human malaria. There are some species within the genus *Anopheles* that do not bite humans. Such a subtlety of species within *Anopheles* was not solved until after Grassi's death by his student Falleroni. Similar statements could be made with respect to the transmission of bird malaria and the genus *Culex* studied by Ross.

Grassi was an inveterate researcher and whenever a question was raised about malaria transmission, his first instinct was to carry out a clarifying empirical demonstration. One such study already mentioned was of Abele Sola who was repeatedly bitten by different mosquito species until the right *Anopheles* culprit was identified.

After locating the correct vector, Grassi replicated the experiment repeatedly with different volunteer subjects using the then identified correct member of *Anopheles*.

A second experimental demonstration was motivated by Robert Koch, the well-known bacteriologist from another chapter. Although Koch also believed in the mosquito-malaria theory, he thought that malaria was passed to the young from their mothers and the mothers themselves did not transmit the disease through subsequent bites. This was consistent with the Theobald Smith demonstration, reported elsewhere, that Texas cattle fever was transmitted through the larvae of the tick. To show this was not the case for malaria, Grassi and six of his colleagues allowed newly-born *Anopheles* mosquitos to freely feed over many days, all having their trouser pant legs pulled up for easy access.

One large-scale real-world experiment was carried out by Grassi to demonstrate that malaria could be prevented by appropriate protections from the bite of mosquitos at night. In the summer of 1900, Grassi went to the malaria-plagued area called the plain of Capaccio and created enclosed and screened living areas for 112 people who were railroad men and their families. These enclosures prevented the entrance of mosquitos during the evening times when they fed. An additional 415 people were housed in non-screened structures. At the end of the summer almost all of the 415 non-screened individuals had contracted malaria. Of those who stayed indoors at night in the heavily screened and protected structures, only five got malaria, and these cases could have been simple relapses from earlier bouts of malaria.

* * *

Patrick Manson guided several experiments himself on his mosquito-malaria theory that now included malaria infection from the actual bite of mosquitos. One involved infecting with mosquitos obtained from Italy his own twenty-three year-old medical student son, Patrick Thurburn Manson, and a second volunteer who was Manson's laboratory assistant, George Warren. A second experiment was done on site in the notoriously malaria infected Roman Campagna. Manson published the results of these two studies in the *British Medical Journal* in 1900 under the title: *Experimental Proof of the Mosquito-Malaria Theory.* This paper is reproduced in an external Appendix.

* * *

The feud between Grassi and Ross, which lasted for the first several decades of the Twentieth Century, was one of the nastiest episodes in the history of the medical sciences. The controversy was started by Ross who accused Grassi of reading his papers on avian malaria transmission before Grassi published his own work on human malaria transmission – but then gave Ross no credit or citation for the idea of malaria transmission through subsequent mosquito bites. Ross sent vicious letters to several journals contending that Grassi was a parasite who survived on the ideas of others. Grassi responded in an equally acrimonious manner – and so it went. The fiery argument over whether both Ross and Grassi should share the 1902 Nobel Prize was adjudicated by the bacteriologist Robert Koch who sided (inappropriately, in my opinion) with Ross and his contention that Grassi was a fraud. This whole odious period and controversy is recounted by Ronald Ross in his self-serving, *Memoirs, with a full*

account of the great malaria problem and its solution (1923).

* * *

We end this chapter on Patrick Manson by discussing a political intervention in 1896 that he was part of and which most likely changed the course of Twentieth Century Chinese history. As noted earlier, one of Manson's first students at the Medical School in Hong Kong was Sun Yat-Sen who would later become the first President of the Chinese Republic after the overthrow in 1912 of the last of the imperial dynasties – the Manchu (1644–1912). After finishing his medical training in Hong Kong, Sun Yat-Sen set up a medical practice in the Portuguese colony of Macao, and began his political activism with the Young China Party. Because of these anti-governmental pursuits, Sun was expelled by the Portuguese authorities from Macao. After leading an abortive revolt against the government in Canton, Sun was forced to flee, first to the United States and then to London, arriving in October of 1896. We take up the story below of Sun's kidnapping in London as recounted in the biography of Manson written by his son-in-law, Philip Manson-Bahr, *Patrick Manson: The Father of Tropical Medicine* (1962):

> Manson's connections with China involved him about this time in a political sensation. Sun Yat-Sen was, it will be remembered, one of Manson's earliest students at the Medical School in Hong Kong, having studied there from 1887 to 1892. At first Sun started a lucrative practice in Macao, the Portuguese settlement at the mouth of the Canton river, and there he began his political activities. He had already organized an association of the leading figures in the Young China party. The Portuguese were unwilling to be compromised with any Chinese factions, and expelled him. Sun

then attempted a military revolt against the Canton Government. When this failed Sun had to flee, and travelling by way of America he eventually reached London on 1 October 1896.

Shortly afterwards he dined at 21 Queen Anne Street, and Manson warned him to keep away from the Chinese Legation which was close by in Portland Place, but he did not appreciate how pertinent this warning was. Some ten days later, while walking down Devonshire Street, Sun was approached by two Chinamen who lured him into the Chinese Legation where he was detained for several days, apparently on orders from Peking to hold him and ship him back to China as quickly as possible. Fortunately he was able to enlist the sympathy of the charwoman, and on 17 October he slipped into her coal-scuttle a note addressed to Manson. Together with Dr. James Cantlie, Manson approached the police authorities but without result. Manson then visited the Foreign Office and saw Sir Halliday McCartney who refused to believe the story, so Manson presented himself at the Chinese Legation and was rebuffed by an official who denied that Sun was in the building. Thereupon Manson replied that he knew that he was there and that the Foreign Office had been informed of his detention. Meanwhile Manson learned through underground channels that Sun was to be smuggled out of London that night and hurried to a ship waiting in the London Docks, whereupon he and Cantlie together hired a hansom cab and posted themselves outside the Legation, waiting all through the night. As nothing happened Manson again went to the Foreign Office and this time saw Lord Salisbury, who insisted on the captive's immediate release, which was granted. Had it not been for Manson's action Sun might have found himself in sore straits, because the Chinese had arranged to stow him away in a barrel and throw him overboard into the Thames.

As is well known he returned to China, recommenced his revolutionary activities, and became the first President of the Chinese Republic.

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Chapter 10

Paul-Louis Simond (Alexandre Yersin)

> But however secure and well-regulated civilized life may become, bacteria, Protozoa, viruses, infected fleas, lice, ticks, mosquitoes, and bedbugs will always lurk in the shadows ready to pounce when neglect, poverty, famine, or war lets down the defenses.
>
> – Hans Zinsser (1878–1940)

> [T]he natural history of the rat is tragically similar to that of man ... some of the more obvious qualities in which rats resemble men – ferocity, omnivorousness, and adaptability to all climates ... the irresponsible fecundity [fertility] with which both species breed at all seasons of the year with a heedlessness of consequences, which subjects them to wholesale disaster on the inevitable, occasional failure of the food supply ... [G]radually, these two have spread across the earth, keeping pace with each other and unable to destroy each other, though continually hostile. They have wandered from East to West, driven by their physical needs, and – unlike any other species of living things – have made war upon their own kind. The gradual, relentless, progressive extermination of the black rat by the brown has no parallel in nature so close as that of the similar extermination of one race of man by another ...
>
> – Hans Zinsser (1878–1940)

The word "plague" in its common usage has come to denote any

form of ongoing trouble or affliction. But in its more restrictive biological meaning, plague refers to an ancient infectious bacterial disease characterized by fever and delirium that typically includes the formation of swollen and inflamed lymph nodes in the armpits and groin. These latter engorged nodes are called buboes and the plague is referred to as bubonic. At times, the plague manifests as an infection of the lungs, called pneumonic, or of the blood in septicemic plague. In all three of these plague types, the bacillus responsible is called *Yersinia pestis*, named for Alexandre Yersin (1863–1943) who first identified the microbe in 1894. A few years later in 1898, the main individual for this chapter, Paul-Louis Simond (1858–1947), identified the rat flea as the major transmission vector for the plague both from rats to rats and from rats to humans. The actual mechanism for transmitting *Yersinia pestis* requires the bacteria to be first transferred from the blood of an infected rat to the rat flea through the latter's bite. The bacillus multiplies in the flea's stomach, eventually blocking it and requiring the flea to somehow remove the blockage or otherwise starve. When the flea next bites a victim, which can include humans as well as other rats and rodents, the consumed blood is regurgitated into the bloodstream of the bitten animal along with all of the bacilli blocking the flea's stomach passageway.

Over the last fifteen-hundred years, the plague has come in the form of three pandemics, each lasting for some extended period of time and having many included epidemic outbreaks. These three pandemics, beginning in the middle Sixth, Fourteenth, and Nineteenth Centuries, are assumed to have different geographical origins. For example, the first pandemic, called the Justinian Plague,

most likely began in central Africa (Ethiopia) and spread north to Egypt and the Mediterranean area more generally, ending up in Constantinople (Istanbul) in the Fall of 541. Between the years 542 and 546, as the disease spread further into Asia, Africa, and Europe, an estimated one-hundred million people died as a direct result. Various major outbreaks from this first pandemic occurred throughout the Middle East and Europe for the next several hundred years.

The second pandemic, commonly called the Black Death, originated in the middle Fourteenth Century presumably in Asia, spread first to the Crimea and then to Europe and Russia. The onset of this second pandemic in Europe is the setting for the famous book by Giovanni Boccaccio called the *Decameron* (1348). This work in its entirety consists of some one-hundred tales told by a group of Florentines who had sequestered themselves in the country to escape the plague. In the introduction to his work, Boccaccio includes the following vivid description of the bubonic symptoms arising from the plague then devastating Florence itself:

> ... in the illustrious city of Florence, the fairest of all the cities of Italy, there made its appearance that deadly pestilence, which, whether disseminated by the influence of the celestial bodies, or sent upon us mortals by God in His just wrath by way of retribution for our iniquities, had had its origin some years before in the East, whence, after destroying an innumerable multitude of living beings, it had propagated itself without respite from place to place, and so, calamitously, had spread into the West.
>
> In Florence, despite all that human wisdom and forethought could devise to avert it, as the cleansing of the city from many impurities by officials appointed for the purpose, the refusal of entrance to all sick folk, and the adoption of many precautions for the preservation of health; despite also humble supplications addressed

to God, and often repeated both in public procession and otherwise, by the devout; towards the beginning of the spring of the said year [1348] the doleful effects of the pestilence began to be horribly apparent by symptoms that shewed [sic] as if miraculous.

Not such were they as in the East, where an issue of blood from the nose was a manifest sign of inevitable death; but in men and women alike it first betrayed itself by the emergence of certain tumours in the groin or the armpits, some of which grew as large as a common apple, others as an egg, some more, some less, which the common folk called gavoccioli. From the two said parts of the body this deadly gavocciolo soon began to propagate and spread itself in all directions indifferently; after which the form of the malady began to change, black spots or livid making their appearance in many cases on the arm or the thigh or elsewhere, now few and large, now minute and numerous. And as the gavocciolo had been and still was an infallible token of approaching death, such also were these spots on whomsoever they shewed [sic] themselves. Which maladies seemed to set entirely at naught both the art of the physician and the virtues of physic; indeed, whether it was that the disorder was of a nature to defy such treatment, or that the physicians were at fault — besides the qualified there was now a multitude both of men and of women who practised without having received the slightest tincture of medical science — and, being in ignorance of its source, failed to apply the proper remedies; in either case, not merely were those that recovered few, but almost all within three days from the appearance of the said symptoms, sooner or later, died, and in most cases without any fever or other attendant malady.

Moreover, the virulence of the pest was the greater by reason that intercourse was apt to convey it from the sick to the whole, just as fire devours things dry or greasy when they are brought close to it. Nay, the evil went yet further, for not merely by speech or association with the sick was the malady communicated to the healthy with consequent peril of common death; but any that touched the clothes of the sick or aught [anything] else that had been touched

or used by them, seemed thereby to contract the disease.

The plague waxed and waned in Europe over the next four centuries including the major outbreak of bubonic and pneumonic plague in London in 1665 and 1666. A fifth of London's population died in this short time period, amounting to some 100,000 individuals. This epidemic was described by Samuel Pepys in his famous *Diary* (1665), and by Daniel Defoe (1722) in his partially fictionalized novel, *A Journal of the Plague Year*.

The third modern plague pandemic originated during the middle Nineteenth Century from the wild rodent reservoir for the disease that was present in Yunnan province, China. By 1894, it had spread to Hong Kong, and by 1896 it was prevalent throughout India. Plague was present in most major ports located on every continent by 1900, all carried by infected rats and fleas traveling the international trade routes on the many newly commissioned steamships from the later 1800s.

As is now well-known, the plague bacillus, *Yersinia pestis*, circulates in animal reservoirs, particularly rodents, which can act as immune hosts for the disease. It is still endemic in various locales throughout North and South America, such as in the region the author currently resides in New Mexico. It is primarily a disease of fleas, particularly for the oriental rat flea (*Xenopsylia cheopis*). Rodents, such as rats, do not themselves start the spread of bubonic plague, and are typically themselves among the first victims. A rodent-borne infection in humans occurs when a person is bitten by a flea that itself has been infected by biting a rodent which in turn had been bitten by a flea carrying the disease or is possibly an immune rodent reservoir. As a recent example of the endemic nature of the plague in New

Mexico, part of a news bulletin is given below from the New Mexico Department of Health reporting on a fatal human plague case in Rio Arriba County in August of 2020:

> The New Mexico Department of Health (NMDOH) reports the death of a man in his 20s from Rio Arriba County of septicemic plague, the first human plague death in New Mexico this year, and the second human plague case overall.
>
> The Rio Arriba County man died after being hospitalized. An environmental investigation will take place at the person's home to look for ongoing risk to immediate family members, neighbors and others in the surrounding community.
>
> Plague is a bacterial disease of rodents and is generally transmitted to humans through the bites of infected fleas but can also be transmitted by direct contact with infected animals, including rodents, wildlife and pets.
>
> Pets that are allowed to roam and hunt can bring infected fleas from dead rodents back into the home, putting household members at risk.
>
> "Plague activity in New Mexico is usually highest during the summer months, so it is especially important now to take precautions to avoid rodents and their fleas which can expose you to plague," said Department of Health Secretary Kathy Kunkel.
>
> To prevent plague, the Department of Health recommends that you:
>
> Avoid sick or dead rodents and rabbits, and their nests and burrows.
>
> Prevent pets from roaming and hunting.
>
> Talk to your veterinarian about using an appropriate flea control product on your pets as not all products are safe for cats, dogs, or your children.
>
> Clean up areas near the home where rodents could live, such as woodpiles, brush piles, junk and abandoned vehicles.
>
> Have sick pets examined promptly by a veterinarian.

See your doctor about any unexplained illness involving a sudden and severe fever.

Put hay, wood, and compost piles as far as possible from your home.

Don't leave your pet's food and water where rodents and wildlife can get to it.

Symptoms of plague in humans include sudden onset of fever, chills, headache, and weakness. In most cases there is a painful swelling of the lymph node in the groin, armpit or neck areas. Plague symptoms in cats and dogs are fever, lethargy and loss of appetite. There may be a swelling in the lymph node under the jaw. With prompt diagnosis and appropriate antibiotic treatment, the fatality rate in people and pets can be greatly reduced. Physicians who suspect plague should promptly report to the New Mexico Department of Health.

This is the first human plague-related death in New Mexico since 2015. There was a single human plague case in 2019 in a 72-year-old man from Torrance County, and no human plague cases in 2018.

There have been two animal plague cases in New Mexico in 2020: one in a dog and one in a cat. Both were from Santa Fe County. There were two animal plague cases in 2019, a dog from Quay County and a cat from Santa Fe County; and three animal plague cases in 2018, two dogs from Santa Fe County and one dog from Torrance County.

* * *

As noted earlier, Alexandre Yersin identified in 1894 the bacillus responsible for the plague in the buboes of human plague victims in Hong Kong; much later, the bacillus was named *Yersinia pestis* in his honor. Yersin had been sent by the Pasteur Institute in Paris with the explicit task of identifying the plague microbe. Yersin proved experimentally that *Yersinia pestis* was the sought for agent by

first injecting guinea pigs with material from the bulboes of plague victims, observing their subsequent deaths, and then identifying the multitude of *Yersinia pestis* that had grown within the guinea pigs prior to their demise.

An account of Yersin's discovery is given in an external Appendix using an excerpt from an informative article written by Ludwik Gross (1904–1999), himself a prominent virologist who discovered several viruses capable of producing cancer. This article appeared in the *Proceedings of the National Academy of Sciences* in August of 1995, under the title: *How the plague bacillus and its transmission through fleas were discovered: Reminiscences from my years at the Pasteur Institute in Paris.*

Besides identifying the plague bacillus, Yersin made a "surprising observation" that lead him to the (abductive) conjecture that rats were also prone to the plague. This observation was the presence of a large number of dead rats lying in the streets and elsewhere immediately before a plague outbreak occurred among humans. Yersin confirmed this suspicion by examining the organs of these dead rats under the microscope, thus becoming the first person to find that they were also full of the same bacilli present in human plague victims. Yersin also took note of the many regional stories that rats appeared to die in great numbers just prior to the occurrence of a plague epidemic among humans. Stated in other words, an epizootic infection in rats typically preceded a human epidemic of plague, with rats having as great a mortality as did humans. What Yersin did not identify was how the plague was actually transmitted from rat to rat or from man to man. That transmission mechanism was to be discovered by Paul-Louis Simond a few years after Yersin's identi-

fication of the plague bacillus. The commentary from Gross in an external Appendix, first deals with Yersin's observations about rats, and then moves on to Simond's explicit discovery of the flea as the primary means of plague transmission between and among rats and humans.

As is apparent from the commentary by Ludwik Gross, Simond's insightful abductive hypothesis that the rat flea was the major means of plague transmission from rat to rat and from rat to human was based on several "surprising" observations that all made "sense" if the flea transmission mechanism was operative. A few of these suggestive observations are reviewed below that led Simond to his "flea hypothesis" and then to the experimental demonstrations that supported the correctness of this conjecture.

To begin, Simond had Yersin's prior work as background that plague is also, or even primarily, a disease of rats, and the same bacillus produces the plague in both rats and in humans; also, a human plague epidemic is commonly foreshadowed by a large die-off of rats. To this understanding, Simond added the following:

a) the plague appeared to be transmittable from sick to healthy individuals separated by some distance and not known to have any physical contact. The popular theories of contagion through the atmosphere and/or from contaminated soil were not as plausible when new victims were at considerable distances away from individuals having the plague.

b) native wisdom held that any contact with sick or dead rats would lead to plague infection. Simond himself had several direct observations of such contact that led to the plague when the rats had newly died but not when the rats had been dead for some period of

time. In these latter cases, all of the fleas had long departed the cold rat carcasses and were in search of still warm hosts. We quote several of these observational instances below that were reported in Simond's seminal paper, *La propagation de la peste* (1898), documenting the discovery of the flea as the principal agent of plague transmission; a few of these were also mentioned in the commentary by Gross:

> ... One day, employees arriving in the morning noticed a large number of dead rats on the floor. Twenty laborers were ordered to clean the floor of the dead animals. Within three days, ten of them developed plague. None of the other employees became ill.
>
> ...
>
> Two weeks later, a mother and daughter received permission to go back to the village to bring clothing from their house. They found several dead rats on the floor of the house. They picked up the rats by their tails and threw them out on the street and then returned to the camp. Two days later, both developed plague.
>
> ...
>
> one more observation: on 13 May 1898, in Bombay, a man walked into a stable to take care of his horse and found there a dead rat on the floor. He picked up the rat by the tail and threw it out. Three days later he developed plague.
>
> ...
>
> On the rats captured alive, and on the rats which had just died, the fleas were thicker than I had every seen them. ... We have to assume that there must be an intermediary between a dead rat and a human. This intermediary might be the flea.

c) healthy rats have very few fleas, and continually groom themselves to keep free of fleas. Sick rats, on the other hand, have many fleas and once a rat dies, the fleas leave immediately to find new hosts, including those that may be human. This partially explained

why rats were especially dangerous when freshly dead but not later when cold — by that time, the fleas have all departed.

d) Simond was able to see the plague bacilli in the stomach of fleas that had fed on infected rats, but was unable to identify such bacilli in fleas taken from healthy rats.

e) Simond noted that the skin of a number of plague patients had blisters (called phlyctena) near their buboes that contained plague bacilli and which appeared to be caused from insect bites such as by fleas. These blisters were in anatomical proximity to plague-infected lymph nodes, suggesting that insects transmitted the pathogen through blood-feeding. Although Simond was not the first to observe these phlyctena on the extremities of plague victims, his actual conjecture that these small lesions might be the result of flea bites illustrates Pasteur's dictum that "in observation and experiment, chance favors only the prepared mind."

f) Simond observed that the introduction of plague-rats into a healthy area was generally followed by an epidemic of plague among humans, but the introduction of an infected man was not often followed by an epidemic. This suggested that transmission generally proceeded from plague infected rats to humans and not by infectious contagion among humans (although it is now known that pneumonic plague can be transmitted from one person to another through infected droplets in the air).

g) Simond showed that rats were not usually infected by eating the infected tissues of other dead rats, but when crushed infected fleas were injected, plague was produced. Also, fleas seemed to remain infected for a considerable time period, which might help explain disease carry-over from season to season. Simond found that in areas

where plague had been epidemic, rats showed a relative immunity to the disease. These immune rats could conceivably remain as longer-term reservoirs for the plague bacillus.

h) Simond noted that in the absence of fleas, rats could not be infected by mere close contact with rats that had died of the plague.

i) By far, the most convincing evidence for the flea transmission of the plague was the experimental cage set-up reviewed by Gross. Simond carried out a number of replications of this procedure that all led to the same conclusion regarding plague transmission from an infected rat to one that was healthy through the mechanism of flea bites. A statement of the crucial experiments in Simond's own (translated) words follow:

> Without delay I proceeded to the experiment I had in mind since the time in Cutch-Mandvi when I had discovered Yersin's bacillus in the digestive tract of fleas taken from plague-ridden rats. I prepared a device consisting of a large glass bottle whose bottom was covered with sand, which would absorb the urine of the rats. The lid consisted of wire mesh covered with fabric held tightly to the neck of the bottle with a drawstring. I was fortunate enough to catch a plague infected rat in the home of a plague victim. In the rat's fur there were several fleas running around. I took advantage of the generosity of a cat I found stalking the hotel premises, borrowing some fleas from it. Once the sick rat was in the bottle, I deposited upon it the cat's fleas from a test tube. I was thus quite sure the rat would be covered with parasites.
>
> After 24 hours the animal I was experimenting on rolled up into a little ball, with its hair standing on end; it seemed to be in agony. I then introduced into the bottle a small metal cage containing a perfectly healthy young Alexandria rat caught several weeks before and kept sequestered from any danger of infection. The cage was suspended with the inside of the bottle several centimeters above

the layer of sand. The cage had three solid sides, but the other three sides were covered by wire screen with a mesh size of about six millimeters. The rat inside the cage could not have any contact with the sick rat, the wall of the bottle or the sand.

The next morning the sick rat had died without having moved from where it had been the day before. I left its body in the bottle for one more day. Then I carefully removed it, plunged it into alcohol and performed an autopsy. The blood and organs all contained an abundance of Yersin's bacillus. During the next four days the other Alexandria rat remained imprisoned in its cage and continued to eat normally. About the fifth day, it seemed to have difficulty moving. By the evening of the sixth day it was dead. An autopsy of this one (previously uninfected rat) revealed buboes both inguinal and axillary. The kidney and liver were swollen and congested. There were abundant plague bacilli in the organs and blood. That day, 2 June 1898, I felt an emotion that was inexpressible in the face of the thought that I had uncovered a secret that had tortured man since the appearance of plague in the world. The mechanism of the propagation of plague includes the transporting of the microbe by rat and man, its transmission from rat to rat, from human to human, from rat to human and from human to rat by parasites. Prophylactic measures, therefore, ought to be directed against each of these three factors: rats, humans and parasites. I subsequently repeated the same experiment with similar results.

Although Simond was the first investigator to demonstrate experimentally the transmission of a bacterial disease by an insect, he readily acknowledged that much more work needed to be done before the full importance of this discovery could be understood. This type of humility is clear in the following summary comments from his 1898 paper:

> While I admit that this theory [transmission by flea] has not yet the full weight of demonstrated fact, we believe that the di-

verse forms of spontaneous plague, in humans and animals, comes normally from a single mode of infection: intracutaneous parasitic inoculation. Nevertheless, new research is needed before we attribute the exclusive role to it. Nor do we know anything about the changes undergone by the microbe in the body of the parasite. Is the virulence increased, preserved or lessened? Is preservation (of virulence) long or short?

One can suspect that the natural history of fleas, their greater or lesser number according to local conditions, ought to play a major role in the development and in the gravity of the epidemic, and perhaps furnish the solution to the problem of recrudescence [recurrence of an undesirable condition] of the disease, as yet incompletely resolved.

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Chapter 11

Carlos Finlay (Walter Reed)

> Havana, Cuba, in which city yellow fever had not failed to make its yearly appearance during the past one hundred and forty years ... Havana was freed from yellow fever within ninety days.
>
> – Walter Reed (1851–1902)

Yellow fever is an acute viral hemorrhagic disease, usually of a fairly short duration, transmitted through the bite of female infected mosquitoes of the species now called, *Aedes aegypti*. The word "yellow" refers to a jaundice that can affect some people through their skin and eye color. General symptoms include fever, severe headache, muscle and back pain, nausea, vomiting, and general fatigue. Once contracted, the virus incubates in the body for some three to six days. The vast majority of people who become infected with the yellow fever virus never experience any symptoms at all, but if they do, their symptoms will generally disappear after three to four days. A small percentage of these latter individuals (about 15%) then enter a second more toxic phase within some twenty-four hours of recovering from their initial set of symptoms; about half of this latter group will then die within seven to ten days. Individuals in this smaller severe cohort invariably develop jaundice from liver damage, produce dark urine accompanied by abdominal pain and the vomiting of black ma-

terial containing blood, all ending with generalized organ failure. It is this last stage of black vomit that provides the Spanish name for yellow fever of *vómito negro*. The only positive aspect of having had yellow fever, no matter how severe, is the lifelong immunity against ever having the disease again.

Yellow fever (or, alternatively, yellow "jack") came to the Americas accompanied by its own mosquito transmission vector in the middle Seventeenth Century as part of the burgeoning slave trade from Africa and the consequent development of sugar cultivation throughout the Caribbean. Some of the first outbreaks of what were most likely yellow fever occurred in the late 1640s on the windward islands of Barbados and Guadeloupe. Many major North American outbreaks followed over the next several hundred years including an especially devastating epidemic in the American capital of Philadelphia in 1793 that forced the whole government including George Washington to abandon the city. The leading explanation at the time for this outbreak was the usual one of miasmatic ("bad air") influences, prominent as a putative cause of disease up to at least the later part of the Victorian Era. As an example of this type of thinking, the most prominent doctor of the time, Benjamin Rush, believed the malady to result from a large batch of rotting coffee from a ship moored in the Philadelphia harbor. This last gruesome episode in American history, including a discussion of the rotting coffee conjecture as a cause, and the shunning of prominent individuals who contracted the disease, such as Alexander Hamilton, is told in detail by J. H. Powell in his 1949 book, *Bring Out Your Dead: The Great Plague of Yellow Fever in Philadelphia in 1793*.

A few years after the major outbreak of yellow fever in Philadel-

phia, one of the more formative events in American history occurred as an indirect result of yellow fever. As most of us learned in high school, the acquisition of a significant portion of the current United States west of the Mississippi was done through the sale of land from France in 1803. At one time, Napoleon had extensive plans for an American empire based on France's presence throughout the Caribbean, and in what would later be known as the Louisiana Purchase, bounded by the Mississippi River in the east and by several major rivers, such as the Rio Grande, further to the west. An 1801 revolt by African slaves in Haiti, however, was the impetus for Napoleon to change his plans. Of the large military force sent to Haiti under Napoleon's brother-in-law, General LeClerc, some 27,000 soldiers died just from yellow fever including General LeClerc himself. The African slaves, on the other hand, being more-or-less immune from childhood, suffered no such devastating casualties.

Besides Haiti gaining its independence from France partially because of the effects of yellow fever on its army, it also refocused Napoleon's empire building efforts elsewhere, such as to the massively unsuccessful invasion of Russia in 1812. In capitalizing on France's re-emphasis away from North America where yellow fever was endemic, President Thomas Jefferson and Secretary of State James Madison negotiated the sale of this enormous area of land known as the Louisiana Purchase for fifteen million dollars, thereby avoiding any further war with European powers in the westward expansion of the United States.[1]

In 1878, and some seventy-five years after the Louisiana Purchase was completed, the worst yellow fever outbreak in North American history emanated from New Orleans and extended throughout the

whole Mississippi River valley up through Memphis. This particular episode is vividly told by Molly Caldwell Crosby in *The American Plague: The Untold Story of Yellow Fever, The Epidemic That Shaped Our History* (2006). Some 20,000 people died during this short period in and around Memphis, completely devastating the city itself. It would take another twenty-five years after this catastrophic epidemic along the whole eastern boundary of the Louisiana Purchase that a solution to the cause of yellow fever would be found.

Although hypothesized in 1881 by one of the main protagonists of this chapter, Carlos Finlay (1833–1918), the mosquito mechanism for the transmission of yellow fever was not demonstrated unequivocally until the early 1900s. The proof came as a direct result of the United States occupation of Cuba after the Spanish-American War that was fought during the last decade of the Nineteenth Century. It became apparent militarily that a solution for controlling yellow fever was needed — many more soldiers were dying of diseases such as yellow fever and malaria than from any actual engagement in combat. Because of this pressing military necessity, the U.S. Army Surgeon General deployed an Army Yellow Fever Commission to Cuba in June of 1900 to search for a way to combat yellow fever, among other diseases. The Commission was lead by an army doctor, Walter Reed (1851–1902), who later became the eponymous benefactor for the large military hospital in Bethesda, Maryland. The Commission included three other doctors known for their medical research skills: James Carroll (1854–1907), Aristides Agramonte (1868–1931), and Jesse Lazear (1866–1900).

A central protagonist for this chapter, as noted earlier, was not any member of the Yellow Fever Commission but rather a Cuban doctor

by the name of Carlos Finlay. It was Finlay's insightful (abductive) conjecture published in 1881 that the mosquito was the mechanism of transmission for yellow fever that motivated Reed and his colleagues to pursue and prove the correctness of Finlay's mosquito hypothesis. The main part of this chapter begins with Carlos Finlay and his 1881 paper that first presented the conjecture that yellow fever was transmitted by the bite of the female mosquito. A discussion then follows of the definitive set of experiments and demonstrations carried out by Reed and his colleagues that finally proved what Finlay had proposed some twenty years earlier but was unable to demonstrate conclusively on his own.

*. *. *

Carlos Finlay (1833–1915) was a Spanish/Cuban doctor and amateur epidemiologist, born in Cuba to a Scottish physician father and a French mother. He received a medical degree in 1855 from the Jefferson Medical College located in Philadelphia, and soon thereafter returned to Havana to set up an ophthalmology practice. Finlay's initial work with yellow fever was carried out in the 1870s; he was the first (or at least among the first) to (abductively) conjecture that the mosquito was the carrier or disease vector for the organism causing yellow fever. When the female mosquito, identified by Finlay as from the genus *Aedes*, bites a yellow fever victim, a subsequent bite of a non-immune individual could transmit the disease.

As noted in Finlay's paper, parts of which are presented in an external Appendix, a number of observations/anomalies led to this abductive conjecture that a transmission agent, such as the mosquito, was necessary for yellow fever to flourish. A major distinction be-

tween yellow fever and other diseases, such as smallpox, was that yellow fever did not seem to be contagious and capable of spreading by person-to-person contact. The evidence for this was present in all the non-immune people who cared for yellow fever patients but never contracted the malady themselves. Also, yellow fever did not appear to be a standard disease of filth, such as cholera or typhoid fever. Sanitary clean-ups done periodically in Havana were effective in the prevention of several diseases but not for yellow fever. What seemed to control yellow fever outbreaks more than sanitary conditions, was the rise and fall of temperature, with yellow fever disappearing with the first frost and being more prevalent during the hot summer months. Altitude also seemed to be a major factor in the presence of yellow fever with higher altitudes less prone to the disease. Presumably, mosquitos had a more difficult time of flying in higher altitudes, particularly when engorged with blood.

Because yellow fever is a blood disease and (female) mosquitos feed on blood, they are an obvious agent to consider for transmission. The observation that yellow fever can transverse oceans and occur in cities far distant from one another also suggests that an agent is needed other than just atmospheric influences. Yellow fever, for example, is particularly rife in marshy areas where mosquitos breed; and generally, there is a strong positive correlation between yellow fever and conditions conducive to the presence of mosquitos.

Finlay presented his mosquito transmission theory of yellow fever to the International Sanitary Conference in 1881. It was published both in Spanish and in an English translation that same year in the *New Orleans Medical and Surgical Journal*. The English translation appeared under the title: *The Mosquito Hypothetically Con-*

sidered As the Agent of Transmission of Yellow Fever. A redacted but still extensive version of Finlay's 1881 article appears in an external Appendix that was reprinted in *Military Medicine* in 2001. This particular translation from the original Spanish was done by Carlos Finlay himself.

Carlos Finlay is typically credited with being the first to conjecture that the mosquito was the likely transmission mechanism for yellow fever, based partly on his observations as to the geographical co-occurrence of the hemorrhagic disease of yellow fever and the ubiquitous presence of mosquitos that fed on blood. Finlay, however, may have had more help in developing his ideas than he otherwise admited. As far as precursors, Finlay merely says: "Finally, by reasons of other considerations which need not be stated here, I came to think that the mosquito might be the transmitter of yellow fever." François Delaporte in his *The History of Yellow Fever* (1991), argues strongly that it was the published work of Patrick Manson (1844–1922) in the late 1870s on the transmission of filariasis, which causes elephantiasis, by parasitic worms through mosquitos that may have been the primary inspiration for Finlay. Or, possibly, Finlay knew of the musings of Louis-Daniel Beauperthuy (1808–1871) working in Venezuela and published in 1854, as to the spread of both malaria and yellow fever through mosquitos. Even somewhat earlier in 1848, Finlay may have been aware of the suggestion of Josiah Nott (1804–1873) as to a possible mosquito insect vector for yellow fever. Irrespective of these possible precursors, it was Finlay who popularized the mosquito transmission theory for yellow fever and worked tirelessly but unsuccessfully to prove it during the last several decades of the Nineteenth Century.

Carlos Finlay may have had the correct idea as to the mosquito being the transmission vector for yellow fever, but he didn't have a complete understanding of all the conditions necessary to effect successful conveyance. Two requirements, in particular, needed to be satisfied: the mosquito had to bite a yellow fever victim within some three days of being symptomatic; and secondly, there was an "extrinsic incubation" period of at least twelve days before the mosquito could be infective. Mosquitos did not merely transmit yellow fever mechanically through a bite as Finlay believed, but rather they had to first serve as intermediary hosts to develop the virus more fully so that it could then be transmitted through their salivary glands. Over the one hundred or so attempted inoculations by mosquito that Finlay attempted in the late 1880s and 90s, none could be shown unambiguously to produce yellow fever. Apparently, Finlay was only able to produce periodically what could be charitably called "abortive yellow fever," as was done in the few cases reported in his 1881 paper.

The concept of "extrinsic incubation" was developed by Henry Rose Carter (1852–1925) through his detailed study in 1898 of the two small communities of Orwood and Taylor in rural Mississippi. Carter was able to determine the time it took between the onset of yellow fever infections among individuals in isolated farmhouses and the occurrence of secondary cases in these same locations. Carter's work in these two Mississippi towns appeared in 1900 in the *New Orleans Medical and Surgical Journal* under the title: *A Note on the Interval Between Infecting and Secondary Cases of Yellow Fever from the Records of the Yellow Fever at Orwood and Taylor, Mississippi in 1898.* It was an understanding of this mandatory period of "extrinsic incubation" that permitted Reed and the Yellow

Fever Commission to be successful in documenting the mosquito as the vector of yellow fever transmission. And conversely, it was the lack of this knowledge that doomed Finlay's attempted demonstrations over the twenty-odd years after his groundbreaking 1881 paper had appeared.

* * *

The Yellow Fever Commission began its work in Cuba during the month of June, 1900. Walter Reed and his assistant, James Carroll, arrived together directly from Washington; both Jesse Lazear and Aristides Agramonte were already stationed in Cuba. Lazear had been assigned to Columbia Barracks several months earlier and placed in charge of the hospital laboratory at the camp. Aristides Agramonte was born in Cuba but raised in the United States after his father had been killed in the battle against the Spanish during the First Cuban War for Independence. He had been stationed for several years in Cuba, tasked with the study of yellow fever. At the time the Commission began its work, Agramonte was in charge of the division laboratory at the Military Hospital Number One in Havana, located next to the University of Havana. It was generally presumed that Agramonte was immune to yellow fever because he had been born in Cuba; such immunity, however, was never tested explicitly during the time the Commission was at work.

One of the first tasks taken on by the Commission was to investigate a claim made in 1896 by an Italian bacteriologist, Guiseppe Sanarelli (1864–1940), that yellow fever was caused by a particular organism he called *Bacillus icteroides*. Sanarelli contended that he was able to isolate consistently the bacillus from yellow fever pa-

tients. Led by the lab work of Agramonte, Sanarelli's bacillus was found in one-third of yellow fever patients and cadavers; it was also present, however, in individuals who suffered from many other diseases. Sanarelli's organism belonged to a group of hog-cholera bacilli and was merely a secondary invader and contaminant whenever it appeared in a yellow fever victim, and therefore, it was not the initial cause of the malady itself.

A second major task taken up by the Commission was Finlay's conjecture as to the mosquito being the means of transmission for the organism causing yellow fever. Experiments involving eleven nonimmune individuals were carried out by allowing mosquitos that had bitten infected individuals to then bite one of the eleven nonimmune volunteers. There were a total of nine negative and two positive results from this process. The two positive cases were from one of the Commission members, James Carroll, and the second from William Dean, an enlisted man residing at the military reservation. There was some slight ambiguity as to the probable cause of yellow fever in the case of Carroll because he had visited several areas of yellow fever activity after being bitten. There was no such ambiguity, however, with respect to William Dean. His movements after being bitten were sufficiently isolated from other possible sources of yellow fever infection to allow a reasonable conclusion of causation between the infected mosquito bite(s) and the subsequent case of yellow fever. In other words, Dean could be considered the first truly controlled experimentally induced case of yellow fever.

Based on these initial results regarding the Sanarelli bacillus and the Carroll and Dean contractions of yellow fever after being bitten by infected mosquitos, the Commission presented a paper to

the American Public Health Association in October of 1900. It was published that same month in the *Philadelphia Medical Journal* under the title: *The Etiology of Yellow Fever — A Preliminary Note*. Parts of this paper are given in an external Appendix that review the mosquito transmission theory and the eleven individuals, including Carroll and Dean, who experimentally received mosquito inoculations. In addition, there is some discussion regarding another Commission member, Jesse Lazear, and his accidental bite by an infected mosquito. Lazear died of yellow fever as a result of this unfortunate accident.

After publication of the *Preliminary Note* and the death of Jesse Lazear, the remaining three members of the Commission continued their work in four distinct areas that all involved how yellow fever could be transmitted:

1) First and foremost was the non-immune human experimentation using the bites of infected mosquitos. This work explicitly took into account the extrinsic incubation period necessary for a mosquito to become infective.

2) As to whether yellow fever could be acquired in ways other than through the bites of infected mosquitos, it was shown that yellow fever could also be passed by the subcutaneous injection of blood from a yellow fever patient to a non-immune individual.

3) The dominant theory of yellow fever transmission at the time was through fomites, defined as objects or materials that are likely to carry infection such as clothing, bedding, furniture, and similar articles that had been in contact with yellow fever patients. This fomite research by the Commission involved a separate building constructed to contain a variety of articles that had been in use with yellow fever

victims, and to house non-immune volunteers for various periods of time.

4) Again, through the use of a specially constructed separate building, the concept of an "infected house" was studied in detail using infected mosquitos and a non-immune individual who spent time in the structure and allowed the contained mosquitos to freely feed.

A second paper entitled *The Etiology of Yellow Fever: An Additional Note* was published in the *Journal of the American Medical Association* in February of 1901. This followup contribution reviewed the results of experimentation in the four areas just mentioned: five cases of yellow fever experimentally induced by the bites of infected mosquitos; the negative results of contact with fomites; the positive result obtained from how a building becomes "infected"; and four cases of yellow fever contraction through the subcutaneous injection of blood obtained from yellow fever patients. Parts of this second article are given in an external Appendix that provide more detail for each of the four areas of experimental study.

Although this second "Additional Note" published in February of 1901 gave rather definitive evidence for how yellow fever could be transmitted, further human experimentation continued at Las Animas Hospital. One set of studies was conducted by the Cuban yellow fever expert, Juan Guitéras; it was intended to produce mild cases of yellow fever that would then provide lifetime immunity against the disease. Unfortunately, three deaths occurred as a result of this last study including a volunteer American Army nurse, Clara Maass. This last death, in particular, led to public pressure to eventually ban all such human experimentation. Because the primary purpose for human experimentation was to prove that yellow fever transmission

could occur through the mosquito, and that had been accomplished, the risk of further death was deemed too high to justify the possible rewards that such experimentation could generate.

Another set of studies at Las Animas Hospital were instituted by James Carroll at about the same time as the death of Clara Maass. These studies centered around the idea that whatever the actual agent was that caused yellow fever, it was so small that it could pass through a porcelain (Berkefeld) filter. If the yellow fever agent had been a bacterium of the type being identified in the late Nineteenth Century by Pasteur and Koch for other diseases, it could not pass through the filter. If it did, it would now be known as a "filterable virus." The first such filterable virus in animals was identified in the late 1800s and produced hoof-and-mouth disease in cattle.

The experiments carried out by Carroll showed that blood serum from a yellow fever patient passed through a porcelain filter was still capable of producing yellow fever when injected subcutaneously into a non-immune individual. Also, when such blood serum was heated appropriately, its ability to produce yellow fever was lost. Carroll's experimentation represented the first transmission of a human disease by a filterable agent, and demonstrated that the etiological cause of yellow fever was so small that it could not be seen with any of the microscopes then available. Such an agent, however, had to be present in the blood serum because it could generate cases of yellow fever after filtration but could be destroyed by appropriate heating. When electron microscopes came into use much later, it was then possible to actually "see" the particular viral agent producing yellow fever.

* * *

One of the more controversial aspects of the Commission efforts to untangle the causes of yellow fever was the necessity of using humans for experimentation. At the time, no animal was known to be susceptible to yellow fever and/or to its transmission through the bite of infected mosquitos, or for that matter, even by the subcutaneous inoculation with blood from a yellow fever victim. This difficulty of having no animal model to help carry out experimentation was explicitly commented on in an editorial that accompanied the "Additional Note" paper that appeared in the *Journal of the American Medical Association*. A short part of this editorial follows:

> At first thought one might be tempted to characterize the experiments carried out on the [sic] human beings as unwarrantable, but as we are assured that everything was done with the full consent and full knowledge of the nature of the experiments on the part of the non-immunes who placed themselves at the disposal of the experimenters, there can be no adequate reason for complaint on this score. Whatever the opinion concerning this phase of the experiments, it in no way modifies the scientific value of the results. The non-immunes that allowed themselves to be bitten by mosquitoes that previously has sucked the blood of yellow fever patients, as well as the persons that slept in the "Infected Clothing and Bedding Building," seem to have submitted themselves unreservedly to the requirements of the experiments. There are examples here of unselfish devotion to the cause of humanity and of science.

Two mitigating factors were present in the use of human subjects in the Commission's work. First, the Commission members were willing to undergo experimentation on themselves, although Agramonte was supposedly immune and Reed was absent whenever such experimentation occurred. Secondly, and possibly for the first time ever, explicit "research consent" forms were used that required a

subject's signature. These forms were done in both English and Spanish and spelled out some of the risks involved. Modern ethicists might question the monetary inducements offered to a poor immigrant population and the questionable argument about getting yellow fever anyway in the course of one's stay in Cuba — so why not get paid for it and have good medical assistance if the disease were contracted? What follows is the English version of the consent form that was used for one individual, Antonio Benigno. Whether if would pass a review today by a university's Institutional Review Board is doubtful:

> We the undersigned, Antonio Benigno, being more than twenty-five years of age ... here states [that] being in the enjoyment and exercise of his own very free will, that he consents to submit himself to experiments for the purpose of determining the methods of transmission of yellow fever, made upon his person by the Commission appointed for this purpose by the Secretary of War of the United States, and that he gives his consent to undergo the said experiments for the reasons and under the conditions below stated.
>
> The undersigned understands perfectly well that in case of the development of yellow fever in him, that he endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his stay in this island, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said Commission the greatest care and the most skillful medical service.
>
> It is understood that at the completion of these experiments, within two months from this date, the undersigned will receive the sum of $100 in American gold and that in case of his contracting yellow fever at any time during his residence in this camp, he will receive in addition to that sum a further sum of $100 in American gold, upon his recovery and that in case of his death because of this disease, the Commission will transmit the said sum (two hun-

dred American dollars) to the person whom the undersigned shall designate at his convenience.

The undersigned binds himself not to leave the bounds of this camp during the period of the experiments and will forfeit all right to the benefits named in this contract if he breaks this agreement.

And to bind himself he signs this paper in duplicate, in the Experimental Camp, near Quemados, Cuba, on the 26th day of November, Nineteen-hundred.

On the part of the Commission:
Walter Reed

The contracting party:
Antonio Benigo

* * *

The tenth conclusion of the Commission had the most practical application.[1] As has been demonstrated continually since that time, the spread of yellow fever can be best controlled by measures directed to the destruction of mosquitoes and to the protection of the sick against the bites of these particular insects. Taking the implication of this conclusion to heart, the Chief Sanitary Officer of Havana, William Gorgas, and the U. S. military engineers under his direction, eliminated yellow fever in Havana in six months starting in February, 1901. The so-called "mosquito brigades" went from house to house destroying whatever mosquito habitat could be identified. Water cisterns were covered with netting to prevent the laying of eggs; and small amounts of kerosene was poured into standing water to suffocate any remaining mosquito larvae. Also, yellow fever patients

[1]From an external Appendix: (10) The spread of yellow fever can be most effectually controlled by measures directed to the destruction of mosquitoes and the protection of the sick against the bites of these insects.

were housed in fully-screened buildings that prevented any access by mosquitos.

The conclusion of the Reed Commission that to prevent yellow fever the transmission vector had to be eliminated, proved crucial outside of Havana in the early 1900s and beyond. William Gorges (1854–1920) oversaw the sanitary measures that needed implementation to complete the Panama Canal. This is in contrast to the French who in the late 1800s could not overcome the difficulties posed by the mosquito-borne diseases of yellow fever and malaria in an earlier attempt to construct a Panama Canal. The last major outbreak of yellow fever in North America occurred in New Orleans in 1905. Again, mosquito eradication stemmed this last outbreak of what had by then become known as the "American Plague."

Yellow fever is still present in parts of Africa and South America in the form of jungle primates and their mosquito transmission vectors. Here, yellow fever is maintained through vertical transmission from female mosquitos to their offspring. Periodically, visitors to these regions who are not vaccinated against yellow fever contract the disease and return to North America with active cases. Given the general absence of the relevant mosquito vectors to serve as a method of further transmission, these isolated instances have not led to any generalized North American outbreaks. However, one still should be vigilant and use the available yellow fever vaccines whenever traveling to these parts of the world where yellow fever is endemic. At present there is still no medical "cure" for an individual who contracts a case of yellow fever.

* * *

Walter Reed died of a ruptured appendix and ensuing peritonitis in November of 1902, soon after the initial papers of the Commission had been published. Although Reed obviously never saw the naming of the major military hospital in his honor, he did recognize clearly the importance of his work and that of the Commission. In a letter to his wife written on New Year's Eve at the turn of the century, he wrote:

> [I]t has been permitted to me and my assistants to lift the impenetrable veil that has surrounded the causation of this most dreadful pest of humanity and to put it on a rational and scientific basis. ... The prayer that has been mine for twenty or more years, that I might be permitted in some way or sometime to do something to alleviate human suffering has been answered!

Notes

[1]The consequences of the Haitian slave revolt and of the subsequent independence of the country were truly horrific. France unbelievably demanded reparations in 1825 for the loss of its land and slaves, or otherwise France would go to war with the nascent state. For the next one hundred and fifty or so years, Haiti was bled dry of resources that could have been used to build the still impoverished country. In the spring of 2022, *The New York Times* ran a series of articles that delineated this unfortunate Haitian history. A lead-in to this complete series is given below, entitled: *6 Takeaways About Haiti's Reparations to France* (Eric Nagourney, May 20, 2022):

How did the modern world's most successful slave revolt give birth to a desperately poor nation? Here is a summary of what a team of *New York Times* correspondents found out.

A failed state. An aid trap. A land seemingly cursed by nature and human nature alike.

When the world looks at Haiti, one of the poorest nations on the planet, sympathy for its endless suffering is often overshadowed by scolding and sermonizing about corruption and mismanagement.

Some know how Haitians overthrew their notoriously brutal French slave masters and declared independence in 1804 — the modern world's first nation born of a slave revolt.

But few know the story of what happened two decades later, when French warships returned to a people who had paid for their freedom with blood, issuing an ultimatum: Pay again, in staggering amounts of cold hard cash, or prepare for war.

For generations, the descendants of enslaved people paid the descendants of their former slave masters, with money that could have been used to build schools, roads, clinics or a vibrant economy.

For years, as *New York Times* journalists have chronicled Haiti's travails, a question has hovered: What if? What if the nation had not been looted by outside powers, foreign banks and its own leaders almost since birth? How much more money might it have had to build a nation?

For more than a year, a team of *Times* correspondents scoured long-forgotten documents languishing in archives and libraries on three continents to answer that question, to put a number on what it cost Haitians to be free. Here are the takeaways from a series of stories appearing this week.

The Double Debt That Started It All

When a French warship bristling with cannons sailed into the port of the Haitian capital in 1825, an emissary from King Charles X came ashore and delivered an astonishing demand: France wanted reparations from the people it had enslaved.

Ordinarily, the defeated are the ones who pay reparations, not the victors. Just a decade earlier, France had been forced to pay them to its European neighbors after the failed military campaigns of Napoleon — the very emperor whose forces were also defeated by the Haitians. But Haiti was virtually alone in the world, with no powerful allies. It was fearful of being invaded and eager to establish trade with other nations, so it agreed to pay.

The demand was for 150 million French francs, to be turned over in five annual payments, far more than Haiti could pay.

So France pushed Haiti to take a loan from a group of French banks to start paying. That Sisyphean weight came to be known as the double debt.

The True Cost to Haiti Then — and Today

The Times tracked each payment Haiti made over the course of 64 years. In all, they added up to about $560 million in today's dollars.

But the loss to Haiti cannot just be measured by adding up how much was paid to France and to outside lenders over the years.

Every franc shipped across the Atlantic to an overseas bank vault was a franc not circulating among Haiti's farmers, laborers and merchants, or not being invested in bridges, schools or factories — the sort of expenditures that help nations become nations, that enable them to prosper.

After reviewing thousands of pages of archival documents, some centuries old, and consulting with 15 of the world's leading economists, our correspondents calculated that the payments to France cost Haiti from $21 billion to $115 billion in lost economic growth over time. That is as much as eight times the size of Haiti's entire economy in 2020.

"Neocolonialism through debt," is how Thomas Piketty, one of the economists we spoke with, put it. "This drain has totally disrupted the process of state building," he said.

And that was only the beginning. The double debt helped push Haiti into a cycle of debts that hobbled the country for more than 100 years.

The French Bank That Struck Gold

The French government sapped Haiti with its demand for reparations, but in later years the French approached Haiti with a different tactic: the outstretched hand of a business partner.

After half a century of crushing payments tied to the double debt, Haitians celebrated the news that at last the country would have its own national bank, the sort of institution that in Europe had financed railroads and factories.

But the National Bank of Haiti was Haitian in name only. It was a creation of Crédit Industriel et Commercial, a Paris-based bank commonly known as C.I.C., and its investors. They controlled Haiti's national bank from Paris and took a commission on nearly every transaction the Haitian government made. Original records uncovered by *The Times* show that Crédit Industriel and its investors siphoned tens of millions of dollars out of Haiti, while saddling the country with still more loans.

It did not take long after the initial celebrations for Haitians to realize that something was wrong.

"Isn't it funny," one Haitian economist wrote, "that a bank that claims to come to the rescue of a depleted public treasury begins not by depositing money but by withdrawing everything of value?"

The U.S. Treated Haiti Like a Cash Register

When the American military invaded Haiti in the summer of 1915, the official explanation was that Haiti was too poor and too unstable to be left to its own devices. Secretary of State Robert Lansing made little effort to mask his contempt for the "African race," casting the occupation as a civilizing mission intended to end "anarchy, savagery and oppression."

But a hint of other motives had come the winter before, when a small team of Marines entered Haiti's national bank and strolled out with $500,000 in gold. Within days, it was in the vault of a Wall Street bank.

"I helped make Haiti and Cuba a decent place for the National City Bank boys to collect revenues," the general who led the U.S. forces in Haiti, said years later, describing himself as a "racketeer for capitalism."

National City Bank was the predecessor of Citigroup, and along with other powers on Wall Street, it pushed Washington to seize control of Haiti and its finances, according to decades of diplomatic correspondence, financial reports and archival records reviewed by *The Times*.

For decades to come, the United States was the dominant power in Haiti, dissolving parliament at gunpoint, killing thousands and shipping a big portion of Haiti's earnings to bankers in New York while the farmers who helped generate the profits often lived near starvation.

Some historians cite tangible gains for Haiti during the U.S. occupation, like hospitals, 800 miles of roads and a more efficient civil service. But they also point to the American use of forced labor, with soldiers tying up workers in ropes, making Haitians build roads for no pay and shooting those who tried to flee.

For a decade, a quarter of Haiti's total revenue went to paying debts controlled by National City Bank and its affiliate, according to nearly two dozen annual reports prepared by American officials and reviewed by *The Times*.

At times, the American officers who controlled Haiti's finances spent more of its money paying their own salaries and expenses than on public health for the entire country of about two million people.

The Scourge Within: Corruption

"They were betrayed by their own brothers, and then by foreign powers."

Those are the words of Georges Michel, a Haitian historian who, like many Haiti experts, says the country's troubles cannot be explained without acknowledging the deeply embedded culture of corruption.

The 19th-century Haitian official who engineered a sweetheart deal for a bank in France — and then retired there?

"That's not the first case of a Haitian official selling the interest of his country for personal gains," Mr. Michel said. "I would say it's almost a rule."

Haiti's leaders have historically ransacked the country for their own gain.

Elected legislators have spoken openly on the radio about accepting bribes and oligarchs sit atop lucrative monopolies, paying few taxes. Transparency International ranks it among the most corrupt nations in the world.

It is a problem of long standing.

In an 1875 loan, the French bankers took a 40 percent cut off the top. Most of the rest went to paying other debts, while the remainder lined the pockets of corrupt Haitian officials who, historians say, enriched themselves at the expense of their country's future.

Nearly a century later, when a bookish doctor named François Duvalier was elected president, the country's prospects looked good. For the first time in more than 130 years, Haiti was unburdened by crippling international debt.

That was in 1957.

For the next 28 years, Duvalier and his son shared a dictatorship notorious for corruption and brutality. Professionals fled the country. A desperate country became still more desperate, and the Duvaliers looted hundreds of millions of dollars.

Haiti was perhaps poorer than ever.

The History the French Don't Teach

The double debt has largely faded into history. Generations of French profited richly from the financial exploits of their forebears, but that is rarely taught in classrooms. *The Times* spoke to more than 30 descendants of families that received payments under Haiti's double debt. Most said they had never heard of it. "This is part of my family history I never knew," said one sixth-generation descendant of Napoleon's first wife.

That is no accident. France has worked hard to bury this part of its past, or at least play it down.

Even in Haiti, the full story was long unknown. Then in 2003, President Jean-Bertrand Aristide stunned Haitians by denouncing the debt imposed by France and demanding reparations.

France moved quickly to try to discredit him. Talk of reparations was alarming to a nation with other former colonies still suffering the legacy of exploitation. The French ambassador to Haiti at the time recalls the reparations demand as "explosive."

"We had to try to defuse it," he says.

Mr. Aristide even offered a precise figure for what France owed, eliciting mockery. But Haiti's long-term losses, *The Times* found, turned out to be surprisingly close to his estimate. He may even have been too conservative.

In 2004, Mr. Aristide found himself being hustled onto a plane in an ouster arranged by the United States and France. The Americans and the French have defended the move by citing the need for stability in Haiti, which was torn by unrest. But with the passage of time, another former ambassador acknowledged that there may have been other factors.

The Haitian president's abrupt removal, he told *The Times*, was "probably a bit about" his call for reparations, too.

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Chapter 12

Theobald Smith

> Research cannot be forced very much. There is always danger of too much foliage and too little fruit.
>
> – Theobald Smith (1859–1934)

> Discovery should come as an adventure rather than as the result of a logical process of thought. Sharp, prolonged thinking is necessary that we may keep on the chosen road but it does not itself necessarily lead to discovery. The investigator must be ready and on the spot when the light comes from whatever direction.
>
> – Theobald Smith (1859–1934)

Texas cattle fever (or, alternatively, Southern cattle fever) is a blood disease in cattle (bovine babesiosis) caused by a single-celled parasite (*Babesia bovis (bigemina)*) that infects and destroys red blood cells. This disease decimated major cattle herds during the Nineteenth Century, particularly throughout the Midwest in the late 1860s right after the end of the Civil War. One prominent example occurred in the summer of 1868 in Champaign County, Illinois. This episode was still part of the area's historical folklore over one-hundred years later when I heard the story while teaching at the University of Illinois. Apparently healthy Longhorn cattle from Texas were shipped up the Mississippi to the river town of Cairo and from there

by rail to various fields in Central Illinois near the towns of Sadorus, Tolono, and Champaign, and intermixed with the already present native cattle. After a relatively short period of time, the native cattle began to die *en masse*; the cattle from Texas, however, remained healthy, and in fact thrived on the fertile fields of Champaign County. As noted in the major report published in 1893 by this chapter's protagonist, Theobald Smith (1859–1934), this widespread midwestern outbreak of cattle fever in 1868 led to the systematic governmental response discussed in Smith's 1893 monograph to first find the cause of Southern cattle fever and then determine how it might be prevented.

In the 1890s, Theobald Smith showed that the organism causing Texas cattle fever was transmitted by the bite of infected larval ticks. The ticks themselves were transported on immune southern cattle brought into more northern regions where the ticks were absent. Smith's extensive research report published in 1893 was the first to document fully the transmission of a disease by an insect vector, foreshadowing similar discoveries several years later for yellow fever, malaria, typhus, and a few other maladies now known to be transmitted primarily through insects. The Smith document clearly characterized the specific protozoan organism causing cattle fever, explicated the life-cycle of the tick that allowed disease transmission, and identified Southern cattle as immune carriers and reservoirs for the disease.

Cattle fever arrived in North America sometime in the 1600s, presumably brought by cattle imported from Mexico and the Spanish colonies in the West Indies. One of the first written accounts of cattle fever occurring in the northern United States was from James

Mease (1771–1846), a prominent Philadelphia physician known for, among other things, the first tomato-based recipe for ketchup (in 1812). In September of 1825, Mease read before the Philadelphia Society for Promoting Agriculture, the following account of cattle fever that appeared in Pennsylvania in 1796. It provides an early vivid description of the devastation that cattle fever brought to the more northern herds, and which would not be completely understood for yet another hundred years:

> Account of a Contagious Disease propagated by a drove of Southern Cattle, in perfect health
>
> By James Mease, M.D.
>
> Read, September 20th, 1825
>
> In the Address which I delivered before this Society in January, 1817, I alluded to the singular circumstance of a drove of cattle, which, while enjoying perfect health, spread disease among all other cattle with which they mixed, and I promised to give a more full account of the facts on a future occasion.
>
> In the month of August of the year 1796, I was on a tour for the recovery of my health, and having called at Anderson's ferry on the Susquehanna, I found the people of the house in great concern on account of the death of some of the cattle, and sickness of others, which had occurred in a few days after a drove from the south had left the place. Upon inquiry I was informed, that the drover merely requested and obtained permission, to confine his cattle for one night in a ploughed [sic] field, and I was assured, that the stock of Mr. Anderson had no intercourse with the drove, which after staying all night, pursued their journey in the morning to Lancaster. There, several head were disposed of to different persons, and in every instance, as I was informed, they communicated disease to the stock with which they mixed. The admission of a single head was enough to give rise to it. As the drove of cattle exhibited no mark of illness, the mystery of the cause was inexplicable, and is

so to this day. They stopped a day or two near to Downing Town, thirty-two miles from Philadelphia, on the western turnpike, and soon after, the field they occupied, received another drove which had been purchased by the late Mr. Strickler of Columbia on the Susquehanna. It consisted of 260 head, and as I was afterwards informed by Mr. S., had been purchased by him in Maryland, in the vicinity of Hagers Town, and between that and the Cove mountain. Sixty of this drove were sold by Mr. S. near the billet in Montgomery county, the greater part of which died. Several others were sold at the Middle ferry on the Schuylkill, eight of them were bought by the late Isaac Coates, above Downing Town, and all died. Some taken to Germantown shared the same fate. Part of the South Carolina drove was sold at the Blue-Bell tavern, a well known sale-place for drove cattle, and of these forty-six head were purchased by Messrs. Weed and Holstein who then rented the meadows on State island, (where I then resided as Lazaretto physician) and were mixed with near 270 others, a part of which had been purchased, half fat, in the month of June preceding. In about four days after the southern cattle had been turned out on the meadows, they were brought up to the yard round the barn, to be branded, and after remaining there a few hours, they were returned to pasture. The disease first appeared after a few days, among the cows in a field near the barn, and which were regularly milked in the yard used to confine the southern cattle until branded, and in a pair of fine working oxen, which were regularly and daily fed and yoked in the same yard. Several other cattle were successively attacked, to the number of at least twenty, all of which except one died. All those purchased half fat in June, died. My advice being asked, I went to the field where several of the cattle lay ill, and was told that the first symptoms were loss of appetite, and weakness of the limbs, amounting to inability to stand. When they fell, they would tremble and groan violently. I saw several in this condition. Some discharged bloody urine, others bled at the nose. The bowels were generally very costive [constipated]. Upon being opened, the kidneys were found

> inflamed, and sometimes in a state of suppuration [pus-filled], and the intestines filled with hard balls. I prescribed strong purgatives. To one I gave two ounces of calomel, in sweet oil, on the second day of the disease, but without producing any evacuation. Bleeding was tried, without success. The blood was in a state of decomposition, and did not coagulate. As a preventive I recommended smearing the nose, horns, forehead, hoofs, and tail with tar, to counteract the contagion of the disease, by creating an artificial atmosphere around the animal, and also the obvious expedient of an entire separation of the old stock from the strangers. None of the southern cattle died. The circumstance of the cattle from a certain district in South Carolina infecting others with the disease above alluded to, has long been known, but the precise locality, or its extent, I have not as yet been able to ascertain, notwithstanding my inquiries on the subject. The country of the long-leaved pine has been said to be the native place of the infection, but with what certainty I am unable to say. The cattle alluded to, are said also to emit a peculiar smell, which is easily perceived on a warm day, and to be well known in South Carolina. The useful deduction of which the foregoing statement admits, is a caution in respect to the mixing northern and southern cattle, without the performance of a kind of quarantine by a strange drove, before they are permitted to associate with the stock already on the farm. ...

* * *

Theobald Smith (1859–1934) was born in July of 1859 in Albany, New York. He received an undergraduate degree from Cornell University in 1881, followed two years later by a medical degree from Albany Medical College. Upon graduation, Smith joined the U.S. Department of Agriculture as director of the pathological laboratory within the newly formed Bureau of Animal Industry (BAI), established by Congress in 1884 to combat the wide range of livestock

diseases then affecting commercial animal husbandry in the United States. Along with two other veterinarian employees at the BAI, F. L. Kilborne and Cooper Curtice, Smith began a systematic study of Texas cattle fever soon after his arrival at BAI that included some four years of extensive field experimentation directed primarily by Kilborne and extensive laboratory work by Curtice on the life-cycle of the tick and how the organism causing cattle fever could be passed through the eggs of a tick and then to non-immune cattle by the hatched larvae. The results of Smith's work on Southern cattle fever were published in 1893, with Kilborne as a second author, under the title: *Investigations into the Nature, Causation and Prevention of Southern Cattle Fever*. This monograph is considered one of the more important in medical history because it showed definitively for the first time how arthropods, such as ticks, might act as vectors of disease transmission from animal to animal.

Several early observations by Smith and colleagues led to the explanatory (abductive) conjecture that the tick was somehow the means of cattle fever transmission. It was known, for example, that cattle fever was not operative after the first frost (when the tick larvae were presumably killed). Also, it had to be something "carried" by otherwise healthy or immune southern cattle when they moved northward because southern cattle lost their infectivity after several weeks on northern pastures or after a prolonged drive — in other words, what they carried must have "dropped away." The infection was not conveyed directly from southern to northern cattle but was passed along by the ground somehow becoming contaminated as southern cattle moved over land that was later traversed by northern cattle. Probably the most significant source of information, however,

that implicated the tick as a possible agent for transmitting cattle fever was a general consensus among southern cattlemen themselves that Cooper Curtice passed along to Smith and Kilborne. It was understood by southern ranchers that the ubiquitous tick was somehow responsible for the malady although there was no understanding just as to how.

Despite the consensus among southern cattle ranchers that the tick must somehow be responsible for cattle fever, the "tick theory" was routinely denigrated by the so-called experts prior to the appearance of the Smith and Kilborne report. One common alternative hypothesis was a transmission theory that operated through southern cattle excreta that somehow contained an agent causing the disease. Non-immune cattle fed on the polluted vegetation and thereby contracted cattle fever. Some of the experiments conducted by Smith and Kilborne that involved cattle ingesting supposedly contaminated vegetation without any effect showed this alternative hypothesis to be wrong. Among those who scoffed openly about the tick as a means of cattle fever transmission, was the chief of the BAI, D. C. Solomon. Nevertheless, in the letter of transmittal written by Solomon for the Smith-Kilborne report, reproduced below, Solomon appears to take credit for the idea of tick transmission once it had been established:

> LETTER OF TRANSMITTAL
>
> U.S. Department of Agriculture
> Bureau of Animal Industry
> Washington, D.C., February 6, 1893
>
> Sir: I have the honor to submit herewith a report covering "Investigations into the Nature, Causation, and Prevention of Texas or Southern Cattle Fever," which have been conducted under my direction by Drs. Theobald Smith and F. L. Kilborne, of this Bu-

reau. These investigations have extended over a period of several years, and it is gratifying to be able to state that they have been successful in discovering the cause of the disease and the means by which it is transmitted.

In the whole list of diseases affecting the domesticated animals, there is none so peculiar in its character or so mysterious in its phenomena as was this one previous to these researches. The dissemination of the deadly contagion by apparently healthy cattle, and the harmlessness in general of the really sick animals were inexplicable by any facts which were furnished by the study of other diseases. Veterinarians who had not had an opportunity to observe this disease were skeptical in regard to the correctness of such conclusions, and some spoke of them as a "romance in pathology." These early observations have not only been confirmed, but the phenomena have been explained, and our knowledge placed upon a scientific basis.

It had long been believed by the cattle-raisers of the West that Texas fever was caused by the ticks which were carried and scattered everywhere by the Southern cattle; but scientists were incredulous, because they could not understand how the bite of these insects could produce such an acute disease, with destruction of the blood corpuscles and lesions of internal organs. It was not until the protozoal microorganism was discovered in the blood corpuscles, and its destructive effects were revealed, that the action of the ticks could be explained.

When the writer investigated the extent of the infected district he was strongly impressed with the fact, which then first became apparent, that this district almost exactly corresponded with the habitat of the suspected tick. This led to the experiments which demonstrated that ticks carried the infection, introduced it into the tissues of the susceptible cattle, and in that way produced the disease. We have to deal therefore, with a complicated infection, in which two very different kinds of parasites play an important part.

Another significant discovery, not less marvelous, is that the mi-

croorganism which constitutes the contagion of the disease is transmitted through the egg to the young tick, and it is this, and not the adult tick carried by the Southern cattle, which finds its way upon susceptible animals and causes the disease. In the absence of the tick, the disease is probably not communicable except by artificial inoculation.

The accompanying report gives all the details of the investigations referred to, and will be found of the greatest interest both to the cattle owner desirous of preserving his animals from this dangerous malady, and to the scientist who wishes to know the various methods by which contagion may be distributed. The researches have been made with great care and thoroughness, and the gentlemen who have conducted them have shown perseverance and scientific ability of the highest order. Their work, as described in these pages, has for its foundation accurate scientific experiments, and, however unexpected may be the results, these may be relied upon as furnishing the basis for the true exposition of the disease.

Very respectfully,
D. E. Salmon, Chief of the Bureau

Parts of the 1893 Smith and Kilborne monograph are given in an external Appendix with an emphasis on the summaries of the field experiments and the various replications that were performed. The field experiments generally involved three distinct types of manipulation: northern cattle placed in the same field with recent arrivals from the south developed the disease several weeks after they were introduced; when all ticks were removed from the southern cattle before they were placed in the field, the northern cattle remained healthy; when northern cattle merely grazed on a field that had been seeded with young ticks procured from a southern grazing area, the northern cattle quickly became infected. In addition to these actual field experiments, several other related demonstrations reinforced the gen-

eral conclusion about tick transmission: Southern cattle fever could be produced by the bites of young ticks raised in the laboratory from eggs laid by female ticks that had lived on infected southern cattle; during the winter and using a heated stable where the ticks remained viable, northern cattle could be successfully infected; on the other hand, however, crushed ticks mixed with hay and used as feed could not produce the disease.

Several other observed phenomena became part of the explanatory mechanism for how Southern cattle fever could be transmitted. First, northern young calves generally contracted only mild forms of cattle fever even though they were grazed on fields fatal to their mothers. This would help explain the apparent immunity of southern cattle who contracted minor forms of the malady when young and which then provided some type of life-long protection against the more serious fatal form of the disease.

Knowledge of the tick life-cycle helped explain some of the apparent anomalies of cattle fever and how it could be passed from southern cattle to non-immune northern cattle. First, why did it take some thirty days for a field be become dangerous? The short answer is that the disease is passed only by the bite of young ticks and it takes some time for these young ticks to be produced. A cattle tick spends its whole life on one host and does not drop off after each molt. When females engorged with blood do drop off, it is then that eggs are laid. After the ticks are hatched, they live in the grass until they are able to crawl on an animal and start the whole process again. In the meantime, the organism causing cattle fever has been passed through the eggs to the young ticks.

The eleven conclusions given at the end of the Smith-Kilborne

monograph provided a definitive explanation for what organism caused Southern cattle fever, how it was transmitted by means of the tick through its eggs and larval offspring, and the best mechanisms for its prevention through the destruction of the ticks on Southern cattle before transport, possibly by means of disinfecting baths:

> (1) Texas cattle fever is a disease of the blood, characterized by a destruction of red corpuscles. The symptoms are partly due to the anaemia produced; partly to the large amount of debris in the blood, which is excreted with difficulty, and which causes derangement of the organs occupied with its removal.
>
> (2) The destruction of the red corpuscles is due to a microorganism or micro-parasite which lives within them. It belongs to the protozoa and passes through several distinct phases in the blood.
>
> (3) Cattle from the permanently infected territory, though otherwise healthy, carry the micro-parasite of Texas fever in their blood.
>
> (4) Texas fever may be produced in susceptible cattle by the direct inoculation of blood containing the micro-parasite.
>
> (5) Texas fever in nature is transmitted from cattle which come from the permanently infected territory to cattle outside of this territory by the cattle tick.
>
> (6) The infection is carried by the progeny of the ticks which matured on infected cattle, and is inoculated by them directly into the blood of susceptible cattle.
>
> (7) Sick natives may be a source of infection (when ticks are present).
>
> (8) Texas fever is more fatal to adult than to young cattle.
>
> (9) Two mild attacks or one severe attack will probably prevent a subsequent fatal attack in every case.
>
> (10) Sheep, rabbits, guinea-pigs, and pigeons are insusceptible to direct inoculation. (Other animals have not been tested.)
>
> (11) In the diagnosis of Texas fever in the living animal the blood should always be examined microscopically if possible.

* * *

Theobald Smith left the BAI in 1895 to join the faculty of Harvard University as a Professor of Comparative Pathology. In 1915 he became the Director of the Department of Animal Diseases at the Rockefeller Institute at Princeton where he remained till retirement. Besides his work on the causes of cattle fever discussed in this chapter and published in 1893, Smith produced seminal work in several areas, and is arguably America's first internationally significant medical research scientist, and at the time, the world's leading comparative pathologist.

Among Smith's other research accomplishments were:

— the differentiation between human and bovine tubercle bacilli;

— the first to identify what is now called anaphylaxis, the severe antibody reaction or hypersensitivity in an animal after the injection of a foreign protein into its body. For some time this was referred to as the "Theobald Smith phenomenon."

— basic research into swine diseases such as hog cholera (intestinal) and swine plague (respiratory).

Since 1942 cattle fever ticks have been considered eradicated from the U.S. although there is a need for continual vigilance along the Mexican border where ticks are still in abundance. With tick eradication comes the prevention of Southern cattle fever. In a similar manner as seen in other chapters, the eradication of other insect vectors removes the chances of contracting the associated maladies they transmit. For example, controlling mosquitos removes the dread of yellow fever and malaria, the elimination of rats and fleas will control the plague in urban areas, and typhus can be prevented by the extermination of body lice.

In a National Academy of Sciences posthumous biographical memoir of Theobald Smith, written by Hans Zinsser and published in 1936, Zinsser summed up the importance of Smith's work on cattle fever and its transmission by means of the tick, as follows:

> The investigations of Smith and his collaborators were, therefore, the first to establish the complete cycle of transmission by arthropod vectors — a discovery which represents one of those fundamental steps forward that alter the entire course of a science, and which has practical consequences of inestimable and permanent importance. We have presented this particular work with a certain degree of emphasis upon the parts played by others than Smith and upon the significance of earlier discoveries which undoubtedly helped to shape Smith's thoughts and experiments. This we have done, not only in the interests of accuracy, but with the feeling that it would be an irreverent disservice to write about this great man's accomplishments in a manner which would have deeply displeased him and which would represent a disregard of other worthy achievements entirely foreign to his own nature.

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Chapter 13

Charles Nicolle

> Chance favors only those who court her.
>
> – Charles Nicolle (1866–1936)

> The disclosure of a new fact, the leap forward, the conquest over yesterday's ignorance, is an act not of reason but of imagination, of intuition.
>
> – Charles Nicolle (1866–1936)

> Nicolle was one of those men who achieve their successes by long preliminary thought before an experiment is formulated, rather than by the frantic and often ill-conceived experimental activities that keep lesser men in ant-like agitation. Indeed, I have often thought of ants in observing the quantity output of 'what-of-it' literature from many laboratories. ... Nicolle did relatively few and simple experiments. But every time he did one, it was the result of long hours of intellectual incubation during which all possible variants had been considered and were allowed for in the final tests. Then he went straight to the point, without wasted motion. That was the method of Pasteur, as it has been of all the really great men of our calling, whose simple, conclusive experiments are a joy to those able to appreciate them.
>
> – Hans Zinsser (1878–1940)

Epidemic typhus is an infectious disease caused by a bacterial organism, *Rickettsia prowazekii*, transmitted from human to human

by the body louse (plural: lice). Historically, typhus has been a classic disease of poverty and filth; it was particularly prevalent under conditions of overcrowding and poor standards of hygiene, especially during wartime. Although human lice live and lay eggs in an individual's clothing, it is actually the infected feces of the louse that is the primary means of typhus transmittal. When a louse bites a typhus victim for a bit of blood and nourishment, it becomes infected and ultimately dies from damage to its digestive organs caused by the rapidly multiplying bacterial organisms. If the louse is able to move to another uninfected person before it dies, the feces might then be rubbed into a scratch, possibly produced by a bite from the louse itself, and thus infect the new host. Also, because louse feces becomes virulent at the same time as the louse bite itself, the bite alone may be sufficient to infect a new host. Typhus may also be passed through breathing louse feces by people who, for example, handle the laundry for those infected.

Hans Zinsser in his rightly famous essay on the louse and typhus (*Rats, Lice, and History*, 1935) provided a view of the man-louse-man transmission situation from the viewpoint of the louse who, in contrast to the human host, always dies:

> The louse shares with us the misfortune of being prey to the typhus virus. If lice can dread, the nightmare of their lives is the fear of someday inhabiting an infected rat or human being. For the host may survive; but the ill-starred louse that sticks his haustellum [proboscis] through an infected skin, and imbibes the loathsome virus with his nourishment, is doomed beyond succor [help]. In eight days, he sickens, in ten days he is *in extremis*, on the eleventh or twelfth his tiny body turns red with blood extravasated [forced out] from his bowel, and he gives up his little ghost.

Man is too prone to look upon all nature through his egocentric eyes. To the louse, we are the dreaded emissaries of death. He leads a relatively harmless life — the result of centuries of adaptations; then, out of the blue, an epidemic occurs; his host sickens, and the only world he has ever known becomes pestilential and deadly; and if, as a result of circumstances not under his control, his stricken body is transferred to another host whom he, in turn, infects. He does so without guile, from the uncontrollable need for nourishment, with death already in his own entrails. If only for his fellowship with us in suffering, he should command a degree of sympathetic consideration.

The louse was not always the dependent, parasitic creature that cannot live away from its host. There were once free and liberty-loving lice, who could look other insects in their multifaceted eyes and bid them smile when they called them "louse." But this was even longer ago than the Declaration of Independence, for it took the louse many centuries to yield up its individualism. (pp. 168–9)

...

However this may be, it is likely from evidence that, somewhere in the legendary past of louse history, an offspring of a free-living form not unlike our book louse found that life could be infinitely simplified if, instead of having to grub for food in straw, under tree barks, in moss or lichen, in decaying cereals and vegetables, it could attach itself to some food-supplying host, and sit tight. It is one of the few instances in which nature seems extremely logical in its processes. The louse sacrifices a liberty that signifies chiefly the necessity for hard work, the uncertainty of food and shelter, and exposure to dangers from birds, lizards, and frogs; loses the fun of having wings, perhaps; but achieves, instead, a secure and effortless existence on a living island of plenty. In a manner, therefore, by adapting itself to parasitism, the louse has attained the ideal of bourgeois civilization, though its methods are more direct than those of business or banking, and its source of nourishment is not its own species. (p. 172)

* * *

A typhus infection manifests itself in several ways: by a high fever, an intense headache, mental stupor, a rash of bright red spots, and all along with a vile stench. Untreated, the mortality rate ranges from ten to forty percent. The earliest documented presence of epidemic typhus in Europe occurred in the early 1490s when the combined Spanish forces of Ferdinand (of Aragon) and Isabella (of Castile) laid siege to Granada, the last Moorish stronghold in Spain. In this first documented European presence, typhus was most likely carried by soldiers coming from Cyprus to participate in the various sieges then ongoing in Spain.

Before the middle of the Sixteenth Century, typhus had an active hand in the politics of Europe through its constant presence in both land and naval forces. Aboard ship it was commonly called "ship fever"; in land forces, it was referred to as "camp fever"; and within an imprisonment setting, it was "jail" or "gaol fever." Typhus was the putative cause for several so-called Black Assizes from the Sixteenth Century, most notably in Oxford (1577) and Exeter (1586). In general, an assize was a court that sat at intervals in each county of England and Wales to administer civil and criminal law. A Black Assize occurred when the prisoners who carried the vile stench of typhus were brought from extremely unsanitary jails into overcrowded courtrooms. The typhus quickly spread from the felons in the dock to those assembled at court, presumably through louse transmission and feces. For example, the Black Assize of Oxford, which shut down the university for some thirty years, involved prominently the trial of Rowland Jenkes, a popish [Catholic] bookseller who was charged with curses against the Queen. On the wall inside the Main Hall

of the Old County Hall of Oxfordshire there is a plaque with the following inscription:

> Near this spot stood the ancient Shire Hall, unhappily famous in history as the scene in July 1577 of the Black Assize, when a malignant disease known as Gaol Fever caused the death within forty days of the Lord Chief Baron of the Exchequer, Sir Robert Bell, the Lord High Sheriff (Sir Robert D'Oyly of Merton) and about three hundred more.
>
> The malady from the stench of the Prisoners developed itself during the Trial of one Rowland Jenkes, a saucy foul-mouthed Bookseller, for scandalous words uttered against the Queen.

Typhus has played a major part in most of the major wars that have occurred after its initial presence at the siege of Granada, including up to the Twentieth Century and World War II. One of the Nineteenth Century's most historically consequential roles for typhus was in Napoleon's disastrous 1812 incursion into Russia and the part it played in obliterating his *Grande Armée*, and destroying his dream of a vast French Empire extending far into Russian territory. A detailed recounting of this Napoleonic saga is given by Stephan Talty in *The Illustrious Dead: The Terrifying Story of How Typhus Killed Napoleon's Greatest Army* (2009).

By the time of World War I the louse was known to be the vector of typhus transmission from the work of Charles Nicolle, the main protagonist for this chapter. Also, various chemical agents were available at that time for the de-lousing of troops and civilians, at least on the Western Front. The Eastern Front was a different matter, however, as reflected in a quote from Lenin near the end of the war in 1919: "Either socialism will defeat the louse or the louse will defeat

socialism." Estimates are that over three million people died from typhus during the Russian Civil War.

World War II saw the widespread use of the insecticide DDT as an extremely effective de-lousing agent. Unfortunately, this was also a period where typhus was rampant in the German concentration camps and Jewish ghettos. The presence of typhus was a convenient excuse for the elimination of Jews and other "undesirable" people, and for effecting Hitler's Final Solution. For a discussion of how typhus played an integral part in the genocide carried out in Nazi Germany during World War II, see Naomi Baumslag, *Murderous Medicine: Nazi Doctors, Human Experimentation, and Typhus* (2005).

* * *

Charles Nicolle (1866–1936) was a French bacteriologist, born in Rouen in 1866, who was awarded the 1928 Nobel Prize in Medicine for his discovery of the body louse as the method (or vector) of transmission for epidemic typhus. After receiving his medical degree from the Pasteur Institute in Paris in 1893, he returned to Rouen and was eventually named director of the local bacteriological laboratory. In 1903, Nicolle became Director the the Pasteur Institute in Tunis, where he began his Nobel-Prize winning research into typhus, particularly in the experimental demonstrations that it was transmitted by way of human body lice.

Typhus was endemic in Tunisia, but it was most severe in years that coincided with famines. Typically, a famine sent unemployed single men to the cities looking for work, who would then wander into the local hospitals and collapse, with puffy faces and darkened

eyes staring out in a stupor. Several observations that Nicolle made about this unfortunate situation and how typhus appeared to operate led him first to the abductive conjecture that it was likely an insect of some sort that was the mode of transmission, and then to the experimental animal trials that confirmed this initial conjecture. Many doctors and staff who came into contact with typhus victims died of the disease, so at this level there was some type of person to person transfer. However, once a typhus sufferer was cleaned up, bathed, and shaven, they were no longer infectious, and when placed in a general hospital ward, the other patients would not contract the malady. So, at this point, person to person contagion seemed to disappear — people were infectious in the receiving areas but not once they were cleaned up. This fact plus the observation that typhus could be contracted by contact with a typhus victim's clothes and personal effects without the presence of the actual victim, suggested an external cause in the transmission — and for Nicolle, the conjecture that appeared most likely was that of an insect or organism that lived in the victim's clothes, which still could do harm even though physically separated from the victim.

As part of Nicolle's experimental work, he first injected blood taken from a thirty-five year-old Tunisian man with typhus into a chimpanzee (a very close primate relative to a human) that he obtained specially from the larger Pasteur Laboratory in Paris. The chimpanzee promptly got sick; this was the first observed nonhuman vertebrate typhus victim. Blood was then taken from the chimpanzee and used to infect a Macaque (Chinese) monkey, who also quickly got sick. Nicolle then placed lice on the back of the sick Macaque, and after a period of time, moved the lice to several healthy mon-

keys. The latter also got sick, demonstrating experimentally the louse transmittal of typhus.

Nicolle and his two colleagues at the Tunis Pasteur Institute, Comte and Conseil, carried out a number of these types of primate typhus transmittals, and jointly published the results of these confirming investigations in 1909. In his Nobel Prize speech given some twenty years later, Nicolle took literary license with his discovery narrative to make it seem more like an epiphany or a"Eureka" moment than what it really was. In actuality, the identification of the body louse as the vector of transmittal for typhus was the result of a tentative (abductive) guess, possibly suggested by his co-author Comte, followed by careful experimental studies with primates. This enlivened part of Nicolle's 1928 Nobel lecture is given below; it is sometimes referred to as the "Door of the Sadiki hospital" discovery narrative — for example, see the comprehensive biography of Nicolle by Kim Pelis (*Charles Nicolle, Pasteur's Imperial Missionary, Typhus and Tunisia*):

> The native hospital in Tunis was the focal point of my research. Often, when going to the hospital, I had to step over the bodies of typhus patients who were awaiting admission to the hospital and had fallen exhausted at the door. We had observed a certain phenomenon at the hospital, of which no one recognized the significance, and which drew my attention. In those days typhus patients were accommodated in the open medical wards. Before reaching the door of the wards they spread contagion. They transmitted the disease to the families that sheltered them, and doctors visiting them were also infected. The administrative staff admitting the patients, the personnel responsible for taking their clothes and linen, and the laundry staff were also contaminated. In spite of this, once admitted to the general ward the typhus patient did not contaminate any

of the other patients, the nurses or the doctors.

I took this observation as my guide. I asked myself what happened between the entrance to the hospital and the wards. This is what happened: the typhus patient was stripped of his clothes and linen, shaved and washed. The contagious agent was therefore something attached to his skin and clothing, something which soap and water could remove. It could only be the louse. It was the louse.

Even if it had not been possible to reproduce the disease in animals and consequently to verify the hypothesis, this simple observation would have been sufficient to demonstrate the way in which the disease was propagated.

Fortunately, it was also possible to provide experimental proof.

My first attempts to transmit typhus to laboratory animals, including the smaller species of monkeys, had failed, as had those of my predecessors, for reasons which I can easily supply today.

I asked my teacher, E. Roux, to get me a chimpanzee, thinking that an anthropoid might be more susceptible to infection than animals of other species. The day I received the chimpanzee I inoculated it with the blood of a patient from Dr. Broc's department at the hospital in Rabta. The chimpanzee contracted a fever. I inoculated a macaco (*M. sinicus*) with blood from the chimpanzee taken during the fever, and he also developed a fever. I cultivated lice on the macaco, which I then transported to other macacos. The latter became infected and subsequently proved to be vaccinated against a test inoculation of the virus.

These decisive experiments did not take very long. I had reproduced typhus in the chimpanzee in June, 1909; I demonstrated the role played by the louse in August. I published these results in September with Charles Comte and Ernest Conseil. This was the yield for the year 1909. During the years that followed I undertook with Conseil and Alfred Conor, and later with Georges Blanc, a more detailed experimental study of the disease and the conditions of transmission.

* * *

Although Nicolle explicitly received the Nobel Prize for his work on the louse transmission of typhus, some would consider his other experimental work at least as important. One such area that Nicolle himself considered his most significant discovery was that of inapparent (or subclinical) infection where a disease (such as typhus) is present in an organism but its symptoms are not. Reminiscent of the same kind of asymptotic carriers of disease discussed by Koch for cholera and typhoid, inapparent infection is characterized by the acquisition and transmission of some malady without any outward signs of illness. The identification of this phenomenon of inapparent infection resulted from a clever abductive conjecture made by Nicolle when faced with the surprising observation of guinea pigs infected with typhus but showing no outward manifestation of the illness, not even a fever. Inapparent infection has been shown both before and subsequent to Nicolle's pioneering work to be a general possibility for many diseases — an organism has some malady and is asymptomatic, but yet still capable of passing it along to others. In the case of typhus, for example, the reservoir for new epidemics are those humans who have typhus asymptomatically but are still capable of passing it along to others and initiating epidemics (assuming the additional presence of the transmitting body louse). That part of Nicolle's Nobel Prize Lecture concerning inapparent infection is given in an external Appendix.

* * *

Even though typhus is no longer the scourge it once was, it still occurs in the colder mountainous regions of central and eastern Africa,

Central and South America, and Asia. Recent outbreaks have taken place in Rwanda, Ethiopia, and Burundi. Generally, typhus can be expected under conditions of poor hygiene and overcrowding, such as that present in refugee camps and prisons. In the United States improved sanitation and hygiene measures have largely eliminated the human body louse vector and epidemic typhus as a public health concern. Some recrudescent [recurring] epidemic typhus, called Brill-Zinsser disease, may reappear some years after a primary typhus infection but usually it is of a milder variety. Most of these cases have been seen in European immigrants to the Northeastern United States. Nevertheless, these delayed relapses could result in new epidemics given the availability of the body louse as a means of transmission.

Over the last one-hundred or so years, typhus has killed a number of researchers who have worked directly with the organism and has infected others, including Nicolle, Zinsser, and many of their collaborators. In 1916, the Brazilian scientist Henrique da Rocha Lima (1879–1956) isolated and named the bacteria responsible for epidemic typhus, *Rickettsia prowazekii*, in honor of two typhus researchers who died of the malady: an American pathologist working in Mexico City, Howard Taylor Ricketts (1874–1910), and Stanislaus Prowazek (1875–1915), an Eastern European zoologist working on typhus during World War I.

The body louse and its relatives that reside in the hair and pubic region (commonly called "crabs") have given rise to a variety of cultural memes and phrases used and understood in everyday communication. In relation to the eggs or nits that are produced by lice, there are the phrases of "going over something with a fine-toothed comb" (to remove the nits); "feeling lousy," or referring to something

as "lousy," meaning very poor or bad; or to "nit pick," implying pedantic fault-finding. There is also the dreaded letter sent home from school to parents about a head lice infestation, and the school yard taunt of boys catching "cooties" from girls.

We end this chapter on Charles Nicolle, typhus, and the human body louse by giving an excerpt from Hans Zinsser's *Rats, Lice, and History* (1935) that relates to the perennial presence of body lice throughout history and to the possibility of typhus epidemics reoccurring in the future as long as the louse exists. This excerpt includes a story about the murder of Archbishop Thomas á Becket (1118–1170) in Canterbury Cathedral by guards sent from Henry II (he of "will no one rid me of this meddlesome priest?" fame):

> The manner of living throughout the Middle Ages made general lousiness inevitable. In England, in the twelfth and thirteenth centuries, the houses of the poor were mere hovels, often with only a hole in the roof to let out the smoke of the central fire; and in cold weather the families were huddled together at night without changing the simple garments — usually a single shift — which they wore in the daytime. Washing was practically out of the question, and the better classes — not very much more comfortable in their badly heated domiciles — wore a great many clothes, which they rarely changed. MacArthur's story of Thomas á Becket's funeral illustrates this: —
>
> The Archbishop was murdered in Canterbury Cathedral on the evening of the twenty-ninth of December. The body lay in the Cathedral all night, and was prepared for burial on the following day. The Archbishop was dressed in an extraordinary collection of clothes. He had on a large brown mantle; under it, a white surplice; below that, a lamb's-wool coat; then another woolen coat; and a third woolen coat below this; under this, there was the black, cowled robe of the Benedictine Order; under this, a shirt; and next to the

body a curious haircloth, covered with linen. As the body grew cold, the vermin that were living in this multiple covering started to crawl out, and, as MacArthur quotes the chronicler: "The vermin boiled over like water in a simmering cauldron, and the onlookers burst into alternate weeping and laughter."

The habit of shaving the head and wearing a wig was no doubt in part due to the effort to hold down vermin. Gentlemen and ladies all over Europe resorted to this, but the wigs they wore were often full of nits. Pepys speaks of this in several places, complaining about a new wig he had bought which was full of nits. "Thence to Westminster to my barber's; to have my Periwigg he lately made me cleansed of its nits, which vexed me cruelly that he should put such a thing into my hands."

Even in the highest society, the questions of lice and scratching were serious problems; and the education of children, even in the highest circles, included a training of the young in relation to their vermin. Reboux, speaking of the education of a princess of France in the middle of the seventeenth century, says: "One had carefully taught the young princess that it was bad manners to scratch when one did it by habit and not by necessity, and that it was improper to take lice or fleas or other vermin by the neck to kill them in company, except in the most intimate circles."

He tells another story illustrative of the universal lousiness even of the aristocracy. The young Comte de Guiche had made himself unpopular with the King by casting amorous eyes upon Madame, the King's sister-in-law. He sent the Comte's father to announce banishment to the son. The latter was not yet out of bed when his father arrived. As the old Marshal stood in front of the bed, a louse crawled out from under his perruque [wig], began to crawl along the deep furrows on the old man's forehead, skirted the edges of the little thickets made by the eyebrows, and crawled back under the hair of the wig. The entire lecture was missed, while the Comte de Guiche was watching the adventures of the insect.

Even long into the eighteenth century, lice were regarded as

necessities. Bacteriologists for a generation have wondered whether the presence of colon bacilli in the intestines might not, because of their universal occurrence, have some physiological purpose. For similar reasons, as wise a man as Linnaeus suggested that children were protected by their lice from a number of diseases.

In the story of George Washington by Rupert Hughes, we find the following paragraph on "Rules of Civility," copied by Washington in his fourteenth year: "Kill no vermin, as Fleas, lice, tics, etc. in the sight of others, if you See any filth or thick Spittle, put your foot Dexterously upon it; if it be upon the Cloths of your Companions, put it off privately, and if it be upon your own Cloths, return thanks to him who puts it off."

Since Colonial days, these things have changed. The louse has been banished completely from fashionable society, and even though — among our middle classes — there may not be a motor car in every garage, there is almost invariably a bathtub in every cottage and flat. And more and more, the habit of keeping the coal in the bathtub is disappearing. The louse is confined, in consequence, to the increasingly diminishing populations of civilized countries who live in distress and great poverty. But there are still many of these with us, and there are regions of the earth where life is still primitive, where bathtubs remain luxuries and bathing amounts to counter-revolution. The louse will never be completely exterminated, and there will always be occasions when it will spread widely to large sections of even the most sanitated populations.

And as long as it exists, the possibility of typhus epidemics remains. (pp. 185–188)

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Part VI

Optional Appendix

Chapter 14

Some Basics of Probability Theory as it Relates to Plausible Reasoning

14.1 Bayes Theorem

The formalism of thought offered by probability theory is one of the more useful portions of any beginning course in statistics in helping promote justifiable quantitative (and plausible) reasoning. As typically presented, we speak of an event represented by a capital letter, say A, and the probability of the event occurring as some number in the range from 0 to 1, written as $P(A)$. The value of 0 is assigned to the "impossible" event that can never occur; 1 is assigned to the "sure" event that will always occur. The driving condition for the complete edifice of all probability theory is one single postulate: for two mutually exclusive events, A and B (where mutual exclusivity implies that both events cannot occur at the same time), $P(A \text{ or } B) = P(A) + P(B)$. As a final beginning definition, we say that two events are independent whenever the probability of the joint event, $P(A \text{ and } B)$, factors as the product of the individual probabilities, $P(A)P(B)$.

Besides the concept of independence, the definition of conditional

probability plays a central role in all uses of probability theory; in fact, many misapplications of statistical/probabilistic reasoning involve confusions of some sort regarding conditional probabilities. Formally, the conditional probability of some event A given that B has already occurred, denoted $P(A|B)$, is defined as $P(A \text{ and } B)/P(B)$. When A and B are independent, $P(A|B) = P(A)P(B)/P(B) = P(A)$; or in words, knowing that B has occurred does not alter the probability of A occurring. If $P(A|B) > P(A)$, we will say that B is "facilitative" of A (or, that A is more plausible than before); when $P(A|B) < P(A)$, B is said to be "inhibitive" of A (or, that A is less plausible than before). As a small example, suppose A is the event of receiving a basketball scholarship; B, the event of being seven feet tall; and C, the event of being five feet tall. One obviously expects B to be facilitative of A (that is, $P(A|B) > P(A)$); and of C to be inhibitive of A (that is, $P(A|C) < P(A)$). In any case, the size and sign of the difference between $P(A|B)$ and $P(A)$ is an obvious raw descriptive measure of how much the occurrence of B is associated with an increased or decreased probability (or, plausibility) of A, with a value of zero corresponding to statistical independence.

A simple form for Bayes theorem that can be used in verifying the three plausible reasoning schemes given in the first introductory chapter begins with the two definitions for the conditional probabilities, $P(A|B)$ and $P(B|A)$:

$P(A|B) = P(A \text{ and } B)/P(B)$

$P(B|A) = P(A \text{ and } B)/P(A)$

These two conditional probability formulas lead to the equivalence:

$P(A \text{ and } B) = P(A|B)P(B) = P(B|A)P(A)$

or, rewriting to eliminate $P(A \text{ and } B)$:

$$P(A|B) = P(B|A)(P(A)/P(B))$$

In the later form this result is a version of what is called Bayes Theorem, one of the most celebrated results in all of probability theory. It provides the relation between $P(A|B)$ and $P(B|A)$; but also, as shown in a later section, this result directly leads to demonstrations of validity for the three plausible reasoning schemes presented in the first chapter.

14.2 Some Useful Terminology Introduced by the O.J. Simpson Murder Trial

The most publicized criminal trial in American history was arguably the O.J. Simpson murder case held throughout much of 1995 in the Superior Court of Los Angeles County, California. The former football star and actor, O.J. Simpson, was tried on two counts of murder after the deaths in June of 1994 of his ex-wife, Nicole Brown Simpson, and a waiter, Ronald Goldman. Simpson was acquitted controversially after a televised trial lasting more than eight months.

Simpson's high-profile defense team, led by Johnnie Cochran, included such luminaries as F. Lee Bailey, Alan Dershowitz, Robert Kardashian, and Barry Scheck and Peter Neufeld of the Innocence Project. Viewers of the widely televised trial might remember Simpson not being able to fit easily into the blood-splattered leather gloves that were found at the crime scene and which supposedly were used in the commission of the murders. For those who might have missed this high theater, there is a YouTube video that replays the glove-trying-on part of the trial; just "Google": OJ Simpson Gloves & Murder Trial Footage

This incident of the gloves not fitting allowed Johnnie Cochran in his closing remarks to issue one of the great lines of Twentieth Century jurisprudence: "if it doesn't fit, you must acquit." One of the questions of interest here is whether one can also turn this statement around to read: "if it fits, you must convict." But before we tackle this explicitly, let's step back and introduce a small bit of formalism in how to deal probabilistically with phrases such as "if P is true, then Q is true," where P and Q are stand-in symbols for two (arbitrary) propositions.

Rephrasing in the language of events occurring or not occurring, suppose we have the following correspondences:

glove fits: event A occurs

glove doesn't fit: event $\bar{A}$ (the negation of A) occurs

jury convicts: event B occurs

jury acquits: event $\bar{B}$ (the negation of B) occurs

Johnnie Cochran's quip of "if it doesn't fit, you must acquit" gets rephrased as "if $\bar{A}$ occurs, then $\bar{B}$ occurs." Or stated in the notation of conditional probabilities, $P(\bar{B}|\bar{A}) = 1.0$; that is, the probability that $\bar{B}$ occurs "given that" $\bar{A}$ has occurred is 1.0; in words, we have "a sure thing."

Although many observers of the O.J. Simpson trial might not ascribe to the absolute nature of the Johnnie Cochran statement implied by $P(\bar{B}|\bar{A})$ being 1.0, most would likely agree to the following modification: $P(\bar{B}|\bar{A}) > P(\bar{B})$. Here, the occurrence of $\bar{A}$ (the glove not fitting) should increase the likelihood of acquittal to somewhere above the original (or marginal or prior) value of $P(\bar{B})$; there is, however, no specification as to how big an increase there should be other than it being short of the value 1.0 representing "a sure thing."

To give a descriptive term for the situation where $P(\bar{B}|\bar{A}) > P(\bar{B})$, we will say in a non-causal descriptive manner that $\bar{A}$ is "facilitative" of $\bar{B}$ (that is, there is an increase in the probability of $\bar{B}$ occurring over its marginal value of $P(\bar{B})$). Alternatively, and as a definition, we will say that $\bar{B}$ becomes *more plausible* in the presence of $\bar{A}$ if and only if $P(\bar{B}|\bar{A}) > P(\bar{B})$. When the inequality is in the opposite direction, and $P(\bar{B}|\bar{A}) < P(\bar{B})$, we say, again in a non-causal descriptive sense, that $\bar{A}$ is "inhibitive" of $\bar{B}$ (that is, there is a decrease in the probability of $\bar{B}$ occurring over its marginal value of $P(\bar{B})$); as a definition, $\bar{B}$ becomes *less plausible* in the presence of $\bar{A}$ if and only if $P(\bar{B}|\bar{A}) < P(\bar{B})$.

Based on the rules of probability, the one phrase of $\bar{A}$ being facilitative of $\bar{B}$, $P(\bar{B}|\bar{A}) > P(\bar{B})$, leads inevitably to a myriad of other such similar statements: $\bar{B}$ is facilitative of $\bar{A}$ and inhibitive of A; $\bar{A}$ is facilitative of $\bar{B}$ and inhibitive of B; B is facilitative of A and inhibitive of $\bar{A}$; A is facilitative of B and inhibitive of $\bar{B}$. To give one example of these latter statements, consider "A being facilitative of B." In a formula, this says that $P(B|A) > P(B)$, or in words, the probability of a conviction (B) given that the glove fits (A) is increased over the marginal or prior probability of a conviction. Most would likely agree that this is a reasonable statement; the point being made here is that once we agree that $\bar{A}$ is facilitative of $\bar{B}$, we must also agree to statements such as A being facilitative of B.[1]

Based on the discussion to this point, we can also now (re)define what it means for two events A and B to be "independent": events A and B are independent if A (or B) is neither inhibitive nor facilitative of B (or A); or, in terms of formulas: $P(A|B) = P(A)$ and $P(B|A) = P(B)$. To give another and more common characteri-

zation of independence, first write $P(B|A)$ as $P(A \text{ and } B)/P(A)$, and set it equal to $P(B)$. This leads to $P(A \text{ and } B)$ factoring as $P(A)P(B)$, which is the more usual definition of event independence.

14.3 The Legend of Cinderella

To provide another illustration of how plausible reasoning might operate, and one that will be used as a clarifying illustration below, we go back to the legend of Cinderella and make one slightly risqué modification. On her hurried way out of the castle just before midnight, Cinderella drops the one glass slipper (but say, she holds on to the other one) and loses all of her fitted clothes and jewelry including tiara, dress, bra, and so on. When the Prince sets off to find Cinderella, the following events are of interest:

person is Cinderella: event A occurs
person is not Cinderella: event $\bar{A}$ (the negation of A) occurs

slipper fits: event B occurs
slipper doesn't fit: event $\bar{B}$ (the negation of B) occurs

In the context of the familiar Disney movie, the Prince's agent first tries the slipper on Cinderella's two ugly sisters but it doesn't fit either. After escaping from the attic (with the help of several friendly mice), Cinderella then appears belatedly to try on the slipper. In the framework of a Peircean abduction scheme, the surprising fact is observed that the slipper now fits. If the person were Cinderella (event A), then the slipper fitting would be a matter of course. Thus, there is reason to suspect that event A is true that the person is Cinderella.

As in the Johnnie Cochran context, the occurrence of the event B (that the slipper fits) increases the likelihood of event A occurring (that the person is Cinderella) over the prior probability of this particular individual being Cinderella. But in our risqué version of the legend, the Prince also has an array of fitted jewelry and clothes that could also be tried on sequentially, with each fitting item being itself facilitative of the event A of being Cinderella. Although one may never reach a "sure thing" and have Cinderella identified "beyond a shadow of a doubt," the sequential weight-of-the-evidence may lead to something at least "beyond a reasonable doubt"; or stated in other words, the cumulative probability of the event A (of being Cinderella) increases steadily with each newly fitting item.[2]

14.4 Inferential (or Evidential) Force and the Strength of Facilitation or Inhibition

Besides knowing that some event may be facilitative or inhibitive of another, it also may be of interest to assess the strength of such a facilitation or inhibition, particularly if it were possible to provide actual numerical values for the probabilities involved. In the Cinderella illustration, for instance, the slipper fitting (event B) is facilitative of the person being Cinderella (event A); that is, $P(A|B) > P(A)$. The absolute difference between the conditional probability, $P(A|B)$, and the prior probability, $P(A)$, is one possible measure of inferential or evidential force. Another relative measure would be the absolute difference between $P(A|B)$ and $P(A)$ in relation to $P(A)$:

$$\frac{|P(A|B) - P(A)|}{P(A)}$$

Presumably, the event of the slipper fitting would have less evidential force than the event of actually producing the exact matching glass slipper, although one might be hard-pressed to say just how much less.[3]

14.5 The Validity of the Three Plausible Reasoning Schemes

The plausible reasoning schemes presented in the first chapter along with demonstrations of their validity were first introduced by George Polya in his remarkable treatise on *Mathematics and Plausible Reasoning, Volume II, Patterns of Plausible Inference*; see, in particular, Chapter XV: *The Calculus of Probability and the Logic of Plausible Reasoning* (Princeton University Press, 1954). Here, we indicate briefly how insights from Bayes theorem lead directly to justifications for these plausible reasoning paradigms. For those who might need some additional background, the beginning of this chapter provides the basic probability theory and terminology necessary to understand Polya's arguments for these three plausible reasoning forms.

As given earlier, the plausible reasoning scheme labeled "Affirming the Consequent" has the form:

If P is true, then Q is true
Q is true
Therefore, P becomes more plausible

Now, however, the propositions, P and Q, being true or not will be replaced by events A and B occurring or not.

Relying on a Cinderella example for concreteness, the first state-

ment reads: "if this person is Cinderella (event A), then the slipper fits (event B)." As a conditional probability, $P(B|A) = 1.0$; that is, when the person is Cinderella, with probability 1.0 the slipper fits. Based on the simple form of Bayes theorem given earlier, and substituting $P(B|A) = 1.0$, we have $P(A|B) = P(A)/P(B)$. Also, because $P(A|B)$ must be less than or equal to 1.0, $P(A) \leq P(B)$. So, as $P(B)$ decreases from 1.0 to $P(A)$, $P(A|B)$ increases from $P(A)$ to 1.0. And therefore, when $P(B) < 1$, $P(A|B) > P(A)$, and A becomes more plausible than it was initially (or alternatively phrased using earlier terminology, B is facilitative of A). Note also that the difference between $P(A|B)$ and $P(A)$ increases as the evidence probability, $P(B)$, gets smaller; thus, the more unusual the evidence, the more "evidential force" it has. Or, stated somewhat differently, the more unexpected a consequent, the more weight its verification carries. So, $P(A|B)$ would presumably be much larger than $P(A)$ when B is the produced matching glass slipper as compared to just the slipper fitting. The plausible reasoning scheme referred to as "denying the antecedent" follows directly because if B is facilitative of A, then $\bar{A}$ is inhibitive of B. Similarly, the third weaker "affirming the consequent" plausible reasoning scheme follows from the fact that if A is facilitative of B, then B is facilitative of A.

As discussed in the context of the Cinderella example, there are multiple sources of evidence that might be used for her identification. These include the many pieces of fitted clothes and jewelry, the slipper to be tried on, and the exact matching glass slipper. Polya extends his plausible reasoning ideas directly to these instances where there are multiple pieces of evidence. To be consistent with Polya's notation, the evidence sources are now labeled $B_1, \ldots, B_n, B_{n+1}$. We

quote several paragraphs taken from his Chapter XV:

> From the very beginning of our discussion we have considered the inductive evidence supplied by the successive verification of several consequences of a proposed conjecture. The extreme cases were the most conspicuous. Let us survey them once more (adding just a little color) and let us focus the moment when, having verified the consequences $B_1, \ldots, B_n$ of a conjecture A, we start scrutinizing a new consequence B_{n+1}.
>
> The new consequence under scrutiny, B_{n+1}, may appear "little different" from the formerly verified consequences $B_1, \ldots, B_n$. Such a case is not too exciting. We confidently expect (by analogy, presumably) that B_{n+1} will be verified like the other consequences (that is, $P(B_{n+1}|B_1, \ldots, B_n)$ is close to 1, its maximum). We scarely expect that the investigation of B_{n+1} will disclose some very new aspect or that it will upset the conjecture A, but also, when B_{n+1} is finally verified, the gain in evidence for A is not much.
>
> On the other hand, the new consequence under scrutiny, B_{n+1}, may appear as "very different" from the formerly verified consequences, $B_1, \ldots, B_n$. Such a case may be exciting. Analogy with $B_1, \ldots, B_n$ gives us little reason to expect that B_{n+1} will be verified ($P(B_{n+1}|B_1, \ldots, B_n)$ is close to its minimum). We realize that the investigation of B_{n+1} risks upsetting the conjecture A, but it has also a chance to disclose some new aspect, and when B_{n+1} is eventually verified, the gain in evidence for A may be considerable.

Given this last discussion, and in the context of how science might generally progress, plausible reasoning schemes serve dual roles. First, there is a usage in the initial abduction of A being the explanatory conjecture for the original surprising observation(s) B: if A is true, then B is true; B is true; therefore, A is more plausible (or $P(A|B) > P(A)$). Secondly, plausible reasoning schemes are central to the verification stage(s) for an explanatory conjecture A. Thus,

if A is true, then B' should occur. And if B' does occur, then A is more plausible (or $P(A|B') > P(A)$). Finally, the plausibility of A increases systematically as more and more of its implications are verified.

It is of interest to note that both Peirce and Polya use the term "induction" to refer to the increase in the plausibility of an event or conjecture, A, as more and more of its implications are verified:

Polya: From the very beginning of our discussion we have considered the inductive evidence supplied by the successive verification of several consequences of a proposed conjecture.

Peirce: The operation of testing a hypothesis by experiment, which consists in remarking that, if it is true, observations made under certain conditions ought to have certain results, and then causing those conditions to be fulfilled, and noting the results, and, if they are favourable, extending a certain confidence to the hypothesis, I call *induction*.

Thus, as our concrete Cinderella example demonstrates, the conjecture that this person is Cinderella becomes more and more plausible based on satisfaction in the sequence of fitting all of the various clothing items.

Notes

[1]A number of alternative words or phrases could be used in place of the terms "facilitative" and "inhibitive." For instance, one early usage of the phrases "favorable to" (for "facilitative") and "unfavorable to" (for "inhibitive") along with demonstrations for all the implications just summarized, is in Kai-Lai Chung's "On Mutually Favorable Events" (*Annals of Mathematical Statistics*, *13*, 1942, 338–349). In an evidentiary context, such as that developed in detail by Schum (1994) [*The Evidential Foundations of Probabilistic Reasoning*], the phrase "positively (or favorably) relevant" could stand for "facilitative," and the phrase "negatively (or unfavorably) relevant" could substitute for "inhibitive."

Rule 401 in the *Federal Rules of Evidence* (FRE) defines evidence relevance as follows:
Evidence is relevant if

(a) it has any tendency to make a fact more or less probable than it would be without the evidence; and

(b) the fact is of consequence in determining the action.

Nevertheless, just because evidence may be relevant doesn't automatically then make it admissible under FRE Rule 403:
Rule 403. Exclusion of Relevant Evidence on Grounds of Prejudice, Confusion, or Waste of Time: Although relevant, evidence may be excluded if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury, or by considerations of undue delay, waste of time, or needless presentation of cumulative evidence.

[2]The Cinderella saga we have laid out may be akin to what occurs in criminal cases where a conviction is obtained when the weight-of-the-evidence has reached a standard of "beyond a reasonable doubt." The tougher standard of "beyond a shadow of a doubt" may be attainable only when there is a proverbial "smoking gun." In Cinderella's case, this "smoking gun" might amount to producing the exact matching glass slipper that she held onto that night. For the O.J. Simpson case, it's unclear whether there could have ever been a "smoking gun" produced; even the available DNA evidence was discounted because of possible police tampering. If the blood-soaked Bruno Magli shoes

had ever been found and if they had fit O.J. Simpson perfectly, then maybe — but then again, maybe not.

[3]In other plausible reasoning contexts, the difference between $P(A|B)$ and $P(A)$ may not be as relevant as the absolute size of $P(A|B)$ by itself. In a genetics context, for example, suppose A and $\bar{A}$ refer to getting or not getting a particular disease, and B and $\bar{B}$ the presence or absence of some genetic marker. It is not generally true that if you have the marker, you must get the disease (that is, $P(A|B)$ is not necessarily 1.0). In genetics, the conditional probability of getting the disease when the marker is present, $P(A|B)$, is called "penetrance," and the magnitude of penetrance alone may drive certain prophylactic practices such as that of breast removal.

Part VII

External Appendices for the Earlier Chapters

Chapter 15

Edward Jenner

Philosophical Transactions

Observations on the Natural History of the Cuckoo
By Mr. Edward Jenner
In a Letter to John Hunter, F.R.S.
Read March 13, 1788

To John Hunter

Dear Sir,

Having at your request, employed some of my leisure hours in attending to the natural history of the Cuckoo, I beg leave to lay before you the result of my observations, with a hope that they may tend to illustrate a subject hitherto not sufficiently investigated; and should what is here offered prove, in your opinion, deserving the attention of the Royal Society, you will do me the honour of presenting it to that learned Body.

The first appearance of Cuckoos in Gloucestershire (the part of England where these observations were made) is about the 17th of April. The song of the male, which is well known, soon proclaims its arrival. The song of the female (if the peculiar notes of which it is composed may be so called) is widely different, and has been so little attended to, that I believe few are acquainted with it. I know not how to convey to you a proper idea of it by a comparison with the notes of any other bird; but the cry of the Dab-chick bears the nearest resemblance to it.

Unlike the generality of birds, Cuckoos do not pair. When a female appears on the wing, she is often attended by two or three males, who seem to be earnestly contending for her favours. From the time of her appearance, till after the middle of summer, the nests of the birds selected to receive her egg are to be found in great abundance but, like the other migrating birds, she does not begin to lay till some weeks after her arrival. I never could procure an egg till after the middle of May, though probably an early-coming Cuckoo may produce one sooner.

The Cuckoo makes choice of the nests of a great variety of small birds. I have known its egg intrusted to the care of the Hedge-sparrow, the Water-wagtail, the Titlark, the Yellowhammer, the green Linnet, and the Whinchat. Among these it generally selects the three former; but shews [sic] a much greater partiality to the Hedge-sparrow than to any of the rest: therefore, for the purpose of avoiding confusion, this bird only, in the following account, will be considered as the foster-parent of the Cuckoo, except in instances which are particularly specified.

The Hedge-sparrow commonly takes up four or five days in laying her eggs. During this time (generally after she has laid one or two) the Cuckoo contrives to deposit her egg among the rest, leaving the future care of it entirely to the Hedge-sparrow. This intrusion often occasions some discomposure; for the old Hedge-sparrow at intervals, whilst she is sitting, not infrequently throws out some of her own eggs, and sometimes injures them in such a way that they become addle; so that it more frequently happens, that only two or three Hedge-sparrow's eggs are hatched with the Cuckoo's than otherwise: but whether this be the case or not, she sits the same length of time as if no foreign egg had been introduced, the Cuckoo's egg requiring no longer incubation than her own. However, I have never seen an instance where the Hedge-sparrow has either thrown out or injured the egg of the Cuckoo.

When the Hedge-sparrow has sat her usual time, and disengaged the young Cuckoo and some of her own offspring from the shell [the young Cuckoo is commonly hatched first], her own young ones, and any of her eggs that remain unhatched, are soon turned out, the young Cuckoo remaining possessor of the nest, and sole object of her future care. The young birds are not previously killed, nor are the eggs demolished; but all are left to perish together, either

entangled about the bush which contains the nest, or lying on the ground under it.

The early fate of the young Hedge-sparrows is a circumstance that has been noticed by others, but attributed to wrong causes. A variety of conjectures have been formed upon it. Some have supposed the parent Cuckoo the author of their destruction; while others, as erroneously, have pronounced them smothered by the disproportionate size of their fellow-nestling. Now the Cuckoo's egg being not much larger than the Hedge-sparrow's (as I shall more fully point out hereafter) it necessarily follows, that at first there can be no great difference in the size of the birds just burst from the shell. Of the fallacy of the former assertion also I was some years ago convinced, by having found that many Cuckoo's eggs were hatched in the nests of other birds after the old Cuckoo had disappeared; and by seeing the same fate then attend the nestling sparrows as during the appearance of old Cuckoos in this country. But, before I proceed to the facts relating to the death of the young Sparrows, it will be proper to lay before you some examples of the incubation of the egg, and the rearing of the young Cuckoo; since even the well known fact, that this business is intrusted to the care of other birds, has been controverted by an Author who has lately written on this subject [The Hon. Daines Barrington]; and since, as it is a fact so much out of the ordinary course of nature, it may still probably be disbelieved by others.

Example I:

The Titlark is frequently selected by the Cuckoo to take charge of its young one; but as it is a bird less familiar than many that I have mentioned, its nest is not so often discovered. I have, nevertheless, had several Cuckoo's eggs brought to me that were found in Titlark's nests; and had one opportunity of seeing the young Cuckoo in the nest of this bird: I saw the old birds feed it repeatedly, and, to satisfy myself that they were really Titlarks, shot them both, and found them to be so.

Example II:

A Cuckoo laid her egg in a Water-wagtail's nest in the thatch of an old cottage. The Wagtail sat her usual time, and then hatched all the eggs but one; which, with all the young ones, except the Cuckoo, was turned out of the nest. The young birds, consisting of five, were found upon a rafter that

projected from under the thatch, and with them was the egg, not in the least injured. On examining the egg, I found the young Wagtail it contained quite perfect, and just in such a state as birds are when ready to be disengaged from the shell. The Cuckoo was reared by the Wagtails till it was nearly capable of flying, when it was killed by an accident.

Example III:

A Hedge-sparrow built her nest in a hawthorn bush in a timber-yard: after she had laid two eggs, a Cuckoo dropped in a third. The Sparrow continued laying, as if nothing had happened, till she had laid five, her usual number, and then sat.

June 20, 1786. On inspecting the nest I found, that the bird had hatched this morning, and that everything but the young Cuckoo was thrown out. Under the nest I found one of the young Hedge-sparrows dead, and one egg by the side of the nest entangled with the coarse woody materials that formed its outside covering. On examining the egg, I found one end of the shell a little cracked, and could see that the Sparrow contained was yet alive. It was then restored to the nest, but in a few minutes was thrown out. The egg being again suspended by the outside of the nest, was saved a second time from breaking. To see what would happen if the Cuckoo was removed, I took out the Cuckoo, and placed the egg containing the Hedge-sparrow in the nest in its stead. The old birds, during this time, flew about the spot, shewing [sic] signs of great anxiety; but when I withdrew, they quickly came to the nest again. On looking into it in a quarter of an hour afterwards, I found the young one completely hatched, warm and lively. The Hedge-sparrows were suffered to remain undisturbed with their new charge for three hours (during which time they paid every attention to it) when the Cuckoo was again put into the nest. The old Sparrows had been so much disturbed by these intrusions, that for some time they shewed [sic] an unwillingness to come to it: however, at length they came, and on examining the nest again in a few minutes, I found the young Sparrow was tumbled out. It was a second time restored, but again experienced the same fate.

From these experiments, and supposing, from the feeble appearance of the young Cuckoo just disengaged from the shell, that it was utterly incapable of displacing either the egg or the young Sparrows. I was induced to believe,

that the old Sparrows were the only agents in this seeming unnatural business; but I afterwards clearly perceived the cause of this strange phenomenon, by discovering the young Cuckoo in the act of displacing its fellow-nestlings, as the following relation will fully evince.

June 18, 1787. I examined the nest of a Hedge-sparrow, which then contained a Cuckoo's and three Hedge-sparrow's eggs. On inspecting it the day following, I found the bird had hatched, but that the nest now contained only a young Cuckoo and one young Hedge-sparrow. The nest was placed so near the extremity of a hedge, that I could distinctly see what was going forward in it; and, to my astonishment, saw the young Cuckoo, though so newly hatched, in the act of turning out the young Hedge-sparrow.

The mode of accomplishing this was very curious. The little animal, with the assistance of its rump and wings, contrived to get the bird upon its back, and making a lodgement for the burden by elevating its elbows, clambered backward with it up the side of the nest till it reached the top, where resting for a moment, it threw off its load with a jerk, and quite disengaged it from the nest. It remained in this situation a short time, feeling about with the extremities of its wings, as if to be convinced whether the business was properly executed, and then dropped into the nest again. With these (the extremities of its wings) I have often seen it examine, as it were, an egg and nestling before it began its operations; and the nice sensibility which these parts appeared to possess seemed sufficiently to compensate [for] the want of sight, which as yet it [was] destitute of. I afterwards put in an egg, and this, by a similar process, was conveyed to the edge of the nest, and thrown out. These experiments I have since repeated several times in different nests, and have always found the young Cuckoo disposed to act in the same manner. In climbing up the nest, it sometimes drops its burden, and thus is foiled in its endeavours; but, after a little respite, the work is resumed, and goes on almost incessantly till it is effected. It is wonderful to see the extraordinary exertions of the young Cuckoo, when it is two or three days old, if a bird be put into the nest with it that is too weighty for it to lift out. In this state it seems ever restless and uneasy. But this disposition for turning out its companions begins to decline from the time it is two or three till it is about twelve days old, when, as far as I have hitherto seen, it ceases. Indeed, the

disposition for throwing out the egg appears to cease a few days sooner; for I have frequently seen the young Cuckoo, after it had been hatched nine or ten days, remove a nestling that had been placed in the nest with it, when it suffered an egg, put there at the same time, to remain unmolested. The singularity of its shape is well adapted to these purposes; for, different from other newly-hatched birds, its back from the scapulae downwards is very broad, with a considerable depression in the middle. This depression seems formed by nature for the design of giving a more secure lodgement to the egg of the Hedge-sparrow, or its young one, when the young Cuckoo is employed in removing either of them from the nest. When it is about twelve days old, this cavity is quite filled up, and then the back assumes the shape of nestling birds in general.

Having found that the old Hedge-sparrow commonly throws out some of her own eggs after her nest has received the Cuckoo's, and not knowing how she might treat her young ones if the young Cuckoo was deprived of the power of dispossessing them of the nest, I made the following experiment.

July 9. A young Cuckoo, that had been hatched by a Hedge-sparrow about four hours, was confined in the nest in such a manner that it could not possibly turn out the young Hedge-sparrows which were hatched at the same time, though it was almost incessantly making attempts to effect it. The consequence was, the old birds fed the whole alike, and appeared in every respect to pay the same attention to their own young as to the young Cuckoo, until the 13th, when the nest was unfortunately plundered.

The smallness of the Cuckoo's egg in proportion to the size of the bird is a circumstance that hitherto, I believe, has escaped the notice of the ornithologist. So great is the disproportion, that it is in general smaller than that of the House-sparrow; whereas the difference in the size of the birds is nearly as five to one. I have used the term in general, because eggs produced at different times by the same bird vary very much in size. I have found a Cuckoo's egg so light that it weighed only forty-three grains, and one so heavy that it weighed fifty-five grains. The colour of the Cuckoo's eggs is extremely variable. Some, both in ground and penciling, very much resemble the House-sparrow's; some are indistinctly covered with bran coloured spots; and others are marked with lines of black, resembling, in some measure, the

eggs of the Yellow-hammer.

The circumstance of the young Cuckoo being destined by nature to throw out the young Hedge-sparrows, seems to account for the parent-cuckoo dropping her egg in the nests of birds so small as those I have particularised. If she were to do this in the nest of a bird which produced a large egg, and consequently a large nestling, the young Cuckoo would probably find an insurmountable difficulty in solely possessing the nest, as its exertions would be unequal to the labour of turning out the young birds. Besides, though many of the larger birds might have fed the nestling Cuckoo very properly, had it been committed to their charge, yet they could not have suffered their own young to have been sacrificed, for the accommodation of the Cuckoo, in such great number as the smaller ones, which are so much more abundant; for though it would be a vain attempt to calculate the numbers of nestlings destroyed by means of the Cuckoo, yet the slightest observation would be sufficient to convince us that they must be very large.

Here it may be remarked, that though nature permits the young Cuckoo to make this great waste, yet the animals thus destroyed are not thrown away or rendered useless. At the season when this happens, great numbers of tender quadrupeds and reptiles are seeking provision; and if they find the callow nestlings which have fallen victims to the young cuckoo, they are furnished with food well adapted to their peculiar state. It appears a little extraordinary, that two Cuckoo's eggs should ever be deposited in the same nest, as the young one produced from one of them must inevitably perish; yet I have known two instances of this kind, one of which I shall relate.

June 27, 1787. Two Cuckoos and a Hedge-sparrow were hatched in the same nest this morning; one Hedge-sparrow's egg remained unhatched. In a few hours after, a contest began between the Cuckoos for the possession of the nest, which continued undetermined till the next afternoon; when one of them, which was somewhat superior in size, turned out the other, together with the young Hedge-sparrow and the unhatched egg. This contest was very remarkable. The combatants alternately appeared to have the advantage, as each carried the other several times nearly to the top of the nest, and then sunk down again, oppressed by the weight of its burden; till at length, after various efforts, the strongest prevailed, and was afterwards brought up by the

Hedge-sparrows.

I come now, Sir, to consider the principal matter that has agitated the mind of the naturalist respecting the Cuckoo: *why, like other birds, it should not build a nest, incubate its eggs, and rear its own young?*

[This next omitted section contains speculations as to why the Cuckoo acts as it does.]

The same instinctive impulse which directs the Cuckoo to deposit her eggs in the nests of other birds, directs her young one to throw out the eggs and young of the owner of the nest. The scheme of nature would be incomplete without it; for it would be extremely difficult, if not impossible, for the little birds, destined to find succour for the Cuckoo, to find it also for their own young ones, after a certain period; nor would there be room for the whole to inhabit the nest.

Thus, Sir, I have, with much pleasure, complied with your request; and here lay before you such observations as I have hitherto been capable of making on the natural history of the Cuckoo; and should they throw some light on a subject that has long lain hid in obscurity, I shall not think my time has been ill employed.

With a grateful sense of the many obligations I owe to the friendship with which you have so long honoured me, I remain, etc.

EDWARD JENNER
Berkeley,
December 27, 1787

On the Origin of the Vaccine Inoculation (*The Medical and Physical Journal*, June, 1801, *5*, 505–508):

The most important discoveries, when familiarized to the mind, are contemplated with indifference. Who now wonders at the discovery of America, or the circulation of the blood? There is, however, a period between the conception of a discovery and its mature birth, fraught with more pangs than war or women know; and there is no light, in which the human mind can be viewed more interesting than during this anxious period. Whenever, therefore, the author of any greatly useful invention details the progress of his own mind, during the completion of his plan, the history is perused with avidity. On these grounds, we conclude that our readers will be much gratified by the following narrative.

I am induced to give the following concise History of the Origin of Vaccine Inoculation, from my frequently observing that those who only consider the subject cursorily, confound the casual Cow Pox with the Disease when excited by Inoculation.

Bond Street, May 6, 1801
EDWARD JENNER

My inquiry into the nature of the Cow-pox commenced upwards of twenty-five years ago. My attention to this singular disease was first excited by observing, that among those whom in the country I was frequently called upon to inoculate, many resisted every effort to give them the Small-pox. These patients I found had undergone a disease they called the Cow-pox, contracted by milking Cows affected with a peculiar eruption on their teats. On inquiry, it appeared that it had been known among the dairies time immemorial, and that a vague opinion prevailed that it was a preventive of the Small Pox. This opinion I found was, comparatively, new among them for all the older farmers declared they had no such idea in their early days — a circumstance that seemed easily to be accounted for, from my knowing that the common people were very rarely inoculated for the Small-pox, till that practice was rendered general by the improved method introduced by the Suttons: so that the working people in the dairies were seldom put to the test of the preventive powers of the Cow-pox.

In the course of the investigation of this subject, which, like all others of a complex and intricate nature, presented many difficulties, I found that some of those *who seemed to have undergone the Cow-pox*, nevertheless, on inoculation with the Small-pox, felt its influence just the same as if no disease had been communicated to them from the cow. This occur[r]ence led me to enquire among the medical practitioners in the country around me, who all agreed in this sentiment, that the Cow-pox was not to be relied upon as a certain preventive of the Small-pox. This for a while damped but did not extinguish my ardour; for as I proceeded, I had the satisfaction to learn that the cow was subject to some varieties of spontaneous eruptions upon her teats; that they were all capable of communicating sores to the hands of the milkers; and that whatever sore was derived from the animal, was called in the dairy the Cow-pox. Thus I surmounted a great obstacle, and, in consequence, was led to form a distinction between these diseases, one of which only I have denominated the *true*, the others the *spurious*, Cow-pox, as they possess no specific power over the constitution. This impediment to my progress was not long removed, before another, of far greater magnitude in its appearances, started up. There were not wanting instances to prove, that when the true Cow-pox broke out among the cattle at a dairy, a person who had milked an infected animal, and had thereby apparently gone through the disease in common with others, was liable to receive the Small-pox afterwards. This, like the former obstacle, gave a painful check to my fond and aspiring hopes: but reflecting that the operations of Nature are generally uniform, and that it was not probable the human constitution (having undergone the Cow-pox) should in some instances be perfectly shielded from the Small-pox, and in many others remain unprotected, I resumed my labours with redoubled ardour. The result was fortunate; for I now discovered that the virus of Cow-pox was liable to undergo progressive changes, from the same causes precisely as that of Small-pox; and that when it was applied to the human skin in its degenerated state, it would produce the ulcerative effects in as great a degree as when it was not decomposed, and sometimes far greater; but having lost its specific properties, it was incapable of producing that change upon the human frame which is requisite to render it unsusceptible of the variolous contagion: so that it became evident a person might milk a cow one day, and

having caught the disease, be forever secure; while another person, milking the same cow the next day, might feel the influence of the virus in such a way, as to produce a sore or sores, and in confluence of this might experience an indisposition to a considerable extent; yet, as has been observed, the specific quality being lost, the constitution would receive no peculiar impression.

Here the close analogy between the Virus of Small-pox and of Cow-pox becomes remarkably conspicuous; since the former, when taken from a recent pustule, and immediately used, gives the perfect Small-pox to the person on whom it is inoculated: but when taken in a far advanced stage of the disease, or when (although taken early) previously to its insertion, it be exposed to such agents as, according to the established laws of Nature, cause its decomposition, it can no longer be relied on as effectual. This observation will fully explain the source of those errors which have been committed by many inoculators of the Cow-pox. Conceiving the whole process to be so extremely simple, as not to admit of a mistake, they have been heedless about the state of the Vaccine Virus; and finding it limpid, as part of it will be, even in an advanced stage of the pustule, when the greater portion has been converted into a scab, they have felt an improper confidence, and sometimes mistaken a spurious pustule, which the Vaccine fluid in this state is capable of exciting, for that which possesses the perfect character.

During the investigation of the casual Cow-pox, I was struck with the idea that it might be practicable to propagate the disease by inoculation, after the manner of the Small-pox, first from the Cow, and finally from one human being to another. I anxiously waited sometime for an opportunity of putting this theory to the test. At length the period arrived. The first experiment was made upon a lad of the name of Phipps, in whose arm a little Vaccine Virus was inserted, taken from the hand of a young woman who had been accidentally infected by a cow. Notwithstanding the resemblance which the pustule, thus excited on the boy's arm, bore to variolous inoculation, yet as the indisposition attending it was barely perceptible, I could scarcely persuade myself the patient was secure from the Small-pox. However, on his being inoculated some months afterwards, it proved that he was secure. This case inspired me with confidence; and as soon as I could again furnish myself with virus from the Cow, I made an arrangement for a series of inoculations.

A number of children were inoculated in succession, one from the other; and after several months had elapsed, they were exposed to the infection of the Small-pox; some by inoculation, others by variolous effluvia, and some in both ways, but they all resisted it. The result of these trials gradually led me into a wider field of experiment, which I went over not only with great attention but with painful solicitude. This became universally known through a Treatise published in June 1798. The result of my further experience was also brought forward in subsequent publications in the two succeeding years, 1799 and 1800. The distrust and skepticism which naturally arose in the minds of medical men, on my first announcing so unexpected a discovery, has now nearly disappeared. Many hundreds of them, from actual experience, have given their attestations that the inoculated Cow-Pox proves a perfect security against the Small-Pox; and I shall probably be within compass if I say, thousands are ready to follow their example; for the scope that this inoculation has now taken is immense. An [sic] hundred thousand persons, upon the smallest computation, have been inoculated in these realms. The numbers who have partaken of its benefits throughout Europe, and other parts of the globe, are incalculable; and it now becomes too manifest to admit of controversy, that the annihilation of the Small-pox, the most dreadful scourge of the human species, must be the final result of this practice.

Chapter 16

John Snow

Snow's discussion of the cholera epidemic in Broad Street (from MCC):

The most terrible outbreak of cholera which ever occurred in this kingdom, is probably that which took place in Broad Street, Golden Square, and the adjoining streets, a few weeks ago. Within two hundred and fifty yards of the spot where Cambridge Street joins Broad Street, there were upwards of five hundred fatal attacks of cholera in ten days. The mortality in this limited area probably equals any that was ever caused in this country, even by the plague; and it was much more sudden, as the greater number of cases terminated in a few hours. The mortality would undoubtedly have been much greater had it not been for the flight of the population. Persons in furnished lodgings left first, then other lodgers went away, leaving their furniture to be sent for when they could meet with a place to put it in. Many houses were closed altogether, owing to the death of the proprietors; and, in a great number of instances, the tradesmen who remained had sent away their families: so that in less than six days from the commencement of the outbreak, the most afflicted streets were deserted by more than three-quarters of their inhabitants.

There were a few cases of cholera in the neighborhood of Broad Street, Golden Square, in the latter part of August; and the so-called outbreak, which commenced in the night between the 31st August and the 1st September, was, as in all similar instances, only a violent increase of the malady. As soon as I became acquainted with the situation and extent of this irruption of cholera, I suspected some contamination of the water of the much-frequented

street-pump in Broad Street, near the end of Cambridge Street; but on examining the water, on the evening of the 3rd September, I found so little impurity in it of an organic nature, that I hesitated to come to a conclusion. Further inquiry, however, showed me that there was no other circumstance or agent common to the circumscribed locality in which this sudden increase of cholera occurred, and not extending beyond it, except the water of the above mentioned pump. I found, moreover, that the water varied, during the next two days, in the amount of organic impurity, visible to the naked eye, on close inspection, in the form of small white, flocculent particles; and I concluded that, at the commencement of the outbreak, it might possibly have been still more impure. I requested permission, therefore, to take a list, at the General Register Office, of the deaths from cholera, registered during the week ending 2nd September, in the subdistricts of Golden Square, Berwick Street, and St. Ann's, Soho, which was kindly granted. Eighty-nine deaths from cholera were registered, during the week, in the three subdistricts. Of these, only six occurred in the four first days of the week; four occurred on Thursday, the 31st August; and the remaining seventy-nine on Friday and Saturday. I considered, therefore, that the outbreak commenced on the Thursday; and I made inquiry, in detail, respecting the eighty-three deaths registered as having taken place during the last three days of the week.

On proceeding to the spot, I found that nearly all the deaths had taken place within a short distance of the pump. There were only ten deaths in houses situated decidedly nearer to another street pump. In five of these cases the families of the deceased persons informed me that they always sent to the pump in Broad Street, as they preferred the water to that of the pump which was nearer. In three other cases, the deceased were children who went to school near the pump in Broad Street. Two of them were known to drink the water; and the parents of the third think it probable that it did so. The other two deaths, beyond the district which this pump supplies, represent only the amount of mortality from cholera that was occurring before the irruption took place.

With regard to the deaths occurring in the locality belonging to the pump, there were sixty-one instances in which I was informed that the deceased persons used to drink the pump-water from Broad Street, either constantly,

or occasionally. In six instances I could get no information, owing to the death or departure of every one connected with the deceased individuals; and in six cases I was informed that the deceased persons did not drink the pump-water before their illness.

The result of the inquiry then was, that there had been no particular outbreak or increase of cholera, in this part of London, except among the persons who were in the habit of drinking the water of the above-mentioned pump-well.

I had an interview with the Board of Guardians of St. James's parish, on the evening of Thursday, 7th September, and represented the above circumstances to them. In consequence of what I said, the handle of the pump was removed on the following day.

Besides the eighty-three deaths mentioned above as occurring on the three last days of the week ending September 2nd, and being registered during that week in the sub-districts in which the attacks occurred, a number of persons died in Middlesex and other hospitals, and a great number of deaths which took place in the locality during the last two days of the week, were not registered till the week following. The deaths altogether, on the 1st and 2nd of September, which have been ascertained to belong to this outbreak of cholera, were one hundred and ninety-seven; and many persons who were attacked about the same time as these, died afterwards. I should have been glad to inquire respecting the use of the water from Broad Street pump in all these instances, but was engaged at the time in an inquiry in the south districts of London, which will be alluded to afterwards; and when I began to make fresh inquiries in the neighborhood of Golden Square, after two or three weeks had elapsed, I found that there had been such a distribution of the remaining population that it would be impossible to arrive at a complete account of the circumstances. There is no reason to suppose, however, that a more extended inquiry would have yielded a different result from that which was obtained respecting the eighty-three deaths which happened to be registered within the district of the outbreak before the end of the week in which it occurred.

The additional facts that I have been able to ascertain are in accordance with those above related; and as regards the small number of those attacked, who were believed not to have drank the water from Broad Street pump, it

must be obvious that there are various ways in which the deceased persons may have taken it without the knowledge of their friends. The water was used for mixing with spirits in all the public houses around. It was used likewise at dining-rooms and coffee-shops. The keeper of a coffee-shop in the neighborhood, which was frequented by mechanics, and where the pump-water was supplied at dinner time, informed me (on 6th September) that she was already aware of nine of her customers who were dead. The pump-water was also sold in various little shops, with a teaspoonful of effervescing powder in it, under the name of sherbet; and it may have been distributed in various other ways with which I am unacquainted. The pump was frequented much more than is usual, even for a London pump in a populous neighborhood.

There are certain circumstances bearing on the subject of this outbreak of cholera which require to be mentioned. The Workhouse in Poland Street is more than three-fourths surrounded by houses in which deaths from cholera occurred, yet out of five hundred and thirty-five inmates only five died of cholera, the other deaths which took place being those of persons admitted after they were attacked. The workhouse has a pump-well on the premises, in addition to the supply from the Grand Junction Water Works, and the inmates never sent to Broad Street for water. If the mortality in the workhouse had been equal to that in the streets immediately surrounding it on three sides, upwards of one hundred persons would have died.

There is a Brewery in Broad Street, near to the pump, and on perceiving that no brewer's men were registered as having died of cholera, I called on Mr. Huggins, the proprietor. He informed me that there were above seventy workmen employed in the brewery, and that none of them had suffered from cholera — at least in a severe form — only two having been indisposed, and that not seriously, at the time the disease prevailed. The men are allowed a certain quantity of malt liquor, and Mr. Huggins believes they do not drink water at all; and he is quite certain that the workmen never obtained water from the pump in the street. There is a deep well in the brewery, in addition to the New River water.

At the percussion-cap manufactory, 37 Broad Street, where, I understand, about two hundred workpeople were employed, two tubs were kept on the premises always supplied with water from the pump in the street, for those

to drink who wished; and eighteen of these workpeople died of cholera at their own homes, sixteen men and two women.

Mr. Marshall, surgeon, of Greek Street, was kind enough to inquire respecting seven workmen who had been employed in the manufactory of dentists' materials, at Nos. 8 and 9 Broad Street, and who died at their own homes. He learned that they were all in the habit of drinking water from the pump, generally drinking about half-a-pint once or twice a day; while two persons who reside constantly on the premises, but do not drink the pump-water, only had diarrhea. Mr. Marshall also informed me of the case of an officer in the army, who lived at St. John's Wood, but came to dine in Wardour Street, where he drank the water from Broad Street pump at his dinner. He was attacked with cholera, and died in a few hours.

I am indebted to Mr. Marshall for the following cases, which are interesting as showing the period of incubation, which in these three cases was from thirty-six to forty-eight hours. Mrs. ——, of 13 Bentinck Street, Berwick Street, aged 28, in the eighth month of pregnancy, went herself (although they were not usually water drinkers), on Sunday, 3rd September, to Broad Street pump for water. The family removed to Gravesend on the following day; and she was attacked with cholera on Tuesday morning at seven o'clock, and died of consecutive fever on 15th September, having been delivered. Two of her children drank also of the water, and were attacked on the same day as the mother, but recovered.

Dr. Fraser, of Oakley Square, kindly informed me of the following circumstance. A gentleman in delicate health was sent for from Brighton to see his brother at 6 Poland Street, who was attacked with cholera and died in twelve hours, on 1st September. The gentleman arrived after his brother's death, and did not see the body. He only stayed about twenty minutes in the house, where he took a hasty and scanty luncheon of rumpsteak, taking with it a small tumbler of brandy and water, the water being from Broad Street pump. He went to Pentonville, and was attacked with cholera on the evening of the following day, 2nd September, and died the next evening.

Dr. Fraser also first called my attention to the following circumstances, which are perhaps the most conclusive of all in proving the connection between the Broad Street pump and the outbreak of cholera. In the "Weekly Re-

turn of Births and Deaths" of September 9th, the following death is recorded as occurring in the Hampstead district: "At West End, on 2nd September, the widow of a percussion-cap maker, aged 59 years, diarrhea two hours, cholera epidemics sixteen hours."

I was informed by this lady's son that she had not been in the neighborhood of Broad Street for many months. A cart went from Broad Street to West End every day, and it was the custom to take out a large bottle of the water from the pump in Broad Street, as she preferred it. The water was taken on Thursday, 31st August, and she drank of it in the evening, and also on Friday. She was seized with cholera on the evening of the latter day, and died on Saturday, as the above quotation from the register shows. A niece, who was on a visit to this lady, also drank of the water; she returned to her residence, in a high and healthy part of Islington, was attacked with cholera, and died also. There was no cholera at the time, either at West End or in the neighborhood where the niece died. Besides these two persons, only one servant partook of the water at Hampstead West End, and she did not suffer, or, at least, not severely. There were many persons who drank the water from Broad Street pump about the time of the outbreak, without being attacked with cholera; but this does not diminish the evidence respecting the influence of the water, for reasons that will be fully stated in another part of this work. (pp. 36–45)

Snow's Grand Experiment (from MCC):

All the instances of communication of cholera through the medium of water, above related, have resulted from the contamination of a pump-well, or some other limited supply of water; and the outbreaks of cholera connected with the contamination, though sudden and intense, have been limited also; but when the water of a river becomes infected with the cholera evacuations emptied from on board ship, or passing down drains and sewers, the communication of the disease, though generally less sudden and violent, is much more widely extended; more especially when the river water is distributed by the steam engine and pipes connected with water-works. Cholera may linger in the courts and alleys crowded with the poor, for reasons previously pointed out, but I know of no instance in which it has been generally spread through a town or neighborhood, amongst all classes of the community, in which the drinking water has not been the medium of its diffusion. Each epidemic of cholera in London has borne a strict relation to the nature of the water-supply of its different districts, being modified only by poverty, and the crowding and want of cleanliness which always attend it.

Although the facts ... afford very strong evidence of the powerful influence which the drinking of water containing the sewage of a town exerts over the spread of cholera, when that disease is present, yet the question does not end here; for the intermixing of the water supply of the Southwark and Vauxhall Company with that of the Lambeth Company, over an extensive part of London, admitted of the subject being sifted in such a way as to yield the most incontrovertible proof on one side or the other. In the sub-districts enumerated ... as being supplied by both Companies, the mixing of the supply is of the most intimate kind. The pipes of each Company go down all the streets, and into nearly all the courts and alleys. A few houses are supplied by one Company and a few by the other, according to the decision of the owner or occupier at that time when the Water Companies were in active competition. In many cases a single house has a supply different from that on either side. Each company supplies both rich and poor, both large houses and small; there is no difference either in the condition or occupation of the persons receiving the water of the different Companies. Now it must be

evident that, if the diminution of cholera, in the districts partly supplied with the improved water, depended on this supply, the houses receiving it would be the houses enjoying the whole benefit of the diminution of the malady, whilst the houses supplied with the [polluted] water from Battersea Fields would suffer the same mortality as they would if the improved supply did not exist at all. As there is no difference whatever, either in the houses or the people receiving the supply of the two Water Companies, or in any of the physical conditions with which they are surrounded, it is obvious that no experiment could have been devised which would more thoroughly test the effect of water supply on the progress of cholera than this, which circumstances placed ready made before the observer.

The experiment, too, was on the grandest scale. No fewer than three hundred thousand people of both sexes, of every age and occupation, and of every rank and station, from gentlefolks down to the very poor, were divided into two groups without their choice, and, in most cases, without their knowledge; one group being supplied with water containing the sewage of London, and, amongst it, whatever might have come from the cholera patients, the other group having water quite free from such impurity.

To turn this grand experiment to account, all that was required was to learn the supply of water to each individual house where a fatal attack of cholera might occur. I regret that, in the short days at the latter part of last year, I could not spare the time to make the inquiry; and, indeed, I was not fully aware, at that time, of the very intimate mixture of the supply of the two Water Companies, and the consequently important nature of the desired inquiry.

...

When the cholera returned to London in July of the present year, however, I resolved to spare no exertion which might be necessary to ascertain the exact effect of the water supply on the progress of the epidemic, in the places where all the circumstances were so happily adapted for the inquiry. I was desirous of making the investigation myself, in order that I might have the most satisfactory proof of the truth or fallacy of the doctrine which I had been advocating for five years. I had no reason to doubt the correctness of the conclusions I had drawn from the great number of facts already in

my possession, but I felt that the circumstance of the cholera-poison passing down the sewers into a great river, and being distributed through miles of pipes, and yet producing its specific effects, was a fact of so startling a nature, and of so vast importance to the community, that it could not be too rigidly examined, or established on too firm a basis.

I accordingly asked permission at the General Register Office to be supplied with the addresses of persons dying of cholera, in those districts where the supply of the two Companies is intermingled in the manner I have stated above. Some of these addresses were published in the"Weekly Returns," and I was kindly permitted to take a copy of others. I commenced my inquiry about the middle of August with two sub-districts of Lambeth, called Kennington, first part, and Kennington, second part. There were forty-four deaths in these sub-districts down to 12th August, and I found that thirty-eight of the houses in which these deaths occurred were supplied with water by the Southwark and Vauxhall Company, four houses were supplied by the Lambeth Company, and two had pump-wells on the premises and no supply from either of the Companies.

As soon as I had ascertained these particulars I communicated them to Dr. Farr, who was much struck with the result, and at his suggestion the Registrars of all the south districts of London were requested to make a return of the water supply of the house in which the attack took place, in all cases of death from cholera. This order was to take place after the 26th August, and I resolved to carry my inquiry down to that date, so that the facts might be ascertained for the whole course of the epidemic. I pursued my inquiry over the various other sub-districts of Lambeth, Southwark, and Newington, where the supply of the two Water Companies is intermixed, with a result very similar to that already given, as will be seen further on. In cases where persons had been removed to a workhouse or any other place, after the attack of cholera had commenced, I inquired the water supply of the house where the individuals were living when the attack took place.

The inquiry was necessarily attended with a good deal of trouble. There were very few instances in which I could at once get the information I required. Even when the water-rates are paid by the residents, they can seldom remember the name of the Water Company till they have looked for the re-

ceipt. In the case of working people who pay weekly rents, the rates are invariably paid by the landlord or his agent, who often lives at a distance, and the residents know nothing about the matter. It would, indeed, have been almost impossible for me to complete the inquiry, if I had not found that I could distinguish the water of the two companies with perfect certainty by a chemical test. The test I employed was founded on the great difference in the quantity of chloride of sodium contained in the two kinds of water, at the time I made the inquiry. On adding solution of nitrate of silver to a gallon of the water of the Lambeth Company, obtained at Thames Ditton, beyond the reach of the sewage of London, only 2.28 grains of chloride of silver were obtained, indicating the presence of 0.95 grains of chloride of sodium in the water. On treating the water of the Southwark and Vauxhall Company in the same manner, 91 grains of chloride of silver were obtained, showing the presence of 37.9 grains of common salt per gallon. Indeed, the difference in appearance on adding nitrate of silver to the two kinds of water was so great, that they could be at once distinguished without any further trouble. Therefore when the resident could not give clear and conclusive evidence about the Water Company, I obtained some of the water in a small phial, and wrote the address on the cover, when I could examine it after coming home. The mere appearance of the water generally afforded a very good indication of its source, especially if it was observed as it came in, before it had entered the water-butt or cistern; and the time of its coming in also afforded some evidence of the kind of water, after I had ascertained the hours when the turncocks of both Companies visited any street. These points were, however, not relied on, except as corroborating more decisive proof, such as the chemical test, or the Company's receipt for the rates.

A return had been made to Parliament of the entire number of houses supplied with water by each of the Water Companies, but as the number of houses which they supplied in particular districts was not stated, I found that it would be necessary to carry my inquiry into all the districts to which the supply of either Company extends, in order to show the full bearing of the facts brought out in those districts where the supply is intermingled. I inquired myself respecting every death from cholera in the districts to which the supply of the Lambeth Company extends, and I was fortunate enough

to obtain the assistance of a medical man, Mr. John Joseph Whiting, ... to make inquiry in Bermondsey, Rotherhithe, Wandsworth, and certain other districts, which are supplied only by the Southwark and Vauxhall Company. Mr. Whiting took great pains with his part of the inquiry, which was to ascertain whether the houses in which the fatal attacks took place were supplied with the Company's water, or from a pump-well, or some other source.

Mr. Whiting's part of the investigation extended over the first four weeks of the epidemic, from 8th July to 5th August; and as inquiry was made respecting every death from cholera during this part of the epidemic, in all the districts to which the supply of either of the Water Companies extends, it may be well to consider this period first. There were three hundred and thirty-four deaths from cholera in these four weeks, in the districts to which the water supply of the Southwark and Vauxhall and the Lambeth Company extends. Of these it was ascertained, that in two hundred and eighty-six cases the house where the fatal attack of cholera took place was supplied with water by the Southwark and Vauxhall Company, and in only fourteen cases was the house supplied with the Lambeth Company's water; in twenty-two cases the water was obtained by dipping a pail directly into the Thames, in four instances it was obtained from pump-wells, in four instances from ditches, and in four cases the source of supply was not ascertained, owing to the person being taken ill whilst traveling, or from some similar cause. The particulars of all the deaths which were caused by cholera in the first four weeks of the late epidemic, were published by the Registrar-General in the "Weekly Returns of Births and Deaths in London" and I have had the three hundred and thirty-four above enumerated reprinted in an Appendix to this edition, as a guarantee that the water supply was inquired into, and to afford any person who wishes it an opportunity of verifying the result. Any one who should make the inquiry must be careful to find the house where the attack took place, for in many streets there are several houses having the same number.

According to a return which was made to Parliament, the Southwark and Vauxhall Company supplied 40,046 houses from January 1st to December 31st, 1853, and the Lambeth Company supplied 26,107 houses during the same period; consequently, as 286 fatal attacks of cholera took place, in the

first four weeks of the epidemic, in houses supplied by the former Company, and only 14 in houses supplied by the latter, the proportion of fatal attacks to each 10,000 houses was as follows. Southwark and Vauxhall 71. Lambeth 5. The cholera was therefore fourteen times as fatal at this period, amongst persons having the impure water of the Southwark and Vauxhall Company, as amongst those having the purer water from Thames Ditton.

It is extremely worthy of remark, that whilst only five hundred and sixty-three deaths from cholera occurred in the whole of the metropolis, in the four weeks ending 5th August, more than one half of them took place amongst the customers of the Southwark and Vauxhall Company, and a great portion of the remaining deaths were those of mariners and persons employed amongst the shipping in the Thames, who almost invariably draw their drinking water direct from the river.

It may, indeed, be confidently asserted, that if the Southwark and Vauxhall Water Company had been able to use the same expedition as the Lambeth Company in completing their new works, and obtaining water free from the contents of sewers, the late epidemic of cholera would have been confined in a great measure to persons employed among the shipping, and to poor people who get water by pailsful direct from the Thames or tidal ditches.

The number of houses in London at the time of the last census was 327,391. If the houses supplied with water by the Southwark and Vauxhall Company, and the deaths from cholera occurring in these houses, be deducted, we shall have in the remainder of London 287,345 houses, in which 277 deaths from cholera took place in the first four weeks of the epidemic. This is at the rate of nine deaths to each 10,000. But the houses supplied with water by the Lambeth Company only suffered a mortality of five in each 10,000 at this period; it follows, therefore, that these houses, although intimately mixed with those of the Southwark and Vauxhall Company, in which so great a proportional mortality occurred, did not suffer even so much as the rest of London which was not so situated.

In the beginning of the late epidemic of cholera in London, the Thames water seems to have been the great means of its diffusion, either through the pipes of the Southwark and Vauxhall Company, or more directly by dipping a pail in the river. Cholera was prevailing in the Baltic Fleet in the early

part of summer, and the following passage from the "Weekly Returns" of the Registrar-General shows that the disease was probably imported thence to the Thames.

"Bermondsey, St. James. At 10, Marine Street, on 25th July, a mate mariner, aged 34 years, Asiatic cholera 101 hours, after premonitory diarrhea 16.5 hours. The medical attendant states: 'This patient was the chief mate to a steam-vessel taking stores to and bringing home invalids from the Baltic Fleet. Three weeks ago he brought home in his cabin the soiled linen of an officer who had been ill. The linen was washed and returned.'"

The time when this steam-vessel arrived in the Thames with the soiled linen on board, was a few days before the first cases of cholera appeared in London, and these first cases were chiefly amongst persons connected with the shipping in the river. It is not improbable therefore that a few simple precautions, with respect to the communications with the Baltic Fleet, might have saved London from the cholera this year, or at all events greatly retarded its appearance.

As the epidemic advanced, the disproportion between the number of cases in houses supplied by the Southwark and Vauxhall Company and those supplied by the Lambeth Company, became not quite so great, although it continued very striking. In the beginning of the epidemic the cases appear to have been almost altogether produced through the agency of the Thames water obtained amongst the sewers; and the small number of cases occurring in houses not so supplied, might be accounted for by the fact of persons not keeping always at home and taking all their meals in the houses in which they live; but as the epidemic advanced it would necessarily spread amongst the customers of the Lambeth Company, as in parts of London where the water was not in fault, by all the usual means of its communication. (pp. 74–82)

Snow's testimony to Parliament on the offensive trades:

Q: Do you practice as a medical man in the Metropolis?

A: Yes, in Sackville Street.

Q: You wish to give some evidence upon the Nuisances Removal and Diseases Prevention Act?

A: I have been requested to give evidence on behalf of the trades people in the south districts of London, more particularly.

Q: Upon what point?

A: I received a request from Mr. Knight. I was asked if I would give evidence on behalf of the manufacturers whose interests are threatened by the Nuisances Removal Act. I have not seen the parties, nor learnt any particulars. From my printed publication they have learnt that my opinion is, that measures necessary to protect the public health would not interfere with useful trades; and I believe it is on that account that they have asked me to give evidence on their behalf, and I have expressed my willingness to do so.

Q: To what points would you desire to draw the attention of the Committee as regards the sanitary question?

A: I have paid a great deal of attention to epidemic diseases, more particularly to cholera, and in fact to the public health in general; and I have arrived at the conclusion with regard to what are called offensive trades, that many of them really do not assist in the propagation of epidemic diseases, and that in fact they are not injurious to the public health. I consider that if they were injurious to the public health they would be extremely so to the workmen engaged in those trades, and as far as I have been able to learn, that is not the case; and from the law of the diffusion of gases, it follows, that if they are not injurious to those actually upon the spot, where the trades are carried on, it is impossible they should be to persons further removed from the spot.

Q: Are the Committee to understand, taking the case of bone-boilers, that no matter how offensive to the sense of smell the effluvia that comes from bone-boiling establishments may be, yet you consider that it is not prejudicial in any way to the health of the inhabitants of the district?

A: That is my opinion.

Q: Does that extend to all animal substances?

A: No. I believe that epidemic diseases are propagated by special animal poisons coming from diseased persons, and causing the same diseases to others, and that they are extremely injurious; but that substances belonging to animals, that is to say, ordinary decomposing animal matter, will not produce disease in the human subject.

Q: Do you apply that, also, to decaying vegetable matter; do you consider that that will not be productive of disease?

A: I do not believe that decaying vegetable matter would be productive of disease; at least, it is a matter open for discussion whether certain decomposing vegetable substances, in marshy districts, may not produce agues; but in London, in any trade I am acquainted with, I do not believe that any decomposing vegetable or animal matters produce disease.

Q: Take the case of a bone-boiling establishment, or a knacker's yard; assuming that there is a large number of horses in a state of decomposition, from which of course there would be very offensive effluvia, as far as the sense of smell is concerned, do you apprehend that that would not be prejudicial to the health of the inhabitants round?

A: I believe not.

Q: Have you never known the blood poisoned by inhaling putrid matter?

A: No; but by dissection wounds the blood may be poisoned.

Q: Never by inhaling putrid matter?

A: No; gases produced by decomposition, when very concentrated, will produce sudden death; but where the person is not killed, if the person recovers, he has no fever or illness.

Q: You mean to say, that the fact of breathing air which is tainted by decomposing matter, either animal or vegetable, will not be highly prejudicial to health?

A: I am not aware that it is, unless it be in such quantities as to produce actually fatal effects at the moment; but to produce those effects it requires that it should be highly concentrated.

Q: Do you not know that the effect of breathing such tainted air often is to produce violent sickness at the time?

A: Yes, when the gases are in a very large quantity, as in a cesspool.

Q: Do you mean to tell the Committee that when the effect is to produce violent sickness there is no injury produced to the constitution or health of the individual?

A: No fever or special disease.

Q: Are you not aware that persons going into vaults where there are a number of dead bodies have suffered very severely, and that sometimes death has been produced by this cause?

A: Yes, when those gases are extremely concentrated, they will actually poison a person and cause death, but not cause disease; those poisons do not reproduce themselves in the constitution.

Q: Are you not aware that, in cases of this kind, illness has sometimes been produced from which persons have suffered for a considerable length of time before death ensued?

A: I am not satisfied upon that point. If illness has followed I think it has been a coincident.

Q: Are you not aware that, in cases of this kind, illness has sometimes been produced from which persons have suffered very severely, and that sometimes death has been produced by this cause?

A: Yes, when those gases are extremely concentrated, they will actually poison a person and cause death, but not cause disease; those poisons do not reproduce themselves in the constitution.

Q: You say that the effluvia arising from living subjects are dangerous?

A: Or even from certain persons who have died from disease.

Q: I understand you to say that such effluvia, when highly concentrated, may produce vomiting, but that they are not injurious to health. How do you reconcile those two propositions?

A: If the vomiting were repeatedly produced, it would certainly be injurious to health. If a person was constantly exposed to decomposing matter, so concentrated as to disturb the digestive organs, it must be admitted that that would be injurious to health; but I am not aware that, in following any useful trade or manufacture, the effects ever experienced.

Q: You consider that occasional sickness would be of no consequence, but that only frequent occurrence of the attacks would be injurious?

A: I am not aware that any occasional sickness is produced in any useful

trade or manufacture.

Q: Do you not know that the effect of a very strong offensive smell often is to produce vomiting?

A: The gases must be very concentrated to do that, except it be by a kind of sympathy. Persons are often much influenced by the imagination.

Q: Where does your practice lie?

A: I am living in Sackville Street, Piccadilly.

Q: I believe you are frequently in the habit of administering chloroform?

A: Yes.

Q: And therefore your attention has been particularly called to the effect of the administration of gases?

A: Yes.

Q: Have you turned your attention to the effects of the late outbreak of cholera in London?

A: Yes, I made special enquiries throughout Lambeth and Southwark and Newington.

Q: Have you satisfied yourself by those inquiries of any particular results of that outbreak of cholera, so as to state your opinion of what has been the mode of propagation of the disease?

A: I have satisfied myself completely, that the chief mode of propagation of cholera in the South district of London, throughout the late outbreak, was by the water of the Southwark and Vauxhall Water Company containing the sewage of London; and containing consequently whatever might come from the cholera patients in the crowded habitations of the poor; and I am satisfied that it spread directly from individual to individual, sometimes in the same family, but by similar means; that is, by their swallowing accidentally what came from a previous sick patient.

Q: Do you believe that there is evidence to show that cholera has been propagated almost entirely by the poison being taken in at the mouth?

A: Yes.

Q: Absolutely swallowed?

A: Yes, it is my belief in every case.

Q: Has your practice lain much amongst the poor?

A: Not so much latterly as it did at one time; but it did very much till

seven years ago.

Q: In what district?

A: In a district near Soho Square, running as far as Seven Dials.

Q: You have stated that in the course of your inquiry you satisfied yourself that water was the principal cause of communicating cholera, after the water had been impregnated by the existence of the cholera. Did you satisfy yourself what was the original cause of cholera in those persons who were not so affected by the water?

A: I consider that the last outbreak of cholera was introduced from the Baltic Fleet into the Thames. I consider that the cause of cholera is always cholera; that each case always depends upon a previous one.

Q: You have stated that, in your opinion, these offensive trades have no injurious effect upon the health; will you state by what means you have arrived at that conclusion; whether it is by lengthened experience derived from medical attendance upon those who carry on these trades or whether it is a theory?

A: It is derived in various ways, but chiefly rather in a negative way; from my having satisfied myself on other causes of disease quite independent of those trades; also from my general medical opinions, and also from my experience amongst trades people who have been exposed to those things.

Q: As your medical practice has not been amongst men who follow those occupations, by what means do you arrive at the fact that their health is not affected by them?

A: I have attended people in every occupation, and my opinion is derived also from reading, and from personal information.

Q: Is your opinion derived from practical experience, or is it mere theory of your own?

A: My theory is derived from practice, and from observation.

Q: Will you state in what particular localities of London you practiced as a medical man, so as to be able to express that opinion so confidently to the Committee?

A: My practice amongst the poor extended chiefly between the Thames and Oxford Street; I have not turned my special attention to any particular trades; I never was called upon, till two or three days ago to consider this

subject particularly.

Q: The point at which we particularly wish to arrive here is the effect of particular trades upon the health of individuals. You say that you believe that these offensive trades have no effect upon the health of individuals; by what means do you arrive at that conclusion?

A: Partly by my own observation, partly by reading.

Q: Will you state where your observation was obtained; because, in the locality that you mention, between the Thames and Oxford Street, there are few, if any, soap-boilers or bone-crushers, or any of those trades?

A: There are people who collect the bones in the rag shops; but in the hospitals I have seen patients from every part of London.

Q: Has your attention ever been directed, as a medical man, to those particular parts of London about Bermondsey, and other districts, on the south side of the water: Have you ever practiced as a medical man there?

A: I have not practiced there; I have visited patients there: but for several weeks in the last autumn I went to the houses of 700 people who had died of cholera, and I knew their actual occupations, and their age, as it was entered in the Registrar General's reports, and I examined the tables at the time.

Q: In what part of London did you make those inquiries?

A: Throughout the whole of Lambeth, St. George's, Southwark, and the whole of Newington, and St. George's Camberwell; I inquired respecting every case of cholera in the first seven weeks of the epidemic.

Q: But you do not practice as a medical man in these particular districts?

A: No, I live in Sackville Street; I have lived there for three years; previously to that I lived in Frith Street, Soho Square. I did not attend those patients on the south side of London, but I went afterwards to the houses making inquiries, to find out the nature of their supply of water; and in doing that I learnt a number of other particulars about them. I always knew the occupation of the deceased person.

Q: Do you dispute the fact that putrid fever and typhus fever hang about places where there are open sewers?

A: Sometimes.

Q: How do you account for that?

A: It is a coincidence. Where there are open sewers you have mostly

a number of people living together under such circumstances that they get fever, which is communicated from one person to another; very often the water of the pump wells is impregnated with the excrements of the people, which soaks into the wells. And the general water supply in certain districts is also very bad.

Q: Did not you make particular inquiries at the houses which were supplied by two companies which take their supply of water from different places?

A: Yes; the one is supplied from Battersea Fields, near Vauxhall Bridge, and the other from Thames Ditton.

Q: Was there a very marked difference between them?

A: There was. In the first four weeks of the epidemic the mortality was fourteen times as great amongst the customers of the Southwark and Vauxhall Company, getting their water in Battersea Fields as in the other, taking into account the number of houses supplied by each company.

Q: You have made very extensive statistical inquiry as to the diseases which you have mentioned?

A: I have.

Q: Have you in any case traced the propagation of those diseases, or of the cholera, to the existence of offensive trades?

A: I have every reason to believe that those trades have not had any influence whatever.

Q: In any single instance that you have visited in those places, were you ever able to trace any case of the propagation of disease by any of the offensive trades?

A: No; on the contrary, I am satisfied that such influences have no effect whatever. Last autumn there was not much cholera about Fore Street, Lambeth, and all that district. That district suffered extremely in 1849; but in 1854 it suffered very slightly. All the other facts remain the same; but that district is now chiefly supplied by the Lambeth Company with improved water.

Q: Is it not possible that the same poisonous qualities which affect the water may be floating in the air?

A: That is possible; but I believe that the poison of the cholera is either swallowed in water, or got directly from some other person in the family, or

in the room; I believe it is quite an exception for it to be conveyed in the air; though if the matter gets dry it may be wafted a short distance.

Snow's *Lancet* (1856) article rebutting an earlier editorial:

The science of public health, like other branches of knowledge, may be as much benefited by the removal of errors which stand in the way of its progress as by direct discovery; and it is with this conviction that I send for publication the result of an examination into a portion of the Registrar-General's very valuable Weekly Returns of Deaths in London. Whilst a number of eminent authors have for a long period attributed the generality of epidemic ... diseases to special poisons passing in some way from one patient to another, an active section of the profession has attributed the greater number of these diseases to a variety of general causes, and in particular has asserted that they were occasioned, or greatly aggravated, by offensive gases proceeding from putrefying materials, even though these materials did not proceed in any way from sick persons.

An opportunity is now afforded of examining this question on, as I believe, a larger scale than previously. For the last eighteen months the Weekly Returns of the Registrar-General have contained the occupations of males aged 20 years and upwards whose deaths have been registered, and at the end of each quarter of a year the aggregate results have been given in a table. The causes of death are not contained in the table; but the diseases which offensive trades are presumed to promote are such as would increase the mortality, and in fact the mortality of persons in any occupation is the best criterion of its salubrity. The entire number of males aged 20 years and upwards in the metropolis at the last census was 632,545, and the number of deaths in this division of the population, in the year and a half just expired, was 22,889, being at the rate of 241 per annum in 10,000. The number of persons aged 20 years and upwards working and dealing in animal substances was 40,004 in 1851, and the number of deaths in the last eighteen months, 1,210, being at the rate of 201 per annum in 10,000, or five-sixths as many as in the entire male population of 20 years and upwards. The greater number of persons working and dealing in animal substances are, however, occupied amongst silk, wool, and hair, which are in no way offensive; and I therefore thought it desirable to separate those trades which I believe to be really offensive, and I have included in the accompanying table all such occupations in which any

Occupations of Males, aged 20 and upwards	Living in London at the Census of 1851	Deaths in 18 Months, ending June 28, 1856	Deaths per annum in 10,000 living in 1851
Tripe dealer, dresser	194	9	
Tallow chandler	1,239	42	226
Comb maker	398	16	
Soap boiler	338	6	
Music-string maker	87	1	
Bone gatherer	34	3	
Bone worker	52	2	
Currier	2,649	79	195
Tanner	1,314	35	177
Fellmonger	202	5	
Grease dealer	67	1	
Cats' meat purveyor	60	3	
Skinner	170	5	
Parchment maker	75	5	
Glue and size maker	64	2	
Total of offensive trades	6,943	214	205
Total working and dealing in animal substances	40,004	1,210	201
Total of males aged 20 and upwards	632,545	22,889	241

death has occurred during the last six quarters. These occupations include 6,943 persons, of whom 214 died, being at the rate of only 205 per annum in 10,000, which is greatly below the mortality of the whole male population of 20 years and upwards. There are some offensive trades in which no death occurred during the last eighteen months. If these trades had been included in the table, the mortality would have been shown to be lower than it appears. Butchers, poulterers, and fishmongers have sometimes been considered to follow offensive trades; but although these persons may occasionally, by a neglect of their duty and interest, be exposed to offensive gases, their proper occupations cannot be considered offensive, and I have therefore not included them in the table.

The Registrar-General has very properly remarked that 'As the persons engaged in various callings are distributed in different proportions through several periods of life, and as the rate of mortality depends on age, an analysis

of the ages of the living and dying must be made before deductions regarding the comparative salubrity of professions can be drawn with safety.' In comparing the mortality of a single occupation, or any group of occupations, with that of the whole population, however, one acts as if all the persons in these occupations had entered them before the age of 20; and therefore any fallacy from the above cause tells against the occupations examined, and not in their favour. For instance, according to the figures in the above table, the expectancy of life for the whole male population of London, at the age of 20 years is $40\frac{4}{10}$ years, or, in other words, the average duration of life in those persons would be over 61 years; whilst in the persons engaged in the offensive trades enumerated in the above table, the expectancy of life at 20 would be over $48\frac{1}{2}$ years, and the average duration of life over $68\frac{1}{2}$ years; but if some persons enter these trades later in life than 20 years, then the expectancy of life at 20 is greater, and the average duration of life is greater in those who have arrived at 20. The mortality amongst the licensed-victuallers and beershop-keepers has been at the rate of 373 per annum in 10,000 during the last eighteen months; but part of this high mortality is undoubtedly due to the circumstance that a great number of persons do not enter these trades till they are advanced much beyond twenty years of age. All these facts tend to show that if the above table does not express accurately the mortality of persons engaged in offensive trades, it errs by making the mortality appear greater, and not less, than it really is. I am quite aware that, as time rolls on, the returns of the Registrar-General will afford a greater body of facts regarding offensive occupations; but, during the six quarters that have already elapsed since these returns were commenced, the results have been pretty uniform, and are, in my opinion, sufficiently important to be commented on. The health of persons employed in any occupation is necessarily the best measure of the effects of any such occupation on the public health. As the gases given off from putrefying substances become diffused in the air, the quantity in a given space is inversely as the square of the distance from their source. Thus, a man working with his face one yard from offensive substances would breathe ten thousand times as much of the gases given off, as a person living a hundred yards from the spot. Currents of air would make a difference; but this would be the average proportion of the gases inhaled re-

spectively by the two individuals. There are, moreover, so many causes which influence the health of a neighbourhood, that it would be almost impossible to judge from that alone of the effect of trades or occupations conducted in it. I of course attribute no benefit to offensive smells; and the reason why the persons employed in the callings I am treating of enjoy a greater longevity than the average, is probably because they are less exposed to privation and less addicted to intemperance than men following many other occupations, and because, as a general rule, they do not lead a sedentary in-door life. It is sometimes argued, that since the gases given off during putrefaction are capable of causing death when in a somewhat concentrated form, they must necessarily be injurious in the most minute quantity; but this by no means follows; for carbonic acid gas, which is a well-known poison when present in large quantity, is a natural constituent of the atmosphere; vapour of ammonia is sniffed without hesitation, and even sulphuretted hydrogen is absorbed, in considerable quantities, by the visitors at Harrogate and some other watering places.

Cholera has not been present during the eighteen months for which the mortality in different occupations has been published; but there are certain facts which bear on the alleged influence of offensive trades on this disease. A great number of skin yards, bone-boiling establishments, and other offensive factories are situated in that part of Lambeth which extends by the river side from Westminster-bridge to Vauxhall-bridge, and constitutes the sub-district called Lambeth Church, 1st part. This part of Lambeth contains also many of the other conditions which are supposed to, or which really, promote the prevalence of cholera. It is crowded with a poor population, wherever the ground is not occupied with the factories above mentioned, and it lies by the river-side, at an elevation of only two feet above Trinity high-water mark, yet the deaths from cholera in 1854 were only 29 to each 10,000 inhabitants, whilst in London at large they were 45 in 10,000; in the sub-district of Kennington, 1st part, less densely inhabited, they were 126, and in Clapham 103 in 10,000, the latter being a genteel, thinly inhabited sub-district, at the elevation of 21 feet. Again, the sub-district of Saffron-hill, with the slaughter-houses, knackers' yards, and catgut factories of Sharp's-alley on its eastern boundary, and the Fleet-ditch, at that time uncovered,

flowing through it, suffered in 1854 a mortality from cholera of only 5 in 10,000; being one-ninth of that of the metropolis generally, and one-twelfth of that of the Belgrave sub-district, where the mortality was 60 in 10,000. These circumstances might be thought to prove a little too much, were it not that the prevalence of cholera is influenced by a variety of circumstances, and in London very much by the nature of the water supply; for in the short but severe epidemic of 1854, the chief medium of its propagation in the metropolis was water, containing whatever passed down the sewers from previous patients. The sub-district of Bermondsey, called the Leather-market, which contains a number of factories for skin-dressing, suffered, in 1854, exactly the same high mortality as the other five sub-districts in the South division of London, which, like it, were supplied exclusively with the impure water of the Southwark and Vauxhall Company. The conclusion to be drawn from all these facts is, that the vicinity of offensive factories leaves the cholera to pursue the same course that it would do in their absence.

Sackville Street, July, 1856.

Farr's report to Parliament on the cholera epidemic of 1866:

The cause of the mortality of cholera in London, whether on the north or the south of the river, up to the rate of 5 in 10,000, it may be admitted on all hands is explained by the diffusion of the cholera-stuff through personal intercourse, sewers, and the slight contamination of the waters either of wells or of the Thames and of the Lea after filtration by the water companies. All those companies had before 1866 professedly carried out extensive works for taking their waters from better sources, for filtering it, for storing it, for distributing it, in conformity with the provisions of the Metropolis Water Companies Act of 1852; and their works had been pronounced very good by three engineers appointed by the President of the Board of Health. "The requirements," said the three engineers, "set forth in the Metropolis Water Act, 1852, have in all essential respects been fully and satisfactorily complied with by the several companies."

The East London water company's works are described in the Engineers' report: in 1850 it had six open reservoirs, one at Lea bridge, one at Stamford Hill, and four at Old Ford; in 1855 the new filter beds at Lea bridge were completed; the filtered water was brought, in a four-feet iron pipe, to Old Ford, into two oval reservoirs, which, used formerly as subsiding reservoirs, were now covered over with brick arches and earth. "The other reservoirs of the company near Old Ford and that at Stamford Hill are," say the reporters, "now thrown out of use. The large depositing reservoirs upon which they had to rely for clearness of the water have now been abandoned, and all communication between them and the [eleven] mains has been cut off."

... The open reservoirs contain water admitted to be unfiltered; and Mr. Greaves the engineer, speaking for the company, in his letter to the *Times*, dated August 1st, 1866, made this statement: "The facts are that the canal having been since 1858 disused for all purposes of supply, is only maintained as a drain from the filter to a lower part of the river; that not a drop of unfiltered water has for several years past been supplied by the company for any purpose."

This was perplexing; but the company, by taking the unfiltered water from the open reservoirs, violated an Act of Parliament, and on the ground, perhaps, that they were not bound to criminate themselves, they, in the

words of their engineer, besides pleading "not guilty," boldly proclaimed their innocence on August 1st. Shortly afterwards Mr. Greaves, however, admitted candidly, that the open reservoirs of unfiltered water could be drawn on; and by the report of Professor Frankland (August 25th) goes a step further. "Communication," Professor Frankland says, "can be established between these reservoirs and the pumping wells supplying the public, but Mr. Greaves assured me that it was never done, except in case of emergency." In his examination before the Pollution of Rivers Commission on December 10th, Mr. Greaves advances another step, and states, that "a small quantity of water was taken out of one of the open reservoirs this spring"; "he had not the date"; "probably June was the latest date," but he could not say definitely. Further revelations were made by the workmen under examination by Captain Tyler; and the story is at length thus told by officers of the company: —

The foreman of the company died quite suddenly of apoplexy early in this year (1866). In appointing a new man, in giving him discretionary instruction as to how he was to manipulate the water, "I described," says Mr. Greaves, "this possibility [of drawing on the open ponds] as something which he must keep in mind, rather than suffer an accident, and so I suppose he may have acted in that sense." He, Mr. Greaves, kept these open ponds in reserve, as the question of quantity was important, "to meet such necessities as might arise."

The Lea, Mr. Beardmore asserts, was full of water in 1866; how then could the supply be in any way deficient in July? This is explained to some extent by Mr. Maine, the manager of the works at Lea Bridge. The rapidity of filtration is very variable; and in the month of July every year a slimy matter is rapidly deposited on the sand, blocking up its pores, and stopping this filtration altogether. In August this slimy matter grows, and no sooner produces green confervoid fibres than the power of the filters is restored; the water flows freely.

The foreman of the works, in his evidence, says that he considered the water in the open reservoirs available as a reserve in the event of the water getting low in the covered reservoir, to prevent the damage of the engine with the higher suction. He kept no notes, but he believed that he allowed the water to run from the open to the covered reservoir not more than three times

during the year 1866; at the latter end of March, at the latter end of June, and some time in the early part of July. The sluice was never opened after cholera broke out; he is certain of that. He had no fear of its doing harm.

A carpenter, twenty-four years at Old Ford, appears to have been the only man who worked the sluice between the open and the closed reservoirs. He did other jobs, but that was his specialty. He opened that sluice frequently in 1864, frequently in 1865, and three times (!) in 1866. He describes in three cases what he did. In March he was at the engine house: the engine began to draw air; and he was ordered by the engineer of the company to open the sluice. He left it open two hours. In June he was about the yard, when the engine driver called to him, and "ordered him to let him have some water." He complied by command of the foreman. About two p.m. early in July, and this may have been the first fatal day, he opened the sluice again, and left it open for about the same period of the day. "He considered the water in the open reservoir to be very good, and had often drunk it."

When this statement is compared with that in Mr. Greaves's letter, and when it is borne in mind that these dependent men were not giving evidence on oath, that the opening of the sluice would be precisely one of those acts of which no record was desired, we can scarcely expect a more explicit statement. It is enough to have in evidence, that immediately before the outbreak in July the foul water of the reservoirs was pumped over the parts of East London where cholera was epidemic.

Again, there was another channel for the entrance of the foul water of the Lea directly into the covered reservoirs supplying the pumps. Professor Frankland sagaciously remarked, that the bottom of these reservoirs, within a few yards of the river, is 16 feet beneath the low ground, which is here only just above the level of spring tides. When the tide was high, and the water of the reservoir was low, the permeation of the water through the gravelly bottom into the reservoir was on hydraulic principles inevitable. Captain Tyler describes graphically how he put this to the proof, and established the fact, by wading over the bottom. The reservoir was on Sunday February 24th, at his instance, pumped, in 36 hours, as low as possible; the bottom was found foul; but the water at last came in faster than it could be pumped out by the powerful engine. The patience of the waiting company was exhausted;

the water still came in.

Cholera flux, with the other excremental matters in the channel of the Lea, thus must have found its way from the reservoirs to the pump wells of the company at Old Ford.

Mr. Greaves himself could not perhaps describe precisely what took place in July; but this is substantially what occurred: — The Lea at Old Ford was much more polluted in the summer of 1866 than it was in 1854; for, besides the sewers emptying into it on the side of East London, the whole sewage of Stratford and West Ham on the Essex side has since 1861 been discharged into the Bow Creek arm of the river at the iron bridge. This sewage is washed up and down the stream by the ebb and flow of the tide twice daily between and in close proximity to the open and the storage reservoirs of the company. The storage reservoir, full, holds 6,000,000 gallons of water in the morning; in the day 8,000,000 gallons flow into it by the iron pipe from Lea Bridge; and as the pumps distribute 11,000,000 gallons in the day, 3,000,000 gallons are left in the reservoir at the close of the day, to be augmented to 6,000,000 in the night when the distributing pumps cease working. But one day, early in July, probably on Monday or Tuesday July 9th or 10th, at 2 o'clock in the afternoon, the storage reservoir was at the lowest ebb, and the dregs of the water were drawn on; the well was scantily filled; the pump gave unmistakeable signs of distress; the engine-driver called out for water; and then the old carpenter opened the sluice, and let in the contents of the northern stagnant pond, with its bottom pervious alike to the waters of the Lea and to the waters of its sister reservoir, which had been recently refilled by soakage from the Lea, and was slightly turbid and milky on the 9th of August. How often this was repeated in July it is impossible to tell, as the engineer did not even know that the pond water had been used at all in that month, and the old carpenter's memory, minute in some respects, reproduced facts too imperfectly to form a basis for a negative argument. If the scanty supply of water was due to slimy obstructions of the Lea Bridge filter bed, Mr. Maine tells us that the slime lasts till its germination in August. Again, if the supply from Lea Bridge in July was less than in May the East London Company must have drawn on its open reservoirs, for in their return they give the quantities supplied at 2,167,885 gallons a day more in July than in

May. They distributed 636,000,000 gallons of water in July; where did it all come from?

The lowness of the water level in the storage reservoir would during the same month let in impurities from the Lea every evening.

Several cases of cholera and choleraic diarrhea had occurred over London in May, and on 27th June, at 12 Priory-street, Bromley, one poor Hedges, a labourer, and his wife, both of the age of 46 years, died of "cholera Asiatica," the former after 15 hours, the latter after 12 hours illness. Their cases are minutely described by Mr. Radcliffe, who traces the discharge into the water-closet of 12 Priory-street, and thence 300 yards down the sewer to its opening into the Lea at Bow Bridge, half a mile below the Old Ford reservoirs. He attaches great importance to these first cases; and they undoubtedly sufficed to pour into the sewers and waters millions of zymotic molecules, which day by day grew more and more frequent in the Lea by every hour's choleraic discharges on both sides of the river. On Wednesday, 11th July, the first four deaths of the explosion occurred, one in each of four distinct sub-districts; and allowing for duration and incubation, it is not improbable that the four persons took the poison early in the week. Nine deaths occurred on the 12th in seven of the East London sub-districts wide apart. On Wednesday the 18th, were 59 deaths, singly, or sometimes in clusters of 8 or 9 deaths in 16 sub-districts of the East London waterfields; a few deaths dropped in here and there in a sub-district of the other waterfields; but this mass of death in East London was due evidently to some superadded agency. It operated mainly in every district supplied by the Old Ford pumps; that is, in Bow, Bromley, Poplar, Limehouse, Mile-End-Old-Town, St. George-in-the-East, Whitechapel, parts of Bethnal Green and West Ham, which Captain Tyler tells us would in the ordinary way be supplied "on the greater part of week days from Old Ford." (pp. xvii–xix)

...

It was precisely in the region of the Old Ford waterfield that cholera raged. There, in three months, it killed little less than 4,000 men, women, and children; while in the Lea Bridge field, and in all the other waterfields of London, the epidemic was kept within such narrow limits of fatality as would be accounted for by diffusion through sewers, direct contact with cholera

matter in various ways, and the slightly contaminated filtered river waters of the other companies. (p. xx)

...

Hippocrates in his great work sought the causes of epidemic diseases in earth, air, and water. The discoveries of the nature of air by Boyle and others fixed attention on that element in the last century; in recent times air has had its sectaries, and so has water; but as the air of London is not supplied like water to its inhabitants by companies the air has had the worst of it, both before parliaimentary committees and royal commissions. For air no scientific witnesses have been retained, no learned counsel have pleaded; so the atmosphere has been freely charged with the propagation and the illicit diffusion of plagues of all kinds; while Father Thames, deservedly reverenced through the ages, and the water-gods of London, have been loudly proclaimed immaculate and innocent. If diseases spread they did it not, it was the air.

In vain did the sewers of London and of twenty towns pour their dark streams into the Thames and the Lea; their waters were assoiled [absolved] from every stain by chemists who had carefully analyzed specimens selected by the water companies, and demonstrated the inevitable effects of the operation of oxygen on all sewage in running streams. One scientific witness who was deservedly trusted at the time in the courts of law, was so convinced of the innocence of his clients, that he stated in evidence how before delivering his lectures it was his practice to drink a glass of the Southwark water, in which Dr. Hassall subsequently detected muscular fibre and the other ingredients of sewage.

Dr. Snow's theory turned the current in the direction of water, and tended to divert attention from the atmospheric doctrine, which in London has received little encouragement from experience. (pp. lxxix–lxxx)

...

The population of London probably inhaled a few cholera corpuscles floating in the open air, and more rising from polluted waters and from the sewers, but the quantity thus taken from the air would be insignificant in its effects in comparison with the quantities imbibed through the waters of the rivers or of ponds into which cholera dejections, either in the diarrheal stage or the stage of collapse, had found their way, and been mingled with sewage by the

churning tides. During the height of the cholera explosion in East London nothing unusual was there visible in the atmosphere; the air was transparent and often bright in the sunshine; but the river Lea, close to the Old Ford reservoirs, and to the ponds from which the water was distributed in those fatal days, looked black, foul, contaminated. ... An indifferent person would have breathed the air without any apprehension; but only a very robust scientific witness would have dared then to drink a glass of the waters of the Lea at Old Ford after filtration.

But there are many facts in favour of the opinion that the disease spreads from person to person, not by contact with the cuticle, but by contact of the colourless, inodorous flux with the mucous membranes. Dirty people in crowded houses take the disease from a first case in unusual numbers; and the soiled linen communicates the disease. (p. lxxxi)

Chapter 17

William Budd

The story of Typhoid Mary by George Soper from *The Military Surgeon*, 1919:

This is the story of the cook who produced a series of epidemics of typhoid fever and was finally discovered and locked up by the New York City Department of Health. Her general history up to that point is widely known, although few details of it can be given by most persons. Her history after her arrest forms a fitting climax to her career. How she disappeared, produced more typhoid and was caught again, is now set down for the first time.

The great amount of attention which the case has received is due entirely to the natural interest which it possesses. The case has never been exploited for the dramatic elements which it contains, although these fairly crowd one another throughout the narrative. The circumstances of Typhoid Mary's discovery were simply announced before the Biological Society of Washington, D. C., April 6, 1907, in a brief paper. This paper subsequently appeared in a medical journal. Since then no authoritative account of the case has been written. Most of the knowledge which the world possesses of it has been obtained from newspaper accounts of some of Mary's interesting movements since her original arrest.

Many inquiries have been received by me as to the history of Typhoid Mary since her first arrest, and although I have had no official connection with the matter since I brought the details to the attention of the New York City Department of Health on March 11, 1907, I seem to be regarded as the person to whom all such inquiries should be addressed.

It is in view of the scientific and popular interest in the subject which has continued now for more than a dozen years, that the following notes are made, the intention being to review the essential facts and to give notice to Typhoid Mary's movements since she was first taken into custody by the New York City Department of Health.

HER DISCOVERY

In the winter of 1906 I was called upon by Mr. George Thompson, of New York City, to investigate a household epidemic which had broken out in the latter part of the preceding August at the Thompson country place at Oyster Bay. The epidemic had been studied by experts immediately after it took place, and there were a number of typewritten reports upon it, but its cause had not positively been ascertained. It was thought by the owner that, unless the mystery surrounding the outbreak could be satisfactorily cleared up, it would be impossible to find desirable tenants for the property during the coming season. The essential facts concerning the investigation follow: Six persons in a household of eleven were attacked with typhoid fever. The house was large, surrounded with ample grounds, in a desirable part of the village, among other handsome places, and had been rented for the summer by a New York banker, Charles Henry Warren.

The first person to be taken sick fell ill on August 27, and the last on September 3. The diagnosis was positive. Two of the patients were sent to the Nassau Hospital at Mineola, and the others were attended by capable physicians at Oyster Bay. None of the subsequent cases apparently resulted from the first. They seemed all to have been original infections. But, whether the disease was transmitted locally or not, the point of interest lay in the origin of the first case.

Typhoid was an unusual disease in Oyster Bay. At the time of the outbreak, [ten] other cases were known. None followed. The milk supply, cream, water and other articles of food which might have been implicated were one by one carefully eliminated as possible causes. The drainage was examined and found satisfactory. Extreme care was used in this part of the investigation in view of the fact that there was a firmly settled belief on the part of many persons that the water had become contaminated from cesspools, a privy vault or stable manure pit. Analyses of the water were made inde-

pendently by two competent chemists and fluorescein was used to study the possibilities of underground percolation. As a result of this particular study it did not seem to me that the water theory was tenable. I was led from the proper track for a time by being informed that the family was extremely fond of soft clams and that supplies of these shell fish had frequently been obtained from an Indian woman who lived in a tent on the beach, not far from the house, and whose supplies of clams were sometimes taken from places that were not improbably polluted with sewage.

But if clams had been responsible for the outbreak, it did not seem clear why the fever should have been confined to this house, because soft clams formed a common article of diet among the native inhabitants of Oyster Bay. On inquiring closely, it was found that no clams had been eaten for six weeks before the outbreak of typhoid, and six weeks was too long a period for an epidemic of this character to remain undeveloped. In my opinion the infectious matter which produced the epidemic had been taken with food or drink on, or before, August 20.

The history of the house with regard to typhoid showed that no case had occurred on the premises or been nursed there, nor was it believed that a convalescent had visited it in thirteen years, and the house had been occupied every summer since then. Attention was then concentrated on the first case of typhoid to determine whether the infection could have occurred during a temporary absence from Oyster Bay, and it was discovered that no person who was taken sick had been on a visit away from Oyster Bay for several weeks prior to the onset of the disease.

The social positions of the persons attacked differed decidedly. The first was a daughter of the family; the next two were maid-servants. Following this, in quick succession, were the wife, and then another daughter of the tenant, and finally a gardener who resided permanently at Oyster Bay and who had lived on the place for years. Believing that some event had occurred in the family or in Oyster Bay, which, properly studied, might give the clue to the cause of the epidemic, the immediate history of the household at this time was carefully inquired into. This gave the key to the situation.

It was found that the family had changed cooks on August 4, about three weeks before the epidemic broke out. Little was known about the new cook's

history. She had been engaged at an employment bureau which gave her a good recommendation. She remained in the family only a short time, leaving about three weeks after the outbreak of typhoid occurred. Her present whereabouts were unknown.

The cook was described as an Irish woman about forty years of age, intelligent, tall, heavy, single and non-communicative. She seemed to be in perfect health. She was not known ever to have had an attack of typhoid.

Here was by all means the most important clue which had come to my notice. If this woman could be found and questioned, it seemed likely that she could give facts from which the cause of the epidemic could be ascertained. I had seen typhoid spread in large epidemics under circumstances which led me to believe that it should be regarded as a contagious disease, and I had so dealt with it when acting as expert for the State of New York in handling the epidemic of 1,300 cases at Ithaca in 1903, and later as expert of the city of Watertown, N.Y., in fighting an epidemic of 600 cases in 1904.

When, after much difficulty, the cook was found, no information of value was obtainable from her. She refused to speak to me or to anyone about herself or her history, except on matters which she found were already known. Her former employers gave freely what information they could, but their minds were not wholly free from bias. Nearly all the epidemics which I was inquiring into had been investigated soon after they occurred and had been explained in a different way. The answers to my questions were therefore unconsciously framed so as to convince me that the original explanations were correct.

Curiously enough the greatest help came from a quarter which was least expected. The office through which Mary had secured some of her situations gave me all the assistance which it possessed. This office, conducted in the name of a woman, was really run by a man. For some good reason he did not allow his own name to be known. Whether by aptitude, training, or both, this person possessed many of the attributes of a good investigator. Without his help Typhoid Mary could not have been found.

In passing, it is interesting to observe that nobody who hired Mary seems to have inquired personally into her references. It seems that the names of some of her former employers were available, but it appears not to be the

custom of the patrons of fashionable employment bureaus to inquire deeply into the personal history of the servants. Mary always was accepted on the recommendation of the proprietor. He was trusted to run a genuine intelligence bureau and it is but right to say that, on the whole, he discharged his obligations admirably.

The effort to work out Typhoid Mary's history was only partly successful. There were many false clues and puzzling circumstances. The mystery which had at first surrounded her continued and was often completely baffling. Sometimes it was somebody's memory which was at fault — few housekeepers seem to know anything about their cooks, much less recall the food which they have eaten weeks and months ago. Yet this information, in some instances, was indispensable.

Sometimes it appears that persons were deliberately refusing to tell what they knew. Twice, I think, I talked with members of Mary's family, but I could never be sure of it. Servants who had been associated with her never gave any help. Try as I would, Typhoid Mary's whereabouts for only part of the ten years before the Oyster Bay outbreak could be determined with unmistakable certainty. About two years of the preceding five remained unaccounted for. In ten years she is known to have worked for eight families and in seven of these typhoid had occurred. She had always escaped in the epidemics with which she had been connected.

A summary of the principal epidemics follows:

In 1904 there was an outbreak at the summer residence of Henry Gilsey, Esq., at Sands Point, N.Y. The household consisted of eleven persons, seven of whom were servants. The house was rented on June 1. On June 8 typhoid began to appear. The first case was that of a laundress. Following this three other persons were taken sick in succession. None of the family was attacked. The Sands Point epidemic was confined to the house where the servants lived. There were no other cases before or after, either in the household or in the village. The cause of the outbreak was believed to be connected in some way with the servants' quarters.

In 1902 a severe outbreak occurred in the family of a New York lawyer at Dark Harbor, Maine. Mr. Coleman Drayton had rented a cottage for the summer and just before leaving New York to occupy it with his family had

engaged Mary Mallon to act as cook. Seven members of this household of nine were presently attacked. In addition, a trained nurse who came in by the day took sick. The first case occurred two weeks after the arrival on June 17. One week later another case occurred; two days later there was a third; the remainder followed rapidly. The only persons who escaped were the cook and Drayton himself, and he had had an attack some years before. These two faced together the burden and anxiety as, one by one, every other occupant of the house fell ill. Drayton felt so grateful to the cook for the help which she gave him during the epidemic that at the end of the epidemic he made her a handsome present of money in addition to her wages, little thinking that the cause of the whole trouble lay at her door.

The Dark Harbor epidemic was investigated at the time and a written report was made upon it. The infection was thought to have been brought to the house by the maid-servant who was the first to be taken ill. It seems that the servants had access to a water tank in the top of the house and it was supposed that this tank became polluted by the first person who was attacked, thus infecting the entire household. How the original case was produced was not explained, but it was assumed with the easy logic which is familiar in many such investigations that it was contracted elsewhere.

Mary Mallon's history before she went to Dark Harbor is not clear. In 1901–02 she lived about eleven months with one family. Here a laundress was taken ill and removed to the Roosevelt Hospital, December 9, 1901. This attack occurred one month after the cook's arrival. Unlike the other outbreaks, the cause of the attack was not investigated at the time, and full information concerning it has not been available.

The earliest record of Mary Mallon's employment is in a New York family which had a summer residence at Mamaroneck, New York. In this instance a young man who made a visit to the family was attacked, his illness dating from September 4, 1904. The cook left a few days after the onset of this illness. It is interesting to observe that she had been in the family for three years without apparently being connected in any way with typhoid before this. It was believed at the time that the young man had contracted his typhoid before he came to visit the family.

Subsequent to her employment at Oyster Bay, Mary Mallon went to live

with a family at Tuxedo, New York. She remained about one month to be exact, from September 21 to October 27, 1906. On October 5, fourteen days after her arrival, a laundress was taken sick with typhoid fever and removed to St. Joseph's Hospital, Patterson. No other case had been known in Tuxedo for several years.

HER ARREST AND EXAMINATION

When at last the cook's final whereabouts were ascertained, it was discovered that two cases of typhoid had recently broken out in the household where she was employed. These occurred a few weeks after her arrival. One patient, a chambermaid, was taken sick January 23, 1907, and removed to the Presbyterian Hospital. The doctor was first called to see the other patient, a daughter of the owner of the house, on February 8. This second case resulted fatally on February 23, 1907, the only fatal case in the record up to this time. A period of two months elapsed between the beginning of the employment of the cook and the first case. There was some doubt about the diagnosis of these cases at the time of my investigation and no opinion had been formed as to their origin. The cook was about to leave the New York house.

It was at this house that I had my first interview with Mary. I expected to find a person who would be as desirous as I was for an explanation of the way in which the typhoid had followed her. Certainly she could not have failed to be impressed by the strange fatality with which the disease had broken out wherever she went. It must have looked as though it was pursuing her. Could she be connected with it in any way? Possibly she had even thought that she had produced the epidemics.

If she were implicated in the outbreaks it was, of course, innocently. I supposed that she would be glad to know the truth and to be shown how to take such precautions as would protect those about her against infection. I thought I could count upon her cooperation in clearing up some of the mystery which surrounded her past. I hoped that we might work out together the complete history of the case and make suitable plans for the protection of her associates in the future. Science and humanitarian considerations made it necessary to clear up the whole matter.

My interview was short. It started in the kitchen and ended almost immediately at the basement door. Reason, at least in the forms in which I was

acquainted with it, proved unavailing. My point of view was not acceptable and the claims of science and humanity were unavailing. I never felt more helpless.

The next interview was staged more deliberately. Mary had a friend whom she often visited at night in the top of a Third Avenue tenement. He kindly offered to manage for the meeting and one night, after her work was done, I awaited her with a physician, Dr. Bert Hoobler, one of my former assistants, whom I had called to help. We waited at the head of the stairs in the Third Avenue house.

At length Mary Mallon came. Dr. Hoobler and I described the situation with as much tact and judgment as we possessed. We explained our suspicions. We pointed out the need of examinations which might reveal the source of the infectious matter which Mary was, to a practical certainty, producing. We wanted a small sample of urine, one of feces and one of blood. The urine and feces were to be tested for typhoid bacilli and the blood for the Widal reaction. We hoped we could get some information from Mary at the same time.

Indignant and peremptory denials met our appeals. We were unable to make any headway. Mary's position was like that of the lawyer who, on being told by the judge that the facts were all against his client, said that he proposed to deny the facts. Mary denied that she was a carrier. She referred to the Dark Harbor outbreak for proof of her helpfulness and to the gift from her employer there as testimony of the same. Far from causing typhoid, she had helped to cure it. Nothing could alter her position. As Mary's attitude toward us at this point could in no sense be interpreted as cordial, we were glad to close the interview and get down to the street. We concluded that it would be hopeless to try again.

Here my investigation came to an end. It was evident that, although I had succeeded in collecting only fragments of her history, there was a remarkable resemblance between these parts. In each instance one or more cases of typhoid had occurred in households after the cook had arrived, or among people who had come to live near her and eaten of the food which she prepared. In every instance the families had ample means and lived well, as the saying is.

The bearing which wealth may have on the chance of infection may not at

once be apparent, but it was taken carefully into account in this investigation. People who live as did the family concerned in these epidemics are almost isolated from infection by their cooks by reason of the fact that nearly everything they eat is subjected to the heat of cooking after it leaves the cook's hands. The heat kills the germs. The cook does not cut the bread or arrange the salad or fruit, for example. All such work is done by a butler, footman or waitress, depending upon the manner in which the housework is organized. The cook comes in much more direct contact with the cooked food of the servants; a fact which probably accounts for the relatively larger number of servants attacked in the several epidemics. Each household had consisted of four or five in the family and from five to seven servants. Four of those attacked had been laundresses, and two gardeners permanently attached to the country places where the epidemics had broken out. All but two of the outbreaks had occurred in the country. The cook had escaped sickness in every instance. In only one case could I find that she had worked in a family where no typhoid occurred, and as this family consisted only of three people of advanced age it is not improbable that they were immune. In all, there were twenty-six cases and one death; twenty-four of these cases had occurred in the preceding five years.

Believing that enough had been learned to show that the cook was a competent cause of typhoid, I laid the facts concerning the four principal epidemics before Dr. Herman M. Briggs, Medical Officer of Health of the New York City Department of Health, with the suggestion that the woman be taken into custody by the department and her excretions made the subject of careful bacteriological examination. I had been unable to obtain her consent to any examination whatever.

The department acted favorably on this suggestion and, after considerable difficulty, during which a number of officers had to be called upon to help, the cook was removed to the Detention Hospital of the Health Department. She reached there on March 19, 1907. She was placed in charge of Dr. Robert J. Wilson, Superintendent of the Department of Hospitals, and Dr. William H. Park, Chief of the Research Laboratories of the Department of Health. Dr. M. Goodwin did the bacteriological work under Dr. Park's direction.

My third and last attempt at an interview was after her arrest. Mary

was in a separate room at the Detention Hospital. I explained that I had come to get some information from her. It was desirable to know whether she had ever had an attack of typhoid and, if so, where and when. Would she consent to give a complete history of her experience with typhoid? The information might help many. It could not possibly hurt her. It might prove very helpful in explaining her case. As matters stood, nobody accused her of deliberately intending any harm. If possible, she was to be freed from her disease-producing capacity.

This interview was shorter than the other two. Without uttering a word Mary retreated with dignity to the toilet, leaving me standing alone in the room.

It was expected by me that the germs might be found in the urine, but more probably in the stools. None was found in the urine. The stools contained the germs in great numbers. Daily examinations made for over two weeks failed only twice to reveal the presence of the Bacillus typhoid and on these occasions the sample taken was perhaps too small to reveal them. The blood gave a positive Widal reaction. The cook appeared to be in perfect health.

The feces were examined on an average of three times a week from March 20 to November 16, 1907, and in only a comparatively few instances did the investigators fail to find the bacilli. During the summer months the culture plates contained only a few typhoid-like colonies. In July there were five consecutive negative tests followed by a positive one.

During August the stool showed no typhoid; in September they began to appear again; from September 11 to October 14, 1907, the feces failed to yield typhoid bacilli. During this time the patient's diet was carefully regulated and she was receiving mild laxatives. On October 16, 1907, a very thorough test showed that the germs were again present. From October 16, 1907, to February 5, 1908, weekly examinations of the stools gave, with only two exceptions, from 25 to 50 per cent typhoid-like colonies on the culture plates. These exceptions were on November 13 and December 4, when no typhoid was found. The implication was plain. The cook was virtually a living culture tube in which the germs of typhoid multiplied and from which they escaped in the movements from her bowels. When at toilet her hands became soiled, perhaps unconsciously and invisibly so. When she prepared a

meal, the germs were washed and rubbed from her fingers into the food. No housekeeper ever gave me to understand that Mary was a particularly clean cook. In the Oyster Bay outbreak, which was studied with more particularity than the others, the infectious matter is believed to have been carried from the cook's hands to the people who were later taken sick by means of ice cream containing cut-up peaches. Mary prepared this herself. In this instance no heat sterilized the washings from her hands. Mary Mallon was kept virtually a prisoner by the Department of Health for three years. At first she was held at the hospital for contagious diseases at the foot of East 16th Street, Manhattan; later she was removed to Riverside Hospital on North Brother's Island in the East River, between Hell Gate and Long Island Sound.

She was employed in various ways, sometimes as laundress. She was allowed to receive friends and enjoyed such privileges as were possible, but she never became reconciled to her detention.

Two legal actions were brought to secure her release. The claims made on her behalf were that she was being deprived of her liberty without ever having committed a crime or knowingly having done injury to any persons or property; she was held without being given a hearing; she was apparently under life sentence; it was contrary to the Constitution of the United States to hold her under the circumstances; such action on the part of the authorities was without precedent. These legal actions were argued with much ability. It was expected that, if she won, she would recover heavy damages.

The case attracted a great deal of public notice, some of the newspapers going to the extent of printing the arguments with illustrations of the unfortunate woman. The courts held that the Department of Health acted within its rights in keeping Mary Mallon in custody and that they were well serving the public interests in refusing to release her. Public sentiment, to judge by the illustrations, was a trifle mixed. On the one hand Mary was pictured as frying deadly typhoid bacilli the size of sausages in preparation for the family meal, and on the other she was shown sitting lone and dejected on her island with a mongrel dog as her solitary companion. *Punch*, the famous English funny paper, devoted a column of poetry to the case.

HER DISAPPEARANCE AND REDISCOVERY

Although the courts refused to order her release, there was a good deal

of sympathy for Typhoid Mary. Whatever could be said of the consequences of her cooking, she had been an innocent offender. She was careless in her personal habits, but so are most cooks. If she was a deadly germ producer, so were thousands of others who were enjoying their liberty. To many persons who did not know Mary it seemed that she ought to be given her liberty.

In the year 1910, soon after a change was made in the administrative head of the Department of Health, Mary Mallon was voluntarily released on her promise not to take employment as a cook nor engage in an occupation which would bring her in contact with food. It was thought that she had learned in three years how dangerous she was and how to avoid infecting people. She was forbidden to cook or otherwise handle the food of others and was required to report periodically to the Department of Health. For awhile she kept her promise. Then she broke her parole and disappeared. She was lost sight of for nearly five years. I have been unable to learn her complete history during this period, but from the fragments which have been collected, it is apparent that she continued to enact her hateful role of typhoid producer. Due to the fact that the woman assumed various names and left little trace behind to indicate her whereabouts, it was not possible to learn all that was desired.

She seems to have produced two cases of typhoid in a sanatorium at New Foundland, N.J., where she was employed in 1914, and another case in New York City in the same year in a small family where she was living under an assumed name with a friend. This, however, is anticipating the end of the story.

Mary Mallon came to light for the second time under circumstances which were the most dramatic of her entire career. In January and February, 1915, an outbreak of typhoid occurred in the Sloane Hospital for Women on West 59th Street, New York City.

In this epidemic there were twenty-five cases; they were mostly among the nurses and other attendants of the institution. The Sloane Hospital is one of the most capably managed institutions of its kind in America, and in its attention to every sanitary requirement is intended to be a model for the teaching of students in the College of Physicians and Surgeons of which it is practically a part. In his conduct of the hospital and in his lectures to his students, it was the custom of Dr. Edwin B. Cragin, Attending Obstetrician

and Gynecologist, to lay his main emphasis upon scrupulous care of the hands. Yet, as Dr. Cragin freely acknowledged, this outbreak was produced by a woman whose hands became soiled with her excrement and who through careless and dirty habits infected the food of the inmates of the institution. Either she at first used sufficient care and later became indifferent is not known, but it is an interesting fact that Mary worked as cook in the hospital for about three months before the first case occurred. She knew, of course, the danger and how to avoid it. She knew that she was violating her agreement with the Department of Health in engaging in the occupation of cook. That she took chances both with the lives of other people and with her own prospect for liberty and that she did this deliberately and in a hospital where the risk of detection and severe punishment were particularly great, argues a mental attitude which is difficult to explain. Aside from such behavior as this, Mary Mallon appears to be an unusually intelligent woman. She writes an excellent hand, and the composition of her letters leaves little room for criticism.

She possesses enough skill as a cook to command high wages and has been able to obtain work in the most desirable situations. Surely a mysterious, non-communicative, self-reliant, abundantly courageous person; a character apart, by nature and by circumstance, strangely chosen to bear the burden of a great lesson to the world. If she had learned and been willing to practice what she learned, she would not have had this costly lesson to teach.

Mary Mallon was officially known in the hospital by the name of Mary Brown, but she was jokingly nicknamed "Typhoid Mary" by her fellow-servants when the epidemic occurred, for there were some who remembered the published accounts of Mary Mallon's unfortunate experience of years ago. It was this nickname, implied in jest, that led the authorities to find her out.

When genuine suspicion began to focus upon her, Mary cleverly disappeared. Before she could be apprehended, she moved to New Jersey and then to a home in Long Island. She was finally traced to the Long Island house and was forcibly removed to the Riverside Hospital of the New York City Department of Health, refusing to go there without compulsion. She has been held by the Department of Health to June, 1919, without any prospect of again being released.

HER LESSON TO CIVILIZATION

Mary's status after her second arrest has been totally different from that which she possessed after her first. This is true both as to the legal aspects and public sympathy. Whatever rights she once possessed as the innocent victim of an infected condition, precisely like that of hundreds of others who were free, were now lost. She was now a woman who could not claim innocence. She was known willfully and deliberately to have taken desperate chances with human life, and this against the specific instructions of the Health Department. She had been treated fairly; she had been given her liberty and was out on parole. She had abused her privilege; she had broken her parole. She was a dangerous character and must be treated accordingly.

The total number of outbreaks of which Typhoid Mary is known to be the cause is ten; the total number of cases, fifty-one. Owing to the fact that only parts of her entire history are known, it is probable that the total number of outbreaks for which she is responsible is much larger than this record indicates. It would surprise nobody to learn that she had produced some extensive epidemics.

The case of Mary Mallon is of exceptional interest for a number of reasons. For one thing it illustrates one of the ways in which typhoid and other diseases may be spread without the real cause being suspected. It also shows that we should be slow in arriving at an opinion as to the origin of an outbreak.

It shows how carefully we should select our cooks, and it calls attention in a startling manner to the fact that we ordinarily know very little about them. It confirms the truth of the adage that the more we pay the less we know about our servants.

The Mallon case affords a striking proof of the fact that our food is not infrequently contaminated by excrement. Here lies, perhaps, a common source of infection. Possibly many of the so-called diarrheas and food poisonings which occur may be ascribed to this cause. Some persons and some families seem to be especially prone to these upsets. Is it not possible that what appears to be special susceptibility is really infection from a nearby carrier in many of these instances?

The story of Typhoid Mary indicates how difficult it is to teach infected people to guard against infecting others. Mary had ample opportunity to know the danger which she constituted toward those whose food she prepared.

She knew from being told and she knew by experience. She was aware of the penalty which she would suffer if she broke her parole and caused another outbreak. That she could have avoided spreading infection by obeying her instructions admits of no doubt. She knew that when she cooked she killed people, and yet she deliberately sought employment as a cook in a hospital. Why did she do this?

The case is least remarkable for the reason that it was the first of its kind to be worked out in America. It is surprising that nobody had discovered a carrier before. They are now known to be rather common.

Somewhat similar investigations bad been made in Germany and I make no claim of originality or for any other credit in her discovery. My interest and experience in the epidemiology of typhoid had been of long standing. I had read the address which Koch had delivered before the Kaiser Wilhelm's Akademie, November 28, 1902, and his investigation into the prevalence of typhoid at Trier and thought it was one of the most illuminating of documents. In fact it had been the basis of much of the epidemic work with which I had been connected.

Koch's address was not the only one printed about this time to show that healthy carriers might exist and give rise to typhoid. Conradi and Drigalski had anticipated Koch and it was probably on the suggestion contained in their paper to the effect that with their new culture medium they had found typhoid bacilli in the stools of several well persons that Koch's flying [sic] laboratory was sent to Trier and the ground prepared for his Kaiser Wilhelm's Akademie address.

...

The literature of carriers has enormously increased in all countries since 1906. Instances of carriers causing large and small epidemics have multiplied by the score. The extent of the danger which is to be apprehended from this source and the steps to be taken to meet it have been discussed pro and con until it would seem that the grounds for a common agreement must long since have been reached.

There is agreement as to nearly everything except how to cure the carrier condition. In some cases the germ focus can be reached and removed, in other cases this has so far proved impossible. The trend of thought has entirely

changed as to the cause of typhoid fever. Before the role of carriers was suspected, water supplies and milk were considered the principal means of transmission. The carrier idea led many to think that here was the principal explanation of the spread of typhoid.

The present thought is that carriers account for a varying proportion of the total typhoid in a region, the exact figure depending largely upon local circumstances. Where water supplies, milk and other common vehicles of typhoid can be satisfactorily excluded from the reckoning carriers probably account for most of the cases.

As a result of research work done in Europe and America, it has been found the from 2 to 3 percent of all persons who have typhoid fever become chronic germ producers. Carriers have been divided into many classes groups some are intermittent, others continuous. A certain proportion permanently free themselves from infection and consequently their power to produce typhoid. Others never become free.

It has thus far been feasible to cure some of the carriers of their unfortunate condition, but there are others who cannot be cured. Experiments at disinfection and even the removal of the gall-bladder, which is generally the focus of the bacteria, have sometimes failed to produce the desired result.

What is to be done in order to protect ourselves from the danger of typhoid carriers?

First, it is desirable to discover the carriers. This is not easy. It is most readily done with the help of a good laboratory. The examination of the feces should be made over and over again.

Second, carriers must be told of their condition. They must be taught to use precautions against soiling the hands with the excretions. They must be taught to wash their hands frequently: always after leaving the toilet and always before handling food; they must never handle the food of others and they must try to give up the senseless habit of shaking hands.

We should all be careful to avoid eating uncooked food which has come in contact with the hands of persons whose history is not known to us and who may have contaminated the food immediately before our getting it.

Those of us who have had typhoid fever should be examined to determine whether we are carriers. If we are carriers, our families should be inoculated

against the particular strain of the typhoid germ which infects us and special precautions should be exercised against the transmission of the bacilli in the household.

Chapter 18

Louis Pasteur

The abstract of Pasteur's (1857) paper on lactic acid fermentation:

My work on the properties of the amyl alcohols and on the very remarkable crystallographic properties of their derivatives has led me to a study of the process of fermentation. Later I will have the honor to present to the Academy observations that show an unexpected relationship between fermentation and the molecular asymmetry of organic molecules found in nature.

The necessary materials for the preparation and production of lactic acid are well known to chemists. It is known that it is only necessary to take a solution of sugar and add chalk, which keeps the medium neutral, a nitrogenous material, such as casein, gluten, animal membranes, etc., in order to have the sugar transformed into lactic acid. But the explanation of this phenomenon is quite obscure, since the way in which the decomposable nitrogenous material acts is completely ignored. Its weight does not change significantly. It does not putrefy. Although it becomes modified and is continually in a marked state of change, it would be difficult to speak of what its composition is.

Careful studies up to the present time have not revealed the development of organized beings during the fermentation process. Those observers who have recognized such beings have always established at the same time that they were accidental and harmful to the fermentation process.

The facts appear therefore to be very favorable for the ideas of Mr. Liebig. In his eyes, the ferment is a substance that is highly alterable, which decomposes and in so doing induces the fermentation because of the alteration that it experiences itself, communicating this agitation to the molecular group

of the fermentable material and in this way bringing about its decomposition. According to Mr. Liebig, this is the principal cause of all fermentations and the origin of the majority of contagious diseases. Each day his opinion receives more favor. ...

I propose to establish in the first part of this work that, in the same way that there exists an alcoholic ferment, the yeast of beer, which is always found wherever sugar is decomposed into alcohol and carbon dioxide, there also exists a particular ferment, the lactic yeast, that is always present when sugar becomes converted into lactic acid. Furthermore, the decomposable nitrogenous material that is able to bring about the conversion of sugar into this acid is used as a convenient nutrient for the development of this ferment.

It is possible to observe in ordinary lactic acid fermentations, on top of the sediment of chalk and nitrogenous material, a gray substance which occurs at the surface of this deposit. Under microscopic examination it can be barely distinguished from the casein, disintegrating gluten, etc. so that nothing indicates that it may be a special material, nor that it has arisen during the fermentation. Nevertheless, it is this substance that plays the principal role in the fermentation. I will shortly reveal the method for its isolation and preparation in a state of purity.

I have extracted from beer yeast its soluble material by boiling it several times with 15 to 20 times its weight of water. This extract is filtered carefully. In this are dissolved 50 grams of sugar per liter, and some chalk is added. Then it is seeded with a trace of the gray material I mentioned above, and a good lactic acid fermentation is obtained of the usual sort. On the next day the fermentation is vigorous and regular. The liquid, which had been perfectly clear at the beginning, becomes turbid, the chalk gradually disappears, and at the same time a deposit is produced which increases continually and progressively at the same rate that the chalk disappears. In addition, all of the characteristics and symptoms of the well-known lactic acid fermentation are observed. In this experiment, it is possible to replace the yeast water with a decoction of any decomposable nitrogenous material, whether fresh or decomposed. Let us now see the nature of this substance that is correlated with all of the phenomena that are included under the words lactic acid fermentation. Its appearance is similar to that of the beer yeast when it is

studied en masse and squeezed or pressed. Under the microscope it is seen to form tiny globules or small objects, which are very short, isolated or in groups of irregular masses. These globules are much smaller than those of beer yeast and move actively by Brownian movement. If washed with a large amount of water by decantation, then diluted into a solution of pure sugar, they immediately begin to make acid, but quite slowly since acid inhibits significantly their action on sugar. If chalk is added so that the medium is maintained at neutrality, the conversion of sugar is considerably accelerated, and even though only a small amount of material is acting, in less than an hour the production of gas is observed and the liquid contains large amounts of calcium lactate and butyrate. Only a small amount of this yeast is needed to convert a large amount of sugar. This fermentation is preferably carried out in the absence of air, since it is inhibited by plants or by parasitic infusoria.

Therefore, the lactic fermentation, like the ordinary alcoholic fermentation, is always correlated with the production of a nitrogenous material that has all the properties of an organized body of the mycodermal type, and is probably closely related to the yeast beer. ...

Pasteur's summary report (1881) on the anthrax vaccination trials:

CLASSICS OF BIOLOGY AND MEDICINE

Summary Report of the Experiments Conducted at Pouilly-le-Fort, Near Melun, on the Anthrax Vaccination

Louis Pasteur (with the Collaboration of Mr. Chamberland and Mr. Roux)

Editorial note: The famous French microbiologist and chemist, Louis Pasteur, pioneered the use of bacterial vaccines for prevention of infectious diseases in animals and humans. One of his early successes was in the development of a vaccine for the agriculturally important disease anthrax, a vaccine that is still in use today for animals worldwide and humans in some countries. He demonstrated the effectiveness of his vaccines often with dramatic public trials, one of the most famous of which was the spectacle at the small French village of Pouilly-le-Fort in May 1881. This paper, translated from the original report in French, describes the set-up and outcome of this public test of anthrax vaccination. Pasteur uses the term virus in its nineteenth century context meaning any agent that transmits disease rather than in its more restricted modern sense. It is interesting to note that neither here nor elsewhere does Pasteur provide a description of the methods of preparation of his vaccine or other experimental details. He kept these confidential. Indeed, recent scholarship (G.L. Geison, *The Private Science of Louis Pasteur*, 1995) shows that his public pronouncements alluding to the success of his method for vaccine preparation are at odds with his laboratory notebooks, which show that he conducted these famous tests at Pouilly-le-Fort not with vaccine prepared by his method of oxygen attenuation, but with vaccine prepared by the bichromate inactivation methods of his competitor Jean-Joseph Henri Toussaint.

In a lecture which I presented to the Academy last February 28, the purpose of which was to discover a method for preparation of attenuated anthrax, I spoke on behalf of myself and my young collaborators:

Each one of our attenuated anthrax microbes is a vaccine for the virulent microbe, that is to say, an adapted virus which produces a more benign variety of disease. After all, what could be easier than to find, among the offspring of the anthrax microbe, some adapted ones which can give the

anthrax fever to sheep, cows and horses without having them perish? We have practiced this procedure with great success in sheep. As soon as the time comes for rounding up the herds in Beauce, we will try to apply this method on a large scale.

Anthrax is responsible for the loss of many millions of animals every year in France. Consequently, it would be desirable to be able to save the ovine, bovine, and equine species if the above method of vaccination can be offered to us almost immediately, and without having to wait for the sheep round-up.

Last April, the president of the Agriculture Society of Melun, Baron de la Rochette, proposed that I conduct a decisive experiment to obtain the results of which I recently presented to the Academy. I was pleased to accept, and on April 28 we met and agreed upon to the following:

1. The Agriculture Society of Melun will put sixty sheep at the disposal of Mr. Pasteur.

2. Ten of these sheep will not undergo any treatment.

3. At an interval of twelve to fifteen days, twenty-five of these sheep will receive two vaccinations of unequally attenuated anthrax.

4. These twenty-five sheep will be inoculated by very virulent anthrax at the same time as the remaining twenty-five (uninoculated sheep), after a new interval of twelve or fifteen days. All twenty-five sheep that were not vaccinated will perish; all twenty-five that were vaccinated will resist infection, and we will ultimately compare them with the ten untreated sheep above. This is to show that vaccination does not prevent the sheep from returning to a normal state.

5. After the general inoculation of very virulent microbe to the two batches of vaccinated and unvaccinated sheep, the fifty sheep will remain together in the same cattle shed; one will distinguish one from the other by punching a hole in the ear of the twenty-five vaccinated sheep.

6. All the sheep which will die of the anthrax will be buried in distinct pits neighboring each other in a pallisaded enclosure.

7. In May 1882, we will put twenty-five new sheep – which have never been subjected to these treatments – in the enclosure in question to prove that the new sheep can be infected spontaneously by the anthrax microbes brought back to the surface of the ground by earthworms.

8. Another twenty-five other new sheep will be herded a few meters away from the enclosure described above. No animals infected with anthrax have ever been interred in this new area, and thus this experiment will show that none of these new sheep will contract anthrax.

Addendum to the preceding agreement:

When the president of the Agriculture Society of Melun asked that these experiments be extended to cows as well, I responded that we were ready to do so. However, I would like to inform the Society that, at the moment, the vaccination experiments in cows are not at as advanced a level as in sheep, so that the results obtained may not be as obviously convincing as with the sheep. In any case, I would like to acknowledge the Society of Melun for having put ten cows at our disposal. Six of these cows were vaccinated and four were not. After receiving the vaccination, the ten cows were inoculated with a highly virulent strain of the microbe (at the same time as the fifty sheep). I hypothesized that the six vaccinated cows would not become very ill, while the four unvaccinated cows would perish or at least become very ill.

I agree that my predictions sounded boldly prophetic, and it is true that my brashness can be excused only by clear successes with these experiments. Several people had the kindness to reproach the scientific imprudence of this approach. However, the Academy must understand that we devised such a scheme without solid, supporting results from previous experiments, despite the fact that none of these previous experiments were as large as the one we are proposing. Fortune, however, favors those who are prepared, and it is in this spirit, I believe, that I might quote the words of the inspired poet: *Audentes fortuna juvat* (fortune favors the bold).

The experiments started on May 5, in the commune of Pouilly-le-Fort, near Melun, in a farm belonging to Mr. Rossignol.

Upon a request by the Agriculture Society, which had undertaken these tests, we agreed to replace two sheep with two goats, and since we had not specified conditions of age or of breed, the fifty-eight sheep were of different ages, breeds and sexes. Of the ten animals from bovine species, there were eight cows, one ox and one bull.

On May 5, 1881, we used a Pravaz syringe to inoculate twenty-four sheep, one goat and six cows each with five drops attenuated anthrax. On May 17,

we revaccinated these twenty-four sheep, the goat and the six cows by more anthrax. While this microbe was also attenuated, it was more virulent than the anthrax used in the previous vaccination.

On May 31, we proceeded to inoculate these animals with the very virulent anthrax which would determine the efficacy of the preventative inoculations given between May 5 and 17. To this end, we inoculated the thirty-one vaccinated animals above [with the very virulent strain], and also twenty-four other sheep, one goat and four other cows, none of which had been exposed to this treatment previously.

The very virulent anthrax used on May 31 was regenerated from spores of the anthrax parasite stored in my laboratory since March 21, 1877.

To make the experiments more definitive, we inoculated both a vaccinated and an unvaccinated animal [with the very virulent anthrax]. With the inoculations completed, all the people present decided to meet again on Thursday June 2, 48 hours after the inoculations with the very virulent anthrax.

When the visitors arrived on June 2, they were astounded. The twenty-four sheep, the goat, and the six cows which had received the vaccinations of attenuated anthrax, all appeared healthy. In contrast, twenty-one sheep and the goat which had not been vaccinated had already died of anthrax; two other unvaccinated sheep died in front of the viewers, and the one remaining sheep died at the end of the day.

The unvaccinated cows had not died [upon exposure to the virulent anthrax]. We have already shown before that cows were less prone than sheep to die of anthrax. However, [within 48 hours], the unvaccinated cows all showed significant edema at the place right behind the shoulder where they were inoculated. In some cases, this edema increased in severity in the following days, to the extent that they contained several liters of fluid: one of these swellings even touched the ground. The temperature of these cows increased 30 C. The vaccinated cows did not show an elevation in temperature, swelling, or even the slightest loss of appetite. This confirms the predicted outcome to be quite as complete for the cows as for the sheep.

On Friday June 3, one of the vaccinated ewes died. An autopsy was performed that same day by Mr. Rossignol and Mr. Garrouste, a military veterinarian. The ewe was pregnant, carrying a full-term lamb which had

died in her womb twelve to fifteen days ago. The opinion of the veterinarians performing the autopsy was that the death of this ewe was due to the death of her fetus.

The experiments which I have come to report have elicited sharp curiosity in Seine-et-Marne and in its neighboring departments. They were witnessed by several hundred people ...

...

I cannot conceal my satisfaction in naming these veterinarians who were brought to Pouilly-le-Fort, to the farm of their colleague Mr. Rossignol, by a desire to know the truth. A large number of them – if not all – had been incredulous at the results of our [previous] treatments. In their conversations and journals, they resisted accepting as true the artificial preparation of our vaccines against fowl cholera and anthrax. Today, these individuals are the most enthusiastic disciples of our new doctrines. One of them – who was much more skeptical at the beginning – trusts our method to the extent that he wants to start a vaccination program himself [Biot]. This is a good omen. They will become proponents of the anthrax vaccination; we have converted them at last. It is particularly important that, at least for the time being, the vaccine cultures are prepared and controlled in my laboratory. A faulty application of the method could compromise the future of a method that promises to be of great service to the field of agriculture.

In summary, we now possess a vaccine of anthrax which is capable of saving animals from this fatal disease; a virus vaccine that is itself never lethal; a live vaccine, one that can be cultivated at will and transported without alteration. Finally, this vaccine is prepared by a procedure that we believe can be generalized since, the first time around, this was the method we used to develop a fowl cholera vaccine. Based on all the conditions that I list here, and by looking at everything only from a scientific point of view, the development of a vaccination against anthrax constitutes significant progress beyond the first vaccine developed by Jenner, since the latter had never been obtained experimentally.

Pasteur's report (1885) on rabies inoculation, as read to the French Academy of Science:

The treatment of rabies, that I have presented in my name and in that of my collaborators, in some previous reports, assuredly constituted real progress in the study of this disease, progress nonetheless more scientific than practical. Its application revealed some irregularities. Of some 20 dogs so treated, I was unable to render refractory to rabies to more than 15 or 16.

It was advantageous, on the other hand, to end the treatment with a final very virulent inoculation, an inoculation with a control virus, in order to confirm and reinforce the refractory state. In addition, prudence dictated that one keep the dogs under observation for a longer time than the duration of incubation of the disease produced by the direct inoculation of this last virus. Hence it was occasionally necessary to wait three to four months in order to be assured of the refractory state to rabies. Such problems would have substantially limited the application of the method. In substance, the method would lend itself with difficulty to immediate application, a condition demanded nevertheless, by the accidental and unexpected rabid bites.

It became necessary, if possible, to develop a more rapid method and one capable of giving perfect security, I dare say, to the dog. And how, furthermore, before this was achieved, could one dare to permit under any circumstance a trial in man? After many numberless experiments, so to speak, I developed a prophylactic procedure, practicable and rapid, which given numerous and assured successes in the dog, has given me confidence in the generality of the method and its use in all animals and man himself. This method rests essentially on the following facts:

The inoculation in the rabbit, by trepanation [the drilling of a hole in a skull], under the dura mater, of spinal cord of a dog suffering from common street rabies, always elicits rabies in these animals after an average incubation period of about fifteen days. If one passes some virus from the first rabbit to a second, from this to a third, and so forth, in the manner of the previous inoculation, there manifests shortly a tendency more and more pronounced in the diminution of the incubation period required for rabies to appear in the successively incubated rabbits.

After twenty to twenty-five passages from rabbit to rabbit, one encounters an incubation period of eight days which is maintained for an additional period of twenty to twenty-five passages. Then one attains an incubation period of seven days, that one discovers with a striking regularity during a new series of passages up to ninety in number. At least this is the number I am at this moment. And it may be that there is a tendency to a length of incubation of a little less than seven days.

This type of experiment, begun in November 1882, and now three years in duration, which has never been interrupted, and which has never had recourse to another virus other than that from rabbits successively dead of rabies. Consequently, nothing is easier to have continually at one's disposition, during a considerable period of time, a rabid virus of perfect purity, always or almost always identical to itself. This then is the practical nub of the method.

The spinal cords of these rabbits are rabid through their length with a constancy in their virulence. If taking the greatest care possible to maintain purity one removes from these cords sections a few centimeters in length, and then suspends them in dry air, virulence slowly disappears until it is finally disappears. The time required for extinction of virulence varies somewhat with the thickness of the cords but above all with the exterior temperature. The lower the temperature, the longer does the virulence last. (Note: If the rabid spinal cord in a humid state is protected from air by carbon dioxide, virulence is conserved more or less for many months without change in its rabid intensity, provided that it is kept from alteration by external microbial agents.) These results represent the scientific center of the method.

Having established these facts, here is the method to render a dog refractory to rabies in a relatively short time. In a series of flasks in which air is maintained in a dry state by means of pieces of potassium hydroxide deposited on the flask bottom, each day one suspends a thickness of fresh rabid spinal tissue taken from a rabbit dead of rabies, rabies developed after seven days of incubation. Each day as well, one inoculates under the skin of a dog one plain Pravaz syringe of sterilized bouillon, in which one has dispersed a small fragment of one of these desiccated spinal pieces, beginning with a piece most distant in time from when it was worked upon, in order to be

quite certain that it isn't at all virulent. (Note of the Translator: A Pravaz syringe consists of a barrel and a metal plunger containing at its base a pair of leather seals. The full syringe can deliver 1 ml of fluid). Preliminary studies made this clear. On the following days, one performed the same procedure with less old spinal tissue, separated by an interval of two days, until one reaches the last most virulent spinal tissue, that was placed for only a day or two in the flask. In this manner is the dog rendered immune to rabies. One can inject it with rabid virus under the skin or similarly on the brain surface by trepanation without rabies appearing.

By the application of this method, I had made fifty dogs of all ages and breeds refractory to rabies without a single failure, when unexpectedly on the 6th of July last, three persons from Alsace presented themselves at my laboratory: Theodore Vone, grocer from Meissengot, near Schlestadt, bitten on the arm 4 July, by his own dog that had become rabid; Joseph Meister, 9 years old, also bitten on 4 July at 8 in the morning by the same dog. This child knocked to the ground by the dog carried numerous bites on the hand, legs, thighs, some rather deep that made his walking difficult. The principal bites had been cauterized only twelve hours earlier with carbolic acid, 4 July at 8 p.m. by Dr. Weber of the town. The third person who hadn't been bitten was the mother of little Joseph Meister.

At the autopsy of the dog killed by his master, one found the stomach full of grass, of straw and pieces of wood. The dog was truly rabid. Joseph Meister had been lifted up from beneath him covered with slaver [saliva] and blood. M. Vone had strong contusions on his arms, but he assured me that his shirt hadn't been pierced by the fangs of the dog. As he had nothing to fear, I told him that he might return to Alsace the same day and he did. But I kept little Joseph Meister and his mother with me.

The weekly meeting of the Academy of Sciences took place precisely on July 6. I saw there our colleague M. Dr. Vulpian to whom I told what had happened. M. Vulpian as well as Dr. Grancher, professor at the Faculty of medicine, were good enough to come to see immediately little Joseph Meister and to establish the condition and number of his wounds. There were not less than 14.

The opinion of our wise colleague and of Dr. Grancher was that by the

intensity and the number of bites, Joseph Meister was almost inevitably to come down with rabies. I then told Vulpian and Grancher the new data that I had obtained in the study of rabies since the lecture that I had given in Copenhagen, a year earlier. As the death of this child appeared inevitable, I decided, not without deep and severe unease, as one can well imagine, to try on Joseph Meister the procedure which had consistently worked in dogs.

My fifty dogs, it is true, hadn't been bitten before I determined their refractory state towards rabies, but I knew that this issue could be dispensed with, as I had already obtained a state resistant to rabies in a large number of dogs after a bite. I had provided evidence this year to the members of the Commission on Rabies of this new and important progress.

In consequence, on July 6, at 8 in the evening, sixty hours after the bites of July 4, and in the presence of Drs. Vulpian and Granter, one injected under a fold of skin in the right hypochondrium, one-half Pravaz syringe of spinal cord of a rabbit dead of rabies on June 21 and conserved since then in a flask of dry air, that is to say for 15 days. The following days new inoculations were made always ... in accord with the conditions which I give here in the table ...

...

Thus, I carried the number of inoculations to 13 and to 10 the number of days of treatment. I will say later on that a smaller number of inoculations would have been sufficient. But one will understand that in this first trial I had to be especially cautious.

...

In the last days, I had thus inoculated Joseph Meister with the most virulent rabid virus, that of the dog made more potent by a great number of rabbit to rabbit passages, a virus that gives rabies to these animals after seven days of incubation, after eight or ten days in dogs. I was warranted in this activity because of what happened to the fifty dogs of which I have spoken. When the state of immunity is attained one may without harm inoculate the most virulent virus and in whatever amount. It always appears that this has no other effect than consolidating the state of refractoriness to rabies.

Joseph Meister has thus escaped, not only from rabies that his bites would have produced, but also from that which I had inoculated him with in order

to check his immunity produced by the treatment – a rabies more virulent than that of ordinary canine rabies. The final most virulent inoculation has again the advantage of reducing the duration of apprehension that one may have following the course of the bites. If rabies might break out, it will be evident more quickly with a more virulent virus that than due to the bites. From the middle of August, I looked forward with confidence to the health of Joseph Meister. As of today, after three months and three weeks elapsed since the accident, his health has left nothing to be desired.

...

I don't have to comment in concluding that perhaps the most serious question to resolve at this moment is the allowable interval between the moment of a bite and when one begins treatment. This interval in the case of Joseph Meister was two and a half days. But it should be expected that this could be much longer. Tuesday last, the 20th of October, with the obliging assistance of M. M. Vulpian and Grancher, I had to treat, under exceptionally serious conditions, a young man of fifteen years, bitten fully six days earlier on each of his two hands. I will commit myself to make known to the Academy what happens in this new trial.

The Academy perhaps cannot hear without emotion the account of the courageous act and the great spirit of the young man which I have begun to treat last Tuesday. This is a villager, of 15 years, his name Jean-Baptiste Jupille, of Villers-Farlay (Jura), who seeing a dog of suspect bearing, of strong stature, threw himself on a group of six of his little friends, all much younger than himself, threw himself, armed only with his whip, in front of the animal. The dog seized Jupille by the left hand. Jupille then threw the dog to the ground, held him beneath him, opened his jaws with his right hand in order to free his left hand, not with receiving many new bites, then with the cord of his whip, he muzzled him and striking him with his shoes, killed him.

Chapter 19

Robert Koch

Koch's (1876) paper on the etiology of anthrax:

The etiology of anthrax, based on the life history of *Bacillus anthracis*

I. Introduction

Since the discovery of rod-shaped bodies in the blood of animals dying of anthrax, there has been much effort directed to attempts to prove that these rod-shaped bodies are responsible for the transmissibility of this disease as well as for the sporadic appearance of it. These studies have sought to determine whether these bodies are the unique contagium of anthrax. Recently Davaine has carried out a number of inoculation experiments with fresh and dried blood containing the rods and has stated decisively that these rods are bacteria, and that only in the presence of these bacteria can a fresh case of anthrax be produced. The lack of proof of the direct transmission of the anthrax disease in man and animals is due to the ability of the bacteria to remain alive for a long time in dry conditions and to be transmitted through the air by insects and the like. It seems here that the mode of transmission of anthrax has been explained.

Nevertheless, these ideas of Davaine have found many opponents. Several workers have obtained experimental anthrax by inoculating blood containing bacteria, but have been unable to show the presence of bacteria in the blood of the diseased animals. Others have been able to induce anthrax by inoculation with blood which could not be shown to contain bacteria, but the diseased animals then had bacteria in their blood. Others have noted that anthrax is

not derived solely from a contagium which is transmitted above ground, but that this disease is related in some way with conditions of the soil. ...

These experiences cannot be explained by the hypothesis of Davaine, and because of this, many people feel that bacteria are of no significance for anthrax.

Since I have had the opportunity several times of examining animals which had died of anthrax, I performed a series of experiments which would clear up the uncertainties in the etiology of anthrax. Through these, I came to the conclusion that the theory of Davaine concerning the transmission of anthrax is only partly correct.

I could show that the rods in the anthrax blood were not so resistant as Davaine had believed. As I will show later, the blood, which contains only rods, keeps its ability to induce anthrax on inoculation only a few weeks in the dry state, and only a few days when moist. How is it possible then for an organism which is so easily destroyed to maintain itself as a dormant contagium for a year in soil and throughout the winter? If bacteria are really the cause of anthrax, then we must hypothesize that they can go through a change in life history and assume a condition which will be resistant to alternate drying and moisture. What is more likely, and what has already been indicated by Prof. Cohn is that the bacteria can form spores which possess the ability to reform bacteria after a long or short resting period. All of my experiments were designed to discover this developmental stage of the anthrax bacterium. After many unsuccessful experiments, I was finally able to reach this goal, and thus to find a basis for the etiology of anthrax.

Since the life history of the anthrax bacterium offers not only botanical interest but also much light on the heretofore uncertain etiology of the soil-related infectious diseases, I am publishing now the most important results of my experiments, although my work is still in progress.

II. Life History of *Bacillus anthracis*

It has not been possible for me to observe the multiplication of the bacteria directly in the animal. But it can be inferred that this occurs from the inoculation experiments which follow. I have used the mouse as my experimental animal, as it is simple to use. ... In most experiments I inoculated them at the base of the tail, where the skin is loose and covered with long hair. ...

I have made a large number of inoculations in this way, using fresh anthrax material, and in every case I have had a positive result, and I believed therefore that the success of the inoculation could be used as an indication of the life or death of the bacilli inoculated. I will show through later experiments that this idea is true.

Partly in order to always have available fresh material, and partly to discover if the bacilli would change into another form after a certain number of generations, I inoculated a number of mice in series, one from the other, each time using a mouse which had just died as a source of the spleenic material. The longest series of mice treated in this way was twenty, which therefore represented that many generations of the bacilli. In all animals the results were the same. The spleen was markedly swollen and contained a large number of transparent rods which were very similar in appearance and were immotile and without spores. This same type of bacillus could be be found also in the blood, but not in so great a number as in the spleen. In these experiments it was shown, therefore, that a small number of bacilli could always develop into a significant mass of individuals of the same type. ... which appeared to reproduce by growing in length and then splitting after they had reached about twice the length of the individual bacilli. These results also indicate that it is highly unlikely that the bacilli would go through some change in form if a longer series of inoculations were made, and therefore it is unlikely that there is ultimately some alternation of generations. ...

It will take us too far afield to consider whether or not the actual cause of the death of the animals is due to the production of carbon dioxide in the blood through the rapid growth of the bacilli there, or, that seems more probable, that death is due to a metabolic product produced by the parasite through its utilization of proteins as nutrients, and that this metabolic product is poisonous to the animal. [Such a metabolic product, known today as a toxin, is usually associated in some way with more infectious diseases, including anthrax.] ...

[To study the life history of the bacilli away from the animal,] a drop of fresh beef serum or aqueous humor from the eye of a cow was placed on a microscope slide. Then a small piece of spleen which contained bacteria and which had been freshly removed from an infected animal was placed in this

and a cover glass placed on top. The microscope slide was then placed in a moist chamber to keep the liquid from evaporating, and this was then placed in an incubator. ...

These preparations were incubated for 15-20 hours at 35-37 C. At the end of this time, in the middle of preparation between the tissue cells could be seen many unaltered bacilli, although in smaller numbers than in fresh preparation. However, away from the tissue in the fluid, one could see bacilli which were 3-8 times longer and showed shallow bends and curvatures ... The closer to the edge of the cover glass, the longer the filaments, and these finally reached a size which was a hundred or more times the length of the original bacilli ... Many of these long filaments had lost their uniform structure and transparent appearance, and their contents had become finely granulated with the regular appearance of strongly light-reflecting grains ... The filaments which lay right at the edge of the cover glass, where the gas exchange with the nutrient fluid was the best, showed the more extensive development. They contained completely formed spores which were imbedded in the substance of the filaments at regular distances and were somewhat oval, strongly light-refracting bodies. In this form the filaments revealed a remarkable appearance, which can best be compared with a string of pearls.

Many filaments had already lost their spores, which can be seen between them as small, free clusters. ... In favorable preparations it is possible to see all of the stages from short bacillus rods, through long, sporulating filaments, to free spores, and this is proof that the latter arises from the former. ... [Because these spores seemed to form most frequently at the edge, it occurred to Koch that they might not actually come from the Bacillus, but be due to contamination from the air, since his preparations were not pure, and he had observed micrococci and bacterium types from time to time. So he decided that the only way to be sure would be to observe the spore formation actually take place.]

Although I had imagined such an experiment would be very difficult to perform, it actually proved quite simple. ... [The preparations were so arranged that they could be observed under the microscope while being incubated continuously.]

Observations every 10-20 minutes revealed that the bacilli at the beginning

were somewhat thicker and seemed to be swollen and hardly showed any changes in the first two hours. Then they began to grow. After 3-4 hours they had already lengthened 10-20 times; they began to curve, to push against each other and make a network. After a few more hours the individual filaments were already so long that they covered several microscope fields. ...

If the free end of the filament was observed continuously for 15-20 minutes, it was quite easy to observe its lengthening and perceive the remarkable spectacle of actually watching the bacillus grow. It was therefore possible to obtain direct evidence of the further development of these filaments. After only 10-15 minutes the contents of the strongest and most luxuriantly growing filaments were finely granular, and soon the small, refractile grains were cut off in regular sequence. These enlarged in the space of several more hours into the strongly refractile, oval-shaped spores. Gradually the filaments disintegrated, fragmented at the ends, and the spores became free. ... In this condition the preparations could remain for weeks without changing. ...

Observations were made to obtain a complete picture of the life history of the *Bacillus anthracis* and to discover whether the spores passed through some intermediate form, such as a swarm spore, or passed directly into a bacillus. In order to do this it was necessary to discover conditions which would permit the spore to develop into the bacillus which would allow for direct microscopic observations.

All efforts to obtain the further development of the spores in distilled water or in well water failed. In serum or aqueous humor, the results were equivocal; bacilli developed without question, and these formed filaments and spores, but their number was small and it was not possible to observe the transformation of single spores into bacilli. Finally I arrived at a procedure which was successful. Preparations were used which revealed under the microscope only a pure culture of *Bacillus anthracis*, and which contained mostly free spore masses. The spores were allowed to dry on a cover glass ... and then a drop of aqueous humor was placed on a microscope slide and the cover glass was laid on it so that the mass of spores was wetted by the fluid. These preparations were placed in the moist chamber and incubated at 35 C.

After a half hour the remains of the filaments began to disintegrate, and after 1 1/2 to 2 hours they had disappeared.

Already after 3-4 hours the development of the spores could be seen. ...

By careful examination at high magnification, it appeared that each spore was oval-shaped and was imbedded in a round transparent mass, which appeared like a small, light ring surrounding the spore. The spherical shape of this ring could be easily seen by rolling the spore in various positions. This material first lost its spherical shape, lengthened itself on one side in the direction of the long axis of the spore and became like a long oval. The spore remained in one of the poles of the cylindrical shaped body. Soon the transparent covering became longer and filamentous, and at the same time the spore began to lose its strongly refractile characteristics. It became quickly pale and smaller, broke apart into many pieces, and finally completely disappeared. ... pictured [is] a mass of spores showing the conversion to filaments.

Later I was able to observe in the same preparation and same drop of aqueous humor the appearance of bacilli from the spores and then later a second generation of spore-containing filaments. ...

It may be assumed that when these spores in some way reach the blood stream of a sensitive animal, a new generation of bacilli will be produced. In order to prove this assumption, the following experiments were performed. ...

By the inoculation of mice with material rich in spores, or with material with few spores, the interesting fact was discovered, that in the first case, with many spores, the mice died after 24 hours, while in the latter case, the mice did not die from anthrax until after three or four days. I have repeated these experiments many times. Such substances containing spores were dried and allowed to stand for a while. When moistened with water and injected, they had not lost their ability to produce anthrax. ...

On the other hand I have inoculated mice with spore masses which had come from cultures in glass cells and which I had ascertained by microscopic examination to have been derived from completely pure cultures of *Bacillus anthracis*, and every time the inoculated animals died of anthrax. It follows, therefore, that only a species of Bacillus is able to cause this specific disease, while other schizophytes have no effects or cause entirely different diseases when inoculated. ...

Koch's (1881) paper on solid media cultivation:

Methods for the study of pathogenic organisms

... After it has been determined that the pathogenic microorganism is present in the animal body, and after it has been shown that the organism can reproduce in the body and be transmitted from one individual to another, the most important experiment remains to be done. This, which is the most interesting part of hygienic studies, is to determine the conditions necessary for the growth and reproduction of the microorganism. As I have mentioned earlier, this problem can only be solved with the help of pure cultures, and I do not believe it is too much to say that the most important point in all studies on infectious diseases is the use of pure cultures.

Since the importance of pure cultures has been known for a long time, it has thus been true that all who have worked in this field of infectious disease have worked the hardest to perfect methods of pure culture. The most recent results have shown that we are not even past the first groping stages in this research. At the most, people have learned to avoid the most obvious errors, and not all have even learned this.

The most important procedures that have been developed for the manipulation of pure cultures can be summarized as follows. A sterilized container is used which has been closed with mold-proof sterilized cotton, and this is filled with a sterilized nutrient liquid of the proper sort. Then this is inoculated with material containing the microorganism which is wanted in pure culture. After suitable reproduction has taken place in this container, a sterile instrument is used to transfer a little of this to a second container. This process may be repeated a number of times. In short, this procedure is analogous to the inoculation of an experimental animal from a diseased animal to transfer an infectious disease.

Naturally in this procedure one has to make several assumptions, of which the first is that the culture vessel is really sterile. How lightly this sterilization has occasionally been treated can be seen from the controversy between Pasteur and Bastian on spontaneous generation, and the well-known question of the former to the latter: Do you flame your glassware before using it? which Bastian had to answer in the negative.

Second, one must assume that the sterile cotton is really mold-proof. As Nageli has shown, this is not always the case.

Third, it must be assumed that the nutrient liquid is both sterile and suitable for the growth of the organism in question. ...

Fourth, it must be assumed that the substance used as inoculum contains no other microorganisms than the one desired. Even a slight contamination of the inoculum with another species which is faster growing than the organism desired will prevent anyone from ever obtaining a pure culture. Buchner has therefore developed his own method for the preparation of an initial material for his studies on the anthrax bacillus. He inoculates the nutrient medium with such a high dilution of anthrax infected material that, through calculations, it can be assumed that only one bacillus is placed in each culture vessel. Then from the characteristic macroscopic appearance of the developing culture, he concludes that he has obtained a pure culture. [This method also has difficulties which I shall go into later.] ...

Fifth, it has to be assumed that during the initial inoculation and also in the subsequent inoculations, that no foreign organism gets into the culture liquid from the air. This is a danger which the experimenter will find difficult to prevent with certainty, even when the protecting cotton plug is exposed to the air for only a very short time. Even if the first, second, and third transfers have been successful, the probability that the culture will get contaminated will increase with the number of transfers. In order to circumvent this eventuality as much as possible, it is customary to prepare a number of replicates, and only use those for further inoculations which appear by macroscopic or microscopic observation to be pure. Unfortunately one cannot even rely on this procedure, because the macroscopic differentiation of several cultures is very uncertain, and even the microscopic examination is fraught with difficulties, since one only knows that the very small drop of culture fluid under the microscope is free of contaminating organisms, and, as well, if the amount of contamination is small, there may be only occasional contaminants amongst the large number of organisms, and this makes them quite easy to miss. Therefore the first initiation of contamination cannot be distinguished either macroscopically or microscopically, and if one by chance uses for further inoculations a culture which is presumed to be pure but which

has already become contaminated, and the contaminating organisms are able to overtake the experimental organism, then the pure culture is completely lost. The microscope will reveal in the next generation, without a doubt, that the culture is contaminated, but now it is too late, because it is impossible at this time to rid oneself of the uninvited guest.

All in all the situation with regard to pure culture techniques is quite disappointing. No one who has cultured microorganisms in the ways currently in vogue and has not avoided completely all of the sources of error that I have indicated, can complain if his results are not accepted as fact by his fellow workers. What has been said above should be heeded by the Pasteur school in its noteworthy but blindly zealous researches, since this renders it doubtful that they have obtained in pure culture the organisms of rabies, sheep pox, tuberculosis, and so forth.

As I have emphasized many times before, pure cultures are indispensable for the further development of knowledge in the field of pathogenic organisms and all that is connected with this, and a practical and exact method must, in some way, be developed. The present methods seem to me to offer no hope for a significant improvement. ...

Therefore I have rejected completely all of the current principles of pure culture technique and have adopted an entirely new way. A simple observation which anyone can repeat has led me to this approach.

If a boiled potato is cut in half and the cut surface is exposed to the air for several hours and then placed in a moist chamber such as a moistened bell jar in order to prevent it from drying, then, depending upon the temperature of the chamber, one will find in the following day or two, on the surface of the potato, a large number of very small droplets, all of which seem to be different from each other. Several of these droplets may be white, others may be yellow, brown, light gray, or reddish, while others appear to be spread out water droplets, or half spheres, or warty. But all of these become larger in time, then appear mycelia of molds, and finally all of the droplets coalesce and the potato soon becomes obviously spoiled. If one examines these droplets under the microscope while they are still isolated, preferably after they have been streaked on a cover glass, heated, and stained, it can be seen that each droplet consists of microorganisms of one particular species. Some reveal

large micrococci, others have small micrococci, in a third the cocci will be in chains. Those which have spread considerably usually consist of bacilli of various sizes and arrangements. Many consist of yeast cells, and here and there is a mold mycelium which has come from a germinated spore. There is no doubt where these different organisms have come from. Another potato is peeled with a flamed knife to remove the peeling which contains soil with bacillus spores which have not been killed by the short heating time. This piece of potato is protected from the air by placing it in a glass beaker with a cotton stopper and then incubated and observed. In this potato no droplets develop, no organisms appear, and the potato remains unchanged until it eventually dries up after several weeks. Therefore, the germs from which the drop-like colonies on the first potato developed could only come out of the air. Indeed, often one can see in the center of the droplet a dust particle or piece of thread which was the carrier of the germ. These germs may be dried but still living bacteria, yeast cells, or spores. ...

What can we conclude from these observations on colonies developing on potatoes? It is possible that two different germs may come to lie close together and develop colonies which quickly coalesce, and it is possible that one dust particle may contain more than one germ and these may develop simultaneously. But these are probably exceptions, and most often each droplet or colony is a pure culture and remains a pure culture until it enlarges to the point that it touches its neighbors. If instead of the potato, a liquid medium of the same surface area were exposed to the air, then undoubtedly the same number and the same kinds of germs would fall as had fallen on the potato, but the development of these germs in the liquid would be different and would follow the manner which has been previously described. The motile bacteria upon dividing would separate from each other. The nonmotile bacteria would probably begin to form tiny colonies, but these would soon be separated by the movements of the motile bacteria. Some of the organisms would sink to the bottom of the liquid, while others would rise to the top. Some of the organisms which would have found places on the potato to grow undisturbed would be choked by the development of other more luxuriantly growing organisms and would never grow. In short, the whole liquid would reveal under the microscope from the beginning a tangled mixture of different

shapes and sizes, which no one would mistake for a pure culture. What is the fundamental difference between the nutrient substratum which the potato and the nutrient liquid offer to the microorganisms? It is only that the potato is solid and prevents the various species, even if they are motile, from becoming mixed, while in the liquid medium there is no chance for the different species to remain apart.

How then can we make use of the advantages which a solid nutrient medium offers for the pure culture practice? A number of colonies which had developed spontaneously on a boiled potato were spread out on other similar potato slices and incubated in the moist chamber. Within one or two days a heavy growth of the seeded microorganism had developed, and these had exactly the same characteristics as those from the original droplet. ... All of them grew quite quickly from very small colonies of the original potato when transferred to other potatoes and appeared to be perfectly pure cultures. Extra-special precautions to prevent air contamination were not necessary here, since if a germ of another organism fell here and there on the potato, it could only develop where it fell and would slowly spread out but would never endanger the whole culture. As well, any contaminating colonies could be easily distinguished by their appearance, so that a contamination of the culture during the next transfer could be easily avoided. ... Here therefore was a very simple method for the production of perfect pure cultures, at least for those organisms which could grow on boiled potato, and this number is not small. ... However, bacteria which had been shown by animal experiments to be pathogenic could not be cultured on potato.

But the principle had been found, and it was only necessary to devise conditions which could be used in all cases. There would be no purpose in outlining all of the experiments which were performed, in order to find a nutrient medium like boiled potato which would suit the pathogenic organisms. I will indicate only the end result of these experiments. In its present form the technique can be used perfectly in the majority of cases where pure cultures are desired, and in time it will undoubtedly be perfected so that all cases will be included.

After I had considered that it would be hardly possible to construct a universal medium which would be equally suitable for all microorganisms,

I limited myself to attempting to use the known media and such new ones as I might develop and converting them to a form which would be firm and rigid. The most useful way to obtain this end is to add gelatin to the nutrient liquid. ... The mixture of nutrient liquid and gelatin, which I will call nutrient gelatin for short, is prepared in the following way: The gelatin is allowed to soak in distilled water and is then dissolved by heating. Both the gelatin and the nutrient liquid are prepared at such concentrations so that when they are mixed in predetermined amounts they will give the desired concentration of gelatin and nutrient in the final medium. I have determined that the best concentration of gelatin for these purposes is 2.5 to 3 percent. ... One can also dissolve the gelatin directly in the nutrient liquid. Gelatin generally gives a slightly acid reaction, and for this reason it is necessary to neutralize the nutrient gelatin with potassium or sodium carbonate or basic sodium phosphate, if the medium is to be used for the culture of bacteria. The neutralized gelatin is again heated, and since there is usually a precipitate formed either during this heating or the preceding neutralization, the mixture is then filtered. This filtration also removes any impurities that were present in the gelatin. In the meantime a container closed with cotton has been sterilized by heating for a long time at 150 C., and this is then filled with the medium and boiled again. The boiling requires only a short time, since it is only necessary to kill the microorganisms which were already present in the nutrient gelatin, and these are easy to kill. The spores which are present can only be killed by prolonged heating, and this cannot be done, since the gelatin then loses its ability to solidify. For the same reason, it is not possible to sterilize with steam under pressure. During these manipulations the nutrient gelatin is therefore not sterilized with certainty, but this makes no difference. If the medium were liquid, the spore forming bacteria would quickly grow and spread throughout the whole liquid, and only reveal themselves through a turbidity on the second or third day. At this time the liquid could no longer be saved, since it would be changed from its original composition, and probably would be full of newly formed spores. But in the nutrient gelatin the situation is quite different, and here can be seen already the tremendous advantage offered by the solid characteristics of the medium for revealing its content of bacteria. In the next day or two one may see dispersed throughout

the transparent, solidified gelatin, a number of very small, translucent little dots, which appear white by reflected light. If one allows the nutrient gelatin to incubate further, then these little dots will soon enlarge into small spheres, and these will continue to increase in circumference, and eventually liquefy the gelatin and convert it into a turbid liquid. These small, white colonies consist of bacilli, which fact can easily be ascertained by a microscopic examination. But if one is aware of this and wishes to sterilize this gelatin, one should not wait until they have achieved such a considerable size, but kill them through boiling of the gelatin when they are just big enough to be seen by the naked eye. Here is a great advantage of the nutrient gelatin, since one cannot overlook the very first beginnings of bacterial development. ... One discovers quickly if this or that particular nutrient fluid when converted into nutrient gelatin is easy or hard to sterilize. Many, as for example alkaline urine or Pasteur's fluid, are easy to sterilize in the form of nutrient gelatin. Others like meat extract or hay infusion are much more difficult; one has to boil them daily for several days. This is because not all of the spores germinate at the same time. Occasional single colonies will develop in the center of the gelatin even days after the last boiling, and their position shows that they were in there from the beginning and did not arrive later. However, if this should be the case, frequent examination of the nutrient gelatin in the first week will allow one to notice these early enough and they can then be killed by another boiling. This frequent examination in the first week should never be omitted.

Because it is so simple and certain to prepare pure cultures using potato slices, I have preferred to prepare the nutrient gelatin in a similar form as a potato slice. It can be poured into flat watch glasses, small glass plates or the like. However, the most useful for the preparation of cultures, and especially for the microscopic examination of these, is to spread the nutrient gelatin as a long, wide drop on a microscope slide, in which form it can be placed under the microscope when so desired. This is done with a previously sterilized pipette, and of course the microscope slide is previously cleaned and sterilized by prolonged heating at 150 C. The drops are about two millimeters thick. The gelatin hardens in a few minutes and the slides are placed on a small glass shelf which will hold two or three slides next to each other. Finally

a number of these shelves are placed in layers over each other and placed in a moist chamber. ... Under such conditions the gelatin drops can be kept two or three weeks before they dry out. The organism to be cultured is seeded by taking a flamed needle or platinum wire, picking up a very small quantity of the liquid or substance containing the organisms, and streaking this in three to six cross lines on the gelatin surface. ... The expression "inoculation" for this operation seems appropriate. ...

The bell jar which serves as the moist chamber is sufficient protection from contamination, even though it does not fit tightly. It sometimes happens that foreign organisms may fall on the gelatin during inoculation or manipulation of the slides. But these can only develop at the place on the gelatin where they have fallen and this is usually not on the inoculation streak. It is hardly possible that all of the cultures of an organism will become contaminated so that they cannot be transferred further, and this possibility is even more reduced if the bell jar is not opened often. Within a few days the pure cultures have developed to their maximum extent and can be inoculated further. There is no purpose in allowing the cultures to stand a long time, and this is especially true when the bacteria being cultured are able to liquefy the gelatin, or when sporulation has set in. In these cases a quick transfer is necessary. If it is necessary to keep single cultures for a long time without transfer, then it is necessary to keep them in a container enclosed with cotton. ...

At low temperatures the development of the cultures proceeds quite slowly, and many organisms require a certain warmth in order to proliferate well. The most luxuriant growth in gelatin cultures has been at 20-25 C., and I have not found any organisms yet which are at all culturable, which could not grow at this temperature. However, if it is necessary to use temperatures over 30 C., where the gelatin is fluid, then one cannot use gelatin or must modify the procedure. ...

A very important operation in the pure culture procedure is the procuring of a completely pure material for the first inoculations. This can be easily performed with the help of nutrient gelatin. With the previous methods this problem was almost impossible to solve. If, for example, blood from a septicemic animal was to be used as culture material to obtain a completely

pure culture of the septicemia bacteria, previously many precautions of sterile procedure would have to be taken to remove the blood from the animal, and still the desired result would not be obtained. Now it is only necessary to take a flamed needle and remove some blood from the opened heart or a convenient blood vessel and streak it a few times on the nutrient gelatin. There will occur growth in colonies of several types of microorganisms, among which will be a greater or lesser number of pure, characteristically mat-like and granular colonies which can be characterized under the microscope as those of the septicemia bacteria. It will be quite easy to culture these further in pure culture. In this case the number of foreign organisms is at a minimum, so that it is quite easy to isolate the pure colonies of the appropriate organism. However, even if this situation were reversed and the sought-for organisms were in the minority, it would still be possible to have success. Although here it would not be as easy, it would be just as certain. It is only necessary to dilute the bacterial mixture considerably and then make a large number of streaks. In such circumstances it is advantageous to inoculate into the still liquid gelatin, in order to spread the various germs over a wide area, and then pour it on the slides and locate the colonies which develop under the microscope. ...

I have carried pathogenic and nonpathogenic organisms over a long series of transfers on boiled potato or nutrient gelatin, without ever once observing any noticeable changes in their characteristics. They maintain their morphological as well as their physiological characteristics, so far as one can determine these, without change through months of growth as pure cultures. ...

In botany and zoology it is a basic rule that all living organisms which have been previously unknown, should be exactly described, named, and tentatively recorded as new species. ... This tried and approved rule, that all new forms which deviate from each other in significant ways, should be considered as separate from each other, has remarkably been often ignored in studies on bacteria. From the very beginning of bacteriological research, from Hallier to Naegel to Buchner, right up to the present time, there has been a tendency to take all of the different kinds of bacteria and throw them into one pile, and make one or at most several species from them. If it is

ever possible to show that one type of bacteria can be converted into another well-known form by merely continued culture, then is the time to consider these demonstrably related forms to be one species. Up until now this proof has not been accomplished, and there is not the slightest basis in bacteriology to deviate from this general maxim of natural science. If at the beginning too many species are assumed, this can be of no disadvantage to the science. But if a priori the utility and necessity of doing research on the different forms of bacteria are denied, making it impossible to acquire knowledge, then a door will be closed on all further research and progress in this field, and this would certainly be a tremendous barrier to the progress in this young and promising subject. ...

It seems to me indispensable in our studies on bacteria ... to adhere to the following concept:

All bacteria which maintain the characteristics which differentiate one from another, when they are cultured on the same medium and under the same conditions, through many transfers or many generations, and which seem to be different from each other, should be designated as species, varieties, forms, or other suitable designation. (italics in the original)

Loeffler's (1907) remembrances of Koch's staining discovery for the tubercle bacillus:

Numerous inoculations of guinea pigs with tuberculous material from various sources gave Koch the same clinical and pathological-anatomical picture and convinced him that he was dealing with a characteristic living agent. Driven forward by this conclusion, Koch set to work to demonstrate the presence of this agent in diseased material. He turned therefore to freshly developed tubercles, which always appeared first upon inoculation. He removed some of this material, streaked it out on cover glasses, and stained it with various dyes, using procedures that we had long used for other bacteria in diseased processes. Ehrlich's methylene blue, which Koch had used for a long time, was his first choice. In such stained preparations, Koch saw very tiny thin rods, about twice as long as wide. He found these rods only in preparations from tuberculous material, and not in controls. Were these rods the sought-for agent? This question was not easy to answer. First, Koch decided to obtain photomicrographs of these bacilli, in order to obtain an objective view of the organism, as he had always done in his earlier work. However, at that time the photographic technique was not very well developed and obtaining good pictures of stained material presented numerous difficulties. The technique that Koch found best was to counterstain his preparations with the brown dye vesuvin [Bismarck Brown] and then to photograph these brown-stained preparations with blue light. The brown-staining parts of the preparation absorbed the blue light and appeared dark on the photographic negative, whereas the blue-stained bacteria appeared to be bright and transparent. Although Koch counterstained the preparation with vesuvin to increase the photographic contrast of the blue-stained rods, when he examined these preparations before photography, he was surprised to discover that in the totally brown background the small rods had retained their blue color. Within the brown background they were now easily visible in large numbers! Extensive further experiments convinced Koch that he had found a new, very valuable method for differentiating the bacteria in tuberculous material from other bacteria, and that it would be possible, with this method alone to distinguish the tubercle bacillus from thousands

of other bacteria. How well I remember that moment when Robert Koch showed me, for the first time, such a brown-stained preparation, with tiny but clearly visible blue-staining rods. However, the brilliant research talent of Robert Koch was soon to be illuminated in even greater degree. After he had used his new technique to demonstrate the presence of the characteristic rods in all possible tuberculous tissues and fluids, he considered it necessary to repeat the whole experiment with freshly prepared dyes. But when he examined his new preparations, which had been stained for 24 hours in fresh methylene blue solution and counterstained with vesuvin, he sought in vain under the microscope for the blue-staining rods. However, using the same samples he could easily demonstrate the presence of the rods using the dye that had been prepared earlier. Therefore, something must have happened to the old dye solution that made it suitable for staining the tubercle bacillus. What? Koch concluded that the dye solution must have absorbed from the air something that made it suitable for the staining technique. One of the most common constituents in the air of a laboratory is ammonia, and Koch quickly concluded that the methylene blue solution had absorbed small amounts of ammonia from the air during its long stay in the laboratory. He then added a small amount of ammonia to his freshly prepared methylene blue solution and found that it now worked satisfactorily for staining the tubercle bacillus. Since ammonia is a strong alkali, the methylene blue solution could be made effective by adding any alkali, such as sodium hydroxide or potassium hydroxide. Through extensive and thorough experiments, Koch determined the optimum concentration of alkali and the proper staining procedure. Koch mentioned nothing about this in his first lecture, nor in the paper that was published soon after. It was Paul Ehrlich, in a paper given at a meeting of *Verin für innere Medizin* in Berlin on 1 May 1882, who improved Koch's staining procedure by using aniline instead of ammonia, and fuchsin instead of methylene blue.

Koch's (1882) paper on the etiology of tuberculosis:

The etiology of tuberculosis

The discovery of Villemin that tuberculosis can be transmitted to animals has been confirmed a number of times, but has also been opposed on seemingly good grounds, so that up until recently it has not been possible to state for certain whether tuberculosis is an infectious disease or not. Since then, Cohnheim and Salomonsen, and later Baumgarten, have achieved success by inoculation in the anterior chamber of the eye, and Tappeiner has been successful with inhalation. These studies have shown without a doubt that tuberculosis must be counted amongst the infectious diseases of mankind.

If the importance of a disease for mankind is measured from the number of fatalities which are due to it, then tuberculosis must be considered much more important than those most feared infectious diseases, plague, cholera, and the like. Statistics have shown that 1/7 of all humans die of tuberculosis. ...

The nature of tuberculosis has been studied by many, but has led to no successful results. The staining methods which have been so useful in the demonstration of pathogenic microorganisms have been unsuccessful here. In addition, the experiments which have been devised for the isolation and culture of the tubercle virus [the word "virus" is used here to mean "infective agent"] have also failed, so that Cohnheim has had to state in the newest edition of his lectures on general pathology, that "the direct demonstration of the tubercle virus is still an unsolved problem."

In my own studies on tuberculosis I began by using the known methods, without success. But several casual observations have induced me to forego these methods and to strike out in a new direction, which has finally led me to positive results.

The goal of the study must first be the demonstration of a foreign parasitic structure in the body which can possibly be indicted as the causal agent. This proof was possible through a certain staining procedure which has allowed the discovery of characteristic, although previously undescribed bacteria, in organs which have been altered by tuberculosis. ...

The material for study was prepared in the usual manner for the study of

pathogenic bacteria. It was either spread out on cover slips, dried, and heated, or cut into pieces after dehydration with alcohol. The cover slips or pieces were placed in a dye solution which contained 200 cc. distilled water with 1 cc. of a concentrated alcoholic solution of methylene blue. They were shaken and then 0.2 cc. of 10% potassium hydroxide added. This mixture should not give a precipitate after standing for days. The material to be stained should remain in this solution for 20-24 hours. By heating this solution at 40 C. in a water bath, this time can be shortened to 1/2 to 1 hour. The cover slips are then immersed in a freshly filtered aqueous solution of vesuvin for 1-2 minutes, and then rinsed in distilled water. When the cover slips are removed from the methylene blue, the adhering film is dark-blue and strongly overstained, but the treatment with vesuvin removes the blue color and the films seem light brown in color. Under the microscope the structures of the animal tissues, such as the nucleus and its breakdown products, are brown, while the tubercle bacteria are a beautiful blue. Indeed, all other types of bacteria except the bacterium of leprosy assume a brown color. The color contrast between the brown colored tissues and the blue tubercle bacteria is so striking, that the latter, although often present in very small numbers, are quite easy to find and to recognize.

The tissue slices are handled differently. They are removed from the methylene blue solution and placed in the filtered vesuvin solution for 15-20 minutes and then rinsed in distilled water until the blue color has disappeared and a more or less strong brown tint remains. After this, they can be dehydrated with alcohol, cleared in clove oil and can be immediately examined under the microscope in this fluid or first placed in Canada balsam. In these preparations the tissue components are brown, and the tubercle bacteria are a most distinct brown.

Further, the bacteria are not stained exclusively with methylene blue, but can take up other aniline dyes with the exception of brown dyes, when they are treated at the same time with alkali. However, the staining is not so clear as with methylene blue. Further, it can be shown that the potassium hydroxide solution can be replaced with sodium or ammonium hydroxide, which shows that it is not the potassium which is especially important, but the strongly alkaline properties of the solution which are necessary. ...

The bacteria visualized by this technique show many distinct characteristics. They are rod-shaped and belong therefore to the group of Bacilli. They are very thin and are only one-fourth to one-half as long as the diameter of a red blood cell, but can occasionally reach a length as long as the diameter of a red cell. They possess a form and size which is surprisingly like that of the leprosy bacillus. ... In all locations where the tuberculosis process has recently developed and is progressing most rapidly, these bacilli can be found in large numbers. They ordinarily form small groups of cells which are pressed together and arranged in bundles, and frequently are lying within tissue cells. They present in places a picture similar to that in tissue which contains leprosy bacilli. Many times the bacteria occur in large numbers outside of cells as well. Especially at the edges of large, cheesy masses, the bacilli occur almost exclusively in large numbers free of the tissue cells.

As soon as the peak of the tubercle eruption has passed, the bacilli become rarer, but occur still in small groups or singly at the edge of the tubercle mass, with many lightly stained and almost invisible bacilli, which are probably in the process of dying or are already dead. Finally they can disappear completely, but this complete disappearance occurs only rarely, and then only in such sites where the tuberculosis process has stopped completely. ...

Because of the quite regular occurrence of the tubercle bacilli, it must seem surprising that they have never been seen before. This can be explained, however, by the fact that the bacilli are extremely small structures, and are generally in such small numbers, that they would elude the most attentive observer without the use of a special staining reaction. Even when they are present in large numbers, they are generally mixed with finely granular detritus in such a way that they are completely hidden, so that even here their discovery would be extremely difficult. ...

On the basis of my extensive observations, I consider it as proven that in all tuberculous conditions of man and animals there exists a characteristic bacterium which I have designated as the tubercle bacillus, which has specific properties which allow it to be distinguished from all other microorganisms. From this correlation between the presence of tuberculous conditions and bacilli, it does not necessarily follow that these phenomena are causally related, However, a high degree of probability for this causal relationship might

be inferred from the observation that the bacilli are generally most frequent when the tuberculous process is developing or progressing, and that they disappear when the disease becomes quiescent.

In order to prove that tuberculosis is brought about through the penetration of the bacilli, and is a definite parasitic disease brought about by the growth and reproduction of these same bacilli, the bacilli must be isolated from the body, and cultured so long in pure culture, that they are freed from any diseased production of the animal organism which may still be adhering to the bacilli. After this, the isolated bacilli must bring about the transfer of the disease to other animals, and cause the same disease picture which can be brought about through the inoculation of healthy animals with naturally developing tubercle materials.

The many preliminary experiments which helped to solve this problem will be passed over, and only the final method will be described. The principle of this method is based on the use of a solid, transparent medium, which can remain solid even at incubator temperature. The advantage of a solid medium for bacteriological research in the production of pure cultures has been discussed by me in an earlier paper. This same procedure has led to the solution of the difficult problem of the pure culture of the tubercle bacillus and is further proof of the value of this method.

Serum from cow or sheep blood, which is obtained as pure as possible, is placed in cotton-plugged test tubes and heated every day for six days, one hour per day at 58 C. Through this procedure it has been possible in most cases to completely sterilize the serum. This serum is then heated for a number of hours at 65 C., until it has solidified completely. The serum appears after this treatment as an amber-yellow, perfectly transparent or lightly opalescent, solid gelatinous mass. When this is placed for a number of days in the incubator, no bacterial colonies develop. ... In order to obtain a large surface for the culture, the serum is allowed to harden while the test tubes are in a slanted position. ...

On this solidified blood serum, the tuberculous materials are placed in the following manner.

The simplest way, and one which is almost always successful, is by the use of an animal which has just died of tuberculosis, or by the use of an animal

suffering from tuberculosis which is killed for this purpose. First the skin of the breast and abdomen is laid to the side with a flamed instrument. Then the ribs are cut in the middle with a flamed scissors and forceps, and a portion of the ribs are removed without at the same time opening the abdominal cavity. The lungs are then to a great extent uncovered. The instruments used here are now discarded and freshly sterilized ones taken up. Single tubercles or particles about the size of a millet seed are quickly cut out of the lung tissue and immediately carried over to the surface of solidified serum in a test tube, with the use of a flamed platinum wire. Naturally the cotton plug should only be exposed to the air for the shortest possible time. In this way, a number of test tubes, perhaps 5-10, are inoculated with tuberculous material. Such a large number are prepared because even with the most careful manipulations, not all test tubes can remain free of accidental contamination. ...

These test tubes are now placed in an incubator and are kept there for a long time at 37-38 C. In the first week, no noticeable changes take place. Indeed, if bacteria develop in the first days, either around the inoculum or away from it, these usually white, gray, or yellowish droplets, which often bring about the liquefaction of the serum, are due to contamination, and the experiment is a failure.

The growth of the tubercle bacilli can first be seen by the naked eye in the second week after seeding, ordinarily after the 10th day. They appear as very small dots, dry and scalelike. This growth arises from the material inoculated, and if the tubercle has been spread around extensively on the surface, then a large amount of growth ensues, while if the tubercles have remained in small patches, then the bacterial growth is less extensive. If there are only very few bacilli in the inoculum, then it is hardly possible to free the bacilli from the tissue and have them growing directly on the nutrient medium. ... With the help of low magnification, 30-40 power, the colonies of the bacilli can already be seen at the end of the first week. ...

The growth of the culture ceases after several weeks, and a further increase probably does not occur because the bacilli have lost their own power of movement, and only spread because of the slow reproduction of the bacilli, being pushed forward on the surface, and because of the slow growth of the bacilli, this spread can only occur to a small extent. In order to keep such a

culture going, it must be brought onto a new medium 10-14 days after the first inoculation. This is done by removing several of the small scales with a flamed platinum wire, and transferring them to a fresh, sterilized serum slant, where the scales are broken up and spread out as much as possible. Further scaly, dry masses then develop which coalesce and cover more or less of the surface of the serum, depending upon the extent of the seeding. In this way the culture can be continued.

The tubercle bacilli can also be cultured on other nutrient substrates, if the latter possess similar properties to the solidified serum. They are able to grow on a solidified gel which remains solid at incubator temperature, prepared by adding agar-agar to a meat infusion or peptone medium. However, on this medium the bacilli form only irregular small crumbs, which are not nearly so characteristic as the growths on blood serum.

Originally I cultivated the tubercle bacilli only from lung tubercles of guinea pigs which had been infected with tubercular material. Therefore the cultures from various sources had first to pass through the intervening stage of the guinea pig before they were obtained in pure cultures. In this way there was a possibility for error, in the same way as in the transfer of a culture from one test tube to another. This might occur through the accidental inoculation of other bacteria into the animal, or through the appearance in the guinea pig of spontaneous tuberculosis. In order to avoid such errors, special precautions are necessary, which can be deduced from observations on the behavior of this spontaneous tuberculosis.

From hundreds of guinea pigs that have been purchased and have occasionally been dissected and examined, I have never found a single case of tuberculosis. Spontaneous tuberculosis develops only occasionally and never before a time of three or four months after the other animals in the room have been infected with tuberculosis. In animals which have become sick from spontaneous tuberculosis, the bronchial glands become quite swollen and full of pus, and in most cases the lungs show a large, cheesy mass with extensive decomposition in the center, so that it occasionally resembles the similar processes in the human lung. ... Animals that have been inoculated with tuberculosis show a completely different picture. The place of inoculation of the animals is in the abdomen, close to the inguinal gland. This first becomes

swollen and gives an early and unmistakable indication that the inoculation has been a success. Since a larger amount of infectious material is present at the beginning, the infection progresses much faster than the spontaneous infection, and in tissue sections of these animals, the spleen and liver show more extensive changes from the tuberculosis than the lungs. Therefore it is not at all difficult to differentiate the artificially induced tuberculosis from the spontaneous tuberculosis in experimental animals. From a consideration of these facts, it can be concluded that the development of tuberculosis in an experimental animal is due to the action of inoculated material, when a number of guinea pigs are purchased and inoculated at the same time in the same way with the same material, and kept separated from other animals in their own cage, and when they show the development of the characteristic tuberculosis symptoms of inoculated animals in a short period of time.

In this way, a substance can be tested for its virulence by inoculating four to six guinea pigs with it, after making use of all precautions, such as previously disinfecting the site of inoculation, using sterile instruments, etc. The results are uniformly the same. In all animals which are inoculated with fresh masses containing tubercle bacilli, the small inoculation site has almost always coalesced on the next day, then remains unaltered for about eight days, then forms a little nodule which may enlarge without breaking open, although it most often changes into a flat, dry abscess. After about two weeks, the inguinal glands and axillary glands on the side where the inoculation has occurred enlarge until they are the size of peas. From then on the animals become progressively weaker and die after four to six weeks, or are killed in order to exclude the later development of spontaneous tuberculosis. In the organs of all of these animals, and most especially in the spleen and liver, the recognizable changes due to tuberculosis occur. That these changes in the guinea pigs are only due to the inoculation of material containing the tubercle bacilli, can be seen from experiments in which inoculation was performed with scrofulous glands or fungus masses from joints, in which no tubercle bacilli could be found. In these cases, not a single animal became sick, while in the animals inoculated with bacilli-containing material, the inoculated animals always showed an extensive infection with tuberculosis after four weeks.

Cultures of tubercle bacilli were prepared from guinea pigs which had

been inoculated with tubercles from the lungs of apes, with material from the brain and lungs of humans that had died of miliary tuberculosis [an acute, systemic form of the disease], with cheesy masses from phthisistic lungs, and with nodules from lungs and from the peritoneum of cows affected with bovine tuberculosis. In all these cases, the disease processes occurred in exactly the same way, and the cultures of bacilli obtained from these could not be differentiated in the slightest way. In all, 15 pure cultures were made of tubercle bacilli, four from guinea pigs infected with ape tuberculosis, four with bovine tuberculosis, and seven with human tuberculosis.

In order to answer the objection that the nature of the bacilli was changed through the preliminary inoculation into guinea pigs, so that they became more similar, experiments were set up to cultivate tubercle bacilli directly from spontaneous cases in man and animals.

This was successful a number of times, and pure cultures have been obtained from the lungs of two people with miliary tuberculosis, as well as one with cheesy pneumonia, twice from the contents of small cavities in phthisistic lungs, once from cheeselike mesenteric glands, twice from freshly removed scrofulous glands, twice from lungs of cows with bovine tuberculosis, and three times from the lungs of guinea pigs that had suffered spontaneous tuberculosis. All of these cultures were quite similar and also resembled those that had been isolated through the preliminary guinea pig inoculation, so that the identity of the bacilli occurring in the various tuberculous processes cannot be doubted. ...

Up until now my studies have shown that a characteristic bacillus is always associated with tuberculosis, and that these bacilli can be obtained from tuberculous organs and isolated in pure culture. It now remained to prove the most important question, namely, that the isolated bacilli were able to bring about the typical tuberculosis disease process when inoculated again into animals. ...

The results of a number of inoculation experiments with bacillus cultures inoculated into a large number of animals, and inoculated in different ways, all have led to the same results. Simple injections subcutaneously, or into the peritoneal cavity, or into the anterior chamber of the eye, or directly into the blood stream, have all produced tuberculosis with only one exception.

Further, the infection was not limited to only isolated nodules, but depending upon the size of the inoculum, large numbers of tubercles were produced. ...

A confusion with spontaneous tuberculosis, or an accidental infection with tubercle virus in the experimental animals, is excluded for the following reasons: (1) Spontaneous tuberculosis or accidental infection cannot develop in so short a time into the extensive eruption of tubercles experienced here. (2) The control animals, which were handled in exactly the same way as the inoculated animals, remained healthy. (3) The typical picture of miliary tuberculosis does not occur when guinea pigs or rabbits are injected with other substances. ...

All of these facts taken together lead to the conclusion that the bacilli which are present in the tuberculous substances not only accompany the tuberculosis process, but are the cause of it. In the bacillus we have, therefore, the actual tubercle virus.

Koch's (1884) paper on the Koch postulates as applied to tuberculosis and anthrax:

The etiology of tuberculosis [Koch's Postulates]

It was first necessary to determine if characteristic elements occurred in the diseased parts of the body, which do not belong to the constituents of the body, and which have not arisen from body constituents. When such foreign structures have been demonstrated, it is further necessary to ascertain if these are organized and if they show any of the characteristics of independent organisms, such as motility, growth, reproduction, and fructification. It is further necessary to determine the relationships of these structures to their surroundings, the behavior of the neighboring tissue substances, the distribution of the foreign substances in the body, their appearance in the various stages of the disease, and such similar circumstances, which would allow one to conclude with greater or lesser probability that there is a causal relationship between these structures and disease. The facts obtained in this study may possibly be sufficient proof of the causal relationship, that only the most skeptical can raise the objection that the discovered microorganism is not the cause but only an accompaniment of the disease. However, many times this objection has a certain validity, and then it is necessary to obtain a perfect proof to satisfy oneself that the parasite and the disease are not only correlated, but actually causally related, and that the parasite is the actual direct cause of the disease, This can only be done by completely separating the parasite from the diseased organism, and from all of the products of the disease which could be subscribed to a disease-inducing influence, and then introducing the isolated parasite into healthy organisms and induce the disease anew with all its characteristic symptoms and properties. An example will clarify the above statements. If the blood of an animal dying of anthrax is examined, one finds in it a large number of regular, rod-shaped, colorless, immotile structures. It is not directly evident that these rods are plant-like, since in fact they were first taken by many to be nonliving, crystalline structures. Only when it was possible to watch these structures grow, form spores, and then form new rods from the spores, could it be concluded with certainty that they were living and belonged to the class of lower plants. Further, if the

rod-containing blood of an animal which had died of anthrax was inoculated in an extremely minute quantity into another animal, this second animal always died of anthrax and its blood contained the characteristic rods, the so-called anthrax bacilli. However, this has not proved that through the inoculation of the rods, the disease was transmitted, because not only the rods were inoculated, but also the other formed and unformed elements of the blood. In order to decide whether it is the bacilli or some other substance of the anthrax blood which causes anthrax, the bacilli must be isolated from the blood and inoculated by themselves. The most certain way of isolating the bacilli is through continued pure culture. For this purpose, a small amount of blood containing bacilli is placed on a solid medium on which the bacilli are able to grow, such as nutrient gelatin, or boiled potato. On these they begin to reproduce quickly and soon are present in large numbers, while the other substances of the blood, the red and white cells and the blood serum, remain unchanged. After two or three days when the bacilli have formed a dense mass of sporulating filaments, a very small amount of this white mass is taken and streaked again on nutrient gelatin or boiled potato. The bacilli reproduce again in the same way as before and form again a dense white covering on the potato, and already in this second culture there are no traces under the microscope of the other elements of the blood. In the same way the culture is transferred a number of times. After the third or fourth transfer, one can consider the bacilli to be completely free from the original blood substances that were inoculated with them. Now if the culture is transferred twenty or fifty times, then it can be assumed with complete certainty that the bacilli no longer are associated with even the slightest amount of disease products from the body. They cannot even have captured these products within their own cells, since the original seeded bacteria are long since gone and the many generations of offspring have taken their nutrients for the production of their necessary substances from the potato itself. The anthrax bacilli in pure culture in this way have therefore no relationships with the first organisms that came out of the blood, or with the disease products which belong to the metabolism of the animal. In spite of this, they are able to induce fatal anthrax as soon as they are inoculated into a healthy animal. The inoculated animal dies just as fast, and with the same symptoms, as one

inoculated with fresh anthrax blood, or one which succumbs to spontaneous anthrax. Also, in its blood appear the characteristic anthrax bacilli in countless numbers. From these facts no other conclusion can be drawn than that the anthrax bacilli are the actual cause of this disease, and not merely an attendant phenomenon or symptom. ... These conclusions are so certain, that no one will dispute them, and the anthrax bacillus will be looked upon by the scientific world as the causal agent of ordinary, typical anthrax infection in both our domestic animals and in man himself.

The process outlined above, which has been successful in proving the parasitic nature of anthrax, and which has led to inescapable conclusions, has been used as the basis for my studies on the etiology of tuberculosis. These studies first concerned themselves with the demonstration of the pathogenic organism, then with its isolation, and finally with its reinoculation.

Koch's (1895) paper on water filtration and cholera:

By all investigators of cholera whose judgment was not disturbed by fantastic dreams about telluric-cosmic influences, or bound by obstinate adherence to theories refuted long ago, more or less great importance has from of old been attached to water as a bearer of the contagious substance of cholera. Only as to the greatness of the influence of water did opinions differ. Some, misled by isolated observations of a specially surprising nature, have gone decidedly too far in this direction, and declared water to be the exclusive bearer of the germ of cholera. To these the designation "Water-Fanatic" or "Water-Theorist," which has been much used of late, may not quite unjustly be applied. That I do not belong to this class of cholera investigators will be admitted at once by everyone who knows what I have said and written about cholera. I have always said that, according to the experience hitherto gained, direct transmission from person to person is possible but to all appearance not very frequent, that, on the other hand, indirect transmissions by many bearers of the germ of cholera play the principal part in the real epidemics and mass-outbreaks of that disease, and that among these bearers water is one of the most important. I have further endeavoured to show by examples that, under certain conditions, water has really played the part ascribed to it. Beyond that, however, I have never, so far as I know, expressed an opinion as to the extent to which this factor is to be regarded as effective. Nor has it been possible hitherto to arrive at a definite judgment on this subject, because investigations of the relations of cholera to water have almost always been undertaken from a one-sided point of view and are therefore generally open to objection. Why, under such circumstances, attempts have been made to stamp me of all people as a "Drinking-Water-Fanatic," I do not clearly understand. It seems almost as if the purpose were to attribute to me by hook or by crook opinions which it is easy to refute.

In the last epidemic indeed, as, I suppose, nobody will seriously dispute, water played a very important part. Nevertheless we cannot yet know even now whether that will be the case in future too, and it is certainly wiser not to pronounce a definitive opinion on the importance of water till we have gathered sufficient experience. Last year, however, has at any rate shown

once more that we have every reason to devote the greatest attention to water-supply.

The cholera epidemic in Hamburg, Altona, and Wandsbeck was extremely instructive in this respect. These three places, which immediately border on one another, and, strictly speaking, form only one single city, do not essentially differ from one another except in the one respect that they are differently supplied with water. Wandsbeck receives filtered water from a lake scarcely exposed at all to pollution with feces, Hamburg takes its water in an unfiltered state from the Elbe at a point above the city, while Altona gets its supply in a filtered state from the Elbe below the city. Hamburg, as is well known, suffered terribly from cholera, whereas Wandsbeck and Altona, if the cases introduced from Hamburg be deducted, hardly suffered at all. The most surprising phenomena of the epidemic came to light on the frontier of Hamburg and Altona. On both sides of the frontier the state of the soil, the buildings, the sewerage, the population, in short all the conditions that are of importance in this connection, are perfectly similar, and yet the cholera in Hamburg spread only to the frontier of Altona, and stopped there. In one street, which forms the frontier for a considerable distance, the Hamburg side was attacked by cholera, while the Altona side remained free of it. In one group of houses, the Hamburger Platz, the cholera even did more than a man could have done with the best maps of the frontier between Hamburg and Altona at his disposal. It found out with sharp precision not the political frontier but the frontier of the water-supplies of the two cities. The said group of houses, densely peopled by workmen's families, belongs to Hamburg, but is supplied with water by Altona, and it remained absolutely free of cholera, whereas numerous cases and deaths occurred in the Hamburg houses all round. Here then we have to do with a kind of experiment, which performed itself on more than a hundred thousand human beings, but which, despite its vast dimensions, fulfilled all the conditions one requires of an exact and absolutely conclusive laboratory experiment. In two large groups of population all the factors are the same except one, namely, the water supply. The group supplied with unfiltered Elbe water suffers severely from cholera, that supplied with filtered water very slightly. This fact gains in significance when we consider that the Hamburg water is taken from a place where the

Elbe is still comparatively little polluted, whereas Altona has to use the Elbe water after it has received all the fluid refuse, including the feces, of nearly 800,000 people. Under such circumstances there is at first sight for all who are accustomed to reflect on the facts of natural science no other explanation whatever than that the difference which the two groups of population show as regards cholera is due to the difference of the water-supply, and that Altona was protected against cholera by the filtration of the Elbe water. It is impossible simply to deny this fact, and all that remains is to try to bring it into harmony with one's views of the nature of cholera. As we have to do in this case with an epidemiological fact of the first rank which lies before us in perfect clearness and transparency, which also, owing to its easy accessibility, can be further tested and supplemented in all directions as regards the correctness of the observations on which it is based, and is therefore in this respect simply unique of its kind, one has a right to demand that every investigator of cholera who claims consideration for his opinion shall tell us what he makes of it.

For the bacteriologist nothing is easier than to give an explanation of the restriction of the cholera to the sphere of the Hamburg water-supply. He need only point out that cholera bacteria got into the Hamburg water either from the outlets of the Hamburg sewers, or, which is much more likely, from the excreta of cholera patients on board the numerous Elbe barges anchoring off the place where the water is taken from the river, and that, after this had happened, cases of cholera, more or less numerous according to the degree of pollution, could not but occur among the people who used that water. The town of Wandsbeck was spared, because its water was not exposed to such pollution, and was also filtered. Altona received water which was originally much worse than that of Hamburg, but which was wholly or almost wholly freed of cholera bacteria by careful filtration. This view is in perfect harmony with all bacteriological experience, and with our present knowledge of infectious substances; it contains no contradictions and nothing forced or artificial.

How people would derive the phenomena of the Hamburg-Altona cholera epidemic from cosmic-telluric or from purely meteorological factors, I am at a loss to imagine; for sky, sun, wind, rain, etc., were distributed with absolute

equality on both sides of the frontier. I hardly believe that the adherents of the cosmic-telluric theory will even attempt to find an explanation.

...

The Hamburg-Altona cholera epidemic, then, irrefutably proved that the filtration of water through sand, in the manner in which it is effected in Altona, affords a practically sufficient protection against cholera contagion. I expressly emphasize the fact that, if filtration is to afford protection, it must be managed as in Altona. I have inspected a considerable number of waterworks with filtering apparatus, and know that but few of them fulfill the prescriptions now valid as regards filtration so strictly as is done in Altona, and I have every reason to believe that cholera would not everywhere have been warded off so successfully as there.

Koch's (1895) paper on the carrier state for cholera:

... it is now certain that among a number of persons who have been exposed to cholera infection, the resultant cases may show the whole scale from the severest and rapidly fatal cases down to the mildest imaginable, demonstrable only by bacteriological investigation. I regard this experience as one of the most important additions to our knowledge of Asiatic cholera, both from the practical and from the theoretical point of view.

It is practically important for the following reasons —

If one rests content, as formerly, with rendering only the clinically suspicious and afterwards bacteriologically ascertained cholera cases harmless by isolation and disinfection, one will doubtless succeed in some cases in extinguishing a cholera focus in course of development; but in other cases, especially in densely crowded city populations, and under circumstances so unfavourable as those in Hamburg were, the efforts to destroy all the cholera germs would be [in] vain. And this method is open to the special objection that precisely the mildest cases, which escape investigation, are the most dangerous of all as regards transmission. This can be most simply explained by some examples. On board each of the two cholera-ships in Hamburg harbour two people fell ill with clinical symptoms which could not but lay them open to the suspicion of cholera; of course they were at once isolated. If now, after disinfecting the ships, one had left the rest of the crews, who seemed to be quite well, unmolested, eight persons whose feces contained cholera bacteria would have had an opportunity of carrying the infectious matter once more from place to place in the environs of Hamburg harbour. Suppose that the crews had not been foreigners but natives, had gone after passing muster to their respective homes, had given rise perhaps at first to the development of mild cases there which escaped recognition, while they themselves had never been ill of cholera from the clinical point of view, the cholera might have been carried in this manner to a considerable distance, and subsequent investigations need not have detected the slightest evidence of its origin. The following circumstances, which occurred in a beggars' inn in Hamburg, seem to me specially noteworthy in this respect. A diarrhea patient from this inn, which had had eight cholera cases during the great epidemic, four of them

fatal, was bacteriologically examined on suspicion of cholera on the 26th of December, and found to be really suffering from that disease. In consequence of this discovery as many of the inmates of the inn as could be laid hold of were also examined, and among them was found a man who had no clinical symptoms justifying suspicion of cholera, but who had cholera bacteria in his feces. When I visited the same inn some days later, it was full of people, by far the greater part of whom had no occupation, some of whom, as they said, had ceased to expect to find occupation, and were on the point of leaving Hamburg again. They were from the most various parts of Germany; natives of the Prussian province of Saxony and of the Kingdom of Saxony were specially numerous among them. One can easily imagine how cholera can be carried by such people from one place to another, and how its traces may not rarely escape the most careful investigation. Had not the cholera been so energetically pursued in Hamburg into its most secret hiding places, and every trace of infectious matter that could be found rendered innocuous, I am convinced that it would have proved impossible to get the upper hand of the kindling matter that had been spread so copiously over the city. In this manner, however, the single sparks were quenched before they could kindle new conflagrations. Every spark of course could not be discovered at once, and the several chains ran on in secret; but they became rarer and rarer, and had also to cease to glow at last. I believe the case which was ascertained on the 27th of May, after an interval of four months, to have been an offshoot of such a chain. It completely justifies the continued caution observed in Hamburg, and thoroughness in the bacteriological investigation of suspicious cases of illness even after the apparent close of an epidemic.

In the theoretic province the demonstration of the mildest cholera cases can be turned to account in two directions.

In the first place, we now know that a not inconsiderable number, nay, if we take the case of the two ships as typical, the majority of persons infected by cholera, show so insignificant symptoms of disease that, under ordinary circumstances, that is, without bacteriological investigation, they would certainly be regarded as in good health. This disposes at once of all the difficulties which have hitherto been found in the fact that human intercourse can propagate cholera, even when only healthy persons are in question. It re-

ally not rarely happens that no notoriously sick people, or inanimate articles, such as linen etc., laden with infectious matter, have come, or at least can be proved to have come, to the infected place. Such cases have been interpreted as indicating that, if cholera can be carried without cholera patients or their feces, a cholera patient is no more fitted to propagate pestilence than any other fraction of human intercourse, and such interpreters have then quite consistently gone the length of declaring cholera patients and their feces comparatively harmless. How overhasty this interpretation of the transmission of cholera by apparently healthy persons is, is now obvious. Whoever maintains that cholera has come to a place without cholera infected persons or their feces having anything to do with it, must now prove that there were no cholera cases of the mildest type among the apparently healthy people who came to the place, and that no articles soiled with cholera feces were brought to it.

Chapter 20

Joseph Lister

On The Antiseptic Principle In The Practice Of Surgery

A paper read before the British Medical Association in Dublin on August 9, 1867; appearing in *The British Medical Journal*, September 21, 1867

In the course of an extended investigation into the nature of inflammation, and the healthy and morbid conditions of the blood in relation to it, I arrived several years ago at the conclusion that the essential cause of suppuration [pus formation] in wounds is decomposition brought about by the influence of the atmosphere upon blood or serum retained within them, and, in the case of contused wounds, upon portions of tissue destroyed by the violence of the injury.

To prevent the occurrence of suppuration with all its attendant risks was an object manifestly desirable, but till lately apparently unattainable, since it seemed hopeless to attempt to exclude the oxygen which was universally regarded as the agent by which putrefaction was effected. *But when it had been shown by the researches of Pasteur that the septic properties of the atmosphere depended not on the oxygen, or any gaseous constituent, but on minute organisms suspended in it, which owed their energy to their vitality, it occurred to me that decomposition in the injured part might be avoided without excluding the air, by applying as a dressing some material capable of destroying the life of the floating particles. Upon this principle I have based a practice of which I will now attempt to give a short account.* (italics added)

The material which I have employed is carbolic or phenic acid, a volatile

organic compound, which appears to exercise a peculiarly destructive influence upon low forms of life, and hence is the most powerful antiseptic with which we are at present acquainted.

The first class of cases to which I applied it was that of compound fractures, in which the effects of decomposition in the injured part were especially striking and pernicious. The results have been such as to establish conclusively the great principle that all local inflammatory mischief and general febrile disturbances which follow severe injuries are due to the irritating and poisonous influence of decomposing blood or sloughs. For these evils are entirely avoided by the antiseptic treatment, so that limbs which would otherwise be unhesitatingly condemned to amputation may be retained, with confidence of the best results.

In conducting the treatment, the first object must be the destruction of any septic germs which may have been introduced into the wounds, either at the moment of the accident or during the time which has since elapsed. This is done by introducing the acid of full strength into all accessible recesses of the wound by means of a piece of rag held in dressing forceps and dipped into the liquid. This I did not venture to do in the earlier cases; but experience has shown that the compound which carbolic acid forms with the blood, and also any portions of tissue killed by its caustic action, including even parts of the bone, are disposed of by absorption and organisation, provided they are afterwards kept from decomposing. We are thus enabled to employ the antiseptic treatment efficiently at a period after the occurrence of the injury at which it would otherwise probably fail. Thus I have now under my care, in Glasgow Infirmary, a boy who was admitted with compound fracture of the leg as late as eight and one-half hours after the accident, in whom, nevertheless, all local and constitutional disturbance was avoided by means of carbolic acid, and the bones were soundly united five weeks after his admission.

The next object to be kept in view is to guard effectually against the spreading of decomposition into the wound along the stream of blood and serum which oozes out during the first few days after the accident, when the acid originally applied has been washed out or dissipated by absorption and evaporation.

...

The next class of cases to which I have applied the antiseptic treatment is that of abscesses. Here also the results have been extremely satisfactory, and in beautiful harmony with the pathological principles indicated above. The pyogenic [pus producing] membrane, like the granulations of a sore, which it resembles in nature, forms pus, not from any inherent disposition to do so, but only because it is subjected to some preternatural [beyond normal] stimulation. In an ordinary abscess, whether acute or chronic, before it is opened the stimulus which maintains the suppuration is derived from the presence of pus pent up within the cavity. When a free opening is made in the ordinary way, this stimulus is got rid of, but the atmosphere gaining access to the contents, the potent stimulus of decomposition comes into operation, and pus is generated in greater abundance than before. But when the evacuation is effected on the antiseptic principle, the pyogenic membrane, freed from the influence of the former stimulus without the substitution of a new one, ceases to suppurate (like the granulations of a sore under metallic dressing), furnishing merely a trifling amount of clear serum, and, whether the opening be dependent or not, rapidly contracts and coalesces. At the same time any constitutional symptoms previously occasioned by the accumulation of the matter are got rid of without the slightest risk of the irritative fever or hectic hitherto so justly dreaded in dealing with large abscesses.

In order that the treatment may be satisfactory, the abscess must be seen before it is opened. Then, except in very rare and peculiar cases, there are no septic organisms in the contents, so that it is needless to introduce carbolic acid into the interior. Indeed, such a procedure would be objectionable, as it would stimulate the pyogenic membrane to unnecessary suppuration. All that is requisite is to guard against the introduction of living atmospheric germs from without, at the same time that free opportunity is afforded for the escape of the discharge from within.

I have so lately given elsewhere a detailed account of the method by which this is effected that I shall not enter into it at present further than to say that the means employed are the same as those described above for the superficial dressing of compound fractures; viz., a piece of rag dipped into the solution of carbolic acid in oil to serve as an antiseptic curtain, under cover of which

the abscess is evacuated by free incision, and the antiseptic paste to guard against decomposition occurring in the stream of pus that flows out beneath it; the dressing being changed daily until the sinus is closed.

...

There is, however, one point more that I cannot but advert to, viz., the influence of this mode of treatment upon the general healthiness of an [sic] hospital. Previously to its introduction the two large wards in which most of my cases of accident and of operation are treated were among the unhealthiest in the whole surgical division of the Glasgow Royal Infirmary, in consequence apparently of those wards being unfavorably placed with reference to the supply of fresh air; and I have felt ashamed when recording the results of my practice, to have so often to allude to hospital gangrene or pyaemia. It was interesting, though melancholy, to observe that whenever all or nearly all the beds contained cases with open sores, these grievous complications were pretty sure to show themselves; so that I came to welcome simple fractures, though in themselves of little interest either for myself or the students, because their presence diminished the proportion of open sores among the patients. But since the antiseptic treatment has been brought into full operation, and wounds and abscesses no longer poison the atmosphere with putrid exhalations, my wards, though in other respects under precisely the same circumstances as before, have completely changed their character; so that during the last nine months not a single instance of pyaemia, hospital gangrene, or erysipelas has occurred in them.

As there appears to be no doubt regarding the cause of this change, the importance of the fact can hardly be exaggerated.

On the Effects of the Antiseptic System of Treatment upon the Salubrity of a Surgical Hospital

BY JOSEPH LISTER, F.R.S.

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London, *Lancet*, 1870

The antiseptic system of treatment has now been in operation sufficiently long to enable us to form a fair estimate of its influence upon the salubrity of an [sic] hospital.

Its effects upon the wards lately under my care in the Glasgow Royal Infirmary were in the highest degree beneficial, converting them from some of the most unhealthy in the kingdom into models of healthiness. The interests of the public demand that this striking change should be made generally known; and in order to do justice to the subject, it is necessary, in the first place, to allude shortly to the position and circumstances of the wards.

Each of the four surgeons of the infirmary had charge of three large wards, two male and one female, besides several small ones for special cases. Of these, the most important were the male accident ward and that for female patients, the former containing the chief operation cases as well as those of injury. The third main ward of each surgeon was devoted to chronic male cases, and was in the old infirmary building; but the other two were in the "New Surgical Hospital," erected nine years ago. This consists of four stories above a basement, each floor containing two large wards communicating with a central staircase, besides several smaller apartments. The wards are spacious and lofty, and in the centre of each are two open fireplaces, in a column which runs straight up to the roof, conveying the chimneys of all the floors, and also collateral ventilating shafts, which are warmed by the chimneys that accompany them, and, communicating with various apertures in the ceilings, form excellent means of carrying off the vitiated atmosphere, while fresh air is amply supplied by numerous windows at both sides, the beds being placed in the intervals between them, at a considerable distance from each other. Except the serious defect that the waterclosets in many cases open directly into the wards, the system of construction seemed all that could be desired.

But, to the great disappointment of all concerned, this noble structure proved extremely unhealthy. Pyaemia, erysipelas, and hospital gangrene soon showed themselves, affecting, on the average, most severely those parts of the building nearest to the ground, including my male accident ward, which was one of those on the ground-floor; while my female ward was on the floor immediately above. For several years I had the opportunity of making an observation of considerable, though melancholy, interest — viz., that in my accident ward, when all or nearly all the beds contained patients with open sores, the diseases which result from hospital atmosphere were sure to be present in an aggravated form; whereas, when a large proportion of the cases had no external wound, the evils in question were greatly mitigated or entirely absent. This appeared striking evidence that the emanations from foul discharges, as distinguished from the mere congregation of several human beings in the same apartment, constitute the great source of mischief in a surgical hospital. Hence I came to regard simple fractures, though almost destitute of professional interest to myself, and of little value for clinical instruction, as the greatest blessings; because, having no external wound, they diminished the proportion of contaminating cases. At this period I was engaged in a perpetual contest with the managing body, who, anxious to provide hospital accommodation for the increasing population of Glasgow, for which the infirmary was by no means adequate, were disposed to introduce additional beds beyond those contemplated in the original construction. It is, I believe, fairly attributable to the firmness of my resistance in this matter that, though my patients suffered from the evils alluded to in a way that was sickening and often heart-rending, so as to make me sometimes feel it a questionable privilege to be connected with the institution, yet none of my wards ever assumed the frightful condition which sometimes showed itself in other parts of the building, making it necessary to shut them up entirely for a time. A crisis of this kind occurred rather more than two years ago in the other male accident ward on the ground-floor, separated from mine merely by a passage 12 ft. broad; where the mortality became so excessive as to lead, not only to closing the ward, but to an investigation into the cause of the evil, which was presumed to be some foul drain. An excavation made with this view disclosed a state of things which seemed to explain

sufficiently the unhealthiness that had so long remained a mystery. A few inches below the surface of the ground, on a level with the floors of the two lowest male accident wards, with only the basement area, 4 ft. wide, intervening, was found the uppermost tier of a multitude of coffins, which had been placed there at the time of the cholera epidemic of 1849, the corpses having undergone so little change in the interval that the clothes they had on at the time of their hurried burial were plainly distinguishable. The wonder now was, not that these wards upon the ground-floor had been unhealthy, but that they had not been absolutely pestilential. Yet at the very time when this shocking disclosure was being made, I was able to state in an address which I delivered to the meeting of the British Medical Association in Dublin, that during the previous nine months, in which the antiseptic system had been fairly in operation in my wards, not a single case of pyemia, erysipelas, or hospital gangrene had occurred in them; and this, be it remembered, not only in the presence of conditions likely to be pernicious, but at a time when the unhealthiness of other parts of the same building was attracting the serious and anxious attention of the managers. Supposing it justifiable to institute an experiment on such a subject, it would be hardly possible to devise one more conclusive.

Having discovered this monstrous evil, the managers at once did all in their power to correct it. The extent of the corrupting mass was so great that it seemed out of the question to attempt its removal; but it was freely treated with carbolic acid and with quick lime, and an additional thickness of earth was laid over it; and, further, a high wall at right angles with the end of the building, and reaching up to the level of the first floor, so as necessarily to confine the bad air most prejudicially, was pulled down, and an open iron railing was substituted for it.

There can be no doubt that these measures must have proved salutary. But even if it were admitted that they cured completely the particular evil against which they were directed, it would still have to be confessed that the situation of the surgical hospital has been far from satisfactory. Besides having along one of its sides the place of sepulture above alluded to, one end of the building is conterminous with the old Cathedral churchyard, which is of large size and much used, and in which the system of "pit burial" of

paupers has hitherto prevailed. I saw one of the pits some time since, having been requested to report upon it by one of the civic authorities, who is also a manager of the infirmary, and who, having accidentally discovered what was going on, at once took steps to prevent for the future the occurrence of anything so disgraceful. The pit, which was standing open for the reception of the next corpse, emitted a horrid stench on the removal of some loose boards from its mouth. Its walls were formed, on three sides, of coffins piled one upon another in four tiers with the lateral interstices between them filled with human bones, the coffins reaching up to within a few inches of the surface of the ground. This was in a place immediately adjoining the patients' airing ground, and a few yards only from the windows of the surgical wards. And the pit which I inspected seems to have been only one of many similar receptacles, for one of the Glasgow newspapers contains a statement that "the Dean of Guild is said to have computed that five thousand bodies were lying in pits, holding eighty each, in a state of decomposition, around the Infirmary." Just beyond the churchyard rises an eminence covered by an extensive necropolis, which, however, from its greater distance, must have comparatively little deleterious influence. When I add that what is called the fever hospital also a long four-storied building, extends at right angles to the new surgical hospital, separated from it by only eight feet, and that the entire infirmary, containing 584 beds, stands upon an area of two acres, and that the institution is almost always full to overflowing, I have said enough to show that the wards at my disposal have been sufficiently trying for any system of surgical treatment. Yet, during the two years and a quarter that elapsed between the Dublin meeting and the time of my leaving Glasgow for Edinburgh, those wards continued in the main as healthy as they had been during the previous nine months. Adding these two periods together, we have three years of immunity from the ordinary evils of surgical hospitals, under circumstances which, but for the antiseptic system, were especially calculated to produce them.

...

Considering, then, the circumstances of the only two cases of pyaemia which have occurred in my department during the three years of the antiseptic period, I am justified in saying that the wards have been completely freed

from their former liability to this frightful scourge.

...

It remains to speak of hospital gangrene. This was formerly both frequent and severe amongst my patients. It often grievously marred the most promising results of surgery, and sometimes committed fearful ravages. Thus, I have known a boy admitted with a small superficial wound near the elbow, in which hospital gangrene occurring caused such destruction of tissue, deeply as well as superficially, in spite of the most energetic treatment, that it became necessary to amputate the limb. Now and then it led to a fatal result, as in one of the amputations before referred to. In that case I removed the arm at the shoulder-joint for injury in a boy, and for some time all went on well, till I regarded him as perfectly safe; but hospital gangrene came on in the stump, and, advancing insidiously in all directions, defied my best attempts to check it, and had reached beyond the sternum before the poor fellow sank exhausted from its effects.

The contrast under the antiseptic system has been most striking. For the first nine months, as before mentioned, we had not a single case of the disease. Since that time it has shown itself now and then, but in a mild form, invariably yielding to treatment, never occurring in recent cases, but only in old sores weakened by the influence of [a] surrounding cicatrix [scar]. But even this has been very rare, and I do not recollect more than one example of it during the last year. In short, hospital gangrene, like pyaemia and erysipelas, may be said to have been banished by the antiseptic system.

Such being the case, I have insensibly relaxed in different ways my former vigilance regarding the wards. I have allowed cribs for children to be introduced without remonstrance [protest], having practically the effect of increasing the number of beds for adults; and I have, in the pressure of deficient accommodation, often permitted two children to be put in one bed— a thing which I should formerly not have thought of. I used to make a point of having both the large fires in each ward kept alight night and day during the heat of summer, for the sake of making the ventilation as perfect as possible. But during the last season the nurses were left to follow their inclination, and kept only one of the fires lighted. I may add that my wards have remained during the three years without the annual cleaning, which used to be thought

essential. On my asking the superintendent the reason for the omission, he replied that, as those wards had continued healthy, and there was nothing dirty in their appearance, it had seemed unnecessary to disturb them. Thus the wards have been in various respects subjected to greater trial than usual, and yet have remained, as I may repeat without any exaggeration, models of healthiness.

That such should have been the case under the unfavorable hygienic conditions above referred to seems at first sight very surprising. The immediate vicinity of a burying-ground such as has been described, together with the position of the wards at the base of an hospital of four stories, with the air confined by neighboring buildings, may seem conditions utterly inconsistent with health in the patients. That these circumstances were very unfavorable is undoubtedly true; and that they were highly injurious before the antiseptic period seems clearly indicated by our experience. But a little consideration will show that it is not unreasonable to suppose them of secondary importance — as aggravators of the evil, rather than the essential causes of it. The corpses in the places of sepulture beside the infirmary were for the most part covered by at least some inches of earth, which has a most powerful effect in checking the evolution of noxious effluvia; and even the foul gases from the open pits were perpetually diluted by the air with which they mingled, so that but a small proportion of them would enter the wards; and accordingly, when the patients were cleared out for the purpose of the annual cleaning, there was nothing in the wards to offend the nose. But the emanations from sores are poured directly into the confined atmosphere in which the patients are; and anyone familiar with the faint sickly smell commonly perceptible in surgical wards under ordinary treatment, and still more with the stench which prevails at the time of the daily dressing, will readily understand that putrid exhalations from the patients may be a source of mischief, compared with which the other circumstances alluded to may be of comparatively trifling consequence.

With the object of getting rid of this great evil as much as possible, I have used antiseptic means, not only where they are of essential importance for the treatment of the individual case concerned, as in recent wounds and abscesses, but also in superficial sores. For though granulating surfaces will commonly

heal well enough under a putrid dressing (for such the cleanly water dressing becomes within a few hours of its application), every case so treated furnishes its quota to the vitiation of the general atmosphere of the ward. Hence, for the sake of the inmates generally, it is obviously desirable that healing sores should be dressed with some application which, while permitting, or, if possible, favoring, cicatrisation [scar formation], should prevent odor. For this purpose some dressing, unstimulating, but at the same time persistent in antiseptic action, is requisite — a combination which I have sought in various different forms to obtain, and, of late more especially, with very satisfactory results, so that while the healing of superficial sores proceeded with greater rapidity than under water dressing, all my sixty patients might sometimes be dressed without the odor of putrefaction being perceptible in one of them.

The result of this great change has been such as to demonstrate conclusively that the exhalations from foul discharges are the essential source of the insalubrity of surgical wards; and that when this is effectually suppressed, other conditions, which we are accustomed to regard as most pernicious, become powerless to produce serious evil.

It is obvious that the facts recorded in this paper are of extreme importance with reference to the vexed question of hospital construction. With the view of assimilating the atmospheric condition of our large hospitals to that of a private dwelling, it has been lately proposed to do away with them altogether in their present form, and to substitute for them congeries of cast iron cottages, capable of being occasionally taken down, cleansed, and reconstructed — a plan which, besides involving enormous expense, would interfere most seriously with efficient supervision of the patients, and with the teaching of students at the bedside. But from what has been related above, it is plain that no material alteration of the existing system will be required. We have seen that a degree of salubrity equal to that of the best private houses has been attained in peculiarly unhealthy wards of a very large hospital, by simply enforcing strict attention to the antiseptic principle. And, considering the circumstances of those wards, it seems hardly too much to expect that the same beneficent change which passed over them will take place in all surgical hospitals, when the principle shall be similarly recognised and acted on by the profession generally. The antiseptic system is continually attracting

more and more attention in various parts of the world; and, whether in the form which it has now reached, or in some other and more perfect shape, its universal adoption can be only a question of time. The noble institutions of which our country is justly proud, admirably adapted alike for the treatment of the sick and the instruction of the student, will then be cleared of the only blot that now attaches to them, the malignant influence of impure atmosphere.

Chapter 21

Patrick Manson (Ronald Ross)

On the Development of *Filaria sanguinis hominis* and on the Mosquito considered as a Nurse

Development cannot progress far in the Host containing the Parent Worm

Fortunately it is an almost universal law, in the history of the more dangerous kinds of Entozoa [internal animal worm parasites], that the egg or embryo must escape from the host inhabited by the parent worm before much progress can be made in development. Were it possible for animals so prolific as *Filaria immitis* of the dog, or *Filaria sanguinis* of man, to be born and matured and to reproduce their kind again in an individual host, the latter would certainly be overwhelmed by the first swarm of embryos escaping into the blood, as soon as they had made any progress in growth. If, for example, the brood of embryo *Filariae*, at any one time free in the blood of a dog moderately well charged with them, were to begin growing before they had each attained a hundredth part of the size of the mature *Filaria*, their aggregate volume would occupy a bulk many times greater than the dog itself. I have calculated that in the blood of certain dogs and men there exists at any given moment more than two millions of embryos. Now the individuals of such a swarm could never attain anything approaching the size of the mature worm without certainly involving the death of the host. The death of the host would imply the death of the parasite before a second generation of *Filaria* could be born, and this, of course, entails the extermination of the species; for in such an arrangement reproduction would be equivalent to the death of both parent and offspring, an anomaly impossible in nature.

The Embryo must escape from the original Host

It follows therefore that the embryo, in order to continue its development and keep its species from extermination, must escape from the first host in some way. After accomplishing this it either lives an independent existence for a time, during which it is provided with organs for growth not possessed by it hitherto; or it is swallowed by another animal which treats it as a nursling for such time as is necessary to fit it with an alimentary system. The former arrangement obtains in the *Filaria* inhabiting the intestinal canal, the *Lumbricus* and thread-worm; the latter is followed by the several species of tapeworm, and also by other kinds of Entozoa. (Throughout this memoir Dr. Manson employs the term "nurse" in the same sense as that in which helminthologists [those who study parasitic worms] use the term "intermediate host.")

I find that in cases where embryo *Filariae* are not in great abundance in the blood, we may infer that there are only one or two parent worms; they often disappear completely for a time, to reappear after the lapse of a few days or weeks. From this circumstance I infer first, that reproduction is of an intermitting and not of a continuous character; and, secondly, that the embryos, after a certain time, are either disintegrated in the blood or are voided in the excretions. The latter does occur, I know from personal investigation, in the urine; and we have Dr. Lewis's testimony that he has found the animals in the tears. In this way they may have an opportunity of continuing development either free (as in the case of the *Lumbricus*) in the media into which the excretions are voided, or in the body of another animal which has intentionally or accidentally fed on these (as in the case of the tapeworms). Man, in his turn, may then swallow this hypothetic animal or other thing containing the embryo suitably perfected, and so complete the circle. This is the history of many Entozoa; but I have evidence to adduce that, if it be one way in which *Filaria sanguinis hominus* is nursed, it is not the only way, and therefore probably not the way at all.

The Mosquito found to be the Nurse

It occurred to me that, as the first step in the history of the hematozoon was in the blood, the next might happen in an animal who fed on that fluid.

To test this idea I procured mosquitos that had fed on the patient Hinlo's blood, and, examining the expressed contents of their abdomens from day to day with the microscope, I found that my idea was correct, and that the hematozoon which entered the mosquito as a simple structureless animal, left it, after passing through a series of highly interesting metamorphoses, much increased in size, possessing an alimentary canal, and being otherwise suited for an independent existence.

History of the Mosquito after feeding on Human blood

I may mention that my observations have been made exclusively on the females of one species of mosquito. I have never, in many hundreds of specimens, met with a male insect charged with blood. This is explained by the arrangement of the appendages and proboscis of the male mosquito, which prevents it from penetrating the skin. As the male is provided with a complete alimentary apparatus, it is presumed that he feeds on the juices and exudations of plants and fruits. There are two species of mosquito found during the summer here: one quite a large insect about half an inch long, with a black thorax and black-and-white banded abdomen; the other about half that size and of a dingy brown colour. The former is rare comparatively; the latter is very common, and is the insect my remarks apply to. After a mosquito has filled itself with blood (which it can do, if not disturbed, in about two minutes), it is evidently much embarrassed by the weight of its distended abdomen, so that it no longer can wheel about in the air. It accordingly attaches itself to some surface, if possible near stagnant water, where it remains in a comparatively torpid condition, digesting the blood, excreting yellow gamboge-looking feces, and maturing its ova. In the course of from three to five days these processes are completed, and the insect now betakes itself to the water, where the eggs are deposited, and on the surface of which they float in a dark-brown mass, looking like a flake of soot. The eggs do not take long to hatch (they are beautifully shaped objects, like an Etruscan vase); and the embryo emerges by forcing open a sort of lid placed at the broad end of the shell. The larvae now escape into the water, where they swim about and feed, and become the "jumpers" we are familiar with, found in every stagnant pool.

If the contents of the abdomen are examined before the mosquito has fed, or after the food has been absorbed, the following parts can easily be distinguished: – two ovisacs containing from sixty to a hundred ova, two large glandular masses (intestine and esophagus), and a very delicate transparent fibrous bag, the stomach. If the blood contained in the dilated stomach is examined soon after ingestion, the blood-corpuscles are seen quite distinct in outline, and behaving very much as when drawn in the ordinary way; but changes rapidly occur. First, the corpuscles lose their distinctness in outline, then crystals of hematin appear: corpuscles and crystals give place to large oil-globules, and the mass is deprived of its fluidity, and before the eggs are deposited all colouring-matter disappears; the white material is absorbed or expelled, and by the time the eggs are deposited the stomach is quite empty but for the embryo *Filariae* it may contain.

How to procure Mosquitos containing embryo *Filariae*

It may be useful to those who wish to repeat and test my observations to know the plan I found most successful in procuring *Filaria* bearing mosquitos, and how their bodies were afterwards treated for microscopic observation. Such details may appear frivolous and unimportant; but by following them the observer will be spared disappointment, and economize his time and patience.

I persuaded a Chinaman, in whose blood I had already ascertained that *Filariae* abounded, to sleep in what is known as a mosquito-house, in a room where mosquitos were plentiful. After he had gone to bed a light was placed beside him, and the door of the mosquito-house kept open for half an hour. In this way many mosquitos entered the "house"; the light was then put out, and the door closed. Next morning the walls of the "house" were covered with an abundant supply of insects with abdomens thoroughly distended. They were then caught below a wineglass, paralyzed by means of a whiff of tobacco-smoke, and transferred to small phials, into some of which a little water had been poured. A cover providing for ventilation was then placed over the mouth of the phial. The effect of the tobacco-smoke, if it has not been applied too long, is very evanescent, and seems to have no prejudicial influence on the posture of the mosquito. From the phials they may be

removed from time to time, as required, by again paralyzing with tobacco and seizing them by the thorax with a fine pincers. The abdomen is then torn off, placed on a glass slide, and a small cylinder, such as a thin penholder, rolled over it from the anus towards the severed thoracic attachment. In this way the contents are safely and efficiently expressed, and observation is not interfered with by the almost opaque integument [outer layer]. If the contents are white and dry a little water should be added and mixed carefully with the mass, so as to allow of the easy separation of the two large ovisacs. These can be removed in this way by the needle, and transferred to another slide for separate examination. A thin covering-glass should be placed over the residue, which will be found to contain the *Filariae* either within the walls of the stomach, or, if these have been ruptured by too rough manipulation, floating in the surrounding water.

Large proportion of *Filariae* ingested by the Mosquito

The blood in the stomach of a mosquito that has fed on a *Filaria*-infested man usually contains a much larger proportion of *Filariae* than does an equal quantity of blood obtained from the same man in the usual way by pricking the finger. Thus six small slides, equivalent to about one drop of blood from the man on whom most of my observations were made, would contain from ten to thirty Hematozoa; whereas the blood drawn by a single mosquito, about as much as would fill one slide only, contained from twenty to thirty as a rule, and sometimes many more. One slide, in which I had the curiosity to count them, had upwards of a hundred and twenty specimens. From this it would appear that the mosquito has the faculty of selecting the embryo *Filariae*; and in this strange circumstance we have an additional reason for concluding that this insect is the natural nurse of the parasite.

All Embryos do not attain maturity

By far the greater number die and are disintegrated, or are expelled in the feces undeveloped. At the end of the third, fourth, or fifth day, when the stomach is quite empty as far as food is concerned, and an embryo could not easily be overlooked, only from two to six are found in the same or slightly different stages of the metamorphosis, which I will now attempt to describe.

The Metamorphosis of the Embryo

The embryo for a short time after entering the stomach of the mosquito retains all the appearances and habits which characterized it when in the human body; that is, it is a long snake-like animal, having a perfectly transparent structureless body enclosed in a delicate and, for the most part, closely applied tube, within which it shortens and extends itself, giving rise, from the collapse of the tube when the body is retracted at either end, to the appearance of a lash at the head and tail. In a very few hours changes commence. The tube first separates from the body by an appreciable interval, giving the appearance of a distinct double outline, and the body itself becomes covered with a delicate but distinct and closely set transverse striation. Oral movements are now very evident, not that they did not exist before, but because the slight increase of shading from the striation renders them more apparent. The indication of a viscus seen in some specimens vanishes at this stage. Presently the tube or sheath is either digested by the gastric juices of the mosquito, or it is cast off as a snake does its skin, and the animal swims about naked, and without any trace of a head- or tail-lash. The striation becomes very marked; but gradually as the blood thickens, and the movements of the embryo become in consequence less vigorous, these markings completely disappear, giving place to a peculiar spotted appearance. Each spot is dark or luminous, according to the focusing of the microscope, and probably depends on some oily material now collecting in the body of the animal.

This concludes the first stage of the metamorphosis, and has taken about thirty-six hours to complete. During all this time the original proportions of the animal have been preserved and vigorous movement maintained. Now, however, it enters on a sort of chrysalis condition, during which nearly all movement is suspended, and the outline and dimensions very much altered. Hitherto the body was long and of graceful contour, but now it becomes shorter and broader, the extreme tail alone not participating in the change. The large spots in the body disappear, gradually giving place to what seems to be a fluid holding numerous minute particles in suspension. I have once or twice detected to-and-fro movements in these. The tail continues to be flexed and extended vigorously, but only at long intervals, whilst all oral

movements cease. By the end of the third day the animal has become much shorter and broader, the small terminal portion of the tail still retaining its original dimensions, and appearing to spring abruptly from the end of the sausage-shaped body. Large cells occupy the previously homogeneous-looking body, and sometimes something like a double outline can be traced. Indications of a mouth present themselves; and if a little pressure is applied to the covering-glass, granular matter and cell-like bodies escape from an orifice placed a little in advance of the tail. The animal now begins to increase in length, and in some specimens to diminish in breadth, the growth seeming to be principally in the oral end of the body. The structure of the mouth is sometimes very evident; it is four-lipped, the lips being either open or pursed up. From the mouth a delicate line can be distinctly traced, passing through the whole length of the body to the opening already referred to as existing near the caudal extremity. Feeble movement may still sometimes be detected in the caudal Appendix; but when the now growing body has attained a certain length the tail gradually disappears.

After this point, specimens of the *Filaria* in its third and last stage are difficult to procure. Most mosquitos die about the fourth or fifth day after feeding; and if their bodies, which fall into the water, are examined, they are soft and sodden and without *Filariae*, these having either decomposed or escaped. Sometimes, however, ovulation does not proceed rapidly, and the mosquito survives to the fifth or sixth day, or perhaps death may not occur, as it usually does, soon after the eggs had been laid, and the insect may survive this operation for two or three days. In such the last stage of the metamorphosis can be studied: four to six days seem necessary for its completion. Out of hundreds of mosquitos watched, I have been successful in finding *Filariae* in this last stage in four instances only. In one of these there was quite a number of embryos in regular gradation, from the passive chrysalis up to the mature and very active embryo, so that there can be no doubt of the relationship of the latter to the former, though their appearances differ so much. Owing to the small number of specimens I have examined, I am not quite certain about the details of this stage of the metamorphosis. As far as I can make out, the body gradually elongates from the hundredth to the fortieth or thirtieth of an inch, and when mature it measures fully a

fifteenth of an inch in length by the five hundredth of an inch in breadth.

When at the above stage large cells occupy the interior; but as development advances these become reduced in size, and accumulate round the dark line I have already mentioned as running from the mouth to the caudal extremity. In this way an alimentary tube is fashioned, and the peculiar and characteristic valve-like termination of the esophagus in the intestine, seen in the *Filariae*, is developed. The mouth may now be seen open and funnel-shaped, and the tail is reduced to a mere stump. Movements, first of a swaying-to-and-fro character, but afterwards brisker, now begin. The body gradually elongates and becomes perhaps slightly thinner; all cellular appearance vanishes, and, owing to the increasing transparency of the tissues, the details can no longer be made out. A vessel of some sort is seen in the centre running nearly the whole length of the body, and opening close to one extremity; this extremity is slightly tapered, and is crowned with three, or perhaps four, papillae; but whether this is the head or tail, and whether the vessel opening near it is the alimentary canal or vagina, I cannot say; the other extremity is also slightly tapered, but has no papillae. There can be no doubt which is mouth and which tail, but the intermediate steps I have failed to trace satisfactorily. There is a stage between these two in which the mouth is closed, and the esophagus can be seen running from it. If the body is compressed, that tube can be forced through the skin and distinctly seen; but about that time the tissues become so transparent that their exact relations cannot be made out.

I cannot say if the three or four papillae round one extremity of the developed embryo constitute the perfected boring-apparatus of the worm, or if it is the boring-apparatus at all; but comparing this with what is found in other species of the same genus, I think it very probable that it either is or will become the piercing-apparatus. Some time ago I operated on an Australian horse for this worm, and had the satisfaction of finding the parasite not very much injured after removal: it was an unimpregnated female possessing all the typical structures of the *Filariae*. Its head was armed with a five- or six-toothed saw, the teeth arranged, like those in some kinds of old-fashioned trephines, in a circle round the mouth. I removed a worm from the same eye of the same horse about three or four weeks previously; the cornea had

healed, and the cloudiness cleared up before the second worm appeared. I infer from this, from the very perfect boring-apparatus, and from the female being unimpregnated, that the eye is not the resting- or breeding-place of the *Filaria* found in it, but that it is sometimes accidentally entered by the worm on its travels in search of the suitable spot. From the fact that one worm succeeded the other I infer that the sexes are brought together in this way (as in the case of *Filaria sanguinolenta* of the dog): when a wandering worm comes across the tract of another, it follows it up; thus several may be found together at the end of the burrow.

Probably, then, these papillae are the boring-apparatus to be used in penetrating the tissues of man and escaping from the mosquito. At this (presumably the final stage of the *Filaria's* existence in the mosquito) it becomes endowed with marvellous power and activity. It rushes about the field, forcing obstacles aside, moving indifferently at either end, and appears quite at home, and in no way inconvenienced by the water in which it has just been immersed. This formidable-looking animal is undoubtedly the *Filaria sanguinis hominis* equipped for independent life and ready to quit its nurse the mosquito.

Future history of the *Filaria*

There can be little doubt as to the subsequent history of the *Filaria*, or that, escaping into the water in which the mosquito died, it is through the medium of this fluid brought in contact with the tissues of man, and that, either piercing the integuments, or, what is more probable, being swallowed, it works its way through the alimentary canal to its final resting place. Arrived there, its development is perfected, fecundation [fertilization] is effected, and finally the embryo *Filariae* we meet with in the blood are discharged in successive swarms and in countless numbers. In this way the genetic cycle is completed

On the nature and significance of the crescentic and flagellated bodies in malarial blood

In malarial blood certain forms of a parasitic organism are invariably present, singly or in association. The bodies referred to consist principally of a pale hyaline [glass-like] substance with or without granules of dark pigment, and are (1) minute nucleated bodies, or spores, which are free in the blood; (2) small epi- or intracorpuscular [within the red blood cells] bodies, presumed to be these spores which have become attached to or have attacked the red blood corpuscles; (3) larger intracorpuscular, pigmented, amoeboid bodies; (4) sporulating intracorpuscular forms, known as "corps en rosace," or "rosette bodies"; (5) the last mentioned outside the blood corpuscles, breaking up and becoming resolved into the first mentioned or free spores; (6) intermediate forms which serve to connect these types and suggest, if not prove, that together they form a complete vital cycle.

The presence of this parasite in the blood precedes and accompanies a special type of fever; the cycle of its development coincides in the main with the cycle of the fever; and it disappears from the blood with spontaneous recovery from or cure of the fever.

The intravenous injection of blood containing this parasite into a healthy individual is followed by the multiplication of the parasite in the blood of the person inoculated, and also by the occurrence in him of the characteristic fever. On these grounds the conclusion that malarial fever is caused by this organism is justified, if not absolutely proved.

Unless in the unnatural way by direct transfusion of blood, the malaria organism and malarial disease are not directly communicable; that is to say, the malaria parasite cannot be acquired by simple proximity to or by contact with an infected individual.

Apart from communication by transfusion of blood, the malaria organism and malarial diseases can be acquired only indirectly either through the air, the water, by food, or by other unknown way.

Malaria can be acquired, and its germ is therefore present, in places where there are few or no inhabitants, and where human beings rarely reside or pass through.

These propositions are all of them fully established facts.

Considering the frequency of the presence of the malaria organism in the human body, that in malarial countries at one time or another almost every individual harbours [sic] it in his blood, that it manifestly flourishes and propagates there, it is unreasonable to suppose that its presence in the human blood is a purely accidental circumstance in the sense that it is an organism which has strayed from its proper habitat, or to suppose that being in the blood, as regards itself, it is in any way abnormally located. On the contrary, it is reasonable to believe that it is present there as being in its normal habitat, in its own interests, in furtherance of its own vital necessities, and as a necessary, or perhaps alternative, condition in the evolution of its life-history as a living propagating organism.

That it can sustain itself and multiply in the blood is proved by its appearance therein in vastly increased numbers after intravenous injection of malaria blood, as well as by direct observation of the process of development and reproduction. But as it has been shown that the malaria organism is not directly communicable (in a normal way) by one individual to another, that it can be acquired in places where there is no human population, it follows that it has a second life, one outside and independent of the human body.

Provision, therefore, must be made in the biological arrangements and economy of this organism, for (1) the life inside the human body, (2) the life outside the human body, (3) for the parasite quitting the human body, and (4) for its entrance into the human body. The life inside the human body is provided for by the forms and developmental changes which culminate in the rosette or sporulating form, and already described.

WHAT IS THE PROVISION MADE FOR THE LIFE OUTSIDE THE BODY?

In certain types of malarial disease, in addition to the forms of malaria parasite already mentioned, another and very different looking form is found – namely, the "crescent" form. The materials entering into the structure of this body are identical in appearance with those composing several of the previously mentioned parasitic forms – namely, a pale hyaline substance forming the matrix and particles of black pigment imbedded in this. The crescentic body, like the above mentioned forms, with the exception of the

free spores, lies inside the red blood corpuscles.

If malaria blood be observed some time after it has been withdrawn from the blood vessels, yet another form is seen – namely, the "flagellated body."

It is important to note that the *flagellated body never appears or comes into view on the microscope field immediately after the withdrawal of the blood from the vessels of the body, but only after the blood has been on the slide for some minutes – generally not before a quarter of an hour.* [Italics in original]

The flagellated body, therefore, cannot exist as such in the circulation, although, potentially, it must be represented there by some of the forms already described as present in freshly-drawn blood.

The flagellated body, if properly and sufficiently searched for, is to be found in all cases of malarial infection; it is, therefore, a constant feature of the parasitism.

The flagellated body has been observed to be evolved in two ways: First, from the crescentic body; second, from certain of the large intracorpuscular amoeboid bodies.

1. Under the microscope the crescentic body can be seen to develop into the flagellated body, thus: first, the crescent becomes straight, next it becomes oval, then spherical, then the centrally-collected pigment becomes arranged as a capsulated ring before being scattered through the sphere, and acquiring peculiar swarming, agitated movements; next the sphere undergoes rapid changes of shape; finally, flagella in varying number burst through the periphery of the sphere. The flagella remain attached to the sphere for some time by one of their extremities, like the tentacles of an octopus, and indulge in rapid, waving, and in peculiar shivering movements.

2. In those forms of malarial infection in which there are no crescents present in the blood the flagellated body can be seen to develop from certain large, pigmented, intracorpuscular forms. Such intracorpuscular forms have been seen to squeeze themselves through an invisible opening in the limiting membrane of the blood corpuscle, very much after the fashion of a leucocyte in diapedesis. When they have effected their escape in this way the pigment they contain becomes agitated, and flagella are subsequently thrown out, as in the corresponding stage of the crescent-derived flagellated body.

Shortly after the appearance of the flagella they break away from the

central body and swim about as free parasites in the liquor sanguinis [blood plasma].

The free flagella, as the attached flagella, have two styles of movement – one a waving, undulating movement, like that of an eel in swimming, which is manifestly subservient to locomotion; the other a rapid, vibrating, shivering movement, indulged in particularly when the flagellum meets with an obstacle, as when it impinges against a blood corpuscle. During the latter movement the flagellum is in the main straight and appears to be more or less rigid.

The crescentic bodies persist in the blood for several days or weeks after the other forms of intracorpuscular bodies and the fever they are associated with have disappeared, whether spontaneously or as a consequence of the action of quinine.

Although some may present signs of degeneration, in freshly-drawn blood the crescentic body never appears as if it had undergone developmental change.

The crescentic body is not attacked by the phagocytes.

These, too, are all well-ascertained facts.

Seeing that the crescentic body is so frequent a feature in malaria blood, so persistent, and so resist[a]nt to the physiological agency for removing foreign bodies from the circulation, its presence cannot be regarded as accidental or as the result of some caprice or freak of Nature. On the contrary, the crescentic body must be regarded as in some way subservient to the interest of the organism to which it evidently belongs.

As it is not observed to undergo development in the circulating blood, its destiny cannot be the propagation of the parasite inside the human body – a requirement sufficiently secured by the rosette form of the parasite.

As the crescentic body is observed to undergo development after it has been removed from the human body, and only then, this circumstance, together with other considerations to be mentioned, points to the conclusion that the crescentic body is intended to carry on the life of the species outside the human body.

If this proposition be correct, then the flagellated organism which proceeds from the crescentic body is the first stage in the life of the malaria organism

outside the human body, and the living moving flagella, into which it breaks up, the second stage. The central sphere, to which the flagella are at first attached and from which they are derived, must be looked on as residual.

Those intracorpuscular bodies which, in certain types of malarial disease, on the withdrawal of the blood from the blood vessels develop into flagellated bodies are to be regarded as analogous to the crescentic bodies, and on the same grounds as bodies destined for the continuation of the species outside the human body. The flagellated organisms which proceed from them have, therefore, a similar destiny to those which proceed from the crescentic bodies.

As the malaria organism has not been found in the physiological or in pathological discharges or excretions from the human body, and as hemorrhage is a very rare occurrence in malarial infection, it may be concluded that those forms of the parasite which have been shown to be destined for the continuation of the species outside the human body do not leave the human body in any of these ways or in such media. The crescentic body, and the analogous intracorpuscular flagellated-organism-producing form, so long as they remain in the blood vessels are perfectly passive, enclosed in blood corpuscles, and manifestly incapable of spontaneously bringing about or actively conducing to their own escape from the body.

Therefore, seeing that neither the physiological arrangements of the human body, nor pathological processes, nor the inherent powers and organisation of the parasite itself provide for its escape from the human body, and seeing that such escape is necessary, some extraneous agency, such as is likely to be frequently, if not constantly, supplied in natural conditions, must come to the assistance of the parasite. What is this extraneous agent which assists the malaria organism to escape from the human body?

A similar problem presented itself to the writer many years ago in connection with the filaria of the blood – *filaria nocturna*. Like the malaria organism, the filaria is at one time of its existence parasitic and circulating in the blood. Like the malaria organism, the filaria, in order to complete its life-cycle and preserve the species, has to pass from one human being to another, and, in order to do this, has to leave the blood vessels. Like the malaria organism, the filaria is not extruded in the secretions, and pathological discharges containing it are not a normal or usual accompaniment of the parasitism. Like

the malaria organism the filaria is incapable of quitting the vessels by its own efforts. As the malaria organism is enclosed in a blood corpuscle so the filaria is enclosed in a sheath – the former to escape the phagocytes, the latter to prevent its leaving the blood vessels. As the malaria organism on being removed artificially from the blood vessels commences, under certain conditions, to enter on its evolutional cycle by first escaping from the enclosing blood corpuscle, so the filaria, under certain conditions, commences to enter on its cycle of development when it is removed artificially from the blood vessels by first escaping from its sheath. In both parasites this first step in development can be brought about experimentally on the microscope slide, and in both parasites a lowering of temperature favours or is associated with the conditions which eventuate in successful experiment.

The parallel is very complete; the conditions, the requirements, and the problem to be solved are apparently identical for both parasites. As the problem and conditions are the same for both organisms, the solution of the problem may also be the same for both. If this be the case, *the mosquito having been shown to be the agent by which the filaria is removed from the human blood vessels, this, or a similar suctorial insect must be the agent which removes from the human blood vessels those forms of the malaria organism which are destined to continue the existence of this organism outside the body.* (Italics added) It must, therefore, be in this or in a similar suctorial [adapted for sucking] insect or insects that the first stages of the extracorporeal life of the malaria organism are passed.

The two classes of movement indulged in by the flagella – the undulating and the vibrating – suggest that these bodies, on breaking away from the residual body or pigment-containing sphere, move in virtue of the locomotive faculty for some distance – say, traverse the blood contained in the insect's stomach – and then in virtue of the vibratory movement penetrate the cells of some organ of the insect. The malaria organism in the human body is an intracellular parasite like a gregarine or a coccidium, and it is probable that outside the human body it retains this habit. It would be idle to attempt to follow the parasite further without the assistance of direct observations; so many possibilities are open to it once clear of the human body. It, may, for all we know, comport itself like the pebrine corpuscle and continue in endless

succession parasitic in the tissues and ova of the insect, then in the larva, and so again in the mature insect. This it is impossible to say. But *the hypothesis I have ventured to formulate seems so well grounded that I for one, did circumstances permit, would approach its experimental demonstration with confidence. The necessary experiments cannot for obvious reasons be carried out in England, but I would commend my hypothesis to the attention of medical men in India and elsewhere, where malarial patients and suctorial insects abound.* (Italics added)

Experimental Proof of The Mosquito-Malaria Theory

Although the theory that the malaria parasite is transmitted from man to man by particular species of mosquito is now accepted by all biologists and medical men who have given adequate attention to the subject, it cannot be said that the general public (including those Europeans who in malarious countries might benefit by the practical application of the theory) unreservedly believe in, much less practically apply it. Endless objections, the outcome of an imperfect acquaintance with the subject and, perhaps, of a disinclination to admit that a pathological puzzle of so many centuries standing could receive so simple an explanation, have been raised by the amateur biologist and sanitarian, so much so that it seemed not improbable that a great principle, pregnant with important issues, might remain barren and unutilised.

Impressed with this fear, and being anxious to see some fruit from a theory which I knew to be true and for which I was in a measure responsible, I cast about for means by which the conversion and cooperation of the public might be secured. I felt that unless the public believed in the efficiency of the sanitary measures so definitely indicated by the mosquito-malaria theory, and, understood the principles on which these measures should be founded, they would not adopt them nor, what is so necessary to the success of all such measures, co-operate heartily in carrying them out. As the histological, biological, and experimental evidence which had satisfied men of science was not understood by the public, it seemed to me that some simple demonstration, such as would be unanswerable and at the same time readily comprehended by laymen, was required.

Grassi in conjunction with Bignami had succeeded in conveying malaria by mosquito bite. Although these experimenters took every care to exclude fallacy, the fact that the experiments were made in Rome, itself of fever repute and in the middle of a highly-malarial district, had an undoubted influence in preventing due appreciation by the public of the conclusive nature of their work. Furthermore, things occurring at a distance and in a strange land do not appeal so strongly as do things happening in our midst. It occurred to me, therefore, that if I repeated Grassi and Bignami's experiments in a more dramatic and crucial manner, that if I fed laboratory-reared mosquitos on a

malarial patient in a distant country and subsequently carried the mosquitos to the centre of London, and there set them to bite some healthy individual free from any suspicion of being malarial, and if this individual within a short period of being bitten developed malarial fever and showed in his blood the characteristic parasite, the conclusion that malaria is conveyed by the mosquito would be evident to every understanding, and could not possibly be evaded.

It also occurred to me that if a certain number of Europeans who had never suffered from malaria kept in good health and free from malaria during an entire malarial season in an intensely malarial locality, where all inhabitants and visitors suffered from malaria, and if they kept well without the use of quinine or other medicinal prophylactic, simply by avoiding mosquito bite, the above conclusion would be accentuated; and, also, that if this immunity were attained by inexpensive means – means which did not interfere seriously with comfort, pleasure, or business – the mosquito-malaria theory would not only be proved to the satisfaction of the public, but the public would be willing to accept the sanitary measures which the theory and experiments indicated.

After having obtained promises of support from the Colonial Office and from the London School of Tropical Medicine, and having secured volunteers for the experiments, still further to accentuate my object and to arrest the attention of those principally interested, I publicly announced in a popular lecture at the Colonial Institute that the above experiments were about to be undertaken, and with the same object in view I ventured to forecast their issue.

EXPERIMENT I – LONDON

Drs. Bignami and Bastianelli very kindly undertook to send me relays of infected mosquitos from Rome. I have to thank these gentlemen for the great care exercised in this somewhat responsible matter. Every case of malaria coming to a general hospital is not suitable for experiment. To have sent mosquitos infected with malignant tertian parasites might have endangered the life of the subject of the experiment; and quartan-infected insects might have conferred a type of disease which, though not endangering life, is ex-

tremely difficult to eradicate. The cases, therefore, on which the experimental insects were fed, had to be examples of pure, benign tertian – a type of case not readily met with in Rome during the height of the malarial season; the absolute purity of the infection could be ascertained only by repeated and careful microscopic examination of the blood of the patient.

When the insects had fed, Dr. L. Sambon, who had gone to Rome on Experiment No. 2, placed them in small cylindrical cages made of mosquito netting stretched on a wire frame. Four such cylinders were packed in a well ventilated box ... and forwarded to the London School of Tropical Medicine through the British Embassy in Rome. The box was 9 inches in depth and 8 1/4 inches on the sides. The wire openings were 3 inches square on each side. The cages were each 8 1/4 inches in length and 3 1/2 inches in diameter. By the courtesy of the Postmaster-General they came forward by the Indian mail so that they arrived in London some 48 hours after leaving Rome. A good many of the mosquitos died on the journey or soon after arrival; a fair proportion survived and appeared to be healthy and vigorous. We are indebted to Dr. Sambon for the method employed of caging mosquitos. Future experimenters will find it very useful. To infect the insect or to become infected by them, the experimenter has merely to place his hand in the cage after carefully untying the netting at one end or, better, by laying the closed cage on his damped hand.

NOTES OF EXPERIMENT

By P. Thurburn Manson, Guy's Hospital.

I am 23 years of age, was born in China, but have lived in this country since I was 3; have never been abroad since, nor in any district in this country reputed to be malarial. I am healthy.

The first consignment of mosquitos arrived at the London School of Tropical Medicine on July 5th. Only some half-dozen had survived the journey. They were in a languid condition, and would not feed satisfactorily. One may have bitten me. By July 7th they were all dead. The second consignment arrived on August 29th. They had been infected in Rome on August 17th, 20th, and 23rd, by being fed upon a patient with a double benign tertian infection. The patient was reported to have had numerous parasites, includ-

ing many gametes, in his blood. On arrival twelve insects were lively and healthy looking. I fed five of them on August 20th, three on August 31st, one on September 2nd, and one on September 4th. They bit my fingers and hands readily. The bites were followed by a considerable amount of irritation, which persisted for two days.

The third consignment arrived on September 10th. They had been fed in Rome on September 6th and 7th on a patient suffering from a simple tertian infection, but with very few parasites in his blood. There were some 50 to 60 mosquitos in good condition. Twenty-five bit me on September 10th, and 10 on September 12th.

Up till September 13th I had been perfectly well. On the morning of the 13th I rose feeling languid and out of sorts with a temperature of 99 F. By midday I was feeling chilly and inclined to yawn. At 4:30 P.M. I went to bed with severe headache, sensation of chilliness, lassitude, pains in the back and bones, and a temperature of 101.4 F. Repeated examinations failed to discover any malarial parasites in my blood.

September 14th: I slept fairly well but woke at 3 A.M. with slight sweating and a temperature of 101 F. During the day my temperature ranged between 101 and 102 F. The symptoms of September 13th were exaggerated and anorexia was complete. Several examinations of the blood were made again with negative result. To relieve headache 10 grains of phenacetin were given at 6 P.M. I perspired profusely but slept indifferently.

September 15th: Woke at 7 A.M. feeling distinctly better, with a temperature of 100.4 F. No malaria parasites were discovered on repeated examinations of my blood by my father. About 2 P.M. I commenced to feel slightly chilly; this soon wore off, and I became hot and restless. By 4:30 P.M. temperature was 103.6 F. It remained about 103 F. till 9 P.M., when profuse sweating set in. I am told there was some delirium.

September 16th: I woke at 8 A.M. feeling quite well; temperature 98.4 F. I made several blood examinations and found one doubtful half-grown tertian parasite. In the afternoon and evening there was a recurrence of fever (temperature 102.8 F), relieved by sweating.

September 17th: Again felt quite well on waking after a good night's sleep; temperature 99 F. At 10 A.M. several half-grown parasites, a gamete, and

two pigmented leucocytes were discovered in the first blood film examined. During the day many tertian parasites were found. Their presence was verified by my father, Dr. Frederick Taylor, Lieutenant Colonel Oswald Baker, I.M.S., Dr. Galloway, Mr. Watson Cheyne, F.R.S., and Mr. James Cantlie, some of whom saw the films prepared.

About 2 P.M. the sensation of chilliness returned. Temperature 101.8 F.

By 5 P.M. temperature had reached 103 F. There was then copious sweating. The edge of the spleen could be felt on deep inspiration, and there was a slight feeling of discomfort in the region of that organ. Dr. Frederick Taylor and Mr. Watson Cheyne confirmed the presence of splenic enlargement. By 9 P.M. the temperature had fallen to 99.2 F., and I was feeling better. Quinine (10 grains) was given.

September 18th: Woke after a good night feeling perfectly well (temperature 97 F.). Ten grains of quinine were taken, and subsequently five grains every eight hours. I continued perfectly well all day. A few three-quarter grown tertian parasites and some gametes were found during the forenoon and afternoon; they were seen by Dr. Oswald Browne, my father, and myself. At 10 P.M. the parasites had disappeared, the last being found at 5 P.M.

September 19th: No parasites discovered. Temperature normal. Feeling quite well. There is no splenic enlargement, and no tenderness. Appetite returned.

September 25th: In good health. No recurrence of malarial symptoms.

EXPERIMENT II – THE ROMAN CAMPAGNA

A wooden hut, constructed in England, was shipped to Italy and erected in the Roman Campagna at a spot ascertained by Dr. L. Sambon, after careful inquiry, to be intensely malarial, where the permanent inhabitants all suffer from malarial cachexia [wasting syndrome], and where the field labourers who come from healthy parts of Italy to reap the harvest after a short time all contract fever. This fever-haunted spot is in the King of Italy's hunting ground near Ostia, at the mouth of the Tiber. It is waterlogged and jungly, and teems with insect life.

The only protection against mosquito bite and fever employed by the experimenters who occupied this hut was mosquito netting, wire screens in

doors and windows, and, by way of extra precaution, mosquito nets around their beds. Not a grain of quinine was taken. Drs. Sambon and Low, Signor Terzi, and their two Italian servants, entered on residence in the hut early in July. They go about the country quite freely always, of course, with an eye on Anopheles —during the day, but are careful to be indoors from sunset to sunrise. Up to September 21st, the date of Dr. Sambon's last letter to me, the experimenters and their servants had enjoyed perfect health, in marked contrast to their neighbours, who were all of them either ill with fever or had suffered malarial attacks.

For the present I content myself with announcing this result. Complete details of their experiences will doubtless be made public by Drs. Sambon and Low at the termination of the malarial season, and of their experiment, at the end of October. Suffice it to say that these gentlemen express themselves as satisfied that protection from mosquito bite protects from malaria, and that protection from mosquito bite is perfectly compatible with active outdoor occupation during the day.

APPLICATION OF THE EXPERIMENTS

It remains for the public to apply the lesson taught by these experiments. Will this be done? Already I have heard objections and difficulties mooted. I saw it advanced recently that it is impossible to avoid mosquito bite in the tropics, and that it was useless trying to do so. One has sometimes to go out in the evening; a doctor, for example, must visit his patient at any hour. This is quite true; but surely because we cannot escape a risk ... altogether this is no reason why we should not try to minimise it. Dr. Daniels, who has recently returned from British Central Africa, tells me that not one mosquito in a thousand in that country carries malarial zygotes, that is to say, is infective. If a man exposes himself therefore in British Central Africa to mosquito bite habitually, so that he gets bitten say ten times every night, the chances are that he is effectually inoculated with malaria some four times a year; but if the same man systematically protected himself from mosquito bite, and, in consequence of his care reduced the chances of being bitten to once a month, he might be a hundred years in British Central Africa before he became infected. This minimising of risk is certainly worth striving for.

The question of expense cannot for a moment be entertained in discussing the means for protection. One life saved one invaliding obviated, would, even in a pecuniary sense: Pay for all the wire gauze and mosquito netting requisite to protect every European house in West Africa.

These experiments, together with the work of Ross, Grassi, Celli, Bignami, Bastianelli, and other Italians, the recent observations on native malaria by Koch, and the representatives of the Malaria Commission of the Royal Society and Colonial Office, plainly indicate that the practical solution of the malaria problem lies in:

1. Avoiding the neighbourhood of native houses – the perennial source of malaria parasites.
2. The destruction, so far as practicable, of Anopheles' breeding pools.
3. And principally: Protection from mosquito bite.

Chapter 22

Paul-Louis Simond

How the plague bacillus and its transmission through fleas were discovered: Reminiscences from my years at the Pasteur Institute in Paris (Ludwik Gross)

This manuscript was prepared in order to describe a few interesting details referring to the initial discovery of the plague bacillus and its mode of transmission from the rat carriers to other rats and to humans.

A few centuries ago, plague represented a massive disaster, killing millions of local populations in India, China, Indo-China, Africa, and, particularly, Europe. The cause of this disease was unknown and was attributed to unfavorable constellations of stars, to comets, to the wrath of supernatural powers, and frequently also to poisoning of wells by Jews, or other ethnic groups of people, who paid for this with tortures inflicted on them by the panicked population.

The mystery of plague was solved fairly recently. Alexandre Yersin, who discovered the bacillus of plague, died in 1943, during World War II. In June 1940, Yersin was in Paris, attending a Pasteur Institute meeting, and left Lutetia Hotel, where he was staying (and where I was staying also at the same time), barely a few hours before the German armies entered the French capital; in fact, Yersin left Paris for Saigon, by air, only 6 hours before the airport was closed. Paul-Louis Simond, who discovered that plague is transmitted by fleas, was collecting plants, and living quietly in retirement, in Valence (province of Drome, south of Lyon), in France, and he very kindly

replied in writing to my letters, which I wrote to him from the Pasteur Institute in 1938, asking him for details of his fundamental discovery.

Since my childhood years, I have always been interested in finding out how the great medical discoveries were made and how the epidemics of transmissible diseases were prevented. In my early postdoctoral years, I had the opportunity, shortly before World War II, to spend several years, as a young guest investigator, at the Pasteur Institute in Paris.

I was intrigued by an isolated laboratory, located in a separate small building, at 25, rue du Docteur Roux. I was told that the upper floor of this small building has a laboratory dedicated to the problem of plague and that it contains notes and records of Yersin, who recognized that this disease infects predominantly rats, and of Simond. I visited this small laboratory several times and studied the notes of Yersin and Simond. In fact, I was working in the same laboratory where Simond worked, some 40 years earlier. In 1938, when I was tracing the data leading to the clarification of the plague transmission puzzle, Simond lived at that time, as a retired French Army Medical Corps general, in Valence. I was helped and guided in my task by Edmond Dujardin-Beaumetz, a former friend of Yersin, who was working in the plague laboratory. I was impressed by these fundamental discoveries, which provided the means to control and prevent pandemics of this devastating disease.

Epidemics of plague have devastated for several centuries not only cities but also entire countries. Millions of people died, populations were decimated, and there were not enough people to bury the dead. People panicked. Medical and church authorities thought that these epidemics were caused by supernatural powers, in retaliation for sins committed by some segments of the population. Innocent groups of people were tortured and killed after being accused of spreading the disease. There did not appear to be any remedy or means to prevent this disaster.

The means of a relatively simple solution leading to the prevention of this devastating disease were found just before the turn of this century. These discoveries did not require complicated methods or techniques, except curiosity, common sense, and good observation by a couple of intelligent and persistent investigators, equipped with good will, a microscope, and letters of recommendation signed by Louis Pasteur and his coworker, Emile Roux.

These letters facilitated dealing with local authorities in Indo-China and other places where plague epidemics were at that time ravaging the local populations. Both Yersin and Simond were trained at the Pasteur Institute in Paris and were strongly encouraged by Pasteur to follow and to try to solve the problem of plague. The story of this fundamental discovery, very briefly, is as follows.

Yersin, born in Switzerland, descendant of French immigrants, studied in France and worked at the Hôtel-Dieu Hospital in Paris; at that time Pasteur just introduced his vaccine treatment for those infected with rabies. Yersin was performing an autopsy on the spinal cord of a patient who died following a bite by a rabid wild dog; during the dissection of the spinal cord, Yersin cut his finger; he immediately proceeded to Pasteur's laboratory. Pasteur called his assistant, Emile Roux, and asked him to start vaccinating Yersin against rabies. That was the beginning of a long friendship that developed between Yersin, Pasteur, and Roux. Yersin became interested in bacteriology and frequently spent time in Pasteur's and Roux's laboratories. He was also assisted by Roux in preparation of his French medical doctorate thesis.

When an epidemic of plague developed in and ravaged Hong Kong, Pasteur suggested that Yersin proceed to Hong Kong to study and attempt to isolate the causative microbe of that devastating disease. Yersin accepted this suggestion enthusiastically. Pasteur requested that the French authorities send Yersin, who was a member of the French medical colonial corps, to Hong Kong. The orders came promptly, by telegram, and Yersin proceeded to Hong Kong.

The problem was not as simple as it might have appeared. Yes, the epidemic was in full swing. People died by the hundreds. The city hospital was full of sick and dying patients. But Yersin had no access to the morgue. The hospital director, Dr. Lawson, did not give him permission. After many interventions and appeals, even to the governor, Yersin finally, as a gesture of good will, received permission to have a small table in a corner of a dark corridor, next to the patients' room, where he could leave his microscope, a notebook, and a few cages with guinea pigs, mice, and rats. That was the limit of his allowance. He had no access to the morgue, where he was anticipating piercing the enlarged lymph nodes (bubo[e]s) of a patient who died from plague in

order to look for the causative bacillus. Frustrated, Yersin in the meantime developed a friendship with an English priest, Father Vigano, who helped him build a small shack outside, but adjoining, the hospital, where Yersin could have a small folding bed and a very small makeshift laboratory. At the advice of Father Vigano, Yersin gave a few dollars to two English sailors who were helping to take care of the morgue at the hospital. Yersin was now able to go with the two sailors into the morgue for a few minutes and have access to the corpse of a patient who just died with plague. Yersin punctured the patient's swollen inguinal lymph node – i.e., bubo – with his sterile pipette and ran to his small laboratory, where one part of the fluid was placed under the microscope, another part was injected into a few guinea pigs, and the rest was prepared for immediate shipment to Roux at the Pasteur Institute in Paris. Yersin was excited after he looked into the microscope; he wrote in his notebook: "June 20, 1894. The specimen is full of microbes, all looking alike, with rounded ends, staining very poorly (Gram-negative); this is without question the microbe of plague." The next note was entered a day or two later: "guinea pigs injected with the plague bubonic fluid all died and their blood and organs were full of the same bacilli." He informed the hospital director of his observations and was now allowed to have access to the morgue.

A new, very important observation followed shortly. Yersin, intrigued by the large number of dead rats lying on the streets, around the morgue, and in hospital corridors, decided to examine, under the microscope, the blood, lymph nodes, and other organs of these rats and found that they were full of the same bacilli that he found in patients dying with plague. He now realized that plague affects not only humans but also, and perhaps predominantly, rats. As a matter of fact, Yersin recorded that rats have long been known to be affected not only at the time of plague epidemics but also often preceding such epidemics in humans; ancient people knew about it, and mountain inhabitants in Chinese villages as well as villagers in parts of mountains in India and also on the island of Formosa knew that when hundreds and thousands of rats lie around on the roads and in houses, they precede the outbreak of the fatal epidemic in humans. In fact, plague was designated, in local languages, as a disease of rats. These fundamental,

historical observations, made in the summer of 1894, established that plague in humans and rats is caused by the bacillus discovered by Yersin but did not clarify yet how this disease is transmitted from man to man, from rat to rat, or from rat to man. Transmission through air, food, and feces mixed with dust was suspected, but not substantiated.

The fundamental observations of Yersin were published the same year in the *Annales de l'Institut Pasteur*, from notes that Yersin mailed to Roux and Albert Calmette.

The mystery of transmission of plague from rat to rat, or from rats to humans, was solved a few years later by Simond, a young French colonial Army physician, who was delegated to Indo-China by Pasteur to take over the research on this devastating disease and to follow and expand the initial observations of Yersin. He worked in the former Metchnikoff's laboratory at the Pasteur Institute in Paris (and where, in fact, I had the privilege of working some 40 years later). Roux suggested to Simond to go to Indo-China to try to follow up Yersin's work and particularly to try to treat patients suffering from plague with a serum prepared from horses immunized with the bacillus isolated by Yersin. Simond accepted with enthusiasm his new mission with the orders from the French government to proceed to Long-Tcheon in Indo-China where plague was ravaging. While Simond was busy with the serum treatment most of the time, his thoughts were elsewhere — he was intrigued by the mysterious manner in which plague appeared to be transmitted from sick to healthy persons, individuals frequently separated by relatively substantial distances and apparently not having any contact with each other. People living in houses separated by a distance of half a mile perhaps from those where plague was observed frequently developed symptoms of this disease, even though they did not seem to have had any contact with those suffering from plague. Simond suspected that rats, which carry the disease, transmit it from man to man. He recalled that Chinese in Yunnan ran away from their homes as soon as they saw dead rats. Furthermore, on the island of Formosa (Taiwan) the inhabitants considered any contact with sick or dead rats as a menace leading to infection with plague. He recorded in his notebook that in one house in Bombay, during the plague epidemic, 75 dead rats were found. He even saw some of these animals running on the

street dragging their legs and falling down and dying. Another observation recorded in his notes: "one day, in a wool factory, employees arriving in the morning noticed a large number of dead rats on the floor. Twenty laborers were ordered to clean the floor of the dead animals. Within 3 days, 10 of them developed plague, whereas none of the other employees became ill." In another observation, made in Chack-Kalal, in April 1898, a high mortality was noticed among rats but not among the human population. The inhabitants of that locality anticipated, however, that plague may be approaching, because of the dead rats observed all over, and much of the frantic population ran away from the village and settled in an isolated camp. "Two weeks later, a mother and daughter received permission to go back to the village to bring clothing from their house. They found several dead rats on the floor of the house. They picked up the rats by their tails and threw them out on the street and then returned to the camp. Two days later, both developed plague. One more observation: on May 13, 1898, in Bombay, a man walked into a stable to take care of his horse and found there a dead rat on the floor. He picked up the rat by the tail and threw it out. Three days later he developed plague." Before long, Simond began to suspect that people become infected with plague only when they approach rats that have just died from plague within a few minutes. People do not become infected, however, if they approach or even touch rats that are already cold, having died perhaps a day ago, or earlier. "We have to assume," theorized Simond, "that there must be an intermediary between a dead rat and a human. This intermediary might be a flea." At least, thought Simond, let me make an experiment with fleas. My experimental laboratory conditions were very primitive, I had only a tent in Bombay during the plague epidemic in a rainy season ... (excerpts from letters to the author). In the tent, I had a microscope and a few cages with rats. I could not do too much under such primitive conditions. Nevertheless, I convinced myself and, in fact, before long I demonstrated that it is the flea that transmits plague. Healthy rats have very few fleas or none at all. If they have any fleas, they get rid of them very fast because they are very careful about grooming their skin and hair and try to keep clean at all times. On the other hand, rats that are sick do not take care of their skin hygiene anymore and that allows them to have many fleas. Immediately after the rat

dies, when its corpse cools off, the fleas leave the dead rat and jump on other healthy rats or, if no rats are available, they jump on men or women. In this manner, one could explain cases of plague transmitted to people who had no contact whatever with patients suffering from that disease. A healthy person, finding the corpse of a rat that died recently of plague, picks up the animal by its tail and throws it out and 3 or 4 days later develops the disease.

Simond was convinced that the rat flea (*Xenopsylla cheopis*) transmits the disease, but he had to prove experimentally that this assumption is correct. He realized the danger of having any contact whatsoever with infected fleas and he devised the whole experiment to be carried out in his tent in Cutch-Mandvi, ... where he was delegated because of the ravaging plague epidemic. His proposed procedure was as follows. He grabbed a rat that had just died because of plague with long forceps and threw it immediately into a paper bag, which in turn would then be dropped into a large container full of warm water saturated with soap. The bag would then be cut open with sharp scissors while it was immersed in water. In this manner, the action of fleas was neutralized. They were attached to the fur of the dead rat. Simond took a few of those fleas from the skin of the rat and placed them under the microscope. He realized at once that their intestines were full of bacilli of plague. In a control study, he checked under the microscope fleas taken from healthy rats and found them free from plague bacilli. He also realized that the danger of an infected flea jumping off the rat is practically limited to the immediate time after the rat dies, when the body of the dead rat is cooling off. The fleas do not tolerate cold and try to leave the dead rats, looking for new hosts with warm skin, preferably for rats, and, if no rats are available, they jump on humans.

A period of excessive heat wave in Cutch-Mandvi lead to the temporary abatement of the plague epidemic. Simond moved to Bombay and Kurrachee, where he could carry out a crucial experiment that he had been planning for a long time. Simond brought to Kurrachee from Saigon a very tall glass jar. On the bottom of this jar he put some sand and a rat sick with plague; the rat was carrying fleas. The top of the jar was covered with a fine mesh net. After 24 hours, the rat was dying. At that time, Simond lifted the cover of the jar and inserted carefully into the jar a small cage dangling in the air held by strings

attached to the center of the cover of the jar. This small cage contained a young healthy rat that had been kept isolated from infection. This small cage was hanging inside of the glass jar, a few inches above the sick rat crouched on the floor of the jar. The bottom of this hanging cage was made out of a screen, with relatively large openings. The healthy rat inside the suspended cage had no contact whatsoever with the sick rat. It was exposed, however, to the fleas, which could have jumped without difficulty from the sick rat, on the bottom of the jar, to the cage hanging above it. Simond determined in separate experiments, that a flea can jump about 4 inches up, vertically. It could reach, without difficulty, the small cage dangling in the air above the floor of the jar.

When the rat with plague, on the bottom of the jar, died, it was carefully removed. Five days later, the rat inside of the hanging cage, also developed plague. That was on June 2, 1898. The problem of plague transmission was solved. Simond sent the summary of all his observations to Roux in Paris. In October 1898, the article appeared in the *Annales de l'Institut Pasteur*.

As a control experiment, Simond placed in the same jar a rat suffering from plague, but carrying no fleas, together with healthy rats. No infection occurred. However, as soon as fleas were introduced from outside, plague developed in the rats placed in the jar.

In this way, the mystery of the long-observed plague epidemics was solved. It also became clear why, as has long been known, the relatively safest places during plague epidemics were in well-maintained hospitals, where no transmission of plague occurred in doctors, nurses, or service personnel, except in cases of very rare pulmonary plague, transmitted directly from patients to healthy people. The bubonic plague, however, is transmitted only through fleas. Once infected, the fleas remain infected for long periods of time, for several weeks, perhaps even months.

These data are based on information I received in July 1938 from Simond, in handwritten letters addressed to my modest laboratory at the Pasteur Institute, where I was at that time a guest investigator in an unrelated field of cancer transmission in laboratory animals. Other data, particularly those referring to the discovery by Yersin of the plague bacillus in human patients and also in rats, I collected from personal notes and records of Yersin, kept

at the Pasteur Institute, and my conversations with Dujardin-Beaumetz.

Chapter 23

Carlos Finlay (Walter Reed)

The Carlos Finlay article on the mosquito as the agent of transmission for yellow fever (1881):

... I feel convinced that any theory which attributes the origin and propagation of yellow fever to atmospheric influences, to miasmatic or meteorological conditions, to filth or to the neglect of general hygienic precautions, must be considered as utterly indefensible. I have, therefore, been obliged to abandon my former ideas, and shall now endeavor to justify this change in my opinions, submitting to your appreciation a new series of experiments which I have undertaken for the purpose of discovering the manner in which yellow fever is propagated.

In this paper I shall not concern myself with the nature or form of the morbific cause of yellow fever, beyond postulating the existence of a material, transportable substance, which may be an amorphous virus, a vegetable or animal germ, a bacterium, etc., but, at any rate, constitutes something tangible which requires to be conveyed from the sick to the healthy before the disease can be propagated. What I propose to consider is the means by which the morbific cause of yellow fever is enabled to part from the body of the patient and to be implanted into that of a healthy person. The need of an external intervention, apart from the disease itself, in order that the latter may be transmitted is made apparent by numerous considerations; some of them already pointed out by Humboldt and Benjamin Rush since the beginning of this century, and now corroborated by recent observations. Yellow fever, at times, will travel across the Ocean to be propagated in dis-

tant ports presenting climatic and topographic conditions very different from those of the focus from which the infection has proceeded, while, at other times, the disease seems unable to transmit itself outside of a very limited zone, although the meteorology and topography beyond that zone do not appear to differ very materially. Once the need of an agent of transmission is admitted as the only means of accounting for such anomalies, it is evident that all the conditions which have hitherto been recognized essential for the propagation of the disease must be understood to act through their influence upon the said agent. It seemed unlikely, therefore, that this agent should be found among Micro or Zoophytes, for those lowest orders of animal life are but little affected by such meteorologic variations as are known to influence the development of yellow fever. To satisfy that requisite it was necessary to search for it among insects. On the other hand, the fact of yellow fever being characterized both clinically and (according to recent findings) histologically, by lesions of the blood vessels and by alterations of the physical and chemical conditions of the blood, suggested that the insect which should convey the infectious particles from the patient to the healthy should be looked for among those which drive their sting into blood-vessels in order to suck human blood. Finally, by reasons of other considerations which need not be stated here, I came to think that the mosquito might be the transmitter of yellow fever. Such was the hypothesis which led me to undertake the experimental investigation which I shall here relate.

Let us first recall the geographical distribution of mosquitoes. They may be said, in general terms, to exist everywhere, except at great altitudes above the sea-level. Many believe that the dipterous insect with which we are concerned, the genus *Culex*, constitutes a special torment of the tropical regions, while in reality it is found in all latitudes. In the polar regions, the Laplanders, just as the inhabitants of the equinoctial regions of America, are prevented from taking their meals and from lying down to sleep within their huts, unless they surround themselves with an atmosphere of smoke in order to escape those pests. In the open, those insects will fly into their mouths and nostrils, and, notwithstanding the hardening of their skin during the previous winters, they find it necessary to use veils steeped in fetid grease and to anoint their bodies with cream or lard as a protection against mosquitoes.

In Canada, in Russia, in England, in France, in Spain, all over Europe, in Siberia, China, the United States, in North and South America, mosquitoes abound. ...

Although mosquitoes are found in all latitudes, their abundance varies in different localities. Humboldt and Bonpland, in their *Travels in Equinoctial America* wrote: "The annoyance suffered from mosquitoes and zancudos in the torrid zone is not so general as most people think. On the high plateaux more than [2500 feet] above the sea-level, and in very dry plains, far from large rivers, such as Cumana and Calabozo, gnats are not much more abundant than in the most populous parts of Europe." The influence of dryness and of a long distance from water-courses, pointed out by those travelers, is easily understood, in as much as the larvae and pupae of the mosquitoes are aquatic, and the winged insect requires water for the laying and hatching of its eggs. The impediment to their propagation at high levels may consist in the exaggeration of the difficulty which those insects must always experience in flying upwards after they have filled themselves with blood; a difficulty which will be much more marked in a species having such small wings as those of the *Culex* mosquito. The rarefaction of the atmosphere at those great heights necessarily increases that difficulty and, under those circumstances, the mosquito will instinctively shun those localities. The above mentioned travelers also relate that a missionary priest, Bernardo Zea, had built himself a room over a scaffolding of palm boards, and they used to go there at night to dry their plants and to write their Diary, adding: "The missionary had rightly observed that those insects are more numerous in the lower strata of the atmosphere, within 12 to 15 feet from the ground." Further on they write: "As one proceeds toward the plateau of the Andes, those insects disappear and the air one breathes becomes pure ... at a height of [1500 feet] mosquitoes and zancudos are no longer feared."

...

Three conditions will, therefore, be necessary in order that yellow fever may be propagated:

1. The existence of a yellow fever patient into whose capillaries the mosquito is able to drive its sting and to impregnate it with the virulent particles, at an appropriate stage of the disease.

2. That the life of the mosquito be spared after its bite upon the patient until it has a chance of biting the person in whom the disease is to be reproduced.

3. The coincidence that some of the persons whom the same mosquito happens to bite thereafter shall be susceptible of contracting the disease.

The first of these conditions ... we may be sure, has never failed to be satisfied in Havana. With regard to the second and third, it is evident that the probabilities of their being satisfied will depend on the abundance of mosquitoes and on the number of susceptible persons present in the locality. I firmly believe that the three above mentioned conditions have, indeed, always coincided in years when yellow fever has made its greatest ravages.

Such is, Gentlemen, my theory; and I consider that it has been singularly strengthened by the numerous historical, geographical, ethnological and meteorological coincidences which occur between the data which I have collected regarding the mosquito and those which are recorded about the yellow fever; while, at the same time, we are enabled by it to account for circumstances which have until now been considered inexplicable under the prevailing theories. Yellow fever was unknown to the white race before the discovery of America, and, according to Humboldt, it is a traditional opinion in Vera Cruz that the disease has been prevailing there ever since the first Spanish explorers landed on its shores. There also, as we have seen, the Spaniards since their first landing have recorded the presence of mosquitoes; and with greater insistence than in any other place in America, in the identical sand-mounds of San Juan de Ulloa (the present site of Veracruz). The races which are most susceptible to yellow fever are also the ones who suffer most from the bites of mosquitoes. The meteorological conditions which are most favorable to the development of yellow fever are those which contribute to increase the number of mosquitoes; in proof of which I can cite several local epidemics regarding which competent authorities assert that the number of mosquitoes during the prevalence of yellow fever was much greater than on other occasions; indeed, it is stated in one instance that the mosquitoes were of a different kind from those which were usually observed in the locality, having gray rings around their bodies. Regarding the topography of the yellow fever, Humboldt points out the altitudes beyond which mosquitoes cease to

appear, and in another passage gives the limits above the sea-level within which the yellow fever may be propagated. Finally, in the notorious case of the U. S. Steamship Plymouth, in which two cases of yellow fever occurred at sea, after the vessel had been disinfected and frozen during winter, four months after the last previous case had occurred on that vessel (the preceding November), the facts can be readily accounted for by the hibernation of mosquitoes which had bitten the former yellow fever patients, and, which, upon finding themselves again within tropical temperatures, recovered from their lethargic condition and bit two of the new men of the crew.

Supported by the above reasons, I decided to submit my theory to an experimental test, and, after obtaining the necessary authorization, I proceeded in the following manner.

On the 30th of last June, I took to the Quinta de Garcini a mosquito which had been caught before being allowed to sting, and there made it bite and fill itself with blood from the arm of a patient, Camilo Anca, who was in the fifth day of a well characterized attack of yellow fever of which he died two days later. I then picked out F.B., one of twenty healthy non-immunes who have continued until now under my observation, and made the same mosquito bite him. Bearing in mind that the incubation of yellow fever, in cases which allow its limits to be reckoned, varies between one and fifteen days, I ordered the man to be kept under observation. On the 9th of July, F.B. began to feel out of sorts, and on the 14th he was admitted to the Military Hospital with a mild attack of yellow fever perfectly characterized by the usual yellowness, and albumin in the urine which persisted from the third till the ninth day.

On the 16th of July, I applied a mosquito at the same Quinta de Garcini, to a patient, Domingo Rodriguez, in the third or fourth day of yellow fever; on the 20th, I allowed the same mosquito to bite me and, finally, on the 22nd I made it bite A.L.C., another of the 20 men who are under observation. Five days later, this man was admitted at the Hospital with fever, severe headache, pain in the loins and injected eyes; these symptoms lasted three days, after which the patient became convalescent without having presented any yellowness nor albuminuria. His case was, however, diagnosed as "abortive yellow fever" by the physician in charge.

The 29th of July, I made a mosquito bite D.L.R. who was going through

a severe attack of yellow fever at Quinta de Garcini, being then in its third day. On the 31st, I made the same mosquito bite D.L.F., another of my 20 men under observation.

On the 5th of August, at 2 a.m., he was attacked with symptoms of mild yellow fever; he subsequently showed some yellowness but I do not think that he developed any albuminuria; his case was, nevertheless, diagnosed "abortive yellow fever."

Finally, on the 31st of July, I applied another mosquito to the same patient, D.L.R. at Quinta de Garcini, his attack having then reached its fifth day and proving fatal on the following one. On the 2d of August I applied this mosquito to D.G.B., another of my twenty non-immunes. Till the present date (12th) this last inoculation has not given any result; but, as only 12 days have elapsed, the case is still within the limits of incubation. I have to state that the persons mentioned above are the only ones who were inoculated with mosquitoes, in the manner described; and that since June 12th, till now (in the course of seven weeks), barring my first three inoculated men, no other case of confirmed or abortive yellow fever has occurred among the twenty non-immunes, whom I have had under observation.

These experiments are certainly favorable to my theory, but I do not wish to exaggerate their value in considering them final, although the accumulation of probabilities in my favor is now very remarkable. I understand but too well that nothing less than an absolutely incontrovertible demonstration will be required before the generality of my colleagues accept a theory so entirely at variance with the ideas which have until now prevailed about yellow fever. In the meantime, I beg leave to resume in the following conclusions the most essential points which I have endeavored to demonstrate.

Conclusions:

(1) It has been proved that the *Culex* mosquito, as a rule, bites several times in the course of its existence, not only when its bite has been accidentally interrupted, but even when it has been allowed to completely satisfy its appetite; in which case two or more days intervene between its successive bites.

(2) In as much as the mouth-parts of the mosquito are very well adapted to retain particles that may be in suspension in the liquids absorbed by that

insect, it cannot be denied that there is a possibility that said mosquito should retain upon the setae of its sting some of the virulent particles contained in a diseased blood, and may inoculate them to the persons whom it afterwards chances to bite.

(3) The direct experiments undertaken to decide whether the mosquito is able to transmit yellow fever in the above stated manner, have been limited to five attempted inoculations, with a single bite, and they have given the following results: One case of mild yellow fever, perfectly characterized, with albuminuria and icterus [jaundice]; two cases diagnosed as "abortive yellow fever" by the physicians in charge; and two ephemeral fevers without any definite characters. From which results it must be inferred that the inoculation with a single bite is insufficient to produce the severe forms of yellow fever, and that a final decision as to the efficacy of such inoculations must be deferred until opportunity is found for experimenting under absolutely decisive conditions, outside of the epidemic zone.

(4) Should it be finally proven that the mosquito inoculation not only reproduces the yellow fever, but that it constitutes the regular process through which the disease is propagated, the conditions of existence and of development for that dipterous insect would account for the anomalies hitherto observed in the propagation of yellow fever, and while we might, on the one hand, have the means of preventing the disease from spreading, non-immunes might at the same time be protected through a mild inoculation. My only desire is that my observations be recorded, and that the correctness of my ideas be tested through direct experiments. I do not mean by this that I would shun the discussion of my opinions; far from it, I shall be very glad to hear any remarks or objections which my distinguished colleagues may be inclined to express.

A *Preliminary Note* from the Yellow Fever Commission:

The writers, constituting a board of medical officers, convened "for the purpose of pursuing scientific investigations with reference to the acute infectious diseases prevalent on the island of Cuba," arrived at our station, Columbia Barracks, Quemados, Cuba, on June 25 of the present year, and proceeded under written instructions from the Surgeon General of the Army, to "give special attention to questions relating to the etiology and prevention of yellow fever."

Two of its members (Agramonte and Lazear) were stationed on the island of Cuba, the former in Habana, and the latter at Columbia Barracks, and were already pursuing investigations relating to the etiology of this disease.

Fortunately for the purposes of this board, an epidemic of yellow fever was prevailing in the adjacent town of Quemados, Cuba, at the time of our arrival, thus furnishing us an opportunity for clinical observations and for bacteriologic and pathologic work. The results already obtained, we believe, warrant the publication, at this time, of a preliminary note. A more detailed account of our observations will be submitted to Surgeon General Sternberg in a future report. The first part of this preliminary note will deal with the results of blood cultures during life and of cultures taken from yellow fever cadavers; reserving for the second part a consideration of the mosquito as instrumental in the propagation of yellow fever; with observations based on the biting of nonimmune human beings by mosquitoes which had fed on patients sick with yellow fever, at various intervals prior to the biting.

...

Having failed to isolate *B. icteroides*, either from the blood during life, or from the blood and organs of cadavers, two courses of procedure in our further investigations appeared to be deserving of attention, viz., first, a careful study of the intestinal flora in yellow fever in comparison with the bacteria that we might isolate from the intestinal canal of healthy individuals, in this vicinity, or of those sick with other diseases; or, secondly, to give our attention to the theory of the propagation of yellow fever by means of the mosquito – a theory first advanced and ingeniously discussed by Dr. Carlos J. Finlay, of Habana, in 1881.

We were influenced to take up the second line of investigation by reason of

the well-known facts connected with the epidemiology of this disease, and, of course, by the brilliant work of Ross and the Italian observers, in connection with the theory of the propagation of malaria by the mosquito.

We were also very much impressed by the valuable observations made at Orwood and Taylor, Miss., during the year 1898, by Surg. Henry R. Carter, U.S. Marine-Hospital Service: A note on the interval between infecting and secondary cases of yellow fever, etc. ... We do not believe that sufficient importance has been accorded these painstaking and valuable data. We observe that the members of the yellow fever commission of the Liverpool School of Tropical Medicine, Drs. Durham and Meyers, to whom we had the pleasure of submitting Carter's observations, have been equally impressed by their importance. ...

The circumstances under which Carter worked were favorable for recording with considerable accuracy the interval between the time of arrival of infecting cases in isolated farmhouses and the occurrence of secondary cases in these houses. According to Carter, "the period from the first (infecting) case to the first group of cases infected, at these houses, is generally from two to three weeks."

The houses having now become infected, susceptible individuals thereafter visiting the houses for a few hours, fall sick with the disease in the usual period of incubation – one to seven days.

Other observations made by us since our arrival confirmed Carter's conclusions, thus pointing as it seemed to us to the presence of an intermediate host, such as the mosquito, which having taken the parasite into its stomach, soon after the entrance of the patient into the noninfected house, was able after a certain interval to reconvey the infecting agent to other individuals, thereby converting a noninfected house into an "infected" house. This interval would appear to be from 9 to 16 days (allowing for the period of incubation), which agrees fairly closely with the time required for the passage of the malarial parasite from the stomach of the mosquito to its salivary glands.

In view of the foregoing observations we concluded to test the theory of Finlay on human beings. According to this author's observation of numerous inoculations in 90 individuals, the applications of one or two contaminated mosquitoes is not dangerous, but followed in about 18 per cent, by an attack

of what he considers to be very benign yellow fever at most.

We here desire to express our sincere thanks to Dr. Finlay, who accorded us a most courteous interview and has gladly placed at our disposal his several publications relating to yellow fever during the past 19 years; and also for ova of the variety of mosquito with which he had made his several inoculations. An important observation to be here recorded is that, according to Finlay's statement, 30 days prior to our visit, these ova had been deposited by a female just at the edge of the water in a small basin, whose contents had been allowed to slightly evaporate; so that these ova were at the time of our visit entirely above contact with the water. Notwithstanding this long interval after deposition, they were promptly converted into the larval stage, after a short period, by raising the level of the water in the basin.

...

Dr. Jesse W. Lazear, acting assistant surgeon, United States Army, a member of this board, was bitten on August 16, 1900 by a mosquito which 10 days previously had been contaminated by biting a very mild case of yellow-fever (fifth day). No appreciable disturbance of health followed this inoculation.

September 13, 1900 (forenoon), Dr. Lazear, while on a visit to Las Animas Hospital, and while collecting blood from yellow fever patients for study, was bitten by a *Culex* mosquito (species undetermined). As Dr. Lazear had been previously bitten by a contaminated insect without aftereffects, he deliberately allowed this particular mosquito, which had settled on the back of his hand, to remain until it had satisfied its hunger.

On the evening of September 18, 5 days after the bite, Dr. Lazear complained of feeling "out of sort," and had a chill at 8 p.m.

September 19, Twelve o'clock noon, his temperature was 102.4, pulse 112. Eyes injected, face suffused; at 3 p.m. temperature was 103.4, pulse 104; 6 p.m., temperature 103.8 and pulse 106; albumin appeared in the urine. Jaundice appeared on the third day. The subsequent history of this case was one of progressive and fatal yellow fever, the death of our much-lamented colleague having occurred on the evening of September 25, 1900.

As Dr. Lazear was bitten by a mosquito while present in the wards of a yellow-fever hospital, one must, at least, admit the possibility of this insect's

contamination by a previous bite of a yellow-fever patient. This case of accidental infection therefore cannot fail to be of interest taken in connection with Cases 10 and 11 ([Carroll and Dean]).

For ourselves, we have been profoundly impressed with the mode of infection and with the results that followed the bite of the mosquito in these three cases. Our results would appear to throw new light on Carter's observations in Mississippi, as to the period required between the introduction of the first (infecting) case and the occurrence of secondary cases of yellow fever.

Since we here, for the first time, record a case [William Dean] in which a typical attack of yellow fever has followed the bite of an infected mosquito, within the usual period of incubation of the disease, and in which other sources of infection can be excluded, we feel confident that the publication of these observations must excite renewed interest in the mosquito theory of the propagation of yellow fever, as first proposed by Finlay.

From our study thus far of yellow fever, we draw the following conclusions:

(1) *Bacillus icteroides* (Sanarelli) stands in no causative relation to yellow fever, but, when present, should be considered as a secondary invader in this disease.

(2) The mosquito serves as the intermediate host for the parasite of yellow fever.

An *Additional Note* from the Yellow Fever Commission:

At the Twenty-eighth Annual Meeting of the American Public Health Association, held in Indianapolis, Ind., Oct. 22–26, 1900, we presented, in the form of a preliminary note, the results of our bacteriologic study of yellow fever, based on cultures taken from the blood in eighteen cases, at various stages of the disease, as well as on those which we had made from the blood and organs of eleven yellow fever cadavers. We also recorded the results obtained from the inoculation of eleven non-immune individuals by means of the bite of mosquitoes ... that had previously fed on the blood of patients sick with yellow fever. We were able to report two positive results, in which the attack of yellow fever followed the bite of a mosquito within the usual period of incubation of this disease.

In one of these cases all other sources of infection could be positively excluded. From our several observations we drew the following conclusions:

1. *Bacillus icteroides* (Sanarelli) stands in no causative relation to yellow fever, but, when present, should be considered as a secondary invader in this disease.

2. The mosquito serves as the intermediate host for the parasite of yellow fever.

Since the publication of our preliminary note, we have continued our investigations, especially as regards the means by which yellow fever is propagated from individual to individual, and as to the manner in which houses become infected with the contagium of this disease. The results already obtained are so positive and striking that, with the permission of Surgeon-General Sternberg, we have concluded to present to this Congress an additional note, in which we will record these later observations. ...

In order to exercise perfect control over the movements of those individuals who were to be subjected to experimentation, and to avoid any other possible source of infection, a location was selected in an open and uncultivated field, about [one] mile from the town of Quemados, Cuba. Here an experimental sanitary station was established under the complete control of the senior member of this Board. This station was named Camp Lazear, in honor of our late colleague, Dr. Jesse W. Lazear, Acting Assistant-Surgeon, U.S.A., who died of yellow fever, while courageously investigating the causation of this

disease. The site selected was very well drained, freely exposed to sunlight and winds, and, from every point of view, satisfactory for the purposes intended.

...

Camp Lazear was established Nov. 20, 1900, and from this date was strictly quarantined, noone being permitted to leave or enter camp except the three immune members of the detachment and the members of the Board. Supplies were drawn chiefly from Columbia Barracks, and for purpose a conveyance under the control of an immune acting hospital steward, and having an immune driver, was used.

A few Spanish immigrants recently arrived at the Port of Havana, were received at Camp Lazear, from time to time, while these observations were being carried out. A non-immune person, having once left this camp, was not permitted to return to it under any circumstances whatever.

The temperature and pulse of all non-immune residents were carefully recorded three times a day. Under these circumstances any infected individual entering the camp could be promptly detected and removed. ...

Observations:

Having thus sufficiently indicated the environment of Camp Lazear and the conditions under which its residents lived, we will now proceed to a narration of the observations thus far made at this experimental station.

...

For the purpose of experimentation, subjects were selected as follows: from Tent No. 2, 2 non-immunes, and from Tent No. 5, 3 non-immunes. Later, 1 non-immune in Tent No. 6 was also designated for inoculation.

...

It should be borne in mind that at the time when these inoculations were begun, there were only 12 non-immune residents at Camp Lazear, and that 5 of these were selected for experiment, viz., 2 in Tent No. 2, and 3 in Tent No. 5. Of these we succeeded in infecting 4, viz, 1 in Tent No. 2 and 3 in Tent No. 5, each of whom developed an attack of yellow fever within the period of incubation of this disease. The one negative result, therefore, was in Case 2 — Moran — inoculated with a mosquito on the fifteenth day after the insect had bitten a case of yellow fever on the third day. Since this mosquito failed to infect Case 4, three days after it had bitten Moran, it follows that

the result could not have been otherwise negative in the latter case. We now know, as the result our observations, that in the case of an insect kept at room temperature during the cool weather of November, fifteen or even eighteen days would, in all probability, be too short a time to render it capable of producing the disease. As bearing upon the source of infection, we invite attention to the period of time during which the subjects had been kept under rigid quarantine, prior to successful inoculation, which was as follows: Case 1, fifteen days; Case 3, nine days; Case 4, nineteen days; Case 5, twenty-one days. We further desire to emphasize the fact that this epidemic of yellow fever, which affected 33.33 per cent of the non-immune residents of Camp Lazear, did not concern the 7 non-immunes occupying Tents No. 1, 4, 6, and 7, but was strictly limited to those individuals who had been bitten by contaminated mosquitoes. Nothing could point more forcibly to the source of this infection than the order of the occurrence of events at this camp. The precision with which the infection of the individual followed the bite of the mosquito left nothing to be desired in order to fulfill the requirements of a scientific experiment. The epidemic having ceased on Dec. 15, 1900 no other case of yellow fever occurred in this camp until we again began to expose individuals to inoculation.

...

In considering the character of the attacks and the course of the disease in these five cases of experimental yellow fever, it must be borne in mind that these infected individuals were all young men, in good general physical condition, and placed amid excellent hygienic surroundings. Further, it must not be forgotten that, upon the earliest manifestation of an approaching infection, they were each and all put to bed at once, and were even carried to the yellow fever wards while occupying the same bed. In other words, these men were kept at absolute rest from the first inception of the disease. Just what bearing this may have had on the subsequent course of the fever, we cannot say, but since so much stress is laid on absolute rest of the patient by those having most experience in the treatment of yellow fever, the influence of this enforced rest, in our cases, upon the subsequent course of the attack, was doubtless of much importance. We reserve a consideration of the clinical side of these cases for a future report.

In our opinion the experiments above described conclusively demonstrate that an attack of yellow fever may be readily induced in the healthy subject by the bite of mosquitoes ... which have been previously contaminated by being fed with the blood of those sick with yellow fever, provided the insects are kept for a sufficient length of time after contamination before being applied to the person to be infected.

Our observations do not confirm Finlay's statement that the bite of the mosquito may confer an abortive attack of yellow fever, when applied to the healthy subject two to six days after it has bitten a yellow fever patient. We have always failed to induce an attack, even of the mildest description, when we have used mosquitoes within less than twelve days from the time of contamination, although the insects were constantly kept at summer temperature. We could cite instances where we have applied mosquitoes at intervals of two, three, four, five, six, nine, and eleven days following the contamination of the insect with the blood of well-marked cases of yellow fever, early in the disease, without any effect whatever being produced by the bite. Thus in one case no result followed the bite of fourteen mosquitoes which four days previously had been contaminated by biting a case of yellow fever on the first day. Again, seven days later, or eleven days after contamination, the surviving seven of these insects failed to infect an individual. On the seventeenth day after contamination, however, the bite of four of these mosquitoes – all that remained of the original fourteen – was promptly followed by an attack of yellow fever in the same individual. These insects had been kept, during the whole of this time, at an average temperature of 82 F.

Our observations would seem to indicate that after the parasite has been taken into the mosquito's stomach, a certain number of days must elapse before the insect is capable of re-conveying it to man. This period doubtless represents the time required for the parasite to pass from the insect's stomach to its salivary glands, and would appear to be about twelve days in summer weather, and most probably about eighteen or more days during the cooler winter months. It follows, also, that our observations do not confirm Finlay's opinion that the bite of the contaminated mosquito may confer immunity against a subsequent attack of yellow fever. In our experience, an individual may be bitten on three or more occasions by contaminated mosquitoes with-

out manifesting any symptoms of disturbance to health, and yet promptly sicken with yellow fever within a few days after being bitten by an insect capable of conveying the infection.

Acquirement of the Disease:

Having shown that yellow fever can be conveyed by the bite of an infected mosquito, it remains to inquire, whether this disease can be acquired in any other manner. It has seemed to us that yellow fever, like the several types of malarial fever, might be induced by the injection of blood taken from the general circulation of a patient suffering with this disease. Accordingly we have subjected four individuals to this method of infection, with one negative and three positive results. Reserving the detailed description of these cases to a subsequent occasion, we may state that in one of the positive cases an attack of pronounced yellow fever followed the subcutaneous injection of 2 c.c. of blood taken from a vein, bend of the elbow, on the first day of the disease, the period of incubation being three days and twenty-two hours; in the second case, 1.5 c.c. of blood, taken on the first day of the disease, and injected in the same manner brought about an attack within two days and twelve hours; while in our third case, the injection of 0.5 c.c. of blood taken on the second day of the disease, produced an attack at the end of forty-one hours.

In the case mentioned as negative to the blood injection, the subsequent inoculation of this individual with mosquitoes already proved to be capable of conveying the disease, also resulted negatively. We think, therefore that this particular individual, a Spanish immigrant, may be considered as one who probably possesses a natural immunity to yellow fever.

It is important to note that in the three cases in which the injection of the blood brought about an attack of yellow fever, careful cultures from the same blood, taken immediately after injection, failed to show the presence of Sanarelli's bacillus. A fourth case of yellow fever, severe in type, has been produced, by the subcutaneous injection of 1 c.c. of blood taken from the general circulation on the second day of the disease, the period of incubation being three days and one hour. The patient from whom the blood was obtained was an experimental case which was in turn produced the injection of blood – 0.5 c.c. – derived from a non-experimental case of fatal yellow fever.

As "controls," Cases 1, 4, 6, and 7 of this report were also injected subcutaneously with 1 c.c. of the same blood without manifesting any symptoms whatever. The blood which produced the fourth case of yellow fever, when transferred at the same time to bouillon tubes in considerable quantities, gave no growth whatever.

Our observations, therefore, show that the parasite of yellow fever is present in the general and capillary circulation, at least during the early stages of this disease and that the latter maybe conveyed, like the malaria parasite, either by means of the bite of the mosquito, or by the injection of blood taken from the general circulation.

Can Yellow Fever Be Propagated in Any Other Way?

We believe that the general consensus of opinion of both the medical profession and the laity is strongly in favor of the conveyance of yellow fever by fomites. The origin of epidemics, devastating in their course, has been frequently attributed to the unpacking of trunks and boxes that contained supposedly infected clothing; and hence the efforts of health authorities, both state and national, are being constantly directed to the thorough disinfection of all clothing and bedding shipped from ports where yellow fever prevails. To such extremes have efforts at disinfection been carried, in order to prevent the importation of this disease into the United States, that, during the epidemic season, all articles of personal apparel and bedding have been subjected to disinfection, sometimes both at the port of departure and at the port of arrival; and this has been done whether the articles have previously been contaminated by contact with yellow fever patients or not. The mere fact that the individual has resided, even for a day, in a city where yellow fever is present, has been sufficient cause to subject his baggage to rigid disinfection by the sanitary authorities.

To determine, therefore, whether clothing and bedding, which have been contaminated by contact with yellow fever patients and their discharges, can convey this disease is a matter of the utmost importance. Although the literature contains many references to the failure of such contaminated articles to cause the disease, we have considered it advisable to test, by actual experiment on non-immune human beings, the theory of the conveyance of yellow fever by fomites, since we know of no other way in which this question can

ever be finally determined.

For this purpose there was erected at Camp Lazear a small frame house consisting of one room 14 x 20 feet, and known as "Building No. 1," or the "Infected Clothing and Bedding Building." The cubic capacity of this house was 2800 feet. It was tightly ceiled [sic] within with "tongue and grooved" boards, and was well battened on the outside. It faced to the south and was provided with two small windows, each 26 x 34 inches in size. These windows were both placed on the south side of the building, the purpose being to prevent, as much as possible, any thorough circulation of the air within the house. They were closed by permanent wire screens of 0.5 mm mesh. In addition sliding glass sash were provided within and heavy wooden shutters without; the latter intended to prevent the entrance of sunlight into the building, as it was not deemed desirable that the disinfecting qualities of sunlight, direct or diffused, should at any time be exerted on the articles of clothing contained within this room. Entrance was effected through a small vestibule, 3 x 5 feet, also placed on the southern side of the house. This vestibule was protected without by a solid door and was divided in its middle by a wire screen door, swung on spring hinges. The inner entrance was also closed by a second wire screen door. In this way the passage of mosquitoes into this room was effectually excluded. During the day, and until after sunset, the house was kept securely closed, while by means of a suitable heating apparatus the temperature was raised to 92 to 95 F. Precaution was taken at the same time to maintain a sufficient humidity of the atmosphere. The average temperature of this house was thus kept at 76.2 F. for a period of 63 days.

Nov. 30, 1900, the building now being ready for occupancy, three large boxes filled with sheets, pillowslips, blankets, etc., contaminated by contact with cases of yellow fever and their discharges were received and placed therein. The majority of the articles had been taken from the beds of patients sick with yellow fever at Las Animas Hospital, Habana, or at Columbia Barracks. Many of them had been purposely soiled with a liberal quantity of black vomit, urine, and fecal matter. A dirty "comfortable" and much-soiled pair of blankets, removed from the bed of a patient sick with yellow fever in the town of Quemados, were contained in one of those boxes. The same

day, at 6 p.m., Dr. R. P. Cooke, Acting Assistant-Surgeon, U.S.A., and two privates of the hospital corps, all non-immune young Americans entered this building and deliberately unpacked these boxes, which had been tightly closed and locked for a period of two weeks. They were careful at the same time to give each article a thorough handling and shaking in order to disseminate through the air of the room the specific agent of yellow fever, if contained in these fomites. These soiled sheets, pillowcases, and blankets were used in preparing the beds in which the members of the hospital corps slept. Various soiled articles were hung around the room and placed about the bed occupied by Dr. Cooke.

From this date until Dec. 19, 1900, a series of twenty days, this room was occupied each night by these three non-immunes. Each morning the various soiled articles were carefully packed in the aforesaid boxes, and at night again unpacked and distributed about the room. During the day the residents of this house were permitted to occupy a tent pitched in the immediate vicinity, but were kept in strict quarantine.

December 12, a fourth box of clothing and bedding was received from Las Animas Hospital. These articles, had been used on the beds of yellow fever patients, but in addition had been purposely soiled with the bloody stool of a fatal case of this disease. As this box had been packed for a number of days, when opened and unpacked by Dr. Cooke and his assistants, on December 12, the odor was so offensive as to compel them to retreat from the house. They pluckily returned, however, within a short time and spent the night as usual.

December 19 these three non-immunes were placed in quarantine for five days and then given the liberty of the camp. All had remained in perfect health, notwithstanding their stay of twenty nights amid such unwholesome surroundings.

During the week, December 20–27, the following articles were also placed in this house, viz.: pajamas suits, 1; undershirts, 2; night-shirts, 4; pillow-slips, 4; sheets, 6; blankets, 5; pillows, 2; mattresses, 1. These articles had been removed from the persons and beds of four patients sick with yellow fever and were very much soiled, as any change of clothing or bed-linen during their attacks had been purposely avoided, the object being to obtain articles

as thoroughly contaminated as possible.

From Dec. 21, 1900, till Jan. 10, 1901, this building was again occupied by two non-immune young Americans, under the same conditions as the preceding occupants, except that these men slept every night in the very garments worn by yellow fever patients throughout their entire attacks, besides making use exclusively of their much-soiled pillow-slips, sheets, and blankets. At the end of twenty-one nights of such intimate contact with fomites, they also went into quarantine, from which they were released five days later in perfect health.

From January 11 till January 31, a period of twenty days, "Building No. 1" continued to be occupied by two other non-immune Americans, who, like those who preceded them, have slept every night in the beds formerly occupied by yellow fever patients and in the nightshirt used by these patients throughout the attack, without change. In addition, during the last fourteen nights of their occupancy of this house they have slept, each night, with their pillows covered with towels that had been thoroughly soiled with the blood drawn from both the general and capillary circulation, on the first day of the disease, in the case of a well-marked attack of yellow fever. Notwithstanding this trying ordeal, these men have continued to remain in perfect health.

The attempt which we have therefore made to infect "Building No. 1" and its seven non-immune occupants, during a period of sixty-three days, has proved an absolute failure. We think we cannot do better here than to quote from the classic work of La Roche. This author says: "In relation to the yellow fever, we find so many instances establishing the fact of the non-transmissibility of the disease through the agency of articles of the kind mentioned, and of merchandise generally, that we cannot but discredit the accounts of a contrary character assigned in medical writings, and still more to those presented on the strength of popular report solely. For if in a large number of well authenticated cases, such articles have been handled and used with perfect impunity – and that, too, often under circumstances best calculated to insure the effect in question – we have every reason to conclude, that a contrary result will not be obtained in other instances of a similar kind; and that consequently the effect said to have been produced by exposure to those articles, must – unless established beyond the possibility of doubt – be

referred to some other agency."

The question here naturally arises: How does a house become infected with yellow fever? This we have attempted to solve by the erection at Camp Lazear of a second house, known as "Building No. 2," or the "Infected Mosquito Building." This was in all respects similar to "Building No. 1," except that the door and windows were placed on opposite sides of the building so as to give through-and-through ventilation. It was divided, also, by a wire-screen partition, extending from floor to ceiling, into two rooms, 12 x 14 feet and 8 x 14 feet respectively. Whereas, all articles admitted to "Building No. I" had been soiled by contact with yellow fever patients, all articles admitted to "Building No. 2" were first carefully disinfected by steam before being placed therein.

On Dec. 21, 1900, at 11.45 a.m., there were set free in the larger room of this building 15 mosquitoes ... which had previously been contaminated by biting yellow fever patients, as follows: 1, a severe case, on the second day, Nov. 27, 1900, twenty-four days; 3, a well-marked case, on the first day, Dec. 9, 1900, twelve days; 4, a mild case, on the first day, Dec. 13, 1900, eight days; 7, a well-marked case, on the first day, Dec. 16, 1900, five days-total, 15.

Only one of these insects was considered capable of conveying the infection, viz., the mosquito that had bitten a severe case twenty-four days before; while three others – the twelve-day insects – had possibly reached the dangerous stage, as they had been kept at an average temperature of 82 F.

At 12, noon, of the same day, John J. Moran – already referred to as Case 2 in this report – a non-immune American, entered the room where the mosquitoes had been freed, and remained thirty minutes. During this time he was bitten about the face and hands by several insects. At 4.30 p.m., the same day, he again entered and remained twenty minutes, and was again bitten. The following day, at 4.30 p.m., he, for the third time, entered the room, and was again bitten.

...

On December 25, 1900, at 6 a.m., the fourth day, Moran complained of slight dizziness and frontal headache. At 11 a.m. he went to bed, complaining of increased headache and malaise, with a temperature of 99.6 F., pulse 88;

at noon the temperature was 100.4 F., the pulse 98; at 1p.m., 101.2 F., the pulse 96, and his eyes were much injected and face suffused. He was removed to the yellow fever wards. He was seen on several occasions by the board of experts and the diagnosis of yellow fever confirmed.

The period of incubation in this case, dating from the first visit to "Building No. 2" was three days and twenty-three hours. If reckoned from his last visit it was two days and eighteen hours. There was no other possible source for his infection, as he had been strictly quarantined at Camp Lazear for a period of the thirty-two days prior to his exposure in the mosquito building.

During each of Moran's visits two non-immunes remained in this same building, only protected from the mosquitoes by the wire-screen partition. From Dec. 21, 1900, till Jan. 8, 1901, inclusive – eighteen nights – these non-immunes have slept in this house, only protected by the wire screen partition. These men have remained in perfect health to the present time.

December 28, after an interval of seven days, this house was again entered by a non-immune American, who remained twenty-five minutes. The subject was bitten by only one insect. The following day he again entered and remained fifteen minutes, and was again bitten by one mosquito. The result of these two visits was entirely negative. As the mortality among the insects in this room, from some unknown cause, had been surprisingly large, it is possible that the subject was bitten by insects not more than thirteen days old, in which case they would probably not infect, since they had been kept for only five days at a temperature of 82 F., and for eight days at the mean temperature of the room, 78 F.

Be this as it may, nothing can be more striking or instructive as bearing upon the cause of house infection in yellow fever, than when we contrast the results obtained in our attempts to infect Buildings No. 1 and No. 2; for whereas, in the former all of seven non-immunes escaped the infection, although exposed to the most intimate contact with the fomites for an average period of twenty-one nights each; in the latter, an exposure, reckoned by as many minutes, was quite sufficient to give an attack of yellow fever to one out of two persons who entered the building – 50 per cent.

Thus at Camp Lazear, of 7 non-immunes whom we attempted to infect by means of the bites of contaminated mosquitoes, we have succeeded in convey-

ing the disease to 6, or 85.71 per cent. On the other hand, 7 non-immunes whom we tried to infect by means of fomites, under particularly favorable circumstances, we did not succeed in a single instance. Out of a total of 18 non-immunes whom we have inoculated with contaminated mosquitoes, since we began this line of investigation, 8, or 44.4 per cent., have contracted yellow fever. If we exclude those individuals bitten by mosquitoes that had been kept less than twelve days after contamination, and which were, therefore, probably incapable of conveying the disease, we have to record eight positive and two negative results – 80 per cent.

Conclusions:

(1) The mosquito ... serves as the intermediate host for the parasite of yellow fever.

(2) Yellow fever is transmitted to the non-immune individual by means of the bite of the mosquito that has previously fed on the blood of those sick with this disease.

(3) An interval of about twelve days or more after contamination appears to be necessary before the mosquito is capable of conveying the infection.

(4) The bite of the mosquito at an earlier period after contamination does not appear to confer any immunity against a subsequent attack.

(5) Yellow fever can also be experimentally produced by the subcutaneous injection of blood taken from the general circulation during the first and second days of this disease.

(6) An attack of yellow fever, produced by the bite of the mosquito, confers immunity against the subsequent injection of the blood of an individual suffering from the non-experimental form of this disease.

(7) The period of incubation in thirteen cases of experimental yellow fever has varied from forty-one hours to five days and seventeen hours.

(8) Yellow fever is not conveyed by fomites, and hence disinfection of articles of clothing, bedding, or merchandise, supposedly contaminated by contact with those sick with this disease, is unnecessary.

(9) A house may be said to be infected with yellow fever only when there are present within its walls contaminated mosquitoes capable of conveying the parasite of this disease.

(10) The spread of yellow fever can be most effectually controlled by measures directed to the destruction of mosquitoes and the protection of the sick against the bites of these insects.

(11) While the mode of propagation of yellow fever has now been definitely determined, the specific cause of this disease remains to be discovered.

Chapter 24

Theobald Smith

Redaction of the 1893 Smith and Kilborne monograph on Southern cattle fever:

HISTORICAL REVIEW

Up to the time at which these investigations were begun, a certain number of very important facts had already been ascertained and repeatedly confirmed concerning the nature of Texas or Southern cattle fever. There were also a number of theories in the field concerning the causation or etiology of this disease, based in part on investigation, in part on speculation.

Of those definitely ascertained facts, we may mention as the most important the one which traced the distribution of the infection to cattle brought from a large but well-defined territory, including most of the Southern states, into more northerly regions. The Southern cattle bearing the infection were, as a rule, free from any signs of disease. It was likewise settled that this infection was carried only during the warmer season of the year, and that in the depth of winter Southern cattle were harmless. It was also known that the infection was not communicated directly from Southern to Northern cattle, but that the ground over which the former passed was infected by them, and that the infection was transmitted thence to susceptible cattle. All that was necessary for the production of disease was the passage of Southern cattle over a given territory and the grazing of Northern cattle over the same or a portion of the same territory during the same season.

It was also discovered that Southern cattle, after remaining for a short time on Northern pastures, lost, in some mysterious way, the power to infect

other pastures and were, for the remainder of their stay north, harmless. Again, cattle driven over a considerable distance lost, after a time on their way, the power to infect pastures. When pastures and trails had been passed over by Southern cattle, it was observed that the disease did not appear at once in the Northern cattle grazing on them, but that a certain period of not less than thirty days elapsed before the native cattle began to die. More curious even than these facts, was the quite unanimous testimony of stock-owners who had had more or less experience with this disease, that native susceptible animals who had become diseased did not transmit the disease to other natives, and that they were harmless. We shall discuss this statement in detail in connection with experiments made to test its accuracy.

If we turn our attention to the opposite aspect of this interesting series of facts which deals with the introduction of Northern cattle into Southern territory, we learn that such cattle may contract Southern cattle fever, and that it is only under considerable risks that Northern cattle can be introduced into what has been called the permanently infected territory.

These interesting facts about a mysterious disease were largely reasoned out by farmers and stock owners in their trying experience with it and were well known before 1868, when the disease began to arouse the attention of the Government, owing to its widespread devastations in the Northern States in that year. The historical record of the development of these ideas is therefore very meager. That Southern cattle in a state of health might bring destruction to Northern herds was observed late in the last century by Dr. Mease. A herd of cattle was driven in 1796 from South Carolina into Pennsylvania, where disease broke out in Lancaster County and other places. This disease was directly traced to the Southern herd by Dr. Mease, who made it the subject of an interesting communication and dwelt particularly upon the fact that the cattle bringing the disease were themselves in good health.

In 1868, Texan cattle shipped up the Mississippi River to Cairo and thence by rail into Illinois and Indiana early in June caused during the summer of that year enormous losses of cattle in these States. Moreover, the East began to be aroused because Western cattle infected with the disease had been shipped eastward for beef and were dying of Texas fever on the way, in the New York stock yards and elsewhere. The question as to the effect of such

diseased flesh upon human health was at that time entirely new and caused much uneasiness. The cattle commissioners of New York State and the board of health of New York City made a vigorous effort to check the importation of diseased cattle from the West, and to their efforts we owe much valuable information of this disease.

...

In addition to this work of accurately defining the territorial distribution of the infection nothing has been done to add materially to the permanently valuable knowledge concerning this malady. Although attempts have been made to discover the cause they were not successful, as we shall be able to show. In 1889 the first systematic experiments were made by the Bureau of Animal Industry and these were at once fruitful in the discovery by one of us of a peculiar microorganism in the red blood corpuscles which corresponds in every respect with what we should expect as the true cause. At the same time the other showed by field experiments that the cattle tick was somehow necessary to the transmission of the disease. These observations were fully confirmed in 1890. In the fall of the same year it was observed that when young ticks hatched artificially are placed on cattle there is a sudden extensive loss of red blood corpuscles accompanied by fever which could in no way be explained by the simple abstraction [sic] of blood. This discovery, at once followed up by additional experiments, brought to light the remarkable fact that Texas fever is caused by putting recently hatched cattle ticks on susceptible cattle. All these results were reconfirmed in the summers of 1891 and 1892.

These investigations have thus far brought to light two important facts:

(1) The constant presence of a blood corpuscle-destroying microorganism in Texas fever, and

(2) the transmission of the disease from cattle to cattle by the cattle tick.

The various experiments and observations which have led to these results are embodied in the following report and Appendix.

...

THE NATURE OF TEXAS CATTLE FEVER

Period of Incubation

This term has no very definite significance in this disease, for it is used to

designate different things. Thus it has been employed to indicate the period elapsing between the exposure of susceptible cattle to Southern cattle, or upon fields infected by them and the appearance of the disease. If taken in this sense it may vary from ten to ninety days. The great variation here observed is readily explained by the life-history of the cattle tick, with which this period is intimately associated. A discussion is therefore postponed until the life-history of this parasite has been described and we content ourselves here by simply mentioning the facts as observed.

This term may also be used to signify the time elapsing between the introduction of the infectious agent into the tissues and fluids of the body and the first appearance of disease. This period is ascertainable by inoculation. In the case of subcutaneous and intravenous injection of blood from cattle suffering with Texas fever, the fever temperature appeared within a few days of the inoculation and outward signs of illness were manifest on or even before the sixth day. It is probable, therefore, that multiplication begins at once after the micro-parasite has been introduced into the body, and when it has attained a sufficient momentum the external symptoms of disease appear. This may be in from six to ten days, depending on the number of micro-parasites originally introduced, the predisposition and age of the animals, and the season of the year.

...

THE PRODUCTION OF TEXAS FEVER IN CATTLE BY THE INOCULATION OF BLOOD FROM CASES OF THE DISEASE

The demonstration that Texas fever is caused by a certain microorganism is not absolutely made by showing that it is always associated with this disease and not observed in health. It may be argued that such bodies are the concomitant rather than the cause of the fever. Nevertheless it may be said that no microorganism constantly associated with a given infectious disease has yet been found which is not demonstrably or presumptively the cause of the disease. Hence the probability that the micro-parasite described is the cause of Texas fever is very high, although the demonstration cannot be made until such organism can be cultivated in some manner outside of the animal body and inoculations made with pure cultures. There is nothing today to encourage us in the hope that parasites so highly adapted as the one

under consideration will ever submit to the crude culture methods successful with many bacteria.

The high probability that we have the cause of Texas fever before us is increased by the fact that when blood from cases of this disease is injected into the circulation of healthy susceptible cattle, the disease is produced and the micro-parasite appears in the blood under the same conditions under which it becomes manifest in the natural disease. There is still the possibility before us that the micro-parasite is transmitted in the diseased blood and that some unknown agent has been transmitted with it which is the true cause of the infection. It is useless to discuss this further, and each reader must form his own opinion of the value of the experimental evidence adduced in this report ...

With these positive results before us we need not hesitate to make the statement that there is something in the blood of cattle during Texas fever which, introduced into the body of healthy susceptible cattle, gives rise to the disease. This something is capable of reproducing itself indefinitely in the blood of susceptible animals. In all cases there had been multiplication of the Texas fever parasite, and these inoculations furnish additional proof that this parasite may be regarded as the cause. These inoculations show, also, that a comparatively small quantity of blood from diseased cattle placed under the skin is capable of causing a severe and even fatal infection. In this respect the microorganism seems to have as powerful an effect as the bacteria which produce acute fatal forms of septicaemia and seems to be capable of almost equally rapid multiplication. The sojourn of three days in a refrigerator did not destroy the vitality of the microorganism as it exists in the blood. The very severe inoculation disease produced in 1891 and 1892, as compared with 1890, is partly to be accounted for by the fact that only old animals were used latterly, while in 1890 the animals were young. The observations made in the field experiments and by former observers, that the susceptibility seems to increase with age, provided there has been no exposure to the disease at any time in life before, is thus indirectly confirmed by inoculation. The very striking susceptibility of cattle to this disease was furthermore demonstrated by the intravenous inoculation of three guinea-pigs at the same time with three of the cases cited above. These animals remained perfectly well, though

they had received relatively to their body weight a very much larger quantity of the defibrinated blood. ...

The inoculations made by us demonstrate that sheep, pigeons, rabbits, and guinea-pigs are to all appearances insusceptible to this disease, whereas in cattle the disease may be invariably produced by the injection of infected blood. It is to be hoped that opportunity will be presented the coming summer to try other species of animals.

...

FIELD EXPERIMENTS TO DETERMINE THE PRECISE RELATION BETWEEN THE CATTLE TICK AND TEXAS FEVER

These experiments were begun in the summer of 1889 and have been continued up to the present. They have been carried on in three different directions:

1) Ticks were carefully picked from Southern animals, so that none could mature and infect the ground. The object of this group of experiments was to find out if the disease could be conveyed from Southern to Northern stock on the same inclosure without the intervention of ticks.

2) Fields were infected by matured ticks and susceptible cattle placed on them to determine whether Texas fever could be produced without the presence of Southern cattle.

3) Susceptible Northern cattle were infected by placing on them young ticks hatched artificially, i.e., in closed dishes in the laboratory.

These three lines were not followed simultaneously because, for instance, the fact that the disease can be produced by placing young ticks on cattle was discovered in 1890, and hence only tried then and thereafter. In giving the details of the various experiments we shall adhere not to the classification given above, but rather to the chronological order in which the experiments were performed. This is necessary in order to describe successively the experiments of the same year which were more or less connected with one another and also to show the process by which the various facts concerning the cattle tick came to our knowledge.

The disease was introduced into one field each year by North Carolina cattle brought here for this purpose. In 1890 a field was infected by cattle from Texas. The field experiments were all conducted on the experiment

station of the Bureau of Animal Industry within half a mile of the limits of the city of Washington. The arrangement of the various experimental fields is shown for each year on a plat of the station grounds. The isolated condition of the field in use in any given season may be seen by an inspection of these plats. They are either separated from one another by a piece of ground remaining permanently free from infection or by a lane or by a strip of ground purposely fenced off between them. No two fields in use are thus separated merely by a fence. In every case, with the exception to be noted, a strip of ground intervenes which is at least 36 feet wide. A small brook passes through a portion of the grounds as is shown in the various plats, and the space between the fields along this brook is about 20 feet wide.

...

GENERAL SUMMARY OF THE FIELD EXPERIMENTS RELATING TO THE CATTLE TICK

We are now in a position to review the results of the field work of the past four summers and determine how far they enable us to draw definite conclusions. In addition to the general control experiments ... by which Texas fever was produced in the natural way in natives which pastured on the same ground with Southern (North Carolina and Texas) cattle, experiments have been carried on in the three directions outlined [earlier]:

(1) Experiments with Southern cattle from which the ticks were picked off were made every year. Those made in 1889 and 1892 were successful. Those made in 1890 and 1891 failed because young ticks appeared subsequently. The conclusion from these experiments that the tick is necessary to cause infection in Northern cattle may be regarded as demonstrated.

(2) Experiments to show that fields may be infected by cattle-ticks alone were made in 1889 and 1890. In both Texas fever was produced.

(3) Experiments to show that young ticks artificially hatched produce Texas fever when placed on susceptible cattle were made in 1890, 1891, and 1892. These were uniformly successful in the summer and fall months. It was observed, however, that the disease induced by such ticks is less fatal than that produced in the fields in the natural way. We are not prepared to account for this difference, unless it be the mode of incubation. The artificial condition of heat and moisture under which the eggs are kept may lead to

a speedy destruction of the micro-parasites which are in some unknown way associated with them.

THE RELATION OF THE CATTLE TICK TO THE "PERIOD OF INCUBATION" OF TEXAS FEVER AND TO THE INFECTIOUSNESS OF SOUTHERN CATTLE

In the foregoing experiment everything points to the cattle tick as the natural transmitter of the disease. It has been definitely demonstrated by our experiments that not only fields may be infected by simply scattering matured ticks over them, but that cattle themselves may be infected in stables away from all infected ground by placing on them young ticks artificially hatched.

We are now in a position to understand the peculiar variability in the period of incubation. We have seen from the experiments related that when native cattle are exposed to Southern cattle on a given field the period elapsing before the disease appears is generally over forty-five days, and the first deaths usually occur one or two weeks later ...

This long period coincides with the time necessary to produce a new generation of ticks. When Southern cattle graze on a certain pasture in early summer, say for a day only, a few ripe ticks drop off. They lay their eggs in about seven days. These are hatched in about twenty days and are at once ready to crawl on cattle. Ten days thereafter the first high temperature usually appears. If we add these figures together we find that the disease may appear about thirty-seven days after the field was infected. To be sure these figures are liable to fluctuations, which may make this period much longer or perhaps a little shorter at times.

When Southern cattle are placed on a certain field and kept there, as in our experiments, the field becomes much more abundantly infected with ticks, for the reason that all the ticks in their various stages ripen and fall on the same ground. Hence there is a continuous infection of the field going on for several weeks, until all the ticks originally attached to the Southern cattle have disappeared. This may increase the severity of the disease.

But how may we account for the fact that cattle placed on infected pastures later may become diseased at the same time and may die in less than fifteen days after the first day of exposure? Simply by taking into account the fact that cattle exposed late are at once attacked by the young ticks already

present on the field. Hence, if we allow ten days for the fever to appear after the ticks have crawled on the cattle the mystery is at once explained.

The explanation of unusually prolonged periods of incubation is equally simple. They are associated with very early importations of cattle and the low temperature retards the development of the young in the egg. We have already shown that this development may be greatly retarded by cold, and we have observed periods of incubation ranging from twenty to forty-five days and have kept eggs over winter which developed when the temperature became warm enough the following spring. ...

There is general unanimity on this point, that a long period elapses between the date of infection of a given pasture and the appearance of the disease, so that further illustrations may be dispensed with. In searching over all the various publications on this subject we have not yet encountered any authentic statement which gave dates to support its claims that Texas fever ever appeared on a field within thirty days of the time that it was entered by tick-bearing cattle. If there are any such outbreaks, they may have been produced either by ticks wintering over in the egg or by an infection of the field earlier than that actually noted. It is not improbable that Southern animals may accidentally carry some eggs of ticks nearly hatched on their feet or other parts of their body. In such a case disease might appear several weeks earlier. The same would be true if ticks which have once attached themselves to cattle may, after being accidentally torn or brushed off, crawl upon natives, provided they are still infections.

The relation of young ticks to Texas fever explains why natives placed in an infected inclosure at various intervals before the appearance of the young ticks will all contract the disease at the same time. They may mingle with freshly arrived Southern stock for twenty or twenty-five days before becoming infected. If removed at the end of this period before the appearance of young ticks they remain healthy. ... We now understand why natives placed on an infected field after the young ticks have appeared will contract Texas fever in ten to fifteen days. The life history of the tick likewise explains the frequently observed fact that Southern cattle lose the power of infecting Northern pastures after a certain number of days. We have already stated that the ticks on Southern cattle gradually disappear as they become matured. It is evi-

dent that when all have dropped off, the power of the cattle to infect fields is lost. It is possible to give the exact period of time required, provided we know the time which has elapsed since Southern cattle left their pastures, where they are being continually infected with young ticks. On the station pastures the time required for all the ticks to disappear was twenty-five to thirty days. Very soon thereafter the young ticks, descended from the ticks which matured first, appeared on all cattle, and the Southern animals again became infectious. The maturation of the second generation may push the period of disease into the fall and thereby rob it of its fatality.

We now likewise understand how cattle driven slowly northward lose their infection after a time. As soon as they have left the territory where ticks abound they receive no more accessions of young ticks and they are continually dropping mature ones. After twenty-five to thirty days, or perhaps sooner, they have parted with all and are henceforth harmless to Northern stock.

Let us now review briefly what occurs when Southern tick-bearing cattle are placed on the same inclosure with natives. If the animals be brought together early in July, as in our experiments, nothing unusual will be noticed for weeks. The ticks on the Southern animals slowly mature, swell up, and drop off, one by one, so that after three or four weeks all have practically disappeared. If during the second week in August the cattle be carefully examined, young ticks will be found, attached to the skin and buried within the coat of hair. They may be overlooked if the examination is superficial and hasty. A week later, generally in the third week in August, the temperatures of all exposed native cattle suddenly rise to 105 or 107 F. within a few days of one another. The ticks at this time are still quite small, and have not yet passed through the second molt. Even at the post-mortem examination of many cases only small, immature ticks are found. If the natives survive the attack, the ticks mature, swell up, and drop off, ready to give birth to a second generation if the season permits.

THE RELATION OF THE CATTLE TICK TO THE MICROORGANISM OF TEXAS FEVER

The hypothesis which seemed most plausible after the experiments of 1889 was that the tick, while withdrawing the blood from Southern cattle, drew

out in it the Texas-fever parasite, which, entering into some more resistant state, perhaps some spore state, was disseminated over the pastures when the body of the mother tick became disintegrated. These spores were then supposed to enter the alimentary tract with the food and infect the body from this direction. The later experiments, however, completely demolished this conception. Neither the feeding of adult ticks and tick eggs nor the feeding of grass from infected pastures gave any positive results. On the other hand, the unmistakable outcome of the experiments was that the young tick introduced the infection into the body. This fact implies two possibilities. Either the tick is a necessary or a merely accidental bearer of the micro-parasite. If a necessary bearer of the infection, we must assume that the latter undergoes certain migrations and perhaps certain changes of state in the body of the adult tick and finally becomes lodged in the ovum. Subsequently it may become localized in certain glands of the young tick and discharge thence into the blood of cattle. This hypothesis assumes a complex symbiosis between the tick and the parasite on the one hand and the cattle and the tick on the other. According to another, simpler hypothesis the tick would be merely an accidental bearer of the infection. The parasite entering the body of the tick with the blood of cattle may be already in the spore state or about to enter upon such a state. The young ticks, as they are hatched near the dead body of the female, may become infected from this. This infection, clinging to their mouth parts, is introduced into the blood of the cattle to which they subsequently attach themselves. Further investigations are necessary before the probable truth of one or the other of these hypotheses can be predicated with any degree of certainty.

It should be stated that the contents of the bodies of ticks in various stages of growth have been examined microscopically with considerable care. The abundant particles resulting from the breaking up of the ingested blood corpuscles obscured the search so that nothing definite has thus far resulted from it. The very minute size of the microorganism renders its identification well-nigh impossible, and any attempts will be fraught with great difficulties.

A question of much interest, but one upon which we have no information, is the relation of the cattle tick to the enzootic Texas fever area. Is the distribution of the tick coextensive with that of the Texas fever micro-parasite, or

does their distribution obey different laws? This question could be solved by a thorough investigation of a small portion of the border line of the enzootic territory. This border line probably depends on the mean annual temperature, and hence we cannot expect to find it very sharply defined. Ticks may extend farther north during some seasons than others, and hence there may be a belt or strip on which cattle are partially insusceptible because of former repeated attacks, although for the time being ticks may be absent. The entire subject is at present speculative, and is simply referred to here to arouse the attention of those who are in a position to record observations concerning it.

THE RELATION OF SOUTHERN CATTLE TO THE TEXAS-FEVER INFECTION

What has already been said concerning the tick makes it certain that all Southern cattle are dangerous when they bear the cattle tick, whether they are sick or healthy. On the experiment-station fields, the North Carolina and Texan cattle which called forth Texas fever during the four years of the investigation were, in general, healthy. Two cows ... were killed. One of these had impoverished blood, although positive signs of Texas fever were not detected. Another died of peritonitis. The remainder were healthy, improved on the pastures, and were sold at the beginning of winter or before.

In the foregoing pages it has been assumed that the tick obtains the micro-parasite from Southern cattle. Without demonstration it might be claimed with equal propriety that the micro-parasite belongs essentially to the cattle tick, and that its multiplication in the body of susceptible cattle is perhaps an accidental phenomenon against which Southern cattle have been amply protected by frequent infection. Experiments made latterly, as well as the microscopic examination of the blood, prove that the micro-parasite is harbored by Southern cattle in a state of health.

...

Whether the Texas fever parasite resides permanently in the bodies of Southern cattle or whether its presence, after all, depends on that of the cattle tick, these experiments do not permit us to decide definitely at present. From an economic standpoint this is of little importance, since in many parts of the permanently infected territory of the South ticks are present during the entire year.

The presence of the parasite in Southern cattle does not seem to materially affect their health although it may maintain a more or less constant breaking up of the red corpuscles on a small scale, which would necessarily tax certain vital organs. The parasite is present in the circulating blood in such small numbers, however, that only after a most tedious microscopic examination is it occasionally encountered. The fact that Southern cattle rid themselves of infectious properties on Northern pastures after twenty-five to thirty days does not, therefore, imply that their blood is no longer infections. It simply signifies that they have rid themselves of the means by which this parasite is transmitted, namely, the cattle tick.

...

PREVENTION

Texas fever in the territory outside of the enzootic region is the result of the distribution of ripe egg-laying ticks by cattle from the enzootic region. Hence such cattle should not be allowed on uninfected territory during the warmer half of the year. It is also evident that all cars carrying Southern cattle contain a larger or smaller number of ticks which have dropped off during the journey and which are ready to lay their eggs. The sweepings of such cars, wherever deposited, may give rise to a crop of young ticks and these, when they have access to cattle, will produce the disease. Wherever Southern tick-bearing cattle are kept within twenty-five to thirty days after their departure from their native fields they are liable to infect such places, since it requires the period mentioned for the smaller ticks to ripen and drop off. But under special conditions even this period is too short and the Southern cattle may remain dangerous a longer time. This would occur when such cattle remain in any one inclosure long enough (four to five weeks) for the progeny of the first ticks which drop off to appear on the same cattle.

The above points are covered in the regulations of the Department of Agriculture concerning cattle transportation. These regulations insist on the complete isolation of cattle coming from the permanently infected territory between March 1 and December 1 of each year and on the proper disinfection of the litter and manure from such cattle during transportation. Furthermore such cattle can only be transported into uninfected territory for immediate slaughter during the prescribed period. These regulations if properly carried

out would prevent the appearance of Texas fever at any time in those areas north of the enzootic territory. The only question which now presents itself with reference to them is the efficiency of the prescribed disinfection. It has been shown that the infection resides only in the cattle ticks and their eggs; hence the destruction of these is absolutely essential to make the disinfection of any value. In the present report this question has not been touched upon; therefore, pending the trial of various disinfectants, which is now going on, any discussion or any suggestions are of little value.

The harmlessness of Southern cattle after being deprived of the cattle tick brings up the very important question whether such cattle can not by some means be freed from ticks so that their transportation may go on without any restriction during the entire year. There are several ways in which experiments might be undertaken. Cattle might be subjected to disinfecting washes of various kinds, or else they might be run through disinfecting baths which expose the whole body to the action of the liquid used. Such processes would require careful attention. The survival of a very few ticks might lead to serious consequences, since a single ripe tick averages about 2,000 eggs.

Cattle may be deprived of ticks on a large scale without the use of any disinfection if the following plan be adopted: Two large fields in a territory naturally free from cattle ticks are inclosed. The tick-bearing cattle are put into the first inclosure and kept there about fifteen days. They are then transferred to the second inclosure for the same length of time. Thirty days after the beginning of their confinement they may be considered free from infection. The reason for this procedure is simple enough. The cattle drop the ticks as they ripen in the inclosures. By being transferred to a second (or even a third) inclosure they are removed from the possible danger of a reinfection by the progeny of the ticks which dropped off first. It is evident that such inclosures can only be used once a season, since the young ticks subsequently hatched remain alive for an indefinite length of time on the ground. Such inclosures must not be located where there is a possibility that the ticks might survive the winter.

For cattle which are introduced into the enzootic territory two modes of prevention may be adopted. Either they are kept entirely free from ticks by confinement in stables or upon pastures known to be free from ticks, or else

they are exposed to the infection in such a way as to become insusceptible to it after a time. The first method is open to the objection that ticks may at some time accidentally gain access to such cattle and produce a fatal disease. The second method seems the more rational, provided it can be successfully carried out. We know that Southern cattle are insusceptible to the disease, and the way in which this insusceptibility has been acquired has been already discussed. Young animals seem to be largely proof against a fatal infection, although they are by no means insusceptible. The repeated mild attacks to which they are subjected finally makes the system indifferent to the virus. The introduction of young animals into the permanently infected territory, though not without danger, is far safer than the introduction of animals older than one year. The danger of a fatal infection increases with the age of the animal and is very great in cows over 5 or 6 years old, as is distinctly shown by the experiments recorded in this report.

The subject of preventive inoculation has already been discussed ... It has been shown that while in general two mild attacks may not prevent a third attack, this will not be fatal. One very acute attack will usually prevent a second severe attack. Hence it is possible to prevent cattle, even when fairly along in years, from succumbing to a fatal attack by several preliminary carefully guarded exposures to a mild infection. This infection may be produced by scattering ripe ticks in an enclosure, or by placing young ticks on cattle in the fall of the year ... Protective inoculation of this kind should be carried on at some locality outside of the enzootic territory carefully chosen for the purpose. A few years of careful experimentation would probably lead to an efficient method which, when definitely formulated in all its details, could be applied in different parts of the country. Such experimentation should, of course, pay special attention to the relative susceptibility of the various higher grades of cattle, a matter which we have been unable to touch upon thus far.

What can the individual farmer or stock-owner do in the event that Texas fever has been introduced into his pastures? From what has been said thus far pastures which have been infected by Southern cattle or ticks from the litter and manure of infected cattle cars should be avoided during the entire summer season. While we know that young ticks may remain alive in jars

for two or three months without food, it would be premature to conclude that such is the case on pastures, as the conditions are quite different. Yet everything seems to point to a long sojourn of young ticks on infected fields, and pending the carrying out of experiments to test this question we would recommend that native cattle be not allowed to graze on infected fields until after the first frosts, for even a mild attack in fall before the ticks have been destroyed by frosts is debilitating to cattle. The period of time during which infected localities remain dangerous varies, of course, with the latitude, and would be shorter the colder the climate.

The infection of stables, stalls, and other structures with the ticks should be counteracted by thorough disinfection. The adult ticks and the eggs must be destroyed. As stated above, we know as yet very little concerning the agents which will destroy the vitality of the eggs of ticks, but the use of water near the boiling point may be sufficient, if liberally applied, to destroy the life of the embryos. In the case of litter and manure heaps the thorough saturation with some strong mineral acid in dilution may accomplish the purpose. Ordinary lime, slaked or unslaked, densely sprinkled over infected places so as to form a continuous layer may be recommended. The slow incrustation of the egg masses with carbonate of lime may be expected, provided the manure is under cover. Otherwise it will be washed away and may leave the eggs unharmed. In regions outside of the enzootic territory the absence of ticks may be accounted for by the severity of the winter; hence in unprotected localities disinfection is unnecessary after the winter has set in. But it may occur that in sheltered places the eggs will winter over and the ticks reappear the following spring. Whether such ticks are likely to produce any serious trouble in the absence of Southern cattle we are unable to state definitely. All that we know is that disease may break out when Southern cattle of the preceding year are in the pasture, as was demonstrated accidentally in our investigations during 1891. Hence all infected material should be freely exposed to the frost, even though treated with disinfectants beforehand.

...

CONCLUSIONS

(1) Texas cattle fever is a disease of the blood, characterized by a destruction of red corpuscles. The symptoms are partly due to the anaemia

produced; partly to the large amount of debris in the blood, which is excreted with difficulty, and which causes derangement of the organs occupied with its removal.

(2) The destruction of the red corpuscles is due to a microorganism or micro-parasite which lives within them. It belongs to the protozoa and passes through several distinct phases in the blood.

(3) Cattle from the permanently infected territory, though otherwise healthy, carry the micro-parasite of Texas fever in their blood.

(4) Texas fever may be produced in susceptible cattle by the direct inoculation of blood containing the micro-parasite.

(5) Texas fever in nature is transmitted from cattle which come from the permanently infected territory to cattle outside of this territory by the cattle tick.

(6) The infection is carried by the progeny of the ticks which matured on infected cattle, and is inoculated by them directly into the blood of susceptible cattle.

(7) Sick natives may be a source of infection (when ticks are present).

(8) Texas fever is more fatal to adult than to young cattle.

(9) Two mild attacks or one severe attack will probably prevent a subsequent fatal attack in every case.

(10) Sheep, rabbits, guinea-pigs, and pigeons are insusceptible to direct inoculation. (Other animals have not been tested.)

(11) In the diagnosis of Texas fever in the living animal the blood should always be examined microscopically if possible.

Chapter 25

Charles Nicolle

Nicolle's Nobel Prize Lecture that discusses inapparent infection:

At the beginning of my research the only animals I knew to be susceptible to the disease were monkeys. All species of monkeys can be infected, provided that a sufficient quantity of virus is inoculated through the peritoneum. The monkey was well suited for preserving the virus. But the monkey is an expensive animal. During the first two years, therefore, I had to be satisfied with studying typhus during the months of its seasonal expansion, experimenting from man to monkey and, exceptionally, from one monkey to another. The discovery that I soon made that the guinea pig was also susceptible to infection made it possible for me, from the third year on, to preserve the virus on this animal. It was then easy for me to conduct my research independently of epidemics, that is, all the time. From the practical point of view, the susceptibility to infection of the guinea pig proved to be the most useful step forward. Today, all laboratories use this animal for preserving the virus.

In man typhus is characterized by a triad of symptoms: fever, rash, nervous symptoms. In animals, fever is the only sign of infection. The fact that the virus is localized more particularly in the brain explains the nervous symptoms to be found in our species.

I demonstrated the characteristics of experimental fever. It appears after an incubation period which is never less than five days. It follows the same pattern as natural fever in man, but is of shorter duration and less pronounced. There follows a period of hypothermia, clearly apparent in the monkey, but less obvious in the guinea pig. In the monkey there are minor

general symptoms and subsequent loss of weight is usual. In the guinea pig the disease would be inapparent if the temperature were not noted. At the time when I was conducting my research there was no known method for taking the guinea pig's temperature. I demonstrated a technique which is now widely used.

I have already mentioned that the virus could be kept indefinitely by injecting guinea pigs. For this purpose, brain tissue gives more constant results than blood.

It can sometimes happen, especially when blood is used, that out of a group of guinea pigs inoculated with the same dose of the same product, certain of them show no signs of fever. At first I attributed this fact to a technical fault or to greater individual resistance. Repeated negative results precluded my continuing to accept these oversimplified explanations. Animals for which the virus is pathogenic present a whole scale of degrees of susceptibility from the grave form, often fatal in adult Europeans, down to the fever, revealed only by the thermometer, in the guinea pig, passing through all the intermediate stages: typhus of the native adult, benign typhus in children, still more benign in monkeys. I wondered if there was not, below the very slight susceptibility of the guinea pig, an even lesser degree in which the only sign of infection was the virulence of the blood during the period when more susceptible animals showed signs of the characteristic fever. This was indeed the case. I was able to ascertain this fact in 1911. A little later I went back to study this problem with Charles Lebailly. It led me to the conception of what I have called inapparent infections. Apyretic typhus, without symptoms, the inapparent typhus presented by the guinea pig, is the first case described and the most well known.

Inapparent typhus in the guinea pig may be a primary infection typhus, as was the case I discovered. The cause in this case is the inoculation of a quantity of virus insufficient to produce fever. Blood from a guinea pig who has contracted inapparent typhus will always produce pyretic typhus in another guinea pig if the dose inoculated is sufficient. The positive result of this inoculation proves in fact that the first guinea pig had contracted typhus, in spite of the lack of fever.

Having ascertained inapparent typhus in cases of primary infection, it was

then easy for me to demonstrate the existence of apyretic typhus in certain guinea pigs that had been reinoculated a fairly long time after contraction of a primary infection of pyretic typhus.

Lebailly and I then went on to demonstrate that inapparent primary infection typhus, which is exceptional in inoculated guinea pigs, is the only form which the disease takes experimentally in the rat and the mouse. This curious disease, which presents no symptoms, which has an incubation period and a period when the blood is virulent, and which confers a certain degree of immunity, can be transmitted from one rat to another. On two occasions I effected twelve such transmissions. At the twelfth, brain tissue from the rats induced pyretic typhus in the guinea pig.

This new concept of inapparent infections that I introduced to pathology is, without a doubt, the most important of the discoveries that I was able to make. In the absence of fever, experimental work on typhus must take into account the possible existence of inapparent forms. We shall see that this concept alone can explain the preservation of the virus in nature and the reappearance of seasonal epidemics. I applied this new concept to measles and certain spirochaete infections, and Georges Blanc has just discovered the existence of inapparent dengue in man, as well as in the monkey and the guinea pig.

Thus my research opened a new chapter, subpathology, which is doubtless a vast field where almost everything remains to be discovered.

We have known for a long time that primary infection of typhus confers immunity in man in almost all cases and that this immunity lasts a lifetime. I established that laboratory animals were subject to a similar immunity; but I also demonstrated that this was of shorter duration than was generally thought before the discovery of inapparent typhus in secondary infections. Although benign, inapparent typhus also confers a certain degree of immunity.

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The role of inapparent typhus in cases of re-infection is indubitably even more important. This alone explains the preservation of the virus in nature when there is no epidemic and the seasonal reappearance of the epidemics themselves. It would be impossible to understand how typhus could remain active if this depended on the louse continually finding different people to

infect. And if this is self-evident in the case of typhus, it is even more so for measles. We have no doubt discovered here the most useful application of the concept of inapparent infections.

Just as the only reservoir for the typhus virus in nature is provided by man, so the only vector of infection is the louse. The bite of the louse is not virulent immediately after the infecting meal. It becomes so only towards the 7th day following infection. On the 9th and 10th days the bite is invariably virulent. It is therefore a necessary condition that the virus should multiply within the louse for it to become dangerous. I have shown that this multiplication takes place in the digestive tract and that louse feces become virulent at the same period as does the bite. This observation was made in 1910.