The Why of Things

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Causality in Science, Medicine, and Life

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TO MY MENTORS
Donald Gallant
Paul McHugh
Philip Slavney
Marshal Folstein

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Preface

The ideas developed in this book were first presented at a clinical teaching presentation to the faculty and students of the Department of Psychiatry and Behavioral Sciences at the Johns Hopkins School of Medicine. In this forum, the lecturer begins by discussing a clinical encounter with a patient and uses the issues raised by that person's situation to address a broader question. In trying to address my patient's question, "Why did this happen to me?" I realized that the same question arises for all of us in the course of work and personal life. That a topic such as causality would be considered an appropriate accompaniment to a clinical teaching presentation is a testament to the vision of the then department chair, Paul McHugh, that the practice of medicine should be rooted in an intellectually defensible and discussable framework. While the rough outline of the schema presented in that 1995 lecture is maintained here, the ideas have evolved in response to the input, questions, and criticisms provided by many colleagues, friends, and family members. To them I owe deep gratitude.

I have had many wonderful and influential teachers dating back to elementary school, and I have no doubt that the ideas presented

here are an outgrowth of their teachings. The four individuals to whom this book is dedicated played a special role in my development as a physician and psychiatrist and shaped how I have approached both the scientific and the clinical work I have done throughout my career. Donald Gallant showed me that psychiatry could be intellectually rigorous, that many patients could be helped, and that bringing care to the places where the most disadvantaged lived would make a difference in the lives of many people. From Paul McHugh and Philip Slavney I learned many things, especially the importance of identifying one's core assumptions, modes of logic, and intellectual predecessors. Marshal Folstein guided my immersion in the interface between psychiatry and the brain and impressed upon me the importance of hypothesis testing.

I began writing this book during a three-month sabbatical in 2001. Its decade-long gestation reflects both the evolution of the ideas and the distillation that comes with many rewrites. The Johns Hopkins Berman Bioethics Institute provided office space during my sabbatical and a forum for presenting these ideas, and to its members I am grateful. Much of the writing and editing took place in the Plum Lake cabin of Marilyn and Peter Julius. Having this extraordinary place away from the distractions of clinical work, teaching, and administration helped me refine my thinking.

Philip Slavney gave a close reading to the first complete draft of the book, and his extensive input improved many aspects of my logic and presentation. My editor, Patrick Fitzgerald of Columbia University Press, was both supportive and critical and helped further improve the writing. The three anonymous reviewers he recruited to vet the typescript made many valuable suggestions, and to them I express gratitude.

My extraordinary family has been supportive throughout the writing of this book. Discussions with them have helped shape my ideas, and they have contributed to the artwork. They continue to inspire and teach me. My wife, Karen, read the final manuscript and, as she has in many of my writings, made significant contributions to the ideas and the writing.

The Why of Things

INTRODUCTION

Men are never satisfied until they know the "why" of a thing.
—Aristotle

On March 11, 2011, a tsunami struck the Fukushima Daiichi power plant on the northeastern coast of Japan. The plant had shut down, as planned, forty minutes previously, when an earthquake occurred just miles off the coast, but the tsunami destroyed the backup sources of electricity that powered the required constant cooling of the reactors. The resultant core meltdown of three of the facilities' five reactors led to a major release of radiation.

What caused this catastrophic failure? The most straightforward answer is the earthquake and tsunami. But subsequent expert analyses cited "technical and institutional weaknesses," such as a weak authority structure at the plant and within the company that managed it and the voluntary nature of the standards by which nuclear power plants are managed and overseen. Still others pointed to the plant designers' failure to provide a mechanism by which cooling could continue in the face of prolonged power loss and their decision to build so many reactors at a single site.

Thirty-two years earlier, in March 1979, the nuclear power plant at Three Mile Island, Pennsylvania, experienced a catastrophic failure. The precipitating event was an open valve that triggered a series

of events ending in reactor failure. In his book on the catastrophe, entitled *Normal Accidents*, the sociologist Charles Perrow concluded that the complexity of modern industrial production facilities, especially nuclear power plants, makes catastrophic failure inevitable and predicted such an accident every decade (Chernobyl and Fukushima have followed in the next thirty-two years). Perrow identified a number of causes that contributed to the Three Mile Island failure, including the multiplicity of interacting elements at the plant and an unwillingness by the many groups of people involved in design, management, political approval, financing, and disaster preparedness to accept the inability of humans to anticipate all potential sources of failure—an attitude best characterized as human hubris.

In my work as a psychiatrist over the past thirty-five years, I have often been asked questions about cause: "Why have I become depressed? Is it something I did or should have done? Or is it some experience of mine in the past?" "Is it genetic since my mother was treated for depression?" "Is this a punishment from God?" "Why do I seem to become friends with people who ultimately turn on me?" "Why do I repeatedly get into trouble with my bosses and lose jobs?"

It is questions such as these that led to the writing of this book. These "why" questions seem so natural to ask, and so important, that many people are convinced that they should be answerable. Yet the answers to questions such as why the Fukushima and Three Mile Island disasters occurred or why a person becomes depressed are complex and multifactorial. How can we include factors as disparate as a valve left open, the inherent complexity of multisystem manufacturing plants, and the inability of humans to anticipate all of the potential errors and adverse events in operating such a complex system? How can genetics, early life experience, and current events be understood as causing depression in one person but not in another with similar experiences and background? How can one choose where to begin? What are the rules or standards by which answers should be judged? Is there even a standard? Is the task impossible because there is no way to judge a correct answer?

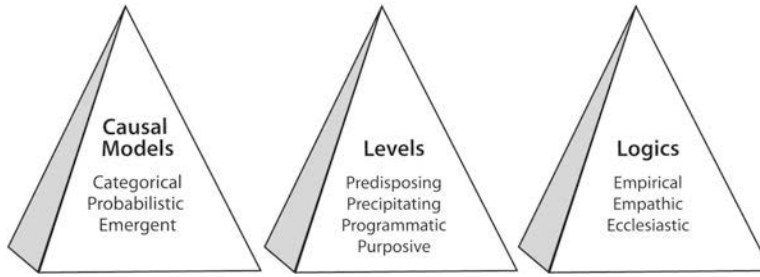
The solution proposed here is a pluralistic approach that assumes that there is a best approach for each question and that it is the job of the seeker to determine which method or combination of approaches

is best suited to the question being asked. This book proposes a three-facet model of causality. As a preview:

- Facet 1 consists of three *conceptual models* of causal logic: the unclosed valve in Three Mile Island is an example of the yes/no or *categorical* model. The genetic contribution to developing depression is likely a graded, *probabilistic* risk rather than an absolute yes/no. A depression that occurs after a relatively minor stress that followed a long string of moderate or severe stressors would be an example of an *emergent* or nonlinear cause.
- Facet 2 describes four *levels of analysis*, an approach first suggested by Aristotle 2,400 years ago. In the Three Mile Island and Fukushima examples, *predisposing* causes were the flawed training and management oversight; the tsunami was a *precipitating* cause. The inherent complexity of the many interacting systems that make up a nuclear power plant is a *programmatic* cause, and human hubris is a *purposive* cause.
- Facet 3 describes the three *logics* by which knowledge of cause is gained. The *empirical* method uses the scientific method, for example, the determination that a genetic variant is present in multiple members of a family in which depression is common. The *empathic* method uses the logic of narrative connectedness to support the reasoning that a specific stressor is negative for one person but not another. *Ecclesiastic* logic would be employed by a believer who attributes cause to an actual lapse in his longstanding participation in the precepts of his religion.

A helpful way to visualize these three facets is as the three sides of a tetrahedron, as shown in the figure here and the diagrams that open each chapter. These diagrams reinforce several important aspects of this approach. First, the three facets are not totally separate but can (and should) be used in combination when appropriate. Second, they are not hierarchical. To help the reader along, each chapter opens with an image of the facet or facets that it will focus on.

The proposed three-facet model is complex, even daunting, and the burden is on the book to justify this complicated approach. I have come to it because several broad challenges must be addressed



by anyone interested in exploring how causal attribution can be justified. First, there is no single definition of cause. Second, the understanding of cause has varied over time and across cultures. And third, one cannot "prove" the existence of the concept of cause or causality. As a result, this book is built on the *premise* that *causes exist* and that *causal relationships can be discovered and confirmed.* This must be stated as an assumption because it is not only impossible to prove but also, as will be discussed later in the book, impossible to disprove. In fact, some well-respected scholars and thinkers claim that the concept of cause is nothing more than a convenience that has no meaning besides its uses in everyday discourse, applied science, logic, or religion. Others cite the widely varying view of causality across cultures as evidence that it is a convention rather than a valid or universal construct.

To make the issue even more complex, there is no single definition or method for determining "the why of a thing." How can it be that there is no one right or best method for determining cause but that causes exist and can be accurately identified and that a best way of approaching a specific question of cause is sometimes possible? I believe an answer to this question emerges when one appreciates that the definition of cause, the history of the concept's development, and the establishment of methods for determining cause are all intertwined. The pluralistic model presented here is built upon an amalgamation of these three big questions. Examples will be used throughout the book to illustrate the types of questions that a particular method or model is useful in addressing. These examples will also illustrate both the strengths and limitations of that approach and

should make it clear that the attempt to identify general principles often oversimplifies what happens in the real world. The reader is encouraged to bring a healthy skepticism to these discussions and to use the examples as checks on whether the arguments that are being put forth have validity.

1

HISTORICAL OVERVIEW

The Four Approaches to Causality

A thing cannot occur without a cause that produces it.

—Pierre Simon de Laplace

The concept of causality is so much a part of our lives that we often think about, discuss, or identify causes without considering the complexity of the underlying concept. Questions about cause touch on issues small and large—questions such as, why did I stumble, what led to that car accident, what caused today's weather? Why are some people happier than others? Why do some individuals become sick while others avoid an illness that "everyone is getting"? What causes poverty, economic cycles, substance abuse, evil? How did the universe come to be?

It is not the goal of this book to answer any of these questions with absolute certainty—that would not be possible. Rather, its goal is to provide *approaches* to answering such questions. We will begin by trying to understand what we mean by the word "cause," since understanding what lies behind the words we use can help focus a search, clarify what is being sought, and settle some of the arguments that arise. This approach shares an assumption, one dating from the ancient Greeks, that human reasoning can be a source of knowledge.

Understanding what we mean by cause is a big question. It is the "why" question asked by two-year-old children, mature adults,

historians, geneticists, clergy, and ethicists. Many great thinkers in disciplines as disparate as theology, philosophy, neurophysiology, history, particle physics, and accident prevention have given thought to what is meant by "a cause." To begin to answer the question, "What do we mean by causality?" we will survey some of the major ideas. This will give the reader an appreciation of how current concepts have developed over time and identify some of the major challenges faced by anyone interested in the question.

However, taking a historical approach in this instance does not mean that ideas and concepts emerged in a specific, ordered sequence or developed in a progressive, linear path. Many of the concepts discussed here developed in widely separated places and reached other parts of the world only centuries later. This is clearly illustrated in the development of similar aspects of causality that emerged in the Eastern and Western worlds at different times and without apparent influence from the other sphere. The benefit of the sequential approach is that it provides a structure upon which disparate ideas can be hung and shows how concepts of causality have changed over time. Perhaps even more importantly, tracing the development of the concept of causality over human written history emphasizes the long struggle that humans have had with the issue and supports the notion that a complete understanding may never develop. A historical review also reveals that our current concepts of causality are an amalgam of ideas that have arisen and developed over thousands of years. They reflect on and derive from long traditions of thought that have engaged many groups and cultures. By necessity, this review will be selective. It will highlight some of the most challenging and contentious issues and set the stage for much of the discussion in succeeding chapters.

HISTORICAL OVERVIEW

The earliest human writings demonstrate the centrality of the concept of causality to humankind. Five-thousand-year-old Sumerian cuneiform tablets and 3,500-year-old Egyptian papyri identify forces or beings that brought about (caused) the world in the way that these cultures (or at least the authors) experienced it. Ancient

religious tracts such as the Hindu Rig Veda and the Aramaic Tanakh or Old Testament do the same. These ancient texts also link events of the present to the influence of the initiating being or force. The identification of an initiating cause as the explanation for the universe as we know it not only persists today in many religions but also is a central tenet of such scientific hypotheses as the Big Bang theory, which ascribes the makeup of the current physical universe to events that occurred at the instant of its formation, and the pantheistic Gaia concept, which describes the Earth as an organism constructed such that a change in one aspect leads to an adjustment in others in order to sustain equilibrium. Thus, what is today labeled a supernatural origin of events can be found in many if not all cultures and must be addressed if a thorough accounting of the concept of causality is attempted. This will be the focus of chapter 10.

The idea that individual humans can cause events has also been present in Eastern and Western thought for thousands of years, although it is not possible to prove that all groups of human beings have conceptualized causality in this fashion. The Hindu concept of karma, which assigns to individuals responsibility for their actions and explains the form into which a person is reincarnated as a result of past choices, implies that individuals are the agents of cause. The oldest extant compilation of laws, the Code of Hammurabi, which dates to 1750 BCE, likewise assigns to individuals the responsibility for their actions, as do the biblical stories of Adam and Eve, the Flood, and the Ten Commandments. The importance of these documents demonstrates that the concept of causal agency has long been a central aspect of human thought.

Several hundred years after the story of Moses is said to have occurred, the Greeks developed the Western tradition of analytic thinking as a source of knowledge. Democritus (c. 400 BCE) conceived of events as having ultimate single causes, although he suggested that causality could be so complex that it was often hidden from human observation or at the least very difficult to discern. At about the same time, Plato proposed that objects like chairs and concepts such as cause exist as ideals against which actual chairs and causes can be measured or compared.

Plato's idea that we use ideal models or "exemplars" as a standard against which an actual event is measured has been shown in recent cognitive neuroscience experiments to be an innate human approach. Inherent in it are two theses that will recur throughout this book. First is the idea that once a standard is identified, it can be approached closer and closer over time, even though perfection is never achieved. Second is the idea that the ideal exists as much in the abstract as in actuality. Plato never applied these concepts to the study of cause. Nevertheless, they underpin the approach taken in this book, which holds that it is possible to develop a model of causality that gets closer to the ideal over time by incorporating into the concept those ideas that improve its accuracy and jettisoning those that are no longer helpful. The implication that the Platonic approach has resulted in an increasingly nuanced and deeper concept of causality is embraced by this book, and so is the recognition that a complete and permanent definition cannot be achieved.

Plato's pupil Aristotle proposed a multifactorial model of cause and effect that describes cause as existing at several different levels of analysis. Table 1.1 lists the four levels of causality that he identified, provides my adaptation of them, and provides a commonly cited example from Aristotle's writings. Aristotle's meaning of "cause" was different than what is generally meant in the present era, but his conception is still strikingly modern. He describes the "cause" of a

Table 1.1 Aristotelian Model of Cause

Aristotelian Term	*New Descriptive Term*	*Definition*	*Bronze Statue of Zeus*
Material	Predisposing	Inherent, preexisting	Strength and malleability of bronze
Efficient	Precipitating	Initiating, provoking	The sculptor
Formal	Programmatic	Systemic, interactional	The beauty of the ideal human body
Final	Purposive	Reason, teleology	To inspire and honor

statue. The *material cause* is the bronze and the unique properties that make that alloy desirable for the production of a representation of a detailed human body. The *formal cause* is the conception of the ideal body and the concept of making an idealized representation. The *efficient cause* is the artisan and the skill the artisan brings to the process. The *final* cause is the purpose of the statue, for example, to exalt the ideal human body or to honor the god represented. "What causes a statue?" is clearly a question about what brought it into being, a question that addresses one aspect of causality, but it is not a question of primary interest today. Although complex, Aristotle's multifactor, multilevel model was extraordinarily influential for almost two thousand years. For example, when Thomas Aquinas (c. 1225–1274) discussed cause in a theological context, he conceptualized God as operating at each Aristotelian level. Chapter 2 will present an expanded and modified version of the Aristotelian model adapted to current questions.

With the emergence and development of the scientific method, the conceptualization of cause and the methods for demonstrating causality have undergone major changes over the past four hundred years. Although the scientific method as we know it today had no single beginning, Francis Bacon (1561–1626), in his *Novum Organum* (1620), is often cited as the first individual to recognize its characteristics and potential. Not an experimentalist himself, Bacon nonetheless recognized that an approach to knowledge that combined the three elements of repeated observation, integration of positive (confirming) and negative (disconfirming) results, and skepticism toward authority as the primary source of accurate information signaled a new way of seeking knowledge. He cited the Danish astronomer Tycho Brahe's voluminous collection of data on the movement of celestial bodies and subsequent 1512 discovery of a nova (which demonstrated that the universe was not static, contradicting a basic Aristotelian precept) as examples of this new approach to knowledge acquisition.

Other discoveries in the sixteenth century further contradicted the Aristotelian model of the universe and undermined the absolute acceptance of Aristotelian intellectual authority. For example, Copernicus's claim that the sun, not the Earth, was at the center of the solar system (his book *De Revolutionibus* was published at the time

of his death in 1543) was supported by Johannes Kepler's (1571–1630) demonstration that the planets' motion could be described mathematically as ellipses, not perfect circles as Aristotle claimed, and Galileo Galilei's (1564–1642) identification of moons revolving around Jupiter contradicted Aristotle's claim that celestial bodies revolved only around the Earth. Furthermore, his belief that moving objects naturally slow down was replaced by Galileo's demonstration that falling bodies accelerate at a uniform rate and by Isaac Newton's (1642–1727) concept of momentum—enshrined as his first law of motion—that objects continue to move in the same direction and at the same velocity unless acted upon by an external force.

Galileo directly attacked the Aristotelian model of cause in his book *Discourse on Two New Sciences* (1638). He proposed that new knowledge is best gained by observation and measurement, not introspection. In the *Discourse*, the character representing Galileo's point of view cites his ability to describe the acceleration of falling bodies mathematically but his concomitant inability to identify the cause of the acceleration as evidence that the search for an Aristotelian final cause is futile.

Galileo's rejection of the Aristotelian idea that cause has multiple meanings and his emphasis on identifying questions or events in which direct measurements can be made (similar to the aspect of cause that Aristotle referred to as "efficient") established a narrowed concept of cause that persists today. I will refer to this narrower definition of cause as the *categorical model* because it seeks as causes single events that are either present or absent. This model will be discussed in detail in chapter 3. As noted earlier, this narrowed concept of cause predated Aristotle, but the Aristotelian model so overshadowed it that the categorical approach only regained a prominent role with the emergence of the scientific method in the seventeenth century.

Another of Galileo's ideas that has been influential in scholarship about causality was highlighted by John Stuart Mill two hundred years later in his use of the phrase "necessary and sufficient." This conception of cause states that A is a necessary and sufficient cause of B *if* A always occurs before B *and* B never occurs without A. This is a very high standard: it implies that an event can have only one cause. This standard cannot be applied in many

situations. However, when it does describe a situation, the likelihood of a causal relationship is high.

While the Galilean view has been presented here as a radical move away from the Aristotelian multifactor, multilevel model of causality, this view becomes absolute only in retrospect. Even the scientists of the time had no sense that the pre-Galilean conceptions of causality had been overthrown. For example, both Isaac Newton and Gottfried Wilhelm von Leibniz, two of the most accomplished and best-known scientists (and sometime rivals) of the seventeenth century, wrote philosophical tracts that identified God as the ultimate cause, much as had Thomas Aquinas four centuries earlier. Newton believed that the regularity of the laws that he discovered demonstrated that they were manifestations of God's work, and Leibniz believed that the organization of the world reflected God's plan and was, therefore, the best possible manner in which the world could be organized. Both Leibniz and Newton saw a role for experimental and mathematical study but remained convinced that God was the ultimate explanation. Neither saw this dual model as a contradiction but rather conceptualized science and religion as complementary causal models that confirmed each other.

While the Galilean criticism of Aristotle might be characterized as a reemphasis on precipitating cause rather than a rejection of the Aristotelian model, the change was a radical one, and it significantly influenced the approach to cause over the next 350 years. It made the search for "sufficient" elements the defining criterion of causality and narrowed the search for causes to observable and testable elements. In effect, it defined the essence of causality as the identification of *precipitating* events. What accounted for—what caused—this dramatic development? I suggest it was the concatenation of events in the West during the sixteenth and seventeenth centuries. They included new technologies, such as the telescope; new methods for gathering and analyzing information, such as probabilistic models; great thinkers such as Leibniz, Newton, and Galileo; economic changes that provided leisure time and fiscal support for brilliant individuals to pursue new knowledge outside of the Church; the development of the printing press, which provided a method of broad and relatively rapid information transfer; and the emergence throughout Europe of

educational institutions in which individuals who could put together the new observations, technologies, and methods worked. (This is an example of narrative logic, discussed further in chapter 9.)

LIMITATIONS OF THE SCIENTIFIC METHOD

Doubts about the scientific method's ability to identify causes quickly followed, however, even among individuals who were practitioners of science. For example, René Descartes (1596–1650), an experimentalist whose contributions included Cartesian two-coordinate geometry, the idea that mathematical relationships underlie the basis of physics, and the concept of momentum, expressed skepticism about the ability to gain knowledge through observation alone. He proposed that one should start from stated principles and *deduce* truths from them. This led to his claim that one could begin from the statement *Cogito ergo sum* (I am thinking, therefore I exist) and deduce both the existence of God and the duality of the mind and the body.

Such skepticism about relying upon the senses can be traced back to the Greek Stoics fifteen hundred years earlier, but it is Descartes's suggestion that the method of deduction is the most useful method for identifying causes that deserves attention here because the deductive method is still with us and because Descartes's applications of it demonstrate that what one claims to deduce is still open to challenge.

Galileo's and Bacon's renewed emphasis on precipitation as the defining feature of causality also came under challenge from the Scottish philosopher David Hume (1711–1776). Hume claimed that causality could never be definitively demonstrated because it relied upon *inductive* reasoning, that is, it required a leap of belief that two events were inevitably linked and, thus, the drawing of conclusions that go beyond the facts. Even if an event B always follows event A, Hume argued, one could only "guess" that A had caused B. Such associations could never *prove* causality.

Hume did not totally dismiss induction, however, but said it could never establish causality with certainty. Hume's skepticism about inductive reasoning persists today, both among scientists who object to seeking broad explanations for natural phenomena and

among antiscientists who reject the scientific method as a means of increasing knowledge and understanding.

As pointed out by Karl Popper two hundred years later, Hume's rejection of induction is itself an induction. Nevertheless, Hume identified an important caveat: inductive reasoning has unavoidable limitations and cannot absolutely "prove" that two events are causally related. It is equally important to emphasize, though, that Hume did not claim that the search for cause is futile. He cited the repeated demonstration that two events occur together and the identification of multiple lines of evidence that point in the same direction as support but not proof of causal relationships.

Even today, though the caveat that the occurrence of two events together (association) does not indicate causality is widely recognized, Hume's identification of this limitation in the search for causal relationships is often ignored. The seduction of inductive reasoning is a trap that easily catches the unwary. Being thoughtful about the meaning of "cause," using caution when claiming such a relationship exists, and requiring multiple lines of evidence can lessen the chance that one will be wrong. Hume's skepticism challenged humankind's readiness to accept causality as a given, but it spurred a refinement of the concept and underlies much of Western thought about the subject during the subsequent two hundred years.

At the same time that Hume was expressing skepticism about the possibility of identifying cause with absolute certainty, the Italian philosopher Giambattista Vico (1668–1744) was expressing similar concerns about the validity of causal knowledge in the discipline of history. Vico noted that most proposed causal mechanisms found in historical writing derived from an analysis of events *after* they had happened. He suggested that a primary distinction should be made between information gathered by scientific and nonscientific methods. His concern will be examined in depth in chapter 9.

IMMANUEL KANT AND THE ROLE OF HUMAN PERCEPTION

Hume's radical dismissal of induction spurred Immanuel Kant (1724–1804) to reformulate the concepts of cause and causality less

than half a century later. Kant proposed that humans impose upon nature basic categories such as causation. Stated in more modern terms, this proposal states that the organization of the nervous system determines the way in which things are perceived. Kant extended this hypothesis to the issue of causality and proposed that the concept of cause is an innate aspect of human thought. Thus, causes exist because the human brain is organized to conceive of causal relationships among events. This extraordinarily radical idea (although it did have precedents among the ancient Greeks) has received support from several lines of modern experiments. Patients who have undergone "split" brain surgery, for example, can be shown to experience and think about causal relationships linking two events differently in each of the disconnected halves of their brain. Research with infants also suggests that the notion of a causal relationship develops between years two and three, but the interpretation of these experiments depends upon agreement that certain behaviors indicate the presence of the concept of causality, an interpretation that is not universally shared. Recent MRI scan studies also suggest a neural basis for human categorization.

MEDICINE OPERATIONALIZES CAUSE

By the latter half of the nineteenth century, new technologies and intellectual approaches built upon the strengths of the "direct-agent" model of cause advocated by Galileo and his successors. This is well illustrated by advances in medical knowledge. For thousands of years, physicians who wrote about medicine focused on individual symptoms such as fever, shortness of breath, seizure, and confusion. Each was considered a specific entity, much as we today consider individual diseases to be distinct conditions. However, in the mid-seventeenth century, the British physician Thomas Sydenham (1624–1689) observed that certain medical symptoms clustered together with regularity in many patients. He suggested that these groupings of medical symptoms, now called *syndromes*, represented actual entities and proposed a test of this hypothesis: they would be found in patients from different parts of the world and in different historical epochs. Furthermore, he proposed, the existence of these entities was proven

by the fact that each would follow a predictable course over time and have a predictable outcome regardless of where or when the person lived. For example, patients who presented with the three symptoms of fever, cough, and sputum production would likely be suffering from pneumonia, a disease of the lungs, while patients with fever, stiff neck, and confusion were likely to be suffering from meningitis, a disease of the lining of the brain and central nervous system.

This dramatic new approach introduced the concept of disease as we understand it today. Two hundred years later, this concept was linked with the autopsy to develop a method called the clinical/pathological correlation by such nineteenth-century physicians such as the German pathologist Rudolf Virchow (1821–1902). This linkage provided a means of demonstrating that many patients with the syndromes identified by Sydenham's method of clustering symptoms had the same bodily abnormalities at autopsy and thus provided a method for demonstrating that a specific bodily abnormality was causative of a specific disease.

More relevant to this discussion, the clinical/pathological approach became a method by which the cause of a specific disease could be established. For example, linking specific abnormalities in bodily structures to specific clinical syndromes led to the abandonment of the beliefs, dating back to the ancient Greeks, that sickness was caused by imbalances of bodily humors (black bile, yellow bile, phlegm, and blood) and environmental substances ("miasmas"). What the autopsy offered was a way to "prove" such linkages and thus to prove the value and specificity of the model proposed by Sydenham. The modern conception of disease that derived from this model is still broadly accepted both within the profession of medicine and by the public. Many of the advances that have occurred in medicine over the past hundred years attest to the strengths of this model of causality, but, as we will see in chapters 4, 5, and 8, some of its failures also derive from the limitations of an overly simple model of disease causality.

Another great medical discovery of the nineteenth century, the germ theory, led directly to a codification of methods for establishing causality in experimental and clinical medicine. In experiments carried out in the middle of the nineteenth century, Louis Pasteur (1822–

1895) and others found that microscopic organisms called bacteria were found to be associated with many syndromes such as pneumonia and meningitis. But how could these causal links be proven?

The microbiologist Robert Koch (1843–1910) proposed three criteria, later termed Koch's postulates, to prove that an organism caused an infection:

1. The organism is repeatedly isolated from individuals with a specific disease;
2. the organism is then reproduced in such a quantity that
3. upon introduction into either animals or human beings, the initial disease is replicated.

This schema contains elements of Hume's suggestion that repeated association strengthens the likelihood of a causal association and of the Galilean idea that causality implies that the relationship between the two events is *necessary*, that is, that the disease would not occur without the agent. The criteria have been modified over the past century and now include an element of *sufficiency*, that is, the idea that the disease never occurs without the agent or that the disease ceases to exist if the agent is removed, for example, by treatment. These criteria describe the essence of the scientific process by which a cause or causes is identified in a biological system. It is a powerful application of the single-cause disease model that will be discussed in chapter 3. Stated more generally, these criteria postulate that A can be demonstrated to be a cause of B if

1. A is *repeatedly* associated with B (correlated or associated with); *and*
2. B occurs regularly when A is introduced (sufficient); *and*
3. The removal of A leads to a resolution of B (necessary).

However, Koch's postulates or causal criteria do not explain several issues in causality that relate to the arena of microbiology and to causality more broadly. Why do some individuals who are inoculated with an organism not develop the disease? Why does the same strain of organism cause variable manifestations in different individuals?

Why do diseases vary in their frequency or prevalence in different geographic areas? These questions reveal that there are limits to the universality of the postulates, but the advances in knowledge that have resulted from their application over the past hundred years are a testament to their power and utility. The rapid linkage of the HIV organism to the immunodeficiency syndrome AIDS, for example, used just such logic, although criterion 3 was not demonstrated in humans for ten years after the virus's discovery.

The questions in the last paragraph that are not answered by Koch's postulates illustrate a much broader issue: *our ability to come up with general rules for establishing causality will always be limited by the specifics of a given causal question*. In the example of proving that a specific infectious agent is the cause of a specific disease, there is variability not only among the organisms known to cause a specific illness (for example, some may have a gene that confers antibiotic resistance while others do not) but also among the individuals who are infected ("host" immune factors) and differences among the environments in which the host and agent are residing. In this example, then, there are three elements in the causal chain, the agent, the host, and the environment, and aspects of all three influence the event of interest (here an infectious illness) and its causal chain. This issue will be encountered in a number of guises throughout this book. It is both frequent and important enough to state as a general statement:

> *The ability to predict cause in a single encounter is influenced not only by specifics of the potential causative agent A and specifics of the object O being acted upon but also by specifics of the environment E in which they occur.*

This limitation in the ability to determine causality echoes Hume's identification of the limits of induction. Every replication of event A is not an exact copy of that event—each instance is unique no matter how carefully the situation is manipulated to make it the same. This limit to replication identifies a limitation of our ability to generalize about cause, but a number of steps can be taken in the experimental situation to minimize greatly any differences. The many successes of microbiology and the successful application in many disciplines of the reasoning encapsulated in Koch's postulates demonstrate