Manuscript Draft

The Unwalled Garden

How the Collision of Disciplines Shaped Modern Discovery

The division of the sciences is an administrative convenience, not a feature of reality.

Complete Manuscript: Introduction, Parts I–IV, & Epilogue

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Introduction: The Invention of the Silo

The Argument at Cambridge

On Monday 24 June 1833 the British Association for the Advancement of Science opened its third annual meeting in Cambridge. The Association was two years old. It had met first at York and then at Oxford, and its founders meant it to do what the Royal Society in London had largely stopped doing: bring together, once a year and in public, the people who studied nature, whatever corner of it they worked on. The president for the year was Adam Sedgwick, the university's professor of geology. Among the Cambridge fellows involved in the meeting was a thirty-nine-year-old clergyman and mathematician of Trinity College named William Whewell.[1]

Whewell was the son of a master carpenter from Lancaster. By 1833 he had written a textbook of mechanics, held Cambridge's chair of mineralogy for four years, published a book on the architecture of German churches and begun a long programme of research on the tides. His work on moral philosophy, and the histories and philosophy of science for which he is best remembered, were still to come. He was also, by temperament, a maker of words. In 1834 Michael Faraday, looking for names for the parts of an electrolytic cell, took Whewell's advice and adopted *anode*, *cathode* and *ion*.[2]

The best-known story about the Cambridge meeting concerns another of his coinages. In the version usually told, the poet Samuel Taylor Coleridge rose during a session to object that the people in the hall had no right to call themselves "natural philosophers": they were practical men, collectors of fossils and makers of experiments, not philosophers. Whewell is said to have answered on the spot that, if those who practise art are artists, those who practise science might be called *scientists*.

The story is probably true in outline, and it has certainly been embroidered. Almost everything we know about it comes from one source, an unsigned review that Whewell published in the *Quarterly Review* in March 1834, of Mary Somerville's book *On the Connexion of the Physical Sciences*. There, in the course of praising Somerville, he noted the lack of any word for "the students of the knowledge of the material world collectively". The difficulty, he wrote, had been felt by members of the British Association at all three of its meetings, at York, Oxford and Cambridge. "Philosophers" had been judged too wide and too lofty, and had been "very properly forbidden them by Mr. Coleridge". "Savans" was French and presumptuous. Facetious alternatives such as "nature-poker" had been rejected. Then "some ingenious gentleman proposed that, by analogy with *artist*, they might form *scientist*", a suggestion that was "not generally

palatable".[3] The review does not say at which meeting Coleridge made his objection, and it does not name the ingenious gentleman. The historian Sydney Ross, who traced the word's history in 1962, identified him as Whewell himself, and Whewell used the word again, this time under his own name, in his *Philosophy of the Inductive Sciences* of 1840, where he also proposed *physicist*.[4] The scene of the poet rising and the polymath replying is a later reconstruction from these sources, and it should be read as one.

The word was not a success for a long time. British men of science went on calling themselves men of science for the rest of the century, and many regarded *scientist* as an ugly American import. As late as December 1894, T. H. Huxley told the magazine *Science-Gossip* that to anyone who respected the English language, it must be "about as pleasing a word as 'Electrocution' ".[5]

What is usually forgotten is why Whewell wanted the word. The sentence that introduces it in the 1834 review follows a complaint. The tendency of the sciences, he wrote, had long been "an increasing proclivity of separation and dismemberment". Mathematicians, chemists and naturalists, he complained, were going their separate ways, and physical science was losing its unity. Somerville's book deserved praise because it showed the connections between branches that were drifting apart. The want of a common name was, in Whewell's telling, a symptom of the disease. *Scientist* was coined to name what the fragments still had in common.[6] The same man went on to name the fragments too. This book is about what happened between those two coinages.

The Fracturing

Whewell was describing a change that had begun before him and would continue long after. Historians of science date the modern discipline, as a social institution rather than a heading in a syllabus, to the decades around 1800. A discipline in this sense is not just a subject. It is a community with its own journals and societies, its own training, its own posts in universities, and its own standards for what counts as a result. Over the nineteenth century such communities formed around chemistry, physics, geology, physiology and a growing list of others, and they proved remarkably stable once formed.[7]

The universities followed, at different speeds. The German universities, reformed in the first half of the century, built their research around professorial chairs and the institutes and laboratories attached to them: Justus Liebig's chemical laboratory at Giessen, which trained a generation of chemists from across Europe; Oswald Schmiedeberg's pharmacology at Strasbourg, where he took up the chair in 1872; Wilhelm Wundt's laboratory of experimental psychology at Leipzig, opened in 1879. Foreign students came to learn the methods and carried them home. Johns Hopkins University, which opened in Baltimore in 1876, was built explicitly on what Americans understood to be the German pattern of graduate research.

It is often said that a "Humboldtian model" of the university, named after the Prussian official who led the founding of the University of Berlin in 1810, swept across Europe and North America in the nineteenth century. Historians have become sceptical of the phrase. Humboldt's

memorandum on the organisation of higher learning was not published until 1903, and the idea of a single Humboldtian model owes more to the celebrations and reform debates of the early twentieth century than to the way German universities actually developed. What spread was a looser set of practices: research as part of a professor's job, the seminar, the teaching laboratory, the doctorate.[8]

The academic *department*, the administrative unit that hires, teaches and examines in one discipline, took its familiar form in the United States. Between about 1870 and 1915, as the modern American research university took shape, the disciplines founded their national societies one after another, and by 1900 most of the leading universities had organised themselves into departments.[9] The social sciences arrived last and least evenly. The University of Chicago appointed Albion Small to head a new department in 1892, often described as the first department of sociology anywhere. In France, Émile Durkheim began teaching "social science" at Bordeaux in 1887, and the title of his Paris chair included the word *sociology* only from 1913. Britain's first chair of sociology was created at the University of London in 1907, for L. T. Hobhouse.[10]

By the end of the century, then, the broad territories of 1800 had been divided, and divided again. Table 1 is a schematic picture of the result. Like any such picture it simplifies: anthropology drew on natural history and medicine as much as on philosophy, geology grew from mineralogy and mining as well as from natural history, and the boundaries were drawn at different times in different countries.

Table 1: The nineteenth-century fracturing of natural philosophy (schematic)

Domain around 1800	**Disciplines by about 1900**	**Characteristic methods**
Natural philosophy	Physics, astronomy, applied mathematics	Differential equations, precision measurement, conservation laws.
Natural history and mineralogy	Botany, zoology, geology, palaeontology	Classification, comparative anatomy, field collection, stratigraphy, evolutionary descent.
Chemistry and medicine (including materia medica)	Organic and physical chemistry, physiology, pharmacology	Quantitative analysis, structural theory and synthesis, animal experiment, bioassay.
Moral and mental philosophy	Economics, sociology, experimental psychology	Marginal and equilibrium analysis, social statistics, laboratory psychophysics.

What the Walls Were For

It would be easy to tell this as a story of loss, with a unified natural philosophy broken up by bureaucrats. That is not what happened, and this book does not argue it.

Specialisation was a response to success. Knowledge grew faster than any one person could follow it, and a community that agreed on its problems, its instruments and its standards of proof could build on its own results without re-arguing first principles in every paper. The economist Benjamin Jones has given the modern version of the argument a name, the burden

of knowledge: as a field accumulates what a newcomer must learn before contributing, people spend longer in training, specialise more narrowly and work more in teams.[11] The narrowing that Whewell lamented is in part the price of depth.

Disciplines also supply something that no individual can: judgement. A discipline is a group of people competent to say whether a piece of work is good. The machinery of that judgement grew up alongside the disciplines. In 1831 Whewell and John Lubbock drew up a report for the Royal Society on a paper by the astronomer George Airy, in what the Society now describes as its first experiment with systematic refereeing; refereeing spread slowly through the century, and the term "peer review" is a coinage of the 1970s.[12] The coiner of *scientist* helped to build the gatekeeping that made specialised science trustworthy.

The chapters that follow bear this out in ways that the usual stories of interdisciplinary triumph leave out. Nearly every border-crosser in this book was first a specialist. John Snow could reason about how cholera entered the body because he was the most experienced anaesthetist in Britain (Chapter 1). Rosalind Franklin read DNA's X-ray patterns with a physical chemist's training in disordered carbons (Chapter 7). Frank Asaro could measure a few parts per billion of iridium in Italian clay because he and Isadore Perlman had spent years perfecting the analysis of ancient pottery (Chapter 9). The receiving fields mattered too. The data that Snow used were collected by William Farr's General Register Office, the most powerful instrument of public health of its day; the method for reading a sudden extinction in the fossil record came from palaeontologists; the structures from which AlphaFold learned were deposited by thousands of crystallographers over half a century (Chapter 12). A crossing needs solid ground on both sides.

Nor are disciplines as sealed as the word "silo" suggests. The sociologist Jerry Jacobs has pointed out that ideas move between fields constantly, and that successful interdisciplinary ventures tend to acquire journals, societies and degree programmes of their own: they become disciplines.[13] This book contains several examples. Epidemiology grew out of the work of Snow and Farr. Molecular biology was built partly by physicists who had crossed into genetics (Chapter 3). The physicists and engineers of the wartime Radiation Laboratory ended the war practising something they called microwave physics (Chapter 5), and the Human Genome Project turned bioinformatics from a specialty into a field with its own departments (Chapter 11). Border crossings do not abolish disciplines. They found new ones.

Yet the walls did carry a cost, and it was less a matter of administration than of habits of mind. As disciplines matured, they developed not only distinct vocabularies but distinct ideas of what counts as an explanation. A physicist tends to be satisfied when a phenomenon can be written as a conservation law or a differential equation; an evolutionary biologist, when a trait's history and its advantage have been identified; a geologist, when the sequence of events can be read in the rocks. Each standard is reasonable on its home ground. Each can make its holders blind to questions that look trivial, or unanswerable, from where they stand. The epigraph of this book puts it bluntly: the division of the sciences is an administrative convenience, not a feature of reality. That is half true. Nature is not divided along departmental lines, but the differences of method and scale that the disciplines track are real, and much of this book is

about what happens when people try to work across them.

The Argument of This Book

The claim of this book is narrower than the one its subtitle might suggest, and, I hope, more useful.

It is not that the great discoveries of the last two centuries all happened at the borders between disciplines. Many did not. Nor is it that border-crossers are wiser than specialists, or that disciplines are illusions to be swept away. The claim is this. In each of the twelve episodes that follow, a decisive step depended on something carried across a disciplinary border: a method, a mathematical structure, or a working language shared by people trained in different fields. That crossing happened in one or more of three recognisable ways, which I call methodological smuggling, structural isomorphism and the trading zone. It succeeded only where it met depth on the receiving side, in the form of good data, competent judges, or a question that the home field had already sharpened. And each crossing carried characteristic costs, which recur from chapter to chapter as reliably as the benefits do.

Twelve episodes cannot show how often discoveries happen this way, and they were not chosen at random. They are famous because they worked, and famous stories attract myths. What they can show is how crossing works when it works, what it costs when it does, and what conditions seem to help. The rest of this Introduction sets out the three mechanisms, explains why the costs belong to the argument rather than standing outside it, and describes how the four Parts of the book build on one another.

Three Ways Across

Methodological smuggling is the transfer of a technique, an instrument or a standard of evidence from the field where it was developed into a field where it was not in use, in order to answer that field's own question. The question stays at home; the tool is foreign. Snow, the anaesthetist, reasoned from the physics of vapours that a poison breathed in should act first on the whole body, whereas cholera acted first on the gut, so it must be swallowed; and to sort the houses of south London by their water company, he borrowed a chemist's test for dissolved salt (Chapter 1). In 1943 Salvador Luria and Max Delbrück showed that bacteria become resistant to viruses by random mutation rather than by an induced response, not with a new microscope but with an argument about the shape of a statistical distribution (Chapter 3). In 1955 James Gray and G. J. Hancock turned the hydrodynamics of slender bodies into a method a zoologist could apply with a ruler and a photograph of a swimming sperm (Chapter 8). In 1978 the analytical technique that Asaro and Perlman had developed for tracing pottery to its clay found thirty times too much iridium in the clay at the end of the Cretaceous (Chapter 9).

What these cases share is that the receiving field could judge the answer by its own standards. A mutation rate, a swimming speed, an iridium concentration and a death rate by water supply

are all things that the people who owned the original question knew how to evaluate. That is the strength of smuggling. Its weakness, which we will meet repeatedly, is that a method arrives with assumptions its new users may not see.

Structural isomorphism is the recognition that two systems studied by different fields obey the same mathematical form, so that what is known about one can be carried over to the other. The word matters. An isomorphism is a claim about equations, and it can be checked; an analogy is a claim about resemblance, and it often cannot. Norbert Wiener and Julian Bigelow, working on anti-aircraft prediction, learned that a feedback system with too much gain and too much delay overshoots and oscillates; by Wiener's later account, the physiologist Arturo Rosenblueth recognised the same behaviour at once in patients with cerebellar damage, whose hands swing back and forth as they reach for a glass (Chapter 6). A sperm cell, a bacterium and a corkscrew sinking through corn syrup all obey the same equations of slow, viscous flow, which is why Edward Purcell could explain bacterial swimming to an audience of physicists with a tank and an overhead projector (Chapter 8). In 1987 Joseph Bryngelson and Peter Wolynes saw that the mathematics devised for spin glasses, disordered magnetic alloys, described the problem a folding protein faces, and what evolution must have done to solve it (Chapter 12). The Santa Fe Institute was founded partly on the hope that such shared structures would be found across cells, economies and cities (Chapter 10).

Isomorphism is the most intellectually exciting of the three mechanisms and the most dangerous. D'Arcy Thompson's *On Growth and Form* (Chapter 2) is the purest example in the book: the recognition that a splash, a soap film, a girder and a shell might obey the same physics. It is also the clearest warning. A physical process that can produce a shape is not thereby shown to be the process that does, and Thompson often slid from the first claim to the second.

The trading zone is a term borrowed from the historian of physics Peter Galison, who used it to describe how theorists, experimenters and engineers manage to work together without sharing a full common language. Groups that must trade without a common language build a *pidgin*, a reduced contact language good enough for the business at hand, which can grow into a full *creole* if the contact lasts.[14] At the wartime Radiation Laboratory in Cambridge, Massachusetts, physicists and radio engineers met around the *equivalent circuit*, a way of reducing the electromagnetic fields in a waveguide to the circuit elements that engineers already used (Chapter 5). Bletchley Park was not one trading zone but a chain of them, in which linguists, mathematicians, engineers and machine operators each passed on to the next a product in a form the next could use (Chapter 4). In 1944 Delbrück persuaded the small community studying bacterial viruses to concentrate on seven phages growing on a single strain of *E. coli*, a modest agreement that gave physicists and biologists a shared object to talk about (Chapter 3). Half a century later, the Critical Assessment of protein Structure Prediction, a competition in which predictions are scored blind against unpublished experimental structures, gave biochemists, physicists, statisticians and computer scientists a single currency in which to compare their methods (Chapter 12).

Galison's term has been stretched to cover almost any collaboration, and Chapter 5 discusses the criticisms. In this book it means something specific: an arrangement, physical or institutional, in which people from different fields coordinate their work around shared objects and

a limited shared language, without having to agree about everything else. Trading zones can be built on purpose, as at Santa Fe (Chapter 10), or improvised under pressure, as at Bletchley. They can be fragile, like the circle around the Macy conferences on cybernetics, which depended on a handful of personal relationships and was badly damaged when one of them broke (Chapter 6). And someone always sets the terms of trade.

The three mechanisms rarely act alone. The discovery of the impact that ended the Cretaceous (Chapter 9) began with smuggling, a nuclear chemist's measurement applied to a geologist's question, and became a trading zone that eventually included palaeontologists, mineralogists, planetary scientists and oil-company geophysicists. The prediction of protein structure (Chapter 12) used all three: statistical physics smuggled into the analysis of sequence alignments, the isomorphism between proteins and spin glasses, and a trading zone organised around a blind test. The mechanisms are a way of seeing what crossed and how, not a set of boxes into which each chapter must fit.

The Costs Are Part of the Argument

Every chapter in this book has a section called "The Costs of Crossing". They are not there to protect the thesis from criticism. They are part of it.

If crossing borders produces discoveries by recognisable mechanisms, it should also produce failures by recognisable mechanisms, and it does. The same moves that succeed in one chapter go wrong in another, and sometimes in the same chapter. Five patterns recur.

Credit is lost to secrecy and to myth. Work that crosses disciplines falls between the habits of attribution of each, and it is easily claimed by whoever tells the story afterwards. The Polish mathematicians who first broke Enigma, the Post Office engineer who built Colossus and the thousands of women who ran the machines at Bletchley were invisible for decades, first because of the Official Secrets Act and then because the story had already been told without them (Chapter 4). The popular account of the Broad Street pump, in which a lone doctor reads a map and ends an epidemic, erases the curate whose knowledge of his parish closed the case (Chapter 1). The story of the double helix as a race, told by one of its winners, shaped how Franklin was remembered for half a century (Chapter 7). A story in which a physicist sweeps into palaeontology and solves its great mystery leaves a dozen chemists, micropalaeontologists, mineralogists and geophysicists in the footnotes (Chapter 9). Myths of this kind are not harmless. They teach that discovery is a matter of individual inspiration, when these histories show it to be a matter of coalitions.

Analogy outruns evidence. Structural isomorphism has a characteristic failure, which is to mistake a resemblance for a shared mechanism. Thompson's physical analogies showed what physics could do, not what organisms actually did (Chapter 2). The cyberneticians found the same feedback loop in guns, nerves and societies, but only the first two came with equations; in 1956 Claude Shannon, whose information theory had become a fashion, warned his own field that it had been inflated beyond its accomplishments (Chapter 6). At Santa Fe, the idea that

evolution drives living systems to the "edge of chaos" spread into the titles of books before its main experimental support was withdrawn by researchers in the institute's own circle, and supposedly universal scaling laws proved to hold only approximately for organisms and, for cities, to depend on where their boundaries were drawn (Chapter 10). Once the impact hypothesis had gained ground, some of its supporters stretched it over a claimed periodicity of extinctions and an unseen companion star to the Sun (Chapter 9).

Insiders often have good reasons. The usual story has an enlightened outsider defeating a hidebound establishment. The chapters rarely support it. The miasmatists who rejected Snow were wrong about cholera, but the sewers they built to remove bad air did more to end the disease in Britain than his theory did (Chapter 1). The palaeontologists who resisted the Alvarez hypothesis were right that the fossil record of land animals was patchy, the volcanists were right that the Deccan eruptions mattered, and both were treated with a contempt that made agreement harder (Chapter 9). Economists who distrusted the physicists' models at Santa Fe had learned, at some cost, to be wary of models that could explain anything (Chapter 10). Franklin's insistence on extracting everything from her data before building models was the standard of her discipline, and it is what eventually confirmed the double helix in detail (Chapter 7).

Imported methods carry blind spots. A technique moved into a new field brings its assumptions with it, and its new users may not know what they are. William Farr brought the best statistical methods of his day to cholera and found a strong, real correlation between low ground and death; the low ground was where the sewage-laden water was supplied, and the elevation law is now a textbook case of confounding (Chapter 1). Physicists' models of microscopic swimmers assumed an infinite, empty fluid; real bacteria live near walls and in mucus, where the physics changes (Chapter 8). A genetic algorithm at the heart of Santa Fe's artificial stock market turned out to contain a bias that manufactured some of the behaviour it was meant to explain (Chapter 10). AlphaFold predicts protein structures with remarkable accuracy, but it does so without explaining how proteins fold, and a field that set out to understand folding may have settled for predicting it (Chapter 12).

Someone sets the terms of trade. Trading zones are not neutral. The Radiation Laboratory's pidgin was shaped by what the armed services wanted to buy, and its institutional heirs lived for decades on military contracts (Chapter 5); cybernetics grew out of gunnery (Chapter 6). The Human Genome Project was sold to legislators in the language of medicine, a promise made by geneticists on behalf of clinicians, and its history includes arguments over patents, ownership and the consent of the people whose DNA was read (Chapter 11). The magnetic and gravity surveys that revealed the Chicxulub crater belonged to an oil company, and the knowledge crossed into academic science only when its owners allowed (Chapter 9). The openness of protein-structure prediction came to depend heavily on the choices of a single company (Chapter 12).

Beneath these patterns lie costs of another kind, borne by people rather than ideas. The collaboration that started molecular biology took place in Nazi Berlin, and two of its three authors spent years in Soviet captivity after the war (Chapter 3). Alan Turing was prosecuted for homosexuality seven years after the war he helped to win (Chapter 4). Walter Pitts, who contributed

perhaps the most original idea in the cybernetics circle, was cut off by the mentor he depended on and died in obscurity (Chapter 6).

The costs are not a reason to stay at home. They are the other half of the evidence about how crossing works, and the Epilogue draws on them as much as on the successes in asking what conditions make crossings go well.

The Shape of the Book

The book is in four Parts, arranged roughly in time. The chapters overlap, and several reach back decades before their main story or forward to the present, but the Parts follow a change in how crossings were organised: from individuals, to coalitions, to institutions, to infrastructures.

Part I, "The First Border Crossings", follows small, improvised coalitions that had little formal support. Snow, an anaesthetist working with a parish curate, a registrar's data and a chemist's test, pieced together physiology, chemistry, statistics and a curate's knowledge of his parish to show how cholera spread (Chapter 1). D'Arcy Thompson, a professor of natural history in Dundee with a classicist's learning and a mathematician's taste, wrote a book that asked biology to look again at physical form, and founded no school (Chapter 2). In the 1930s a few physicists, drawn into biology by Niels Bohr's speculation that life might set a limit on physical explanation, joined geneticists in Berlin and bacteriologists in America to measure the gene and found the phage group, which was less an institution than an agreement about how to work (Chapter 3). What these crossers lacked was institutional support of the kind later chapters describe. What they had was freedom from the standards of the field they entered, which helped and hurt them in about equal measure.

Part II, "The Crucible of Crisis and the Post-War Boom", begins with the Second World War, when governments put people from incompatible fields in the same buildings and gave them a single goal, a deadline and a clear test of success. At Bletchley Park mathematicians, linguists, classicists, engineers and some nine thousand staff, most of them women, broke the German ciphers (Chapter 4). At the Radiation Laboratory physicists and engineers learned to speak a common technical language while building microwave radar (Chapter 5). After the war some of the same people tried to keep the conversation going without the compulsion: the Macy conferences brought mathematicians, engineers, neurophysiologists, psychiatrists and anthropologists together ten times between 1946 and 1953 to look for a common science of control and communication (Chapter 6). The double helix (Chapter 7) belongs here too, as a meeting of physicists and physical chemists, several of them shaped by war work, with genetics and biochemistry. Part II shows how much coalitions can achieve under pressure, and how rarely their working arrangements survive intact once the pressure is removed, even when their people and institutions do.

Part III, "Scales, Systems, and Invisible Worlds", turns to crossings that took decades and needed institutions to sustain them. The physics of swimming microbes (Chapter 8) grew from a fluid dynamicist's calculation of 1951 into a field, through the slow meeting of hydrodynamics,

cell biology and the experimental physics of single cells. The impact hypothesis (Chapter 9) required geologists, physicists, chemists, palaeontologists and industrial geophysicists to argue for more than a decade before a crater was found. The Santa Fe Institute (Chapter 10) was designed from the start, more deliberately than any earlier institution in this book, to be a trading zone, with no departments and no tenure, and its record is the clearest test of what such design can and cannot do. The common thread is scale: these are problems in which the world behaves differently from everyday intuition, too small, too slow, too rare or too collective for any one discipline's habits.

Part IV, "The Age of Big Data and Convergence", follows crossing as it became industrial. The Human Genome Project (Chapter 11) required biologists, chemists, engineers, mathematicians, programmers and ethicists to read three billion letters of DNA, and its most lasting decisions, about open data, patents and consent, were made by people who were not sequencing anything. The prediction of protein structure (Chapter 12) brought biochemistry, statistical physics, game design and machine learning together around an archive of experimental structures and a blind test, and ended with a Nobel Prize divided between a biochemist and two researchers from an artificial-intelligence company. In Part IV the crossing is carried as much by shared infrastructure, by databases, benchmarks and software, as by people in a room, and machines begin to take part in it. Each Part depends on the one before. The individuals of Part I showed what crossing could do; the coalitions of Part II showed it could be organised; the institutions of Part III tried to make it permanent; and the infrastructures of Part IV made it possible on a scale none of the earlier crossers could have imagined, with costs to match.

How to Read This Book

Each chapter tells one story, and the chapters can be read in any order, though later ones sometimes refer back to earlier ones. Each opens with a scene and then, in one or more sections headed "The Science", explains what the field knew beforehand and the scientific idea that the reader needs. Equations appear only where they earn their place, and every symbol is explained. Shaded boxes headed "Science Primer" work through a key concept in more detail, usually with real numbers; readers in a hurry can skip them without losing the thread. Each chapter ends with three sections in the same order: "Outcomes and Legacy", on what the work led to and where things stand now; "The Costs of Crossing", described above; and a short Coda. Notes, gathered at the end of each chapter, give sources for specific claims and flag places where accounts disagree. Each chapter closes with an annotated list of further reading for anyone who wants to go deeper into its story.

Notes

[1] The date of the opening and Sedgwick's presidency are recorded in *Lithographed Signatures of the Members of the British Association for the Advancement of Science, Who Met at Cambridge, June 1833, with a Report of the Proceedings at the Public Meetings during the Week* (Cambridge: John Smith, 1833), transcribed by Darwin

Online, https://darwin-online.org.uk/converted/Ancillary/BeagleLibrary/1833_BAAS_A746.html.

[2]On Whewell's career, see Laura J. Snyder, "William Whewell," *Stanford Encyclopedia of Philosophy*, https://plato.stanford.edu/entries/whewell/; and the MacTutor biography, https://mathshistory.st-andrews.ac.uk/Biographies/Whewell/. Faraday's acceptance of the terms is in his letter to Whewell of 15 May 1834, Epsilon: The Faraday Collection, https://epsilon.ac.uk/view/faraday/letters/Faraday0720.

[3][William Whewell], review of Mary Somerville, *On the Connexion of the Physical Sciences*, *Quarterly Review* 51 (March 1834): 54–68. The review was anonymous, as was usual in the *Quarterly*; its attribution to Whewell is not in doubt.

[4]Sydney Ross, "Scientist: The Story of a Word," *Annals of Science* 18, no. 2 (1962): 65–85; William Whewell, *The Philosophy of the Inductive Sciences, Founded upon Their History*, 2 vols. (London: John W. Parker, 1840). The dramatised version of the Cambridge exchange is best known from Laura J. Snyder, *The Philosophical Breakfast Club: Four Remarkable Friends Who Transformed Science and Changed the World* (New York: Broadway Books, 2011), which tells the story in its fullest form; Snyder dates the exchange to 24 June 1833 in "Inventing the Scientist," 2011, https://www.laurajsnyder.com/2011/01/inventing-the-scientist/. For Coleridge's objection and the wider debate over what to call men of science, see Richard Yeo, *Defining Science: William Whewell, Natural Knowledge and Public Debate in Early Victorian Britain* (Cambridge: Cambridge University Press, 1993).

[5]Huxley's letter, one of several on the word that *Science-Gossip* published in December 1894, is transcribed in Charles Blinderman and David Joyce, *The Huxley File*, Clark University, https://mathcs.clarku.edu/huxley/UnColl/PMG/PMGetal/Scientist.html. On the slow British acceptance of the word, see Ross, "Scientist."

[6]Whewell, review of Somerville. On the review and its context, see James Secord, "Mary Somerville's Vision of Science," *Physics Today* 71, no. 1 (January 2018).

[7]Rudolf Stichweh, "The Sociology of Scientific Disciplines: On the Genesis and Stability of the Disciplinary Structure of Modern Science," *Science in Context* 5, no. 1 (1992): 3–15.

[8]Sylvia Paletschek, "Verbreitete sich ein 'Humboldt'sches Modell' an den deutschen Universitäten im 19. Jahrhundert?," in *Humboldt international: Der Export des deutschen Universitätsmodells im 19. und 20. Jahrhundert*, ed. Rainer Christoph Schwinges (Basel: Schwabe, 2001), 75–104; Mitchell G. Ash, "Bachelor of What, Master of Whom? The Humboldt Myth and Historical Transformations of Higher Education in German-Speaking Europe and the US," *European Journal of Education* 41, no. 2 (2006): 245–67.

[9]Louis Menand, *The Marketplace of Ideas: Reform and Resistance in the American University* (New York: W. W. Norton, 2010).

[10]On Small, see the American Sociological Association, "Albion W. Small," https://www.asanet.org/albion-w-small. On Durkheim's appointments, see "Emile Durkheim: His Life and Work," University of Chicago, https://durkheim.uchicago.edu/Biography.html.

[11]Benjamin F. Jones, "The Burden of Knowledge and the 'Death of the Renaissance Man': Is Innovation Getting Harder?," *Review of Economic Studies* 76, no. 1 (2009): 283–317.

[12]Royal Society, "Peer Review from the Archive," blog, September 2015, https://royalsociety.org/blog/2015/09/peer-review-from-the-archive; Noah Moxham and Aileen Fyfe, "The Royal Society and the Prehistory of Peer Review, 1665–1965," *Historical Journal* 61, no. 4 (2018): 863–89.

[13]Jerry A. Jacobs, *In Defense of Disciplines: Interdisciplinarity and Specialization in the Research University*

(Chicago: University of Chicago Press, 2013).

[14]Peter Galison, *Image and Logic: A Material Culture of Microphysics* (Chicago: University of Chicago Press, 1997). Chapter 5 discusses Galison's account and its critics in more detail.

Further Reading

Laura J. Snyder, *The Philosophical Breakfast Club: Four Remarkable Friends Who Transformed Science and Changed the World* (Broadway Books, 2011). A lively group biography of Whewell, Charles Babbage, John Herschel and Richard Jones, and of the reform of British science in their time. It tells the Cambridge story more dramatically than the sources strictly allow.

Richard Yeo, *Defining Science: William Whewell, Natural Knowledge and Public Debate in Early Victorian Britain* (Cambridge University Press, 1993). The scholarly study of Whewell's attempt to define what science was and who could speak for it.

Rudolf Stichweh, "The Sociology of Scientific Disciplines," *Science in Context* 5 (1992). A short, clear account of how disciplines formed as communities, and why they have proved so stable.

Peter Galison, *Image and Logic: A Material Culture of Microphysics* (University of Chicago Press, 1997). The source of the trading-zone idea. Long and demanding; the chapters on wartime radar and on trading zones can be read on their own.

Jerry A. Jacobs, *In Defense of Disciplines: Interdisciplinarity and Specialization in the Research University* (University of Chicago Press, 2013). The best-argued case for disciplines, and a useful corrective to easy talk of silos.

Part I

The First Border Crossings (1854–1944)

Chapter 1

The Doctor, the Mapmaker, and the Ghost Map (1854)

Thirty-First of August

Broad Street, in the parish of St James, Westminster, was not a slum in the way the Victorians used the word. It was something more ordinary and more crowded: a working street of tailors and shoemakers, small workshops and lodging houses, a few hundred yards north of the elegant squares of Mayfair and a short walk from the theatres of the Strand. Its houses had been built for single families in the eighteenth century and subdivided, floor by floor and room by room, as London's population swelled past two and a half million. A family of six might occupy a single back room. Beneath the cellars lay a honeycomb of old cesspools, many of them unemptied for years, because the newer sewers that ran under the street were meant to carry rainwater, not the contents of privies.

At the corner of Broad Street and Cambridge Street stood a public pump. Water was drawn from a well some twenty-eight to thirty feet deep, and the pump had a local reputation for producing the best drinking water in the neighbourhood: cold, clear, and pleasantly sharp to the taste. People walked past nearer pumps to use it. Coffee-shop keepers mixed its water with sherbet powders and sold the drink by the glass. Factories along the street kept tubs of it for their workers on hot days. And the last days of August 1854 were very hot.

On the night of Thursday 31 August, people along Broad Street began to fall ill. The illness came on in hours, sometimes in minutes: a violent, painless diarrhoea, then vomiting, then cramps so severe that the limbs locked. The fluid that poured out of the sick was thin, pale, and flecked with white particles, like water in which rice had been boiled. Within a few hours the patient's skin had turned cold and slack, the eyes had sunk into the skull, the voice had shrunk to a whisper, and the lips and fingernails had gone a dusky blue. Many were dead within a day of the first symptom. Some were dead before the night was out.

Everyone in London knew the name of this disease. It was cholera, and it had come to Britain twice before.

On 2 September alone, 127 people died. Within ten days there had been more than five hundred fatal attacks among people living within about 250 yards of the pump, and around three-quarters of the surviving residents had fled.[1] Shops were shuttered. Black-edged notices went up. Carts carried the dead to the burial grounds by day and night. In absolute numbers it was not the deadliest outbreak London had suffered; in concentration, it was the worst the city had seen. A single street had lost a large share of its population in a little over a week.

Within that same week, a doctor from Sackville Street, a fifteen-minute walk away, began knocking on doors. His explanation for what was happening was one that almost every authority in British medicine considered wrong. To make it convincing, he would have to borrow from fields that rarely spoke to medicine at all: the physics of gases, the statistics of the General Register Office, the street knowledge of a parish clergyman, and the geometry of the map.

The Science: What Cholera Is

It helps to know, before following the people of 1854, what they could not: what cholera actually is, and why it kills.

Cholera is caused by a bacterium, *Vibrio cholerae*, a curved, comma-shaped organism a few thousandths of a millimetre long, which lives naturally in brackish water and estuaries and moves by spinning a single whip-like flagellum. Most strains are harmless. A few carry the genes for a protein called cholera toxin, and these are the strains that cause epidemics. The bacteria reach the human gut in contaminated water or food. Because most are killed by stomach acid, a healthy adult typically needs to swallow a very large number of them to fall ill; volunteer studies in the 1970s put the figure at around a hundred million organisms. That detail matters for the history. It means cholera does not usually leap from person to person through casual contact. It travels in bulk, through water.

The survivors of the stomach colonise the small intestine and release their toxin. The toxin's mechanism was worked out only in the second half of the twentieth century, and it is worth describing because it explains the symptoms that so frightened Victorian doctors. One part of the toxin molecule binds to the surface of the cells lining the intestine; another part enters them and chemically jams a molecular switch (a protein called G_s) into the "on" position. That switch controls the production of a signalling molecule, cyclic AMP. With the switch stuck on, cyclic AMP floods the cell, which responds by opening channels that release chloride ions into the gut. Sodium follows the chloride, and water follows the salt by osmosis. The result is a secretory diarrhoea of extraordinary volume: a severely ill adult can lose a litre of fluid an hour. The "rice-water" stools are the lining of the intestine being rinsed by this flood.

The patient does not die of the bacterium, which never invades the bloodstream. The patient dies of dehydration and the collapse of the body's salt balance: the blood thickens, the pressure falls, the kidneys fail, and the heart, starved of potassium, stops. Untreated, severe cholera kills roughly half of those it strikes.[2] With simple rehydration, which we will come to at the end of this chapter, fewer than one in a hundred die.

None of this was known in 1854. The microscope existed, and at least two investigators that very year were peering at the rice-water fluid and seeing small curved bodies in it. But nobody had a theory that could connect a microscopic organism to a disease, and nobody could culture one, isolate it, or prove that it caused anything. What London's doctors had instead was the disease's history, and a set of explanations built to fit that history.

The Science: What London Thought It Was

Cholera had been endemic in the Ganges delta for centuries. In 1817 it broke out of Bengal and began to travel along the routes of trade, war, and pilgrimage that the nineteenth century was building. It reached Russia in 1830 and the port of Sunderland, in north-east England, in October 1831. The epidemic of 1831–32 killed more than twenty thousand people in Britain. A second wave in 1848–49 was worse: some fifty thousand dead in England and Wales, around fourteen thousand of them in London. The third visitation began in 1853 and was still under way when Broad Street erupted.

Victorian medicine had two broad families of explanation for epidemics like this, and neither fitted cholera well.

The first was *contagion*: the idea that disease passed from the sick to the healthy by touch, breath, or contact with clothing and bedding. Contagion explained smallpox well. But cholera seemed to behave differently. Doctors and nurses who sat with cholera patients often stayed healthy, while people who had never been near a patient fell ill in a street half a mile away. And contagionism carried political baggage: if cholera was contagious, the remedy was quarantine, which was expensive, unpopular with merchants, and had demonstrably failed to keep cholera out of Europe.

The second family of ideas, and the dominant one, was *miasma*: the idea that epidemic disease arose from an atmospheric poison generated by decaying organic matter. Cesspools, open drains, rotting refuse, overcrowded graveyards, and the tidal mud of the Thames all exhaled "effluvia" that could, in the right conditions of heat and stagnation, corrupt the air and the bodies that breathed it. The leading sanitary reformer of the age, Edwin Chadwick, summed up the position in a phrase he repeated to Parliament: all smell is disease. Miasma theory had real strengths. It explained why cholera clustered in poor, crowded, filthy districts. It explained why it struck in summer. It did not require anyone to see an invisible agent. And it pointed towards reforms (cleaning streets, draining cesspools, removing refuse) that were plainly good things to do.

The most sophisticated version of the miasmatic view belonged to William Farr, the compiler of abstracts at the General Register Office. The GRO had been created in 1837 to record every birth, marriage, and death in England and Wales, and Farr, a physician trained in statistics, had turned its weekly returns into the most powerful instrument of public health in the world. Every death in London was recorded with its date, its address, its age, its occupation, and its cause, and published within days. Farr classed cholera among what he called *zymotic* diseases, from

the Greek for fermentation: illnesses caused by some organic matter that multiplied in the body as yeast does in dough, and which was produced and spread most readily by filth.

In his 1852 report on the epidemic of 1848–49, Farr tested this idea against an enormous body of data. He tabulated cholera mortality in every registration district of London against wealth, density of housing, water supply, and elevation above the high-water mark of the Thames. The strongest and most consistent relationship he found was with elevation. Districts lying low on the river had the most deaths; mortality fell steadily as the ground rose, and Farr found that it fell roughly in inverse proportion to height. To a miasmatist, this made perfect sense: the poisonous vapours of the river mud would be densest at the bottom of the valley and thin out up the slopes.[3] It was a careful piece of quantitative work, conducted by the best medical statistician of his generation, and it was wrong in a way that will matter later in this chapter.

So in 1854 the question of what cholera was had three plausible answers, each held by serious people: a contagion passed from person to person, a poison in the air, or a ferment bred in filth. What almost nobody believed was that it was a living thing that multiplied in the human gut, left the body in the evacuations, and found its next victim through the drinking water.

The Anaesthetist

John Snow did not come from the world that governed British medicine. He was born in York in 1813, the eldest of nine children of a labourer in the city's coal yards, in a riverside parish that flooded with the Ouse. At fourteen he was apprenticed to a surgeon-apothecary in Newcastle upon Tyne, and during the epidemic of 1831–32, still a teenager, he was sent to tend miners at the Killingworth colliery during the first cholera epidemic to reach Britain. He saw what the disease did up close, and he noticed something about the pits that would stay with him: the miners worked long shifts underground with no privies and no water to wash in, and they ate their food with their hands where they worked.

He was an unusual young man in other ways. For some years he was a vegetarian and a teetotaller (after a serious illness in his thirties he returned, on medical advice, to meat and an occasional glass of wine), and he reputedly drank only water that he had boiled or distilled, which tells us something about the turn of his mind even then. In 1836 he went to London to complete his training, reputedly walking much of the way, and studied at the Hunterian school of medicine in Great Windmill Street, a few streets from Broad Street. He qualified as a surgeon in 1838, took his medical degree at the University of London in 1844, and set up practice in Soho. He never married. He was reserved, earnest, and not especially good at the clubbable sociability by which London medical careers were built.

What made his name was not cholera but anaesthesia. In December 1846 news reached London from Boston that surgeons there had operated painlessly on patients who had inhaled the vapour of ether. Within weeks, London surgeons were trying it, often badly: some patients barely went under, others went too deep and stopped breathing. Snow recognised the problem as a physical one. The amount of ether a patient breathed depended on how much of it the air

could hold, and that depended on temperature. He measured the vapour pressure of ether at different temperatures, worked out the percentage of vapour that air would carry when saturated, and designed an inhaler with a water bath that held the ether at a constant temperature so that the dose could be controlled. He did the same for chloroform when it was introduced in late 1847, and he worked out, through careful experiments on animals and himself, how the depth of anaesthesia depended on the concentration of vapour in the blood.

By the early 1850s he was the most experienced anaesthetist in the country, and in April 1853 he gave chloroform to Queen Victoria at the birth of her eighth child, Prince Leopold. (He would do so again in 1857, for Princess Beatrice.) The royal endorsement did more than anything else to make pain relief in childbirth respectable in Britain.

The work matters to this story because it trained Snow to think about disease in physical terms. An anaesthetist thinks constantly about routes of entry: how a substance gets into the body, where it goes first, what concentration it reaches, and how quickly. When Snow turned his attention back to cholera in the epidemic of 1848–49, that habit of mind made him sceptical of miasma for a specific reason. A poison carried in the air would enter through the lungs and reach the blood first; its first effects should be general, felt throughout the body, as the effects of ether and chloroform were. Yet cholera's first effects were local and intestinal, and the general symptoms (the cold skin, the collapse, the thick blood) looked like consequences of fluid loss from the gut rather than causes of it. To Snow's mind, the poison was not being breathed. It was being swallowed.

And if it was being swallowed, and if, as the symptoms suggested, it multiplied in the gut and left in the evacuations, then it could reach new victims in two ways: on unwashed hands, as among the miners of Killingworth, or in the water supply, if sewage found its way into wells and rivers from which people drank.

In August 1849 Snow published these arguments in a pamphlet of some thirty pages, *On the Mode of Communication of Cholera*.[4] It contained no maps and few numbers. It made its case from the clinical course of the disease and from a set of local outbreaks in which the water supply seemed to be the common factor, such as a terrace of houses in south London whose wells had been contaminated by an overflowing drain. Reviewers were polite and unconvinced. The argument was ingenious, they said, but it had not been proved: other explanations fitted the same cases, and the theory was too narrow to explain everything that cholera did. They were right that it had not been proved. Snow spent the next five years looking for a way to prove it.

The Grand Experiment

In 1854 London's water was supplied by private companies, several of which drew it straight from the Thames, into which the city's sewers also emptied. South of the river, two of these companies had competed for customers street by street for years. Their mains ran side by side under the same roads, so that one house might take water from the Southwark and Vauxhall Company and its neighbour from the Lambeth Company, often because of decisions made by

landlords years before.

In 1852 the Lambeth Company moved its intake upriver to Seething Wells, near Thames Ditton, above the reach of London's sewage and above the tide. The Southwark and Vauxhall Company continued to take its water from the river at Battersea, in the middle of the city's sewage. When cholera returned in the summer of 1854, Snow realised that London had, without meaning to, set up an experiment on a scale no physician could have arranged. As he put it, the two companies' customers numbered around three hundred thousand people of both sexes and every age and occupation, who differed in essentially one respect: one group was drinking water contaminated with sewage, the other was drinking water that was relatively clean.[5]

The difficulty was finding out which company supplied each house where a cholera death occurred. Residents often did not know: many were tenants who never saw the water bills. Snow started in August 1854, working at first on his own, by walking to every address in the GRO's weekly lists of cholera deaths in south London and asking. Later he hired an assistant, John Joseph Whiting, to extend the inquiry. When residents could not say, he asked for receipts. When there were no receipts, he took a sample of the water and tested it chemically. The Southwark and Vauxhall water carried a great deal of dissolved salt: by Snow's measurements, around forty times as much as the Lambeth water. Snow believed that most of it came from sewage, salt that had passed through the bodies of London's inhabitants. Adding a drop of silver nitrate to a sample produced a heavy white cloud of silver chloride in Southwark and Vauxhall water and almost none in Lambeth water. A test borrowed from the analytical chemist's bench became a way to sort households for an epidemiological study.

The result, published in the second edition of his book in 1855, is the table that has been reproduced in epidemiology textbooks ever since.

Table 1.1: Snow's "Grand Experiment": cholera deaths in the first seven weeks of the 1854 epidemic by water supply (after Snow, Table IX)

Water supply	Houses	Cholera deaths	Deaths per 10,000 houses
Southwark & Vauxhall Company	40,046	1,263	315
Lambeth Company	26,107	98	37
Rest of London	256,423	1,422	59

Houses supplied with sewage-laden water suffered between eight and nine times the cholera mortality of houses supplied with cleaner water. Snow's table compared the companies' whole supply areas, but in the many districts where the two networks were intermixed, the contrast held between neighbouring houses, among people of the same classes, breathing the same air, at the same elevation above the river.

Science Primer: Rates, not counts

Snow's table looks simple, but it rests on two ideas that epidemiology still depends on.

The first is that *counts mislead and rates inform*. Southwark and Vauxhall houses had 1,263 deaths and the rest of London had 1,422; on counts alone, the two look similar. But the rest

of London had more than six times as many houses. Dividing deaths by the population at risk gives a *rate*, and rates can be compared. Snow used houses as his denominator because he had no census of individuals for each company; it is a rough measure, but the same for both groups.

The second is the *rate ratio*, today called the relative risk: the rate in the exposed group divided by the rate in the unexposed group. Here it is

$$\frac{315}{37} \approx 8.5,$$

meaning that a Southwark and Vauxhall household was about eight and a half times as likely to suffer a cholera death. A related measure, the *attributable fraction* $(315 - 37)/315 \approx 0.88$, estimates that roughly 88 per cent of the cholera deaths in Southwark and Vauxhall houses would not have occurred if those houses had drunk Lambeth water.

Snow's design is what we now call a *natural experiment*. He did not assign the water supply; history did. Its strength is that the assignment was largely unrelated to the other things that might cause cholera (poverty, elevation, smell). Its weakness is that it was not random, so a critic could always suggest some hidden difference between the two groups. The best answer to that criticism is the one Snow gave: show that the groups were mixed together in the same streets, so that most other explanations would have to apply to one house and not its neighbour.

It was a powerful result, and Snow knew it. But the analysis took months, and the published table would not appear until 1855. Meanwhile, at the end of August 1854, with the south London survey half finished, cholera erupted a few streets from his own front door.

Ten Days in Golden Square

Snow lived at 18 Sackville Street, just off Piccadilly. When he heard of the outbreak, he suspected the Broad Street pump almost at once, because it sat at the heart of the affected area and was the most heavily used water supply in it. On the evening of Sunday 3 September he took a sample. To his disappointment, the water looked clean: only a few small white flecks, nothing like the visible impurity he had expected. He examined it again over the next two days and found the particles more noticeable, but he knew that appearances proved nothing either way.

So he turned to the method that William Farr's office had made possible. He applied to the General Register Office for the list of every cholera death registered in the subdistricts of Golden Square, Berwick Street, and St Ann's, Soho in the week ending 2 September. There were eighty-nine, and he went to every address. Eighty-three of the deaths had occurred in the last three days of that week. Of these, seventy-three had occurred in houses that were nearer to the Broad Street pump than to any other public pump. In sixty-one of those cases, Snow was told by relatives or neighbours that the dead person had habitually drunk the Broad Street water,

either always or sometimes. Of the ten deaths in houses nearer to another pump, five were in families who sent to Broad Street because they preferred its water, and three were children who went to school near it.[6]

Just as telling were the places that should have suffered and did not. The parish workhouse on Poland Street, three-quarters surrounded by houses where people had died, held 535 inmates; only five of them died of cholera. The workhouse had its own well, and its inmates never needed to send to Broad Street. The brewery on Broad Street itself, owned by Messrs Huggins, employed some seventy men, and not one of them died. The proprietor told Snow that his men were allowed a ration of malt liquor and, as far as he knew, never drank water at all; in any case the brewery had its own deep well.

And then there were the deaths far away from Broad Street that pointed straight back to it. Snow heard of a widow, Susannah Eley, who had died of cholera on 2 September in Hampstead, a high and healthy suburb several miles to the north, where there was no cholera at all. Her late husband had owned a percussion-cap factory on Broad Street, which her sons still ran. Snow went to see them. They told him that their mother had lived in Broad Street years before and liked the taste of its water so much that a cart brought her a large bottle of it every day. She had drunk from the bottle delivered on Thursday 31 August, fell ill the following evening, and died the next day. A niece who was staying with her drank the same water, went home to Islington, another district free of cholera, and died there too. At the factory, eighteen of the workmen, who drank from tubs of pump water kept on the premises, also died.

On the evening of Thursday 7 September, Snow went before the Board of Guardians of St James's parish, which was meeting to discuss the emergency, and presented his findings. He asked them to take the handle off the pump. The Guardians were not persuaded by his theory, but they had nothing better and the request was cheap. The handle was removed the next day, Friday 8 September.

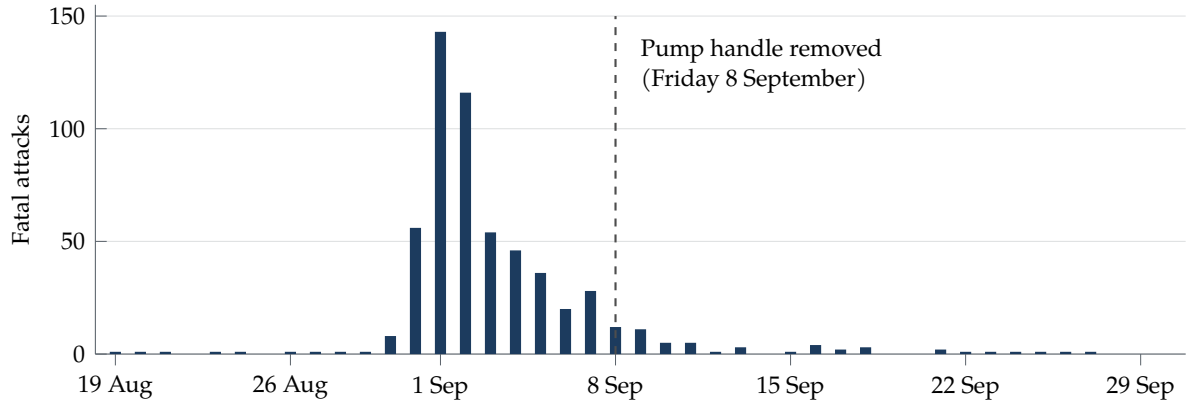


Figure 1.1: Fatal attacks of cholera by date of onset in the Broad Street outbreak, 19 August to 30 September 1854. A further 45 fatal attacks had no known date. The epidemic had peaked on 1 September, a week before the handle was removed. Data from Snow's Table 1 (1855), as transcribed in the R package `HistData`.

What happened next is the most famous moment in the history of public health, and it is not quite what the legend says. The legend says that the outbreak stopped when the handle

came off. Snow himself said otherwise. When he tabulated the dates on which each fatal case had begun, he found that the attacks had peaked on 1 September, with 143 cases that day, and had been falling steeply ever since. By 8 September, the day of the removal, there were twelve new fatal attacks; over the following days, the numbers dwindled into single figures and then to nothing. Many residents had fled. Many of the heaviest drinkers of the pump water were already dead. Snow conceded in print that the epidemic had already been much on the decline before the handle came off, and that it was impossible to know how much difference the removal had made.[7]

That honesty cost him. If the outbreak was already ending, what had the pump handle proved? To the authorities, the waterborne theory remained what it had been in 1849: one ingenious hypothesis among several. To convince them, Snow would need more than his own door-to-door count. As it turned out, the decisive evidence came from a man who set out to prove him wrong.

The Curate

Henry Whitehead was twenty-eight in 1854, an Oxford graduate and the assistant curate of St Luke's, Berwick Street, a parish church in the heart of the district. He was a sociable, energetic young man who spent his days visiting the homes of his parishioners, and he knew Broad Street intimately: who lived on which floor, who worked where, who drank at which public house, whose children were sick. During the outbreak he went from house to house among the dying, and afterwards he wrote a short pamphlet, *The Cholera in Berwick Street*, describing what he had seen. He regarded the epidemic, as most of his parishioners did, as a visitation that probably had something to do with the air and the drains, and possibly with the hand of Providence. When he read Snow's suggestion that the pump was to blame, he thought it unlikely: he knew people who had drunk the water and recovered, and he had himself drunk it during the outbreak without harm.

In the autumn of 1854 the vestry of St James's parish set up a Cholera Inquiry Committee to establish what had happened, and appointed Whitehead to it. He resolved to settle the question of the pump. Over the following months he did what no one else could have done: he tracked down almost everyone who had lived on Broad Street at the time of the outbreak, including many who had fled to other parts of London, and asked each of them the same questions. Had they been ill? Had they drunk the pump water, and when? In the end he gathered information about 497 residents of the street, more than half its population.

His results, laid out as a simple cross-tabulation, did what he had not intended.

Among people known to have drunk the water, more than half fell ill. Among those known not to have drunk it, about one in fifteen did. The ratio between the two proportions, roughly 8.7, was almost exactly the ratio Snow had found between the two water companies in south London: two entirely different studies, at entirely different scales, giving the same answer. Whitehead also noticed that of the fifty-six fatal cases that began in the first three days of the outbreak, only

Table 1.2: Henry Whitehead's survey of Broad Street residents: attacks of cholera among those who did and did not drink the pump water (from the Cholera Inquiry Committee report, 1855)

	Attacked	Escaped	Total	Proportion attacked
Drank the pump water	80	57	137	58%
Did not drink the pump water	20	279	299	7%

two were said with any confidence not to have used the pump.[8]

Whitehead had been converted. But he had also found the hole in Snow's case. If the pump was the source, how had the water become poisoned in the first place, and why so suddenly, at the end of August?

The answer lay in the death register, where Whitehead found an entry that everyone else had overlooked: a five-month-old girl, Frances Lewis, who had died at 40 Broad Street on 2 September of "exhaustion, after an attack of diarrhoea four days previous to death." Number 40 was the house immediately next to the pump. Whitehead went to see the child's mother, Sarah Lewis. She told him that the baby had fallen ill in the last days of August, before the great outbreak began, and that while nursing her she had soaked the soiled napkins in pails of water and emptied the pails partly into a sink in the back yard and partly into a cesspool in the area at the front of the house.

The vestry ordered the parish surveyor, Jehosephat York, to excavate the site. He found that the wall of the cesspool vault practically abutted the well, that the house drain passed within two feet eight inches of the well's brickwork, that the brickwork of both was decayed, and that the ground between them was saturated with sewage. Faecal matter from the house had been seeping into the drinking water of the whole neighbourhood.

There was one more detail, and it gave the pump handle a vindication of sorts. The baby's father, Thomas Lewis, a police constable, fell ill with cholera on 8 September, the very day the handle was removed, and died on 19 September. His wife, nursing him, would presumably have disposed of his evacuations as she had disposed of their daughter's. If the pump had still been in use, a second outbreak might well have followed the first. The removal of the handle may not have ended the epidemic of 1854; it may well have prevented another one.

Whitehead remained Snow's friend and defender for the rest of Snow's short life, and kept a portrait of him in his study for many years afterwards. He later recalled Snow telling him that neither of them might live to see the day, but that the time would come when great outbreaks of cholera would be things of the past, because the knowledge of how the disease spread would make them impossible.

The partnership between them is the core of this chapter's argument. Snow brought a physiological hypothesis, a chemist's test, and a statistician's habit of counting. Whitehead brought something no amount of method could replace: the trust of the people of Broad Street, who told their curate things they would never have told an outside doctor, and a detailed knowledge of the social life of a single street. Neither could have closed the case alone.

The Map and the Line

Snow's map of Soho is the most reproduced image in the history of epidemiology. On a street plan of the district, each death is marked by a small black bar drawn against the house where it occurred, the bars stacking up outward from the building line as the deaths in a single house mount. Thirteen public pumps are marked. The bars gather densely around the pump on Broad Street and thin out with distance in every direction. It is a picture that almost explains itself, and that is part of the trouble with it, because the story usually told about it gets the order of events backwards.

Snow did not discover the pump by drawing the map. He identified the pump in the first week of September from the death register and his door-to-door inquiries, before any map existed. The map was made afterwards, as an argument for an audience: Snow first showed it at a meeting of the Epidemiological Society of London in December 1854, and published it in the second edition of *On the Mode of Communication of Cholera* early in 1855. The base map and its lithography were the work of a professional draughtsman, Charles Cheffins. Nor was it the first map of the outbreak. In September 1854, Edmund Cooper, an engineer working for the Metropolitan Commission of Sewers, had already plotted the deaths on a plan of the district as part of an inquiry into its drainage, which also addressed a popular theory that the sewers, newly dug through ground believed to contain a seventeenth-century plague pit, had released the infection. Mapping disease was not new either: physicians had plotted yellow fever cases in New York in the 1790s and cholera deaths in several British towns in the 1830s and 1840s.[9]

What Snow added that was genuinely new appeared in a second version of the map, which he prepared for the parish Cholera Inquiry Committee and which was published in its report in 1855. On this version, a dotted line winds irregularly around the Broad Street pump. In Snow's words, it marked the various points that careful measurement had shown to be at an equal distance, by the nearest road, from the Broad Street pump and from the surrounding pumps. Every house inside the line was closer to Broad Street, on foot, than to any other public water supply. And the deaths, with a handful of explicable exceptions, lay inside the line.[10]

Science Primer: Snow's line and the Voronoi diagram

Suppose you have a set of points on a plane (here, pumps) and you want to divide the plane into regions such that every location in a region is closer to that region's point than to any other. The result is called a *Voronoi diagram*, after the Russian mathematician Georgy Voronoy, who studied such divisions formally in 1908. (They are also called Dirichlet or Thiessen tessellations; Descartes sketched something similar in the seventeenth century.)

If "distance" means straight-line distance, the boundaries are straight: each one is the perpendicular bisector of the line joining two neighbouring points, and the regions are convex polygons. But a person fetching water does not walk through walls. Snow measured distance *along the streets*, which mathematicians call a network or graph distance. Under that measure, boundaries bend around blocks, and a house can be a few yards from one pump as the crow flies but further from it on foot than from another pump round the corner.

That is why Snow's line is irregular rather than polygonal.

The point of the line was to turn a picture into a test. If the pump was the source of infection, deaths should concentrate inside the region of houses for which Broad Street was the most convenient water, and fall off sharply at its edge, not simply decline smoothly with distance as an airborne poison spreading from a central source would. That is what Snow's map showed. Modern reanalyses using geographical information systems, which recompute walking distances along the 1854 street network, have broadly confirmed his result.

The dotted line is the moment in this story when a fourth discipline enters, almost unnoticed. Snow was not a mathematician and did not think of his line as geometry. But the question it answers (which source is nearest to each location, measured along a network?) is a geometrical one, and the answer it gives is a structure that mathematicians would formalise, and name after Voronoy, half a century later. It is also the ancestor of a family of methods that public-health agencies now use routinely, from defining hospital catchment areas to locating the source of an outbreak from the addresses of its victims.

Rejection

The Cholera Inquiry Committee reported in the summer of 1855. It concluded unanimously that the outbreak was in some manner attributable to the impure water of the Broad Street well, and it paid full tribute to Whitehead's work, though it stopped short of endorsing Snow's wider theory of how cholera spread. Even so, when the full vestry voted in August 1855 on whether to receive the report, the vote was tied, and the chairman's casting vote carried it.

The national authorities were less convinced. The General Board of Health had appointed its own Committee for Scientific Inquiries into the 1854 epidemic, with William Farr among its members, and it reported in 1855 as well. It rejected Snow's explanation. It did not find it established that the Broad Street water had been contaminated in the way Snow alleged, and it concluded that the influences that spread cholera belonged less to the water than to the air; impure water, at most, made people more vulnerable. The microscopic bodies that the physician Arthur Hassall had seen in the evacuations of cholera patients were dismissed as products of decomposition rather than causes of disease.[11]

The argument was not unreasonable. Snow had no organism to point to, no mechanism other than inference, and an outbreak that had already been ending when his intervention was made. He was a specialist in anaesthesia, not an established authority on epidemics. And his theory asked the sanitary movement to accept that its central doctrine, the danger of bad air, was mistaken about the most feared disease of the age.

Snow kept working. He published a fuller account of the south London study in 1856 and defended his theory at every opportunity. He continued to give anaesthetics, and he began work on a large book on the subject. On 10 June 1858 he suffered a stroke while writing it, and he died

at his home in Sackville Street on 16 June, aged forty-five. *The Lancet*'s obituary was a few lines long. It noted that his researches on chloroform and other anaesthetics had been appreciated by the profession. It did not mention cholera. The journal published a correction in April 2013.[12]

Outcomes and Legacy

Snow's theory was eventually accepted, but not because the Broad Street map persuaded anyone. It won through a slow accumulation of evidence from other places and other disciplines.

The first came from the same office whose data Snow had used. In the summer of 1866, a final cholera epidemic struck London, and it was concentrated, to a startling degree, in the East End. By then Joseph Bazalgette's new system of intercepting sewers was carrying most of the city's sewage downstream, but the East End's section was not yet complete. Farr, examining the weekly returns, saw that the deaths were confined almost exactly to the area supplied by the East London Water Company, and investigation revealed that the company had been drawing water from a reservoir at Old Ford, on the River Lea, that was contaminated by sewage. Farr's report on the epidemic accepted that water had carried the disease. Snow had been dead for eight years.[13]

The second came from the laboratory. In 1854, the year of Broad Street, the Florentine anatomist Filippo Pacini had described curved microscopic organisms in the intestines of cholera victims and called them *vibrioni*; his paper was ignored outside Italy, and the bacterium's formal name, *Vibrio cholerae* Pacini 1854, was adopted in his honour only in 1965. In 1883–84, Robert Koch, working first in Egypt and then in Calcutta, isolated the "comma bacillus" in pure culture, found it consistently in cholera patients and never in healthy people, and traced it to a contaminated village water tank. Koch's germ theory supplied what Snow had lacked: an agent that could be seen, grown, and followed.

The third came from a natural experiment even cleaner than Snow's. In 1892 cholera struck Hamburg, which took unfiltered water from the River Elbe. The neighbouring city of Altona, immediately downstream, took water from the same river but passed it through slow sand filters. Hamburg suffered around eighteen thousand cases and more than eight thousand deaths in ten weeks. Altona, which was more downstream and so drew dirtier water, had a few hundred cases, most of them traced to contact with Hamburg. In places the border between the two cities ran down the middle of a street, and the disease followed the water mains rather than the street.[14] The great Munich hygienist Max von Pettenkofer, who held that germs alone could not cause cholera without the right conditions of soil and groundwater, responded by swallowing a culture of Koch's bacillus in October 1892. He suffered only diarrhoea and claimed vindication. The water filters, not the argument, settled the question.

The longer outcomes are larger than any of these episodes. Cholera never again became epidemic in Britain after 1866, and it retreated from most of Europe within a few decades, not mainly because of medicine but because of engineering: sewers, protected water intakes, filtration, and, from the early twentieth century, chlorination. Ironically, Bazalgette's sewers, the

single greatest public-health investment in Victorian London, were approved in 1858 after the "Great Stink" of that summer, when the smell of the Thames became so bad that Parliament could barely sit. They were built to remove miasma. They worked because they also kept sewage out of the drinking water.

The treatment of cholera was transformed by another collision of fields a century later. In 1959, the Indian pathologist Sambhu Nath De, working in Calcutta, showed that a bacteria-free filtrate of *V. cholerae* culture could by itself cause fluid to pour into the intestine, demonstrating that the disease was caused by a toxin. Meanwhile, physiologists studying how the gut absorbs nutrients had discovered that sodium and glucose are carried across the intestinal wall together by a transport protein, and that this pathway keeps working even when cholera toxin has jammed the cell's chloride channels open. A solution of salt and sugar in clean water, drunk in the right proportions, could therefore replace the fluid that cholera removed. Trials in Dhaka and Calcutta in the late 1960s proved it, and in 1971 the physician Dilip Mahalanabis used oral rehydration in refugee camps during the Bangladesh Liberation War, where intravenous fluids were desperately short; deaths among his cholera patients fell to around 3 per cent, against 20 to 30 per cent in camps relying on intravenous treatment.[15] Oral rehydration therapy, cheap enough to be mixed at home, is credited with saving tens of millions of lives since.

Cholera has not gone away. In 2025, countries reported more than 450,000 cases and nearly 7,900 deaths to the World Health Organization, the highest annual death toll reported since 1999, and the true numbers are certainly far higher.[16] The disease persists wherever war, displacement, and poverty break water and sanitation systems. When cholera reached Haiti in October 2010, months after the earthquake, investigators combined classic outbreak epidemiology with whole-genome sequencing of the bacterium to show that the strain had almost certainly been introduced from Nepal, by way of a camp of United Nations peacekeepers whose sewage drained into a tributary of the Artibonite River. The methods were new; the logic of following the bacterium to its source through water was Snow's.

Finally, there is the discipline itself. Snow was a founding member of the Epidemiological Society of London in 1850, and epidemiology as a body of practice (counting cases against populations, comparing rates between exposed and unexposed groups, looking for natural experiments, testing explanations against the places where they predict cases should and should not occur) grew out of the work of people like him, Farr, and their contemporaries. A replica of the pump, without a handle, now stands on what is today Broadwick Street. The public house on the corner is named after Snow.

The Costs of Crossing

This book argues that discoveries happen at the borders between disciplines. The Broad Street story is the classic example, which is exactly why its complications deserve attention. Four of them bear directly on the argument.

Being right was not enough. Snow's border-crossing produced the correct answer more

than a decade before it was accepted, and for most of that time it changed nothing. The establishment's resistance was not mere prejudice. A theory assembled from several fields can be harder to evaluate than one built inside a single discipline, because no one reviewer is competent to judge all of its parts, and Snow could not supply the one piece of evidence (a visible, culturable agent) that would have made the case compelling to his contemporaries. Insights at the border need a community able to receive them. In 1855 that community did not exist.

The wrong theory did a great deal of good. The miasmatists were mistaken about cholera, but the reforms their theory demanded (clearing filth, draining cesspools, building sewers) were exactly the right things to do, and in the long run they did more to defeat cholera than Snow's insight did. Here a mistaken idea, held firmly within one discipline, produced the right action at scale. That is an uncomfortable fact for any story in which the outsider is simply right and the insiders simply wrong.

Imported methods can mislead as easily as they illuminate. William Farr brought the most rigorous statistical apparatus of his day into medicine, and it led him to the elevation law. His correlation was real: low-lying districts did have more cholera. But the low-lying districts of south London were also the ones that drank the sewage-laden water of the tidal Thames, because that was where the companies that drew from the tidal river supplied. Elevation was a stand-in for water supply. Statisticians now call this *confounding*, and Farr's error is a textbook example of it. The same smuggling of method across borders that made Snow's case also produced one of the period's most persuasive mistakes. A method borrowed from another field carries that field's blind spots with it.

Heroic stories hide the coalition. The popular version of this chapter, in which a lone genius looks at a map, identifies a pump, and ends an epidemic, misstates nearly every part of what happened. Snow did not need the map to find the pump; the epidemic was already ending; and his case depended on Farr's registration system, a chemist's test for salt, a surveyor's excavation, an engineer's earlier map, and, above all, Henry Whitehead's knowledge of his parish. The myth survives because it is a good story. But it teaches the wrong lesson about how discovery works, and a book about collaboration across disciplines should be especially wary of it.[17]

Coda

What, then, does the Broad Street story show? Not that a single outsider broke a single orthodoxy, but that a problem as large as an epidemic in a crowded city was beyond the reach of any one field. The physiology of gases gave Snow his hypothesis. The registration system gave him his data. Chemistry let him sort the houses of south London. Whitehead's parish work found the people the data could not reach, and the index case that explained the sudden start. The geometry of the dotted line turned a picture into a test. Each of those pieces had existed separately before 1854. The discovery lay in putting them together, and in the willingness of a sceptical curate to follow the evidence where it led.

Notes

[1]Snow's own account gives more than five hundred fatal attacks in ten days within 250 yards of the pump, and reports that most residents fled within a week; the 127 deaths on 2 September are from his Table 1: John Snow, *On the Mode of Communication of Cholera*, 2nd ed. (London: John Churchill, 1855). The final total of 616 deaths is the count most often used by historians; see Peter Vinten-Johansen et al., *Cholera, Chloroform, and the Science of Medicine: A Life of John Snow* (New York: Oxford University Press, 2003).

[2]The fifty per cent figure for untreated cholera is the conventional estimate; see Michael Emmans Dean, "Selective Suppression by the Medical Establishment of Unwelcome Research Findings: The Cholera Treatment Evaluation by the General Board of Health, London 1854," *Journal of the Royal Society of Medicine* 109, no. 5 (2016): 200–205.

[3]William Farr, *Report on the Mortality of Cholera in England, 1848–49* (London: HMSO, 1852). For Farr's thinking more generally, see John M. Eyler, *Victorian Social Medicine: The Ideas and Methods of William Farr* (Baltimore: Johns Hopkins University Press, 1979).

[4]John Snow, *On the Mode of Communication of Cholera* (London: John Churchill, 1849). Snow's prior career in anaesthesia, and its influence on his thinking about cholera, is treated in detail in Vinten-Johansen et al., *Cholera, Chloroform, and the Science of Medicine*.

[5]Snow, *On the Mode*, 2nd ed.

[6]Snow's figures for the deaths registered in the week ending 2 September are given in *On the Mode*, 2nd ed., and in his report to the parish inquiry: Cholera Inquiry Committee, *Report on the Cholera Outbreak in the Parish of St. James, Westminster, during the Autumn of 1854* (London: J. Churchill, 1855).

[7]Snow, *On the Mode*, 2nd ed.; Snow's Table 1 lists fatal attacks by date of onset. The daily figures in Figure 1.1 match the transcription in the `Snow.dates` dataset of Michael Friendly's `HistData` package for R. On the significance of the decline before the handle was removed, see Howard Brody et al., "Map-Making and Myth-Making in Broad Street: The London Cholera Epidemic, 1854," *The Lancet* 356, no. 9223 (2000): 64–68.

[8]Henry Whitehead, "Mr. Whitehead's Report of His Special Investigation of Broad Street," in Cholera Inquiry Committee, *Report*. Whitehead's numbers are presented as "80 to 57" and "20 to 279"; the proportions and ratio are my calculation. On Whitehead's life, see S. P. W. Chave, "Henry Whitehead and Cholera in Broad Street," *Medical History* 2, no. 2 (1958): 92–108; and the Cumbrian Lives project, `https://www.cumbrianlives.org.uk/lives/the-rev-henry-whitehead.html`.

[9]On the precursors and the two versions of the map, see Tom Koch, *Cartographies of Disease: Maps, Mapping, and Medicine* (Redlands, CA: ESRI Press, 2005); and, for the dates of the two maps, the UCLA John Snow site, `https://epi-snow.ph.ucla.edu`.

[10]The boundary appears on the map published with Snow's report in the Cholera Inquiry Committee's *Report* (1855), not on the map in the second edition of *On the Mode* (January 1855); some modern accounts conflate the two. See the John Snow Archive and Research Companion at Michigan State University, `https://johnsnow.matrix.msu.edu`, which reproduces both maps.

[11]Dean, "Selective Suppression," discusses the work of the General Board of Health's committees in 1854–55.

[12]The *Lancet*'s 1858 obituary and its 2013 correction are discussed in Paul Raeburn, "The Lancet Corrects the Obituary of a Pioneering Epidemiologist—after How Many Years?," Knight Science Journalism Tracker, MIT, 12 April 2013, `https://ksj.mit.edu/tracker-archive/lancet-corrects-obituary-p`

ioneering-epid/.

[13]William Farr, *Report on the Cholera Epidemic of 1866 in England*, supplement to the Twenty-Ninth Annual Report of the Registrar-General (London: HMSO, 1868); see also Eyler, *Victorian Social Medicine*.

[14]Figures from Robert Koch, *Professor Koch on the Bacteriological Diagnosis of Cholera, Water-Filtration and Cholera, and the Cholera in Germany during the Winter of 1892–93*, trans. George Duncan (Edinburgh: David Douglas, 1894). The standard history is Richard J. Evans, *Death in Hamburg: Society and Politics in the Cholera Years, 1830–1910* (Oxford: Clarendon Press, 1987).

[15]Sambhu Nath De, "Enterotoxicity of Bacteria-Free Culture-Filtrate of *Vibrio cholerae*," *Nature* 183 (1959): 1533–34; Dilip Mahalanabis et al., "Oral Fluid Therapy of Cholera among Bangladesh Refugees," *Johns Hopkins Medical Journal* 132 (1973): 197–205.

[16]World Health Organization figures for 2025, released 30 September 2026, as reported in "Cholera Remains a Challenge, Deaths Increased by 30% in 2025: WHO," *Down To Earth*, 30 September 2026.

[17]The development of the Snow legend is examined in Kari S. McLeod, "Our Sense of Snow: The Myth of John Snow in Medical Geography," *Social Science & Medicine* 50, no. 7–8 (2000): 923–35; and Nigel Paneth, "Assessing the Contributions of John Snow to Epidemiology: 150 Years after Removal of the Broad Street Pump Handle," *Epidemiology* 15, no. 5 (2004): 514–16.

Further Reading

John Snow, *On the Mode of Communication of Cholera*, 2nd ed. (London: John Churchill, 1855). The primary source, and still readable. Snow's prose is plain and his reasoning easy to follow; the Grand Experiment and the Broad Street investigation are both here. Facsimiles are freely available online.

Peter Vinten-Johansen, Howard Brody, Nigel Paneth, Stephen Rachman, and Michael Rip, *Cholera, Chloroform, and the Science of Medicine: A Life of John Snow* (Oxford University Press, 2003). The definitive scholarly biography, by a team of historians and epidemiologists. Best on Snow's anaesthesia work and on how his reasoning developed.

Steven Johnson, *The Ghost Map* (Riverhead, 2006). A vivid narrative of the outbreak, especially good on Whitehead and on the city itself. More dramatic than the scholarly accounts, and occasionally more confident than the evidence.

Sandra Hempel, *The Medical Detective: John Snow and the Mystery of Cholera* (Granta, 2006). A shorter, well-researched popular account that places Broad Street within the longer history of cholera in Britain.

Tom Koch, *Cartographies of Disease: Maps, Mapping, and Medicine* (ESRI Press, 2005). For readers interested in the map: its precursors, its two versions, and what it did and did not show.

John M. Eyler, *Victorian Social Medicine: The Ideas and Methods of William Farr* (Johns Hopkins University Press, 1979). The best account of Farr, which corrects the popular picture of him as Snow's antagonist.

Richard J. Evans, *Death in Hamburg: Society and Politics in the Cholera Years, 1830–1910* (Clarendon Press, 1987). A classic of social history, built around the 1892 epidemic and the Hamburg–Altona comparison.

Stephen Halliday, *The Great Stink of London: Sir Joseph Bazalgette and the Cleansing of the Victorian Metropolis* (Sutton, 1999). The engineering side of the story.

Online: the John Snow Archive and Research Companion (Michigan State University), https://johnsnow.matrix.msu.edu, and the John Snow site of the UCLA Department of Epidemiology, https://epi-snow.ph.ucla.edu. Transcriptions of Snow's and Whitehead's reports, the maps, and much

else.

Chapter 2

On Growth and Form: The Geometry of Life (1917)

The Rookeries

In the summer of 1896 a thirty-six-year-old professor of natural history from Dundee travelled to the Pribilof Islands, whose two main islands, St Paul and St George, lie in the middle of the Bering Sea, to count seals. Every summer the northern fur seals of the eastern Pacific came ashore on the islands' beaches to breed, in crowded colonies known as rookeries. The bulls held territories along the shore, the cows came in to give birth and mate, and the pups stayed on land while their mothers went out to sea to feed. The herd was the basis of a valuable fur trade, and it had been shrinking for more than a decade.

The United States, which had bought the islands with Alaska in 1867, leased them to a company that drove young males inland and killed them for their skins. Sealing schooners, many of them from British Columbia and sailing under the British flag, shot seals in the open ocean, a practice called pelagic sealing. Each side blamed the other for the decline. An international tribunal sitting in Paris had imposed regulations on the sealers, which came into force in 1894, but the herd went on falling. In 1896 both governments sent scientists to the islands to find out why, and the expert sent at the request of Lord Salisbury's government was D'Arcy Wentworth Thompson. He went back for a second season in 1897.

The investigators' main tool was counting. Because a pup stays near the spot where it was born for its first weeks of life, a count of pups on a rookery is in effect a census of the breeding females that used it. They counted harems, cows and pups; they also counted the dead, including many thousands of starved pups in 1896. Most of the seals killed at sea were females, many of them nursing mothers that had swum out to feed, and their pups, waiting on shore, could not survive without them. In 1897 Thompson recounted one rookery on his own. His figures implied a fall of about nine per cent in a single year, against twelve per cent from the official joint counts, and the experts treated his lower figure as the minimum.

From 10 to 17 November 1897 the experts met in Washington. Thompson and James Ma-

coun, for Britain and Canada, and David Starr Jordan and Charles Hamlin, for the United States, signed a joint statement of fact: the herd had been declining since 1884; the killing of males on land was not to blame; and pelagic sealing, because it took females, was a significant cause. The herd was not yet close to extinction, they agreed, but it was yielding little return either to the island lessees or to the sealing fleet.[1] Thompson was made a Companion of the Order of the Bath the following year. He brought home for his teaching museum in Dundee, among other things, the skeleton of a Steller's sea cow, a giant sea cow related to the dugong and manatee that had been hunted to extinction in the eighteenth century.

This is not the picture most readers have of D'Arcy Thompson, if they have one at all. He is remembered for a single book, *On Growth and Form*, which he finished in Dundee during the First World War and signed off with a prefatory note dated December 1916. The book, he wrote there, had little need of a preface, being "all preface" from beginning to end.[2] It ran to nearly eight hundred pages. It asked a question that the biology of its day had largely stopped asking (why do living things have the shapes they have?) and gave an answer drawn from physics, engineering and geometry: that a great deal of biological form is the visible result of physical forces acting on growing matter. It is one of the purest examples in this book of what the Introduction called structural isomorphism, the recognition that a soap film, a splash, a girder and a shell may obey the same mathematics. It is also a lesson in how far such a recognition can carry a science, and where it stops.

The Science: What Biology Asked of Form

By 1900, four decades after Darwin's *On the Origin of Species*, the study of animal form was dominated by one kind of question. Comparative anatomists and embryologists worked to reconstruct the family tree of life. They compared bones, organs and embryos across species to identify *homologies*, structures inherited from a common ancestor, and they arranged living and fossil groups into lineages. When a morphologist asked why an animal had a particular shape, the expected answer was historical: because its ancestors had a related shape, modified by descent. A second kind of answer was functional: the shape had been favoured by natural selection because it did something useful.

Both answers were reasonable, and both left something out. Neither said how a shape was actually produced. The chambers of a shell, the cells of a honeycomb or the branching of a bone are made by physical processes in real materials, and those processes have their own rules. A shell is secreted by a mantle; a cell divides; a liquid surface pulls itself tight. To say that selection favoured a form is to say why it persisted, not how it was built.

Some biologists were asking the second kind of question. A German school of experimental embryology, *Entwicklungsmechanik* (developmental mechanics), associated with Wilhelm Roux and before him Wilhelm His, tried to explain embryonic shapes by the pushes and pulls of growing tissue. Anatomists had compared the internal struts of bone to the lines of stress in engineering structures: in 1866 and 1867 the engineer Karl Culmann and the anatomist Hermann von Meyer noticed that the trabeculae inside the head of a human femur followed much

the same pattern as the stress lines that Culmann's new graphical methods drew for a curved crane. Statisticians of the biometric school around Karl Pearson measured variation in populations with great precision. But in mainstream morphology the physics of form was a marginal interest.

On Growth and Form opens with Kant. Of the chemistry of his own day, Thompson recalled, Kant had declared that it was "a science, but not science", because the test of a true science lay in its relation to mathematics. Chemistry had since earned the title. Physiology, Thompson thought, was earning it by adopting the methods of physics. But zoologists and morphologists had hardly begun, and when a zoologist saw a near-perfect sphere or spiral in a shell, he tended to assume that it must be something more than a sphere or a spiral, and to look for its meaning in its history or its use.

Thompson's complaint, set out in the opening pages of his book, was that biology had neglected one kind of cause for the sake of another. The vocabulary came from Aristotle, whose biology Thompson knew intimately: Aristotle distinguished the *efficient* cause of a thing (the agent or process that produces it) from its *final* cause (the end it serves). Darwinism, Thompson argued, had replaced the old argument from design with an argument from selection that still explained forms by their purposes. Borrowing a phrase from earlier critics, he said that biology had arrived at a "teleology" without a *telos*, a doctrine of purposes without an end in view. What it lacked was the efficient cause. "Cell and tissue, shell and bone, leaf and flower," he wrote, "are so many portions of matter", shaped in obedience to the laws of physics.

He put the programme in a phrase that has outlived most of his specific claims. The form of an object, he said, is a "diagram of forces": from the shape of a thing we can infer the forces that have acted on it, and from known forces we can predict a shape. A raindrop is round because surface tension pulls a liquid into the smallest surface that will hold its volume; a hanging chain takes a curve fixed by gravity and its own weight. Thompson asked how far the same reasoning could go with living things.

The Science: Size and Surface

The book's first substantial argument concerns size. Thompson credited it to Galileo, who in his *Two New Sciences* of 1638 had shown that neither a house nor an animal can be scaled up indefinitely while keeping its proportions and materials. Galileo noted that a horse falling a few cubits may break its legs while a cat or dog survives a greater fall, and that a giant ten times the height of a man could exist only if his bones were thickened out of all normal proportion. Herbert Spencer had applied the same principle to biology in the nineteenth century. The idea was not lost and in need of reviving; what Thompson did was to place it at the foundation of a whole account of biological form, and to follow it in both directions, up to whales and down to bacteria.[3]

The principle is now called the square–cube law. If a body keeps its shape while its length grows, its surface area grows as the square of the length and its volume, and therefore its weight,

as the cube. The strength of a bone or muscle depends on its cross-sectional area, which is also a square. So as an animal grows larger, its weight outstrips the strength of its supports. Thompson noted that the elephant was already showing, in the thickness of its limb bones, signs of approaching the limit that physics sets for a land animal. Large animals are not simply small animals magnified. They have to be built differently. (Chapter 10 follows the same question of scale into the metabolic scaling laws of the 1990s.)

Going down in scale, the law works the other way. Surface grows in importance relative to volume, and forces that act on surfaces come to dominate forces that act on mass. The most important of these is surface tension. The molecules at the surface of a liquid are pulled inwards by their neighbours more strongly than they are pulled outwards, so a liquid surface behaves rather like a stretched elastic skin that tries to make itself as small as possible. For a puddle or a pond, surface tension is negligible compared with gravity. For a droplet a millimetre across it is the controlling force. Thompson put the consequence directly: the form of small organisms is largely independent of gravity, and largely if not mainly due to surface tension.

Science Primer: The square–cube law in numbers

Take an animal and scale it up by a factor k in every direction, keeping its shape. Its length becomes k times as large, every area (including the cross-section of each bone) becomes k^2 times as large, and its volume and weight become k^3 times as large. The *stress* in a leg bone, the load it carries divided by its cross-sectional area, therefore grows as

$$\frac{k^3}{k^2} = k.$$

Galileo's giant, ten times the height of a man ($k = 10$), would weigh a thousand times as much, stand on bones with a hundred times the cross-section, and load every square centimetre of bone ten times as heavily. To bring the stress back to normal, the bones' cross-sectional area would have to grow as fast as the weight, as k^3, so their diameter would have to grow as $k^{3/2}$. For $k = 10$ that is about 32 times the original diameter on a skeleton only 10 times as long: bones roughly three times as thick in proportion. That is Galileo's "monstrosity", and it is why an elephant's legs are not a scaled-up gazelle's.

Now go the other way. Surface tension, γ, is a force per unit length (about 0.072 newtons per metre for water at room temperature). It competes with gravity, which acts on volume. A useful comparison is the *capillary length*,

$$\ell_c = \sqrt{\frac{\gamma}{\rho g}},$$

where ρ is the density of the liquid (1,000 kilograms per cubic metre for water) and g is the acceleration due to gravity (9.8 metres per second squared). For water,

$$\ell_c = \sqrt{\frac{0.072}{1000 \times 9.8}} \approx 0.0027 \text{ m},$$

or about 2.7 millimetres. Structures much larger than this are shaped mainly by gravity; structures much smaller, mainly by surface tension. Most cells are hundreds or thousands of times smaller than ℓ_c, and most of the protozoan skeletons that Thompson studied, typically a fraction of a millimetre across, are well below it.

The same arithmetic explains why getting wet is trivial for us and dangerous for an insect, a point J. B. S. Haldane made in a famous essay in 1926. A person stepping out of a bath, he wrote, carries a film of water about one-fiftieth of an inch (half a millimetre) thick, weighing roughly a pound: under 1 per cent of body weight. The film's thickness is set by the water, not by the animal, so for a fly about 250 times shorter than a person, the water it carries shrinks as k^2 while its body shrinks as k^3. Its burden relative to its weight is about 250 times larger, which puts it above the fly's own weight. (These are rough figures, but the ratio is the point.)

Thompson's guide to the physics of surfaces was the Belgian physicist Joseph Plateau. Plateau believed he had damaged his eyes in 1829 by staring at the sun during an experiment on vision, and by 1843 he was completely blind. He spent the next quarter-century studying liquid films and drops through the hands and eyes of assistants, among them his son and his son-in-law, and published the results in 1873 as a two-volume treatise on the statics of liquids under molecular forces.[4] He dipped wire frames into soapy glycerine solutions and described the films that formed. A wire cube, for instance, does not fill with six films on its faces or with films running into its centre; instead it holds thirteen films, twelve running inwards from the edges to meet a small four-sided film suspended in the middle. A soap film, like any liquid surface, settles into the shape of least area that its boundary allows: a *minimal surface*. And when films meet, they obey a small set of rules, now called Plateau's laws. Films meet only in threes, along an edge, at equal angles of 120°. Those edges meet only in fours, at a point, at the angle of about 109.5° found between the bonds of a tetrahedral molecule. Plateau found these rules by observation. They were proved mathematically, as properties of minimal surfaces, only in 1976, by the American mathematician Jean Taylor.

Thompson saw Plateau's rules everywhere in living tissue. Cells packed together in a sheet tend to meet in threes, like bubbles in a froth. The first divisions of a frog's egg produce partitions that look like soap films in a container. He drew on the work of the Belgian botanist Léo Errera, who had argued in the nineteenth century that a dividing plant cell lays down its new wall as a soap film would, along the surface of least area. He compared the arrangement of cells in plant tissues and corals to bubble rafts.

The most famous test case was the honeycomb. Darwin had treated the hexagonal cell of the honeybee as a triumph of natural selection: a shape that stores the most honey for the least wax, perfected over generations. Thompson argued instead that the hexagons arose from physical forces acting on the soft wax as cells pressed together, much as bubbles become hexagonal in a raft, and that the bee was not economising at all. The argument has not ended. In 2013 a team led by engineers at Cardiff University reported that cells start out circular and become rounded hexagons as wax, warmed by worker bees, flows under surface tension at the junc-

tions. Entomologists have replied that bees build and shape the cells actively, following simple building rules. The science writer Philip Ball, reviewing the dispute in 2017, scored that round to Darwin.[5]

A Classicist among the Bones

D'Arcy Wentworth Thompson was born on 2 May 1860 at 3 Brandon Street in Edinburgh. His father, also D'Arcy Wentworth Thompson, was a classics master at the Edinburgh Academy. His mother, Fanny Gamgee, died within days of his birth. When the boy was three his father left to become professor of Greek at Queen's College, Galway, and the young D'Arcy spent much of his childhood in Edinburgh in the household of his maternal grandfather, Joseph Gamgee, a veterinary surgeon who encouraged his interest in natural history. From his father he took a lifelong love of the classics; from the Gamgee side of the family, which also produced the physiologist Arthur Gamgee, he took a taste for science.

He went to the Edinburgh Academy, where his classmates included the future marine biologist William Herdman and the physiologist John Scott Haldane, and then studied medicine at Edinburgh University. There he came under the influence of Sir Wyville Thomson, recently returned from the scientific voyage of HMS *Challenger*, and turned from medicine towards zoology. In 1880 he went to Trinity College, Cambridge, at first as a sizar (a student admitted on reduced fees) and then as a scholar. He took first-class honours in both parts of the Natural Sciences Tripos and spent a year as a demonstrator in physiology under Michael Foster. To help pay his way he translated Hermann Müller's work on the fertilisation of flowers by insects, which appeared in English in 1883 with a preface by Charles Darwin, one of the last things Darwin wrote.

In 1884, still in his early twenties, he was appointed to the new chair of biology at University College, Dundee, which had been founded in 1881 with a gift from Mary Ann Baxter, of a Dundee textile family, and had opened its doors in 1883. The chair was renamed natural history in 1888, and in 1897 the college became part of the University of St Andrews. Dundee had no zoological museum, so Thompson built one, buying, begging and collecting specimens for teaching. He wrote to his grandfather in 1885 that additions to his museum were numerous, including two bagfuls of monkeys, all dead of course. Dundee's whaling captains brought him Arctic material, and the museum's strength in Arctic zoology became unusual. Thompson married Maureen Drury in 1901, and they had three daughters.

He did not spend those years writing *On Growth and Form*. For most of his career his scientific reputation rested on practical natural history and on classical scholarship. After the Bering Sea, he served from 1898 as a scientific member of the Fishery Board for Scotland, and when the International Council for the Exploration of the Sea was founded in 1902 he became one of Britain's representatives, serving on its council and editing its statistical bulletin until 1947. He compiled fisheries statistics and charted sea temperatures. At the same time he published *A Glossary of Greek Birds* (1895), an annotated translation of Aristotle's *Historia Animalium* (Oxford, 1910), and *On Aristotle as a Biologist*, the Herbert Spencer lecture he gave at Oxford in February

1913. His *Glossary of Greek Fishes* appeared in 1947, the year before his death. The two lives were not separate. To identify the birds and fishes named by Aristotle, Thompson had to know both the Greek and the animals, and his Aristotle was a careful field naturalist, not only a philosopher. The classical training mattered in another way. Thompson read Plato, Euclid and Archimedes as working texts, and the geometry he brought to biology was the geometry of the Greeks, of ratios, similar figures and gnomons, rather than the calculus of the physics laboratory.

His colleagues remembered him as tall and bearded (the curator of his museum today puts his height at about six foot three) and as a spellbinding lecturer who would produce an object from his pocket and talk about it. In old age in St Andrews he was known to walk about town with a parrot on his shoulder; one acquaintance remembered his heavy overcoat streaked on the right shoulder where the parrot had left its mark. He reputedly gave his last lecture, at eighty-seven, with a live chicken under his arm. These stories are recorded by people who knew him and seem reliable, though like most such stories they have been polished in the retelling.

Thompson was elected a Fellow of the Royal Society of Edinburgh in 1885 and of the Royal Society in 1916. Later honours reflected both of his worlds. He was president of the Classical Association in 1929, a rare distinction for a scientist, and president of the Royal Society of Edinburgh from 1934 to 1939. He was knighted in 1937, received the Linnean Society's gold medal in 1938 and the Royal Society's Darwin Medal in 1946, and was made an honorary member of the Edinburgh Mathematical Society in 1933. None of these were mathematical prizes; his mathematics was largely self-taught and, by his own account, modest.[6]

Writing the Book

The idea that became *On Growth and Form* had been forming for years. In 1911 Thompson used his presidential address to the zoological section of the British Association, which he called "Magnalia Naturae", to describe the problems that drew him most strongly: those on the borderline between morphology and physics, which involved mechanics, mathematical laws and physical processes. He had already offered Cambridge University Press a small book on the subject, around 1910. By 1915, with the war giving him time to write, he had produced something much larger, and he signed a contract for it. The book was published in 1917, in an edition of 500 copies, at 793 pages. Reviewers were respectful and sometimes enthusiastic. J. Arthur Thomson, reviewing it for *Nature* in September 1917, compared its patience and learning to Darwin's and praised it as substantial and stately, though he doubted Thompson's claim that physical science was the only guide to the living body. The mathematician R. C. Archibald called it "one of the most notable and most readable" scientific books of the decade, while correcting some of its mathematical history.[7] The first edition sold out by the early 1920s, and Thompson refused to allow a reprint until he had revised it.

The book is organised by scale. It begins with magnitude and the rate of growth, moves through the forms of single cells and tissues to the skeletons of protozoa and sponges, then to shells, horns and teeth, the arrangement of leaves, the shapes of eggs, and the engineering of bone, and ends with the chapter on transformations. It is written in long, allusive sentences,

with untranslated quotations in Latin, Greek, French, German and Italian, and its footnotes range from Plato to the physics journals of the day. Thompson was candid about the limits of his mathematics. "I pretend to no mathematical skill," he wrote in the prefatory note, "but I have made what use I could of what tools I had." His tools were classical geometry and algebra. He made almost no use of calculus, and years later, while revising it, he asked the young St Andrews mathematician Walter Ledermann to explain a problem involving differential equations, which Ledermann worked out for him at his desk.

What he did have was a network. Thompson's surviving correspondence, now at St Andrews, shows him asking mathematicians, physicists and engineers for help on problem after problem. John Marshall, a St Andrews-educated mathematician, sent him annotated notes in 1914 on the coordinate transformations he would use in the last chapter. The engineer Thomas Claxton Fidler supplied the analysis of bridges and girders that Thompson applied to skeletons, and some of Fidler's notes passed into the book almost word for word. His Dundee colleague the physicist William Peddie was another source. Thompson acknowledged many of these debts in the book. The historian of mathematics Deborah Kent, who has studied the letters, argues that the book grew out of extensive and continuing collaboration, some of it perhaps unwitting, rather than from one solitary mind.[8] In the terms of this book, Thompson's study in Dundee was a small trading zone, run by post.

Splashes, Skeletons and Spirals

Some of the book's most memorable comparisons came from the work of Arthur Mason Worthington, a physicist who taught at the Royal Naval Engineering College in Devonport. Worthington had begun photographing drops falling into liquids in the 1890s, showing his first pictures at a lecture at the Royal Institution in 1894. Each image was lit by the flash of an electric spark, discharged from Leyden jars, that lasted by his estimate less than three-millionths of a second, short enough to freeze the motion. In 1908 he published the results as *A Study of Splashes*. His images showed a falling drop throwing up a crown-shaped rim with a ring of points, each of which might pinch off into a droplet. Thompson set these beside drawings of the cup-shaped cases (calycles) of campanularian hydroids, small colonial relatives of jellyfish whose cups have scalloped or toothed rims. He also compared the forms taken by a drop of one liquid sinking through another, which spreads into a bell or ring as it falls, to the bells of medusae.

The point of such comparisons was not that a hydroid *is* a splash. It was that the same physical conditions (a liquid or semi-liquid surface under tension, perturbed by motion) tend to produce the same family of forms, and that living tissue, at an early and soft stage of growth, might be subject to similar forces. As a hypothesis it was suggestive. As an explanation, as we will see, it promised more than it could deliver.

The same reasoning drove Thompson's chapters on skeletons. He drew heavily on the plates of the German zoologist Ernst Haeckel, whose report on the radiolarians collected by the *Challenger* expedition had described thousands of species of these single-celled marine organisms,

with their intricate skeletons of silica: lattice spheres, spiked stars, little cages and helmets. One, *Aulonia hexagona*, is a sphere covered in a net of mostly hexagonal meshes. Another, *Callimitra*, has a skeleton of bars and thin windows that Thompson set beside the soap films that form inside one of Plateau's wire frames. Thompson argued that the silica was laid down along the boundaries of a froth of tiny bubbles or vesicles in the organism's living substance, so that the skeleton was a mineralised cast of a foam and took its geometry from Plateau's laws. If so, the pattern owed more to the physics of froths than to anything specific to the species.

At the other end of the scale, where gravity rules, Thompson turned engineer. In his chapter on form and mechanical efficiency he took up the comparison of the femur with a crane, describing the spongy bone inside the head of the femur as nothing more nor less than a diagram of the lines of stress in the loaded structure. With Fidler's help he went further and treated the skeleton of a large four-legged animal, a horse or a dinosaur, as a bridge: its backbone the main girder of a double-armed cantilever like the Forth Railway Bridge, carried on the piers of the fore and hind legs. Here the analogy was closer to an explanation than in the case of splashes, because bone is a structural material that is known to remodel itself in response to load. Biomechanists still analyse skeletons in broadly this way.

The most elegant of the book's arguments concerned spirals. Many shells, horns and tusks grow by adding new material at one end without remodelling what is already there. A snail cannot rebuild its old shell; it can only extend the lip. Thompson pointed out that if such a structure is to keep the same shape as it grows, it must follow a particular curve: the *equiangular* or *logarithmic* spiral. The curve had a long mathematical history. René Descartes described it in 1638, and Jakob Bernoulli, who called it the *spira mirabilis*, asked for it to be carved on his tombstone with the motto *Eadem mutata resurgo* ("though changed, I shall arise the same"); the mason carved the wrong spiral. In 1838 the mathematician Henry Moseley had shown that the whorls of the chambered nautilus and many other shells grow in geometrical progression, which is to say along a logarithmic spiral.[9] Thompson took up Moseley's work and extended it to horns, tusks, the spiral tests of foraminifera and the growth of teeth.

Thompson linked the spiral to an idea from Greek geometry, the *gnomon*: a figure which, added to another figure, produces a larger figure of the same shape. The chambers of a nautilus are gnomons of the shell. Each new chamber is larger than the last, but the shell as a whole is the same shape at every age.

Science Primer: Why growth by accretion gives a logarithmic spiral

Describe a curve in polar coordinates: $r(\theta)$ is the distance from a fixed centre to the curve at angle θ. Suppose the curve is *self-similar*: turning it through any angle ϕ has the same effect as enlarging it by some factor $c(\phi)$. In symbols,

$$r(\theta + \phi) = c(\phi)\, r(\theta) \quad \text{for all } \theta \text{ and } \phi.$$

Differentiate both sides with respect to ϕ and then set $\phi = 0$. Writing $b = c'(0)$ (a constant)

gives

$$\frac{dr}{d\theta} = b\,r,$$

which says that the radius grows at a rate proportional to its own size. The only solutions are

$$r(\theta) = a\,e^{b\theta},$$

where a fixes the overall size and b how tightly the spiral is wound. This is the logarithmic spiral, and the argument shows that, apart from the circle (the case $b = 0$), it is the only plane curve with this property. (In three dimensions, a shell can also drift along its axis as it coils, giving a helico-spiral, as in a snail; the same reasoning applies to its growth.)

The spiral is also *equiangular*. The angle ψ between the curve and the line from the centre satisfies $\tan\psi = r/(dr/d\theta) = 1/b$, the same at every point. A growing shell keeps the same angle between its new edge and its radius throughout its life.

A worked example. When the mathematician Clement Falbo measured nautilus shells, he found that their spirals fitted nested rectangles with sides in the ratio of about 1.33 (the range was 1.24 to 1.43), not the golden ratio of 1.618. For a logarithmic spiral, that ratio is the factor by which the radius grows in each quarter turn. Then $e^{b\pi/2} \approx 1.33$, so $b \approx 0.18$, and in a full turn the radius grows by $1.33^4 \approx 3.1$. The angle $\psi = \arctan(1/0.18) \approx 80^\circ$. The "golden spiral" often claimed for the nautilus would grow by 1.618 per quarter turn, or about 6.9 per whorl, more than twice as fast. Real nautiluses are logarithmic spirals, but not golden ones.

The spiral argument is Thompson at his strongest. It does not say that natural selection plays no part in shells; selection can and does act on how fast the spiral expands, how the tube is shaped, and whether the coils touch. What the geometry does is fix the family of shapes available to any animal that grows by accretion without remodelling, so that the resemblance between a ram's horn and a nautilus needs no separate adaptive story. In the 1960s the palaeontologist David Raup turned this insight into a computer model in which a handful of coiling parameters generate shell shapes; when he plotted real shells within the space of possible ones, large regions turned out to be empty, and he asked whether those forms were impossible to build or simply unused.

Thompson was more sceptical about the arrangement of leaves, or phyllotaxis. Botanists since the 1830s had noticed that the spirals of scales on a pine cone or seeds in a sunflower head usually come in two sets, winding in opposite directions, whose numbers are consecutive terms of the Fibonacci sequence (1, 1, 2, 3, 5, 8, 13, 21, 34 and so on, each term the sum of the two before). The ratio of consecutive terms converges on the golden ratio, about 1.618, and a great deal of speculation had grown up around it. Thompson acknowledged the regularity but would have nothing to do with mystical interpretations. Nor would he accept that the pattern had been selected because it was useful, for instance by spacing leaves to catch the most light: its supposed usefulness, and the hypothesis that natural selection had introduced it, he wrote, "deserve no place in the plain study of botanical phenomena." The numbers arose, he said, for

mathematical reasons.[10] He compared the plant to a bricklayer building a factory chimney, who lays his bricks in a steady, orderly way with no thought of the spiral patterns that order produces. But he did not say what the mathematical reasons were, and he treated the recurrence of the particular numbers as closer to a coincidence than botanists supposed. On that point, as we will see, he was wrong.

The Theory of Transformations

The final chapter of *On Growth and Form*, "On the Theory of Transformations, or the Comparison of Related Forms," is the one most people remember. Its method is simple to describe. Draw the outline of an animal, or of one of its bones, on a square grid. Then draw the outline of a related species on a second grid that has been deformed (stretched, sheared, bent) so that corresponding points of the two animals fall in corresponding cells. If a simple, smooth deformation of the grid turns one form into the other, Thompson argued, the two forms differ not by a long list of separate changes in separate parts but by a single, coordinated change in the pattern of growth. He traced the idea to the proportion studies of Albrecht Dürer, who had distorted grids to change the proportions of human faces and figures.

Table 2.1: Some of the transformations in the 1917 edition of *On Growth and Form*

Forms compared	**Kind of grid**	**Comment**
Hatchetfishes *Argyropelecus* and *Sternoptyx*	Rectangular grid to oblique grid	A shear: straight lines stay straight and parallel lines parallel (an affine map).
Parrotfish *Scarus* and angelfish *Pomacanthus*	Rectangular grid to a coaxial system of curves	Lines become curves: a non-linear map.
Porcupinefish *Diodon* and sunfish *Orthagoriscus* (now *Mola*)	Vertical lines bent into concentric arcs	Non-linear. One of the book's best-known figures.
Pelvis of *Archaeopteryx* and of the Cretaceous bird *Apatornis*	Deformed grid, with intermediates found by interpolation (after Gerhard Heilmann)	Intermediate pelves drawn between the two.
Skulls of *Eohippus* and *Equus*	Coordinate diagrams with actual and hypothetical intermediates (Heilmann)	Compared with real fossil horses.
Pelvic girdles of *Stegosaurus* and *Camptosaurus*	Deformed grid	Used to reconstruct a missing part of the *Camptosaurus* pelvis.
Human skull with the skulls of chimpanzee, baboon and dog	Cartesian grid reprojected for each	Strongly curved grids; the fit is approximate.

The method had first been set out in a long paper, "Morphology and Mathematics", which Thompson published in the *Transactions of the Royal Society of Edinburgh* in 1916. Some of its best examples came from an unexpected collaborator. Gerhard Heilmann was a Danish artist

and palaeontologist working outside the universities who was writing, in a series of Danish articles, a study of the origin of birds. The American ornithologist R. W. Shufeldt brought Heilmann's work to Thompson's attention; Thompson wrote to him in 1915, Heilmann took up the grid method, and the two corresponded throughout the war. Heilmann used the grids to do something Thompson had not: to draw hypothetical intermediates. If the grid that turns the pelvis of the Jurassic *Archaeopteryx* into that of the much later bird *Apatornis* can be deformed by stages, then each stage gives a predicted intermediate pelvis. Thompson reproduced Heilmann's drawings of the two pelves and three interpolated forms in the book, and Heilmann's similar series of intermediate horse skulls between *Eohippus* and *Equus*. Heilmann tested the horse series against real fossils and found that some fitted and one did not. Thompson himself used a transformed *Stegosaurus* pelvis to restore the missing part of a *Camptosaurus* pelvis.[11]

Science Primer: Grids, shears and splines

A transformation grid is a picture of a mapping: a rule that sends every point (x, y) of one drawing to a point (x', y') of another. The simplest useful family is the *affine* maps,

$$x' = ax + by + e, \qquad y' = cx + dy + f,$$

where a to f are six constants. Affine maps can stretch, squeeze, rotate and shear a figure, but they keep straight lines straight and parallel lines parallel, so a square grid becomes a grid of identical parallelograms. Thompson's hatchetfishes are related this way: draw *Argyropelecus* on a square grid, tilt the vertical lines to about 70°, and the grid fits *Sternoptyx*.

Most of Thompson's famous examples are not affine. When he turns the porcupinefish *Diodon* into the sunfish *Mola*, he bends the vertical lines of the grid into a set of concentric arcs, so that the back half of the fish is expanded far more than the front. No choice of six constants can do that. Such non-linear maps have, in principle, infinitely many degrees of freedom, which is both their power and their weakness: with enough freedom almost any outline can be mapped onto almost any other, so a good fit means something only if the deformation is simple.

Thompson drew his grids by hand and never specified exactly which points on the two animals he took to correspond. Modern *geometric morphometrics* begins by fixing that: it uses *landmarks*, points that can be identified on every specimen (the tip of the snout, the joint between two bones). The *thin-plate spline*, introduced to biology by the statistician Fred Bookstein in 1989, finds the smoothest map that carries one set of landmarks exactly onto another. It borrows its mathematics from engineering: it is the shape a thin metal plate would take if pinned at the landmark positions, the one that minimises the total bending. Applied to a square grid, it produces a picture very like Thompson's, but one that any two researchers starting from the same landmarks will draw identically.

The transformation grids made a point that the anatomy of the day had trouble expressing. A comparative anatomist listed differences part by part: this bone longer, that process shorter. Thompson's grids showed that many such differences could be the result of one change in the rel-

ative rates of growth in different directions, applied to the whole animal. That suggested something about how evolution might proceed, through changes in the coordinated programme of growth rather than in independent parts. It also suggested, in Thompson's hands, something more contentious: that because the deformations were smooth and the forms related by simple mathematics, the steps between them need not be gradual or individually adaptive. In the second edition he went further, arguing that discontinuous variation was a natural feature of the world of forms.

Outcomes and Legacy

The second edition. Thompson would not let the sold-out first edition be reprinted without revision, and the revision took him many years. The second edition appeared in 1942, in the middle of another war, in two volumes and 1,116 pages. It added new material on growth, new references and, among other things, high-speed photographs of splashes that Harold Edgerton had taken at the Massachusetts Institute of Technology with his stroboscopic flash. At the end it touched briefly on the stripes of the zebra. The new edition won Thompson the Daniel Giraud Elliot Medal of the United States National Academy of Sciences. It also exposed how far biology had moved since 1917. Reviewers noted that genetics was barely mentioned. Thompson had read about genes; he simply did not think the subject could yet be brought within his framework, and said that biology was still too much "in the dark" about the forces acting on chromosomes to say more.[12]

The abridgement. In 1961 the American biologist John Tyler Bonner, who studied the development of slime moulds, produced an abridged edition of 346 pages. It cut the book to roughly a third and dropped several chapters, including the one on leaf arrangement. Many readers since have known only this version, which has been reprinted repeatedly.

Allometry, and a festschrift. The book's influence on biology was real but diffuse. Julian Huxley's *Problems of Relative Growth* (1932), which laid the foundations for the study of what came to be called *allometry*, the way the proportions of an organism change as it grows, was dedicated to Thompson. In 1945, to mark sixty years since Thompson's first appointment, a group of biologists presented him with a volume of *Essays on Growth and Form*, edited by Wilfrid Le Gros Clark and Peter Medawar, with contributions from Huxley, the insect physiologist Vincent Wigglesworth, the neuroscientist J. Z. Young, the philosopher of biology Joseph Woodger and others. Medawar had himself published a paper in 1944 on how the shape of the human body changes with age, applying quantitative methods to the kind of problem the transformation chapter had posed. Later he described the book as "beyond comparison the finest work of literature in all the annals of science" recorded in English, while arguing, as early as 1945, that the transformation method's true field of application lay in development, not evolution.[13] Thompson died at his home in St Andrews on 21 June 1948. He had held a professorial chair, first in Dundee and then in St Andrews, for some sixty-four years.

Turing. The best-known link between Thompson and later science is also the one most often overstated. Alan Turing, whom we will meet at Bletchley Park in Chapter 4, turned to biology

after the war. His paper "The Chemical Basis of Morphogenesis", received by the Royal Society in November 1951 and published in 1952, proposed that two or more chemicals ("morphogens") reacting with each other and diffusing through a tissue at different rates could turn an initially uniform state into a pattern of spots or stripes. He suggested applications to the tentacles of *Hydra*, the whorls of leaves, and dappled coats. Thompson did not teach Turing, and there is no record that the two men met; Thompson died four years before the paper appeared. What is documented is narrower. Turing's paper has a short reference list of six works, and one is the 1942 edition of *On Growth and Form*, alongside C. H. Waddington's *Organisers and Genes* and C. M. Child's *Patterns and Problems of Development*. Thompson is not discussed in the body of the paper. Turing's unpublished work in his last years, much of it on the problem of why Fibonacci numbers appear in plants (he named some of his computer programs after fir cones), takes up a question that Thompson had made famous, and the historian Sara Franceschelli has argued that in those writings Turing set his work in continuity with Thompson's questions about form. How and when Turing first read the book is not recorded; a plausible route is through Waddington, whom he cited alongside Thompson.[14]

There is a postscript. In 1953 a Manchester student, Bernard Richards, began working with Turing on morphogenesis, and Richards extended Turing's equations to three dimensions and solved them on the university's Ferranti computer. The shapes that came out resembled radiolarians, and Turing told Richards that such forms were described and drawn in the reports of the *Challenger* expedition, the same source of Haeckel's plates that Thompson had mined. The work was finished in 1954, the year Turing died.[15]

Waddington and developmental biology. C. H. Waddington, the embryologist and geneticist whose picture of development as a ball rolling down a branching "epigenetic landscape" became one of the field's central images, drew on Thompson's work and reviewed the 1945 festschrift for *Nature*; in 1969 he and a colleague produced one of the first computer simulations of pigment patterns on shells. Developmental biology as a discipline, however, grew mainly from experimental embryology and, after the 1970s, from molecular genetics. For decades Turing's paper itself was little followed up: the equations were hard to solve without computers, and after 1953 the attention of biologists turned to DNA. Thompson's book sat on the shelf as an admired classic.

Vindications. When the physical approach to form returned, it returned with experiments Thompson could not have done. In 1995 Shigeru Kondo and Rihito Asai showed that the stripes of the marine angelfish *Pomacanthus* rearrange themselves as the fish grows in the way a reaction–diffusion system predicts, widely taken as the first strong evidence for a Turing pattern in a living animal. It was the same genus that Thompson had drawn on a curved grid in 1917. In 1992 the physicists Stéphane Douady and Yves Couder dropped magnetised droplets of ferrofluid, one at a time, into the centre of a dish of oil; as the drops repelled each other and drifted outwards, they arranged themselves, for suitable rates of dropping, in spirals whose numbers followed the Fibonacci sequence. The pattern, they showed, emerges whenever each new element forms in the largest available gap left by its predecessors, a rule the botanist Wilhelm Hofmeister had proposed in 1868. In 2003 plant biologists identified a mechanism by which plants carry out such a rule: new leaves form where the hormone auxin accumulates,

and existing leaf primordia drain auxin from their surroundings. The Fibonacci numbers were neither mystical nor coincidental. Thompson had been right that their cause was not utility, and wrong that there was nothing systematic to explain.

In mechanobiology, the study of how physical forces shape cells and tissues, his "diagram of forces" has become a working programme. In 2013 a team led by Clifford Tabin and L. Mahadevan at Harvard showed, working mainly with chick embryos, that the finger-like villi lining the gut begin as folds produced when the growing inner lining is compressed by the muscle layers around it, buckling like a sheet pushed from its edges; similar principles appeared to operate in frogs, mice and snakes. Such work differs from Thompson's in one essential respect: it identifies and measures the forces, and traces them to the tissues that generate them.[16]

Morphometrics. The transformation grids had their own revival. In 1977 Fred Bookstein published a long paper on "the study of shape transformation after D'Arcy Thompson", which tried to make the grids quantitative, and in 1989 he introduced the thin-plate spline described in the primer above, with an explicit nod to Thompson. Combined with methods for superimposing landmark configurations and analysing their variation statistically, these tools became geometric morphometrics, now standard in palaeontology, anthropology and evolutionary biology.[17] It would be an exaggeration to say that Thompson anticipated this field. The grids gave it a picture and a question; its methods came from statistics and computing.

Art and architecture. Outside biology, the book's influence was larger and faster. Henry Moore later said he had come across it as a student, and his transformation drawings of bones, roots and lobster claws from the early 1930s are often read as showing its mark, though the link rests more on resemblance than on documents. In 1951 the artist Richard Hamilton, introduced to the book by his fellow student Nigel Henderson, organised an exhibition called *Growth and Form* at the Institute of Contemporary Arts in London as the institute's contribution to the Festival of Britain. Mies van der Rohe is said to have put the book on his students' reading lists, and it has remained a set text in architecture schools, where its soap films and skeletons fed an interest in lightweight structures.

The Costs of Crossing

On Growth and Form is often held up as the founding text of mathematical biology and as proof that an outsider's eye can see what specialists miss. Both claims hold some truth. Four complications deserve equal weight.

The border-crosser turned his back on the neighbouring field. Thompson brought physics into biology, but he kept genetics out, and he treated natural selection less as a partner than as a rival. He was not opposed to evolution, and he admired Darwin; but he wrote as though explanations by physical force and by selection competed for the same territory, so that every form explained by surface tension was a form taken away from Darwin. The second edition appeared in 1942, the same year as Julian Huxley's *Evolution: The Modern Synthesis*, and treated the new union of genetics and selection as someone else's business. That made it easy for biologists to

treat Thompson as an elegant anachronism. The modern view, that physics constrains which forms are possible and that genes and selection work within and through those constraints, would have suited his insight better than his own framing did. Interdisciplinarity that crosses one border while fortifying another is only half an achievement.

Analogy is not mechanism. The jellyfish is not a falling drop. A medusa's bell is made of cells and a jelly-like matrix shaped by growth, and its resemblance to a drop of ink in water is, in the end, a resemblance. Radiolarian skeletons are not simply casts of a passive foam: the silica is deposited within a living sheath of cytoplasm that the cell controls, and the cytoplasm's activity, not surface tension alone, sets the final geometry. Even the honeycomb, one of his most famous cases, remains disputed. A physical analogy that reproduces a shape can show that a given physical process is *sufficient* to make it; it cannot show that this is how the organism actually makes it. Thompson often slid from the first to the second, and the slide is the characteristic error of structural isomorphism. When a 2020 study tried to reproduce his crab transformations with modern image analysis, it found that only the simplest worked well, and concluded that his approach had no reliable predictive power.[18]

It inspired more than it directed. For half a century the book was revered and rarely used. The evolutionary biologist George C. Williams called it "a work widely praised, but seldom used".[19] There are good reasons. Thompson founded no school and disliked directed research; the grids were laborious and subjective to draw before computers; and the book posed problems without supplying the experimental methods to attack them. It offered a way of seeing, not a research programme. Even its admirers have struggled to point to a line of research that leads back to it directly: as Medawar observed, its influence was diffuse and pervasive, felt in the questions people asked rather than in the methods they used. The later fields that claim descent from it (pattern formation, morphometrics, mechanobiology) were built by people who supplied what it lacked: equations that could be solved, measurements that could be repeated, and molecular mechanisms. To credit Thompson with "anticipating" them, as popular accounts often do, is to confuse a question with an answer.

The grids are not pictures of evolution. The transformation chapter invites the reader to imagine one species flowing into another. But no adult porcupinefish ever turned into a sunfish. Evolution changes the developmental programme that builds each generation from an egg; it does not deform an adult. The developmental biologist Wallace Arthur has put the point directly: the transformations Thompson drew have not taken place in evolution, which cannot convert one species' adult form into another's.[20] A geometrical relation between two shapes is a clue to look for a common developmental cause. It is not that cause.

Coda

The man who counted seal pups on the Pribilof Islands and the man who drew fish on bending grids were the same man, and the habits that served him on the rookeries served him in the book: careful observation, a willingness to count and measure, and a refusal to let one discipline's questions define what was worth asking. *On Growth and Form* did not found a science.

It kept alive, through decades when biology was concerned with other things, the question of how physical forces make living shapes, and it did so in prose good enough to be read for pleasure. When the tools arrived to answer that question, in the form of computers, imaging and molecular biology, the people who used them found that Thompson had already drawn the pictures. Many of his answers were wrong. His question has outlasted them.

Notes

[1]Joint statement of the British and American delegates, Washington, 17 November 1897, in *Papers Relating to the Foreign Relations of the United States, 1897* (Washington, DC: Government Printing Office, 1898), available at https://history.state.gov/historicaldocuments/frus1897/d305; and "The Scientific Expert and the Bering Sea Controversy," *Popular Science Monthly* 54 (March 1899), which describes Thompson's recount of a single rookery. Thompson's two seasons, as scientific adviser to the British delegation, are described in "December 10 – Seals, Pribilof Islands," *Echoes from the Vault* (University of St Andrews Special Collections blog), https://special-collections.wp.st-andrews.ac.uk/?p=18982. The sea cow skeleton is mentioned in D. R. R. Burt, "D'Arcy Wentworth Thompson," in *Veterum Laudes*, ed. James B. Salmond (Edinburgh: Oliver and Boyd, 1950).

[2]D'Arcy Wentworth Thompson, *On Growth and Form* (Cambridge: Cambridge University Press, 1917), Prefatory Note. Quotations from the 1917 edition follow the text transcribed by Project Gutenberg, https://www.gutenberg.org/ebooks/55264.

[3]Galileo Galilei, *Dialogues Concerning Two New Sciences*, trans. Henry Crew and Alfonso de Salvio (New York: Macmillan, 1914; first published in Italian, 1638); Thompson, *On Growth and Form* (1917), chap. 2, which credits both Galileo and Spencer; J. B. S. Haldane, "On Being the Right Size," *Harper's Magazine*, March 1926.

[4]Joseph Plateau, *Statique expérimentale et théorique des liquides soumis aux seules forces moléculaires*, 2 vols. (Paris: Gauthier-Villars, 1873). Jean Taylor's proof is "The Structure of Singularities in Soap-Bubble-Like and Soap-Film-Like Minimal Surfaces," *Annals of Mathematics* 103 (1976): 489–539.

[5]Bhushan L. Karihaloo, Kai Zhang, and Jianjun Wang, "Honeybee Combs: How the Circular Cells Transform into Rounded Hexagons," *Journal of the Royal Society Interface* 10, no. 86 (2013): 20130299; Benjamin P. Oldroyd and Stephen C. Pratt, "Comb Architecture of the Eusocial Bees Arises from Simple Rules Used during Cell Building," *Advances in Insect Physiology* 49 (2015): 101–21; Philip Ball, "Did Darwin Miss Something?," *Prospect*, 29 June 2017.

[6]The main biographical sources are Ruth D'Arcy Thompson, *D'Arcy Wentworth Thompson: The Scholar-Naturalist, 1860–1948*, with a postscript by P. B. Medawar (London: Oxford University Press, 1958), by his eldest daughter; and the biography and obituaries collected in the MacTutor History of Mathematics archive, University of St Andrews, https://mathshistory.st-andrews.ac.uk/Biographies/Thompson_DArcy/. Sources differ slightly on how soon after his birth his mother died, on whether he studied medicine at Edinburgh for two years or three, and on the year of his Classical Association presidency (most give 1929; the *Dictionary of Scientific Biography* gives 1928). Thompson's posts and honours are summarised in his entry in the *Dictionary of National Biography*, reproduced at https://mathshistory.st-andrews.ac.uk/DNB/Thompson_DArcy.html; D'Arcy Wentworth Thompson, *On Aristotle as a Biologist, with a Prooemion on Herbert Spencer* (Oxford: Clarendon Press, 1913); *A Glossary of Greek Fishes* (London: Oxford University Press, 1947). The recollections of Alexander Peacock and Hamish Watt are gathered in the University of Dundee Museum's exhibition "...and a Bag Full of Monkeys," https:

//app.dundee.ac.uk/museum/exhibitions/zoology/bagful/; Thompson's height is given by Matthew Jarron, curator of the D'Arcy Thompson Zoology Museum, in an interview with *The Node* (Company of Biologists), 2017.

[7]On the book's origins and publication, see Matthew Jarron, " 'A Single and Indivisible Principle of Unity': *On Growth and Form* in Context," *Biological Theory* (2023), https://doi.org/10.1007/s13752-023-00449-x; and Stephen Wolfram, "Are All Fish the Same Shape If You Stretch Them? The Victorian Tale of *On Growth and Form*," *Stephen Wolfram Writings*, 25 October 2017, which gives the first print run. J. Arthur Thomson, "On Growth and Form," *Nature* 100 (13 September 1917): 21–22; R. C. Archibald, review of *On Growth and Form*, *Bulletin of the American Mathematical Society* 24 (1918): 403–7.

[8]Deborah Kent, "Questions of Collaboration and Credit in D'Arcy Thompson's *On Growth and Form*," lecture, Mathematical Institute, University of Oxford, 11 May 2022. The correspondence is discussed in two student projects hosted by MacTutor: Alice Gowenlock and Indre Tuminauskaite, "D'Arcy Thompson and Mathematics," and Heather Dickinson and Barbora Cernokova, "An Investigation of Some of D'Arcy Thompson's Correspondence," both at https://mathshistory.st-andrews.ac.uk/Darcy/; Walter Ledermann's recollection is reproduced at https://mathshistory.st-andrews.ac.uk/Extras/Ledermann_DArcy_Thompson/.

[9]H. Moseley, "On the Geometrical Forms of Turbinated and Discoid Shells," *Philosophical Transactions of the Royal Society of London* 128 (1838). On nautilus proportions, see Ivars Peterson, "Sea Shell Spirals," *Science News*, 1 April 2005, reporting measurements by Clement Falbo.

[10]Thompson, *On Growth and Form* (1917), chap. 14, "On Leaf-Arrangement, or Phyllotaxis." For a modern assessment of the Fibonacci claims, see Todd J. Cooke, "Fibonacci Numbers in Phyllotaxis," *Botanical Journal of the Linnean Society* 150 (2006): 3–24.

[11]D'Arcy Wentworth Thompson, "Morphology and Mathematics," *Transactions of the Royal Society of Edinburgh* 50, no. 4 (1916): 857–95. The correspondence is described in Dickinson and Cernokova, "An Investigation of Some of D'Arcy Thompson's Correspondence"; on Heilmann's grids and their later omission from his English book, see Darren Naish, "Heilmann, Thompson, Beebe, Tetrapteryx and the Proavian," *Tetrapod Zoology*, 1 January 2019, https://tetzoo.com/blog/2019/1/1/heilmann-thompson-beebe-tetrapteryx-and-the-proavian. The pelves of *Archaeopteryx* and *Apatornis* appear in Thompson, *On Growth and Form* (1917), chap. 17.

[12]D'Arcy Wentworth Thompson, *On Growth and Form*, new ed., 2 vols. (Cambridge: Cambridge University Press, 1942). J. W. Buchanan's review in *Physiological Zoology* 16, no. 1 (1943): 135–37, noted how little the book said of genetics. Thompson's remark about chromosomes is discussed in Enrico Coen, Richard Kennaway, and Christopher Whitewoods, "On Genes and Form," *Development* 144 (2017): 4203–13.

[13]P. B. Medawar, "D'Arcy Thompson and *Growth and Form*," first published as the postscript to Ruth D'Arcy Thompson, *The Scholar-Naturalist* (1958), and reprinted in Medawar, *The Art of the Soluble* (London: Methuen, 1967); W. E. Le Gros Clark and P. B. Medawar, eds., *Essays on Growth and Form Presented to D'Arcy Wentworth Thompson* (Oxford: Clarendon Press, 1945). Medawar's 1945 remark on development and evolution is quoted in Coen, Kennaway, and Whitewoods, "On Genes and Form."

[14]A. M. Turing, "The Chemical Basis of Morphogenesis," *Philosophical Transactions of the Royal Society of London B* 237, no. 641 (1952): 37–72. On Turing's reading, see Hajo Greif, Adam Kubiak, and Paweł Stacewicz, "Turing's Biological Philosophy: Morphogenesis, Mechanisms and Organicism," *Philosophies* 8, no. 1 (2023): 8; and Andrew Hodges, *Alan Turing: The Enigma* (London: Burnett Books, 1983). Sara Franceschelli, "The 'Imaginary Organism' and Turing's Delicate Art of Non-linear Modelling," seminar abstract, Mathematical Institute, University of Oxford, June 2026, https://www.maths.ox.ac.uk/node/80793; on the fircone programs, see Andrew Hodges, Alan Turing Scrapbook, https://www.turing.o

rg.uk/scrapbook/wondrous.html.

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[16]Shigeru Kondo and Rihito Asai, "A Reaction–Diffusion Wave on the Skin of the Marine Angelfish *Pomacanthus*," *Nature* 376 (1995): 765–68. S. Douady and Y. Couder, "Phyllotaxis as a Physical Self-Organized Growth Process," *Physical Review Letters* 68 (1992): 2098–2101; Didier Reinhardt et al., "Regulation of Phyllotaxis by Polar Auxin Transport," *Nature* 426 (2003): 255–60. Amy E. Shyer et al., "Villification: How the Gut Gets Its Villi," *Science* 342, no. 6155 (2013): 212–18.

[17]Fred L. Bookstein, "The Study of Shape Transformation after D'Arcy Thompson," *Mathematical Biosciences* 34 (1977): 177–219; Bookstein, "Principal Warps: Thin-Plate Splines and the Decomposition of Deformations," *IEEE Transactions on Pattern Analysis and Machine Intelligence* 11, no. 6 (1989): 567–85; Bookstein, *Morphometric Tools for Landmark Data: Geometry and Biology* (Cambridge: Cambridge University Press, 1991).

[18]Gerhard Scholtz, David Knötel, and Daniel Baum, "D'Arcy W. Thompson's Cartesian Transformations: A Critical Evaluation," *Zoomorphology* 139 (2020): 293–308. On the radiolarian skeleton, see O. Roger Anderson and Shyam M. Gupta, "Evidence of Binary Division in Mature Central Capsules of a Collosphaerid Colonial Radiolarian: Implications for Shell Ontogenetic Patterns in Modern and Fossil Species," *Palaeontologia Electronica* 1, no. 1 (1998): art. 1.1.2A.

[19]George C. Williams, review of *On Growth and Form*, *Quarterly Review of Biology* 68, no. 2 (1993): 267–68. See also Philip Ball, "In Retrospect: *On Growth and Form*," *Nature* 494 (2013): 32–33.

[20]Wallace Arthur, "D'Arcy Thompson and the Theory of Transformations," *Nature Reviews Genetics* 7 (2006): 401–6; Arthur, "D'Arcy Thompson's Morphological Transformations: Issues of Causality and Dimensionality," *Biological Theory* (2023), https://doi.org/10.1007/s13752-023-00438-0.

Further Reading

D'Arcy Wentworth Thompson, *On Growth and Form* (Cambridge University Press, 1917; new edition, 1942). The 1917 text is freely available through Project Gutenberg. Long, digressive and beautifully written; the chapters on magnitude, the logarithmic spiral and transformations are the best entry points.

D'Arcy Wentworth Thompson, *On Growth and Form*, abridged edition, ed. John Tyler Bonner (Cambridge University Press, 1961; Canto edition, 1992, with a foreword by Stephen Jay Gould). The version most readers know, about a third of the length. Bonner's brief introductions to each chapter are useful; it omits the chapter on leaf arrangement.

Ruth D'Arcy Thompson, *D'Arcy Wentworth Thompson: The Scholar-Naturalist, 1860–1948* (Oxford University Press, 1958). A biography by his eldest daughter, affectionate and detailed, with a postscript by Peter Medawar on the book's place in biology.

Matthew Jarron, Catherine Caudwell, and Meic PierceOwen, *Growing and Forming: Essays on D'Arcy Thompson* (Abertay Historical Society, 2017). A short centenary volume by the curator of his Dundee museum and colleagues, good on the museum, the correspondence and the book's afterlife in art.

Matthew Jarron, " 'A Single and Indivisible Principle of Unity': *On Growth and Form* in Context," *Biological Theory* (2023). The best short scholarly account of how the book was written and received, including its influence on art and architecture.

Philip Ball, *The Self-Made Tapestry: Pattern Formation in Nature* (Oxford University Press, 1999). A popular account of pattern formation from soap films to animal markings, written by an admirer of Thompson who is clear about where he went wrong.

Fred L. Bookstein, *Morphometric Tools for Landmark Data: Geometry and Biology* (Cambridge University Press, 1991). For technically minded readers: the book that turned Thompson's grids into a statistical method.

Gerhard Scholtz, David Knötel, and Daniel Baum, "D'Arcy W. Thompson's Cartesian Transformations: A Critical Evaluation," *Zoomorphology* 139 (2020). An open-access test of Thompson's grids against real crabs, with a clear account of what they can and cannot show.

Online: the D'Arcy Thompson pages of the MacTutor History of Mathematics archive, `https://mathshistory.st-andrews.ac.uk/Darcy/`, including student projects on his correspondence with mathematicians and with Gerhard Heilmann, and an interactive tool for drawing transformation grids.

Chapter 3

The Quantum Mechanical Cell (1930s–1944)

The Rising Lectern

On 15 August 1932, Niels Bohr gave the opening address to the Second International Congress on Light Therapy in Copenhagen. It was a natural place for such a meeting: in 1903 the Danish physician Niels Finsen had won the Nobel Prize for treating skin disease with concentrated light, and the therapy his work launched was still in wide use. Bohr, who had shaped the new quantum theory of the atom and who thought harder than most about its philosophical consequences, took the invitation seriously. He called his lecture "Light and Life".

Among the audience was a twenty-five-year-old German theoretical physicist named Max Delbrück, who had made a short trip to Copenhagen to hear it, in the company of the Belgian physicist Léon Rosenfeld. Our picture of how the lecture went comes mainly from Delbrück's recollection, given in an interview more than forty years later, and by that account it was not a smooth performance. Bohr, he remembered, mislaid his place behind the lectern, fidgeted with it, and set off a mechanism that raised the reading desk until the speaker slowly vanished behind it, in front of an audience that included the Danish Crown Prince. Bohr spoke, as usual, in a voice so low that some listeners could not tell whether he was speaking English or Danish.[1]

What he said, once the lectern was lowered, stayed with Delbrück for the rest of his life. Bohr argued that the lesson of quantum mechanics, which he called *complementarity*, might apply to biology. In atomic physics, he said, the act of observation sets limits on what can be known: an electron can be described as a wave or as a particle, depending on the experiment, but no single experiment can show both aspects at once. Perhaps life posed a similar limit. To trace the role of every atom in a living organism, Bohr said, we should doubtless have to kill it. The conditions needed for an atomic description and the conditions needed for life might exclude one another, so that the existence of life would have to be taken in biology as an elementary fact, in the way that the quantum of action was taken as an elementary fact in physics, not something to be derived from anything more basic. Bohr was careful to say that this was not vitalism; he

was not proposing a life force. He was proposing that biology might set a limit on physical explanation.

Physicists, Delbrück recalled, largely ignored the lecture, and biologists, who knew no atomic physics, had no way to engage with it. Delbrück took it as a challenge. What struck him was that Bohr, usually so careful to hedge, had for once said something definite enough to be tested and, if necessary, shown to be wrong. If there was a paradox at the heart of living matter, someone trained in the new physics ought to be able to find it. Within three years he had co-written one of the founding papers of molecular biology. Within ten he had helped turn the study of bacterial viruses into a quantitative science. He never found the paradox he was looking for. This chapter is the story of how a search for something that was not there produced something that was.

The Science: What a Gene Was in 1930

The biology that Delbrück proposed to enter was in the middle of its own revolution. Mendel's laws of inheritance, rediscovered in 1900, said that traits were passed from parents to offspring by discrete factors that came in pairs and separated cleanly in each generation. In 1909 the Danish botanist Wilhelm Johannsen gave those factors a name, *genes*. Over the next two decades a group of researchers at Columbia University in New York turned the gene from a bookkeeping device into something that could be located.

The group worked under Thomas Hunt Morgan in a crowded laboratory in the zoology department, known as the Fly Room, and their organism was the fruit fly *Drosophila melanogaster*. Flies were cheap, bred every two weeks, and had only four pairs of chromosomes. In 1910 Morgan found a male with white eyes instead of red, and showed that the trait was inherited along with the fly's sex, which meant that the gene for eye colour travelled with the X chromosome. His students Alfred Sturtevant, Calvin Bridges and Hermann Muller followed through. Genes that sat on the same chromosome tended to be inherited together, but not always, because chromosomes exchange segments during the formation of eggs and sperm. The further apart two genes were, the more often they would be separated. In 1911 Sturtevant, then an undergraduate, used the frequencies of separation to construct the first genetic map, an ordered list of genes along a chromosome with the distances between them. By the 1920s the Morgan school had mapped a great many genes in the fly.

The maps were a triumph of inference. They showed that genes were arranged in a line, like beads on a string, at definite positions. But they said nothing about what a gene was made of, how large it was, or how it acted. Morgan himself was famously agnostic. In his Nobel lecture of 1934 he said that there was still no consensus among geneticists about what genes were, or "whether they are real or purely fictitious", and that for the practical work of genetics it made no difference. For a working geneticist, the gene was defined by its effects: by the eye colours, wing shapes and lethal defects whose inheritance it explained.

A minority wanted more. The most insistent was Muller, by then a professor at the Univer-

sity of Texas. Muller argued from the early 1920s that the gene had a unique property that made it the key to life itself: when it changed, by mutation, it went on copying itself in its changed form. Whatever a gene was physically, it was a structure that could make copies of its own variations. In a 1922 paper he noted that the bacterial viruses recently described by the French-Canadian microbiologist Félix d'Hérelle seemed to share this property, and speculated that if they were indeed something like naked genes, "perhaps we may be able to grind genes in a mortar and cook them in a beaker after all." It was an extraordinary forecast, and two decades early.

Muller also found the first way to intervene in genes at will. In 1926 and 1927, using a clever breeding scheme that revealed lethal mutations on the X chromosome by the absence of male offspring, he exposed flies to X-rays and counted the results. In one experiment, irradiated flies produced lethal mutations at roughly 150 times the spontaneous rate. He announced the result in *Science* in 1927 under the title "Artificial Transmutation of the Gene", borrowing the physicists' word for the conversion of one element into another, and presented the full data at a genetics congress in Berlin later that year.[2] Muller received the Nobel Prize in Physiology or Medicine for it in 1946.

X-ray mutagenesis mattered for this story in two ways. It gave geneticists an experimental handle on mutation, which until then had been a rare and capricious event. And it brought genetics into contact with physics, because an X-ray is a precisely measurable physical agent. Radiologists could say how much energy a given dose deposited and how many atoms it ionised. If mutations could be counted as a function of dose, then perhaps the gene could be measured with a physicist's ruler.

The Science: Why Physicists Were Restless

Between 1925 and 1928 Werner Heisenberg, Erwin Schrödinger, Max Born, Paul Dirac, Wolfgang Pauli and Bohr himself built quantum mechanics: a theory that explained, at least in principle, how electrons arrange themselves in atoms, why atoms bond into molecules, and why matter is stable at all. The achievement was so complete that Dirac, in a paper of April 1929, wrote that the physical laws needed for much of physics and "the whole of chemistry are thus completely known". The remaining difficulty, he added, was only that the equations were too complicated to solve exactly.[3] That was a confident thing to say about chemistry, and chemists did not all agree. But it captured a mood among young theoretical physicists. The heroic phase was over. What remained in atomic physics looked like approximation and calculation, while the frontier was moving inward to the nucleus, where the experiments were expensive and the theory murky.

For a few of them, biology looked like the next place where something fundamental might be hiding. The reasons were partly temperamental and partly philosophical. Bohr's complementarity offered one programme: if physics had been forced to accept that some of its concepts could not be used together, perhaps the study of life would force a similar renunciation, and so reveal something new about physics. A more sober programme asked whether the gene, which

geneticists described so precisely but could not see, might be a physical object whose properties could be estimated from the outside, as physicists had estimated the size of atoms from the behaviour of gases long before anyone could image one. The two programmes would turn out to have very different fates.

A Physicist in Search of a Paradox

Max Ludwig Henning Delbrück was born in Berlin on 4 September 1906, the youngest of seven children, into one of the city's leading academic families. His father, Hans Delbrück, was a professor of history at the University of Berlin and a well-known military historian; his mother, Lina Thiersch, was a granddaughter of the chemist Justus von Liebig. The family lived in the suburb of Grunewald, among a circle of professors' households that included the Bonhoeffers; Karl Friedrich Bonhoeffer, the eldest son of that family and later a distinguished physical chemist, became Delbrück's mentor and lifelong friend.

Delbrück's first love was astronomy. He began university at Tübingen in 1924, then moved between Berlin and Bonn before settling in 1926 at Göttingen, which was just then the centre of the new quantum mechanics. He began a thesis in astrophysics, on a type of exploding star, and abandoned it. Trying to understand the physics of stars led him into quantum theory, and he took his doctorate in theoretical physics under Max Born in 1930, with a thesis on the chemical bond in the lithium molecule. He later said it was not exciting science. From 1929 he spent about eighteen months at Bristol, working with the theoretical chemist John Lennard-Jones and sharing lodgings with the future Nobel laureate Cecil Powell. In 1931 a Rockefeller Foundation fellowship took him to Bohr's institute in Copenhagen, and then for six months to Pauli in Zurich. Copenhagen in those years was the world capital of theoretical physics, and its intellectual atmosphere was set by Bohr's habit of turning every problem into a question about the limits of description. Delbrück absorbed it, and started reading Kant on causality.

In 1932 he returned to Berlin as assistant to Lise Meitner at the Kaiser Wilhelm Institute for Chemistry in Dahlem, where she and Otto Hahn would soon begin bombarding uranium with neutrons. His job was in effect to be the institute's theoretical consultant. He chose Berlin partly to be near the biological institutes of the Kaiser Wilhelm Society. He had already decided, as he put it later, that taking Bohr seriously meant learning some biology.

Here a familiar story needs a correction. Popular accounts often say that Delbrück abandoned physics for biology because Bohr's lecture had persuaded him that biology would reveal new laws of physics. The historian Daniel McKaughan has argued that this version owes more to Schrödinger's later book, discussed below, than to Bohr. What Bohr offered, and what Delbrück hoped for, was subtler: not a new force or a new equation, but a limit, a point at which physical and chemical analysis of a living thing would stop being possible and a complementary kind of description would be needed.[4] The difference matters, because a search for a limit tells you to keep pushing reductive analysis as hard as you can, to see where it fails. That is what Delbrück did for the next forty years.

Ten Hours at a Time

The Berlin that Delbrück came back to was about to change beyond recognition. Within months of Hitler's appointment as chancellor in January 1933, the civil service law drove Jewish scholars out of German universities and research institutes. Delbrück, who was not Jewish, kept his post, but the scientific community around him was being hollowed out. From about 1934 he gathered a small private group of theoretical physicists, five or six in number, who met for discussions, often at his mother's house in Grunewald. At his suggestion they began to invite biologists and biochemists. Out of these contacts grew a smaller working group. One of its members, the radiation physicist Karl Günter Zimmer, later recalled that they met two or three times a week, mostly at Timoféeff-Ressovsky's home in Berlin, and that the talk could run for ten hours or more.

Zimmer and the other biologist in the group worked on the northern edge of the city, at the Kaiser Wilhelm Institute for Brain Research in Berlin-Buch. Nikolai Vladimirovich Timoféeff-Ressovsky was a Russian geneticist, born in 1900, who had trained in Moscow at Nikolai Koltsov's Institute of Experimental Biology under Sergei Chetverikov, a pioneer of the genetics of natural populations. In 1925 the neurologist Oskar Vogt had invited him to Berlin to set up a genetics department, and he and his wife Elena, also a geneticist, had stayed. By the early 1930s Timoféeff-Ressovsky was one of the leading experts in the world on radiation-induced mutation in *Drosophila*. Muller himself spent the academic year 1932–33 working in his department. The Russian nickname by which he came to be known, *Zubr*, means the European bison.

Zimmer was the youngest of the three, born in Breslau in 1911. He had trained in physics and photochemistry in Berlin and had begun to collaborate with Timoféeff-Ressovsky, unpaid at first, in 1933. His speciality was dosimetry: measuring exactly how much radiation a sample of flies had received. That might sound like a technician's task. In the work that followed, it was the hinge on which everything turned.[5]

The three men were a nearly ideal trading zone in miniature. Timoféeff-Ressovsky had the flies, the mutants and the breeding methods. Zimmer had the dosimeters and a working knowledge of how radiation interacted with matter. Delbrück had quantum mechanics. None of them could have written the paper that came out of their conversations alone.

The Three-Man Paper

The paper was published in 1935 in the biology series of the *Nachrichten* of the Gesellschaft der Wissenschaften in Göttingen, under the title "Über die Natur der Genmutation und der Genstruktur" ("On the Nature of Gene Mutation and Gene Structure"). It came to be known as the *Dreimännerarbeit*, the Three-Man Paper, and to some geneticists as the Green Pamphlet. It was in four parts: Timoféeff-Ressovsky summarised the genetic experiments, Zimmer analysed them using the theory of radiation "hits", Delbrück proposed an atomic-physical model of the gene, and a final joint section drew the three together into a theory of gene mutation and gene structure.

The experimental findings, summarised at the end of Timoféeff-Ressovsky's section in some fifteen lettered points, came from years of irradiating flies and counting the mutations that appeared in their offspring. Four of them carried the argument.

First, the number of induced mutations was *directly and linearly proportional to the dose*, over the whole range tested, from a few hundred to several thousand roentgens. Double the dose and you doubled the mutations. There was no threshold below which radiation did nothing.

Second, the yield depended only on the *total* dose, not on how it was delivered. Flies given a dose all at once, or spread thinly over a long time, or in several separate fractions, showed the same number of mutations.

Third, the yield was the same for X-rays of different wavelengths and for the much harder gamma rays of radium, provided the dose was measured in the same units: what mattered was how much ionisation the radiation produced, not what kind of radiation it was. Nor did the temperature at which flies were irradiated make any difference.

Fourth, and in a different direction, the *spontaneous* mutation rate, the rate at which mutations arose without any radiation, did depend on temperature. After correcting for the faster development of flies in warm conditions, the authors found that it rose by a factor of about five for each ten degrees Celsius, the kind of temperature dependence that chemists associate with an ordinary chemical reaction.[6]

Zimmer's section read the first three results through the lens of *target theory*. The idea had grown up in radiology in the 1920s, in the work of the German physicist Friedrich Dessauer and the British physicist J. A. Crowther, among others. Ionising radiation does not deposit its energy smoothly, like heat. It deposits it in discrete packets, each one the stripping of an electron from an atom to make an *ion pair*, scattered at random through the irradiated material. Crowther, writing in 1926, compared the rays to bullets fired at random into a swarm: the question was how many hits a sensitive target had to take to be put out of action. If one hit was enough, the yield would rise linearly with dose and would not care how the dose was spread over time, because each hit was an independent event. If two or more hits were needed, the yield would rise more steeply than linearly at low doses, and it would fall if the dose were stretched out, because one hit might be undone before the next arrived. The fly data fitted the one-hit pattern exactly. A single ionisation, or a small cluster of them, within some small sensitive volume was enough to produce a mutation.

That inference turned a count of flies into a measurement of size. If the probability of a mutation per unit dose is known, and the number of ionisations that one unit of dose produces per unit volume is known (Zimmer's dosimetry supplied this), then the size of the sensitive volume follows by simple division. The primer below works through the arithmetic, using later and more precise figures than the authors had.[7] The answer the three authors arrived at, as Schrödinger later summarised it, was a volume about ten average atomic distances on a side, which would contain about a thousand atoms.

Science Primer: One-hit target theory in numbers

Suppose a dose D of radiation scatters ionisations at random through tissue, with an average of n ion pairs per cubic centimetre for each unit of dose. A target of volume v will then receive, on average, $\lambda = v\,n\,D$ ionisations. Because the ionisations are independent and rare, the actual number in the target follows a *Poisson distribution*, and the probability that the target receives none at all is $e^{-\lambda}$. If a single hit is enough to change the target, the fraction of targets left unchanged after dose D is

$$S = e^{-vnD} = e^{-D/D_{37}}, \qquad \text{where } D_{37} = \frac{1}{vn}.$$

D_{37} is the dose at which e^{-1}, about 37 per cent, of targets escape, hence its name. For small doses, the fraction that *is* hit is $1 - e^{-D/D_{37}} \approx D/D_{37}$: exactly proportional to dose, and independent of how fast the dose is given.

Now some rough numbers. The roentgen, the dose unit of the 1930s, was defined by the ionisation it produces in air: about 2.1×10^9 ion pairs in a cubic centimetre of air at normal temperature and pressure. Tissue is nearly 800 times denser than air and absorbs slightly more energy per gram, so one roentgen produces roughly $n \approx 1.7 \times 10^{12}$ ion pairs in each cubic centimetre of tissue. Later measurements of mutation at particular genes in *Drosophila* sperm found rates of a few times 10^{-8} per gene for each roentgen (or rad, a nearly equal unit); take $\mu = 4 \times 10^{-8}$. Then the target volume is

$$v = \frac{\mu}{n} = \frac{4 \times 10^{-8}}{1.7 \times 10^{12}} \approx 2.4 \times 10^{-20}\ \text{cm}^3.$$

Since a cubic centimetre is 10^{24} cubic ångströms (an ångström, 10^{-8} cm, is about the diameter of an atom), this is about 24,000 cubic ångströms: a cube some 30 Å on a side. Allowing roughly 10 cubic ångströms per atom in organic matter, the target holds a few thousand atoms. The 1935 estimate was of the same order: about a thousand atoms. Note that $D_{37} = 1/\mu$ here is some 2.5×10^7 roentgens, far beyond any dose a fly could survive, so in practice only the straight, low-dose start of the curve is ever seen.

The arithmetic is simple. The assumptions are not. The calculation treats every ionisation within the target as a hit and every one outside it as harmless, and it measures the size of whatever is sensitive, which need not be the whole gene.

Delbrück's section asked what kind of physical object could behave like this. Here the fourth finding, the temperature dependence of spontaneous mutation, became crucial. A gene was evidently extraordinarily stable: Timoféeff-Ressovsky's figures put the chance that a particular normal gene would mutate in a given generation at between about one in a hundred thousand and one in a million. Yet it was not perfectly stable, and its rate of change rose with temperature in the way a chemical reaction's does.

Quantum mechanics gave Delbrück a natural explanation. In a molecule, atoms are held in definite positions by chemical bonds. To rearrange them into a different stable configuration,

an *isomer*, the molecule must pass over an energy barrier. Thermal agitation supplies energy at random, in quantities typically of order kT, where k is Boltzmann's constant and T the absolute temperature; at room temperature kT is about one-fortieth of an electron-volt. If the barrier W is many times larger than kT, the molecule will wait a very long time, on average, before a random thermal kick is large enough to carry it over. The rate goes as $e^{-W/kT}$, the Arrhenius law of chemistry. A factor of five for ten degrees at room temperature corresponds to a barrier of a little over one electron-volt, nearly fifty times kT, a typical size for the energy needed to rearrange chemical bonds. (The figure of about 1.2 electron-volts is my calculation from the published temperature coefficient.) An ionisation, by contrast, delivers energy of order tens of electron-volts in a single event, enough to push the molecule over the barrier at once, which is why radiation produced mutations regardless of temperature.

The conclusion was that a gene was a molecule, or a well-defined assembly of atoms within a larger structure, and that a mutation was a transition between two stable configurations of its atoms: in physicists' language, a quantum jump. That sounds unremarkable now. In 1935 it was a bold claim. Many biologists thought of genes as properties of the chromosome as a whole, or as something more like a physiological state than an object, and the physical nature of the hereditary material was entirely unknown.

The paper was, as Delbrück later put it, given "a funeral first class".[8] It appeared in a little-read journal, chosen because the society would supply plenty of reprints that the authors could send to anyone they thought interested, and it was written in a mixture of genetics and physics that few readers of either kind could follow. Delbrück himself became critical of its argument. In his oral history he said that it was not strong: it could not tell whether radiation caused point mutations or small deletions, nor whether induced and spontaneous mutations were really the same kind of event. Later commentators judged the gene-size calculation, which assumed a spherical target, unconvincing. The paper might have stayed obscure. What rescued it was a physicist in neutral Ireland, who read a reprint during the war.

The Foundation and the Refugees

Delbrück's route out of Germany ran through an American philanthropy. In 1932 the Rockefeller Foundation appointed Warren Weaver, a mathematician who had chaired the mathematics department at the University of Wisconsin, as director of its Division of Natural Sciences, created four years earlier under Max Mason. Weaver set the division on a long-term programme to support what he called experimental biology: research that applied the instruments and methods of physics and chemistry (X-rays, the ultracentrifuge, radioactive isotopes, mathematics) to living matter. He chose grantees personally, without formal peer review, and he favoured physicists and chemists willing to work on biological problems. In the Foundation's report for 1938 he gave the field a name, describing a new branch of science, "molecular biology", that was beginning to uncover the secrets of the living cell. He later claimed, in a letter to *Science* in 1970, to have coined the term.

Delbrück had held a Rockefeller fellowship in physics in 1931. In 1936 he completed his

Habilitation, the qualification needed for a German university career, but was denied the right to teach; the authorities did not consider him politically mature enough, and he believed it was because he had been too open in his dislike of the regime. In 1937 the Foundation gave him a second fellowship, this time in biology, which took him to the United States. He chose the California Institute of Technology in Pasadena, because Morgan had moved there in 1928 and built the leading centre of *Drosophila* genetics in the country.[9] He was not a refugee in the sense that his Jewish colleagues were. He left on a fellowship, and when it ended in September 1939, with Europe at war, he stayed.

Thousands of scholars left under far worse conditions. The Rockefeller Foundation's Special Research Aid Fund for Deposed Scholars, set up in 1933, typically paid half the salary of displaced academics whom European and American institutions agreed to employ; by 1945 the Foundation's refugee programmes had helped some three hundred scholars. Among those who reached Britain and the United States in the 1930s were scientists who would later shape molecular biology, such as Max Perutz, a young Viennese chemist who arrived in Cambridge in 1936. Salvador Luria, who will enter this story shortly, reached New York in 1940 and found work at Columbia University on a Rockefeller fellowship arranged by Enrico Fermi. The émigré story is often told as a gain for the receiving countries, which it was. It was also a loss, inflicted by violence, and the gain was paid for by those who could not get out.

Something Like Atoms

Delbrück's first months in Pasadena were frustrating. He found the specialised vocabulary of *Drosophila* genetics, with its hundreds of named mutants, hard to master quickly, though Sturtevant and Bridges helped him. What he wanted was a system in which a single, simple act of biological self-copying could be watched and measured, with the precision that physicists brought to atoms.

He found it by accident. He had missed a seminar given by Emory Ellis, a Caltech biochemist who had taken up bacteriophages, the viruses that infect bacteria and that d'Hérelle had described two decades before. Ellis was interested in viruses as a possible cause of cancer and had turned to phage because animal experiments were slow and expensive. Delbrück went to Ellis's laboratory to find out what he had missed. Ellis showed him how phages could be counted. A drop of a phage suspension is spread on a lawn of bacteria growing on a dish of nutrient jelly; wherever a single phage particle lands, it infects a bacterium, multiplies, bursts out, and infects the neighbours, until a clear spot, a *plaque*, appears in the cloudy lawn. Each plaque marks one original particle. Count the plaques and you have counted the viruses. Ellis remembered that Delbrück's first reaction was disbelief. Delbrück himself recalled that phage seemed to offer, beyond his wildest hopes, simple experiments on what amounted to the atoms of biology.

Together Ellis and Delbrück designed what became the founding experiment of phage biology, the *one-step growth* experiment. They mixed phage with bacteria, allowed a few minutes for the viruses to attach, and then diluted the mixture so heavily that any new phages released

would be unlikely to meet a fresh bacterium. Samples plated at intervals then showed what happened inside a single cycle of infection. For a period, the number of plaques stayed flat: each infected bacterium still made only one plaque, however many viruses were growing inside it. Then, within a short span, the count jumped, as the infected cells burst and released their progeny. The flat stretch, the *latent period*, varied with temperature in the same way as the division time of the bacteria; the size of the jump gave the average yield per cell, about sixty phage particles, though individual cells released anywhere from a few to about two hundred. Delbrück brought Poisson statistics to bear on the efficiency of plating and the rate at which phages attached to bacteria.[10] The paper, published in 1939, was the only one they wrote together. Ellis returned to his tumours, and Delbrück was left alone with phage.

When the fellowship ran out, the Foundation helped again. Delbrück took a post as an instructor in physics at Vanderbilt University in Nashville, Tennessee, where he stayed from 1940 to 1947; the Foundation paid half his salary, on condition that he spent half his time on biology. Vanderbilt had no tradition in phage work and gave him no biology students. What he needed were collaborators.

Slot Machines in Bloomington

Salvador Luria was born in Turin in 1912 and graduated in medicine from the university there in 1935. He had no wish to practise. Encouraged by his friend the physicist Ugo Fano, he sought training in radiology as a way of combining biology with physics, and after military service he spent 1938 at the University of Rome, among the physicists around Enrico Fermi, studying physics and concluding that he would remain an amateur at it. In Rome he first encountered Delbrück's work on radiation and the gene, and a bacteriologist, Geo Rita, whom he met by chance on a stalled tram, introduced him to bacteriophage. Mussolini's racial laws of 1938, which excluded Jews from Italian academic life, sent him to Paris, where he worked on the effects of radiation on phage at the Institut du Radium. When the German army approached Paris in June 1940 he left by bicycle, made his way to Marseilles for an American visa, and sailed from Lisbon, reaching New York on 12 September 1940.

At the end of December 1940, at the annual meeting of the American Physical Society, he met Delbrück, and they spent New Year's Day together in Luria's laboratory at Columbia. The description of Luria, often repeated, as a "physician turned physicist" is not quite right. He was a physician with radiological training who had learned enough physics to talk to physicists, and he remained, by temperament and appointment, a microbiologist. That combination was exactly what Delbrück lacked.

The third member of the partnership came from a different direction. Alfred Day Hershey, born in Michigan in 1908, had taken a degree in chemistry and a doctorate in bacteriology at Michigan State College, and since 1934 had worked in the department of bacteriology and immunology at Washington University in St Louis, where he studied the immune reactions to phage. Delbrück and Luria had been reading his papers, and in early 1943 Delbrück invited him to Nashville. Delbrück's notes on the visit recorded that Hershey drank whiskey but not

tea, was simple and to the point, and liked independence.[11] Hershey was a chemist by first training and a bacteriologist by profession, not a "physical chemist". With Delbrück and Luria he formed the nucleus of what came to be called the Phage Group.

The most celebrated result of these years, however, came from Luria and Delbrück alone, and it concerned an old and basic question about bacteria. When a culture of bacteria is exposed to a phage, nearly all the cells are killed, but a few survive and grow into a resistant population. Where do the resistant cells come from? One possibility, favoured by many bacteriologists, was that contact with the virus *induced* resistance in a small fraction of cells, an adaptive response to the challenge. The other was that resistance arose by random *mutation*, before any contact with the virus, in a few cells that the virus then selected. Bacteria have no visible chromosomes and no sex in the ordinary sense, and many biologists doubted that they had genes at all. The question mattered far beyond bacteria: it was a test, in the simplest organisms available, of whether heritable change was directed by the environment, as Lamarck had suggested, or arose blindly and was sifted by selection, as Darwin had.

Luria had moved to Indiana University in Bloomington in January 1943. Soon afterwards, at one of the monthly faculty dances held at the Bloomington Country Club, he found himself watching a colleague feed dimes into a slot machine. As he later told it, the machine paid out mostly nothing, occasionally small amounts and rarely a jackpot, and it struck him that the two hypotheses about bacterial resistance predicted different patterns of payout. He wrote to Delbrück proposing an experiment, and Delbrück replied with the mathematics.

The design was simple. Grow many small cultures of bacteria in parallel, each started from a small number of cells, and plate each culture, or a fixed sample of it, with phage. Separately, grow one large culture and plate many equal samples from it. Count the resistant colonies on every plate. If resistance is induced on contact with the virus, every plate is in the same situation, and the counts should vary only by chance, in the way that the number of raindrops falling on equal paving slabs varies. If resistance arises by mutation during growth, the independent cultures should differ wildly: one in which a mutation happened early would contain a large clone of resistant descendants, while most would contain few or none.

Science Primer: The fluctuation test

Suppose each bacterium exposed to phage has a small, fixed chance of becoming resistant on contact. Then the number of resistant colonies on a plate is the sum of many independent rare events, and it follows a *Poisson distribution*, whose defining property is that its *variance* (the average squared deviation from the mean) equals its *mean*. Plates with a mean of 10 colonies would typically show between about 4 and 16.

Now suppose resistance arises by random mutation during growth. In Luria and Delbrück's experiments each small culture was started from between 50 and 500 bacteria and grown until it held hundreds of millions, which takes some twenty generations. A mutation in the first of those generations leaves hundreds of thousands of resistant descendants; a mutation in the last generation leaves one. Because cells are far more numerous in late

generations, most mutations happen late and produce small clones, but the rare early ones produce huge ones: jackpots. The distribution has a long tail, and its variance is far larger than its mean.

In one experiment (their Experiment 16) Luria and Delbrück grew 20 parallel cultures of 0.2 cubic centimetres, each of which ended with about 5.6×10^8 bacteria, and plated a sample of 0.08 cubic centimetres from each. The numbers of resistant colonies were

$$1,\ 0,\ 3,\ 0,\ 0,\ 5,\ 0,\ 5,\ 0,\ 6,\ 107,\ 0,\ 0,\ 0,\ 1,\ 0,\ 0,\ 64,\ 0,\ 35.$$

The average is 11.35 per sample, and the variance the authors reported is 694, some sixty times the mean. In a separate experiment, ten samples taken from a single large culture gave

$$14,\ 15,\ 13,\ 21,\ 15,\ 14,\ 26,\ 16,\ 20,\ 13,$$

with a mean of 16.7 and a variance of 15: close to the mean, as a Poisson process predicts. The sampling itself was not the source of the scatter; the scatter came from the history of each culture.

Delbrück's analysis also turned the scatter into a measurement. From the average number of resistant bacteria per culture (28.4 in Experiment 16), the number of bacteria, and the theory of how clones grow, the paper estimated a mutation rate of about 1.1×10^{-8} for this experiment. A second method used only the cultures with no resistant bacteria at all. If mutations occur at random, the number of mutational events in a culture is itself Poisson, so the fraction of cultures with *no* mutation is $P_0 = e^{-m}$, where m is the average number of mutations per culture. This works only when whole cultures are tested, so that a zero really means no mutant. In Experiment 23, 29 of 87 whole cultures had none: $P_0 = 29/87 \approx 0.33$, so $m = -\ln 0.33 \approx 1.1$ mutations per culture, which the authors converted to about three mutations to resistance in every thousand million cell divisions (0.32×10^{-8} per division).

The paper, "Mutations of Bacteria from Virus Sensitivity to Virus Resistance", appeared in *Genetics* in November 1943.[12] Its conclusion was that resistance arose by spontaneous mutation, independent of the virus, and that bacteria therefore had genes that mutated much as the genes of flies did. It is generally counted as the founding paper of bacterial genetics. It was also one of the clearest examples in this book of methodological smuggling. The biological question was old; the instrument used to answer it was a statistical argument about the shape of a distribution, of a kind that came naturally to a physicist used to thinking about counting errors and fluctuations, and that had not occurred to the bacteriologists. The experiment needed nothing more elaborate than test tubes, dishes and patience.

It did not convince everyone at once. Some bacteriologists objected that the statistics were indirect, and the Lamarckian alternative lingered until it was dislodged by experiments that showed the resistant mutants directly. In 1949 Howard Newcombe showed that respreading colonies before exposure to phage multiplied the number of resistant colonies, as it should if

the mutants already existed. In 1952 Joshua and Esther Lederberg used a velvet stamp to copy a plate of colonies onto several others, and found resistant colonies at the same positions on every copy, even though none of the bacteria on the master plate had ever met the selecting agent.

The Treaty and the Course

The Phage Group was never an institution. It was a network of people who agreed to work in a particular way. Its meeting place, from the summer of 1941, was the Cold Spring Harbor laboratory on the north shore of Long Island, where the geneticist Milislav Demerec gave Delbrück and Luria space to work in the summers. (Delbrück married Mary Bruce in Pasadena in August 1941 and spent the honeymoon there.) In the winter of 1941–42 Luria and the electron microscopist Thomas Anderson took some of the early electron micrographs of phage particles; in Berlin, Helmut Ruska had begun imaging phages in the same way a little earlier.

In 1944 Delbrück negotiated what became known as the phage treaty. Until then, each laboratory had worked with its own phages and bacterial strains, so that results could seldom be compared. The treaty concentrated work on seven phages, named T1 to T7, all growing on a single strain of the bacterium *Escherichia coli*, strain B, under standard conditions. It was a small act of discipline, and an essential one: it made phage biology cumulative.

In the summer of 1945 Delbrück taught the first phage course at Cold Spring Harbor, a short, intensive training in the methods of phage work that drew in many physicists and chemists who wanted to move into biology. He was its principal instructor for the first three years, and the course ran annually for twenty-six years, training more than four hundred students. Annual phage meetings began in 1947, with eight people in Nashville.[13] The style of the group was Delbrück's: quantitative, sceptical, informal and impatient with loose reasoning. He became an American citizen in 1945 and returned to Caltech as professor of biology in 1947.

The course and the group were a trading zone of an unusual kind. They were not a meeting of equals from different fields, each bringing a skill. They were a deliberate conversion programme, which taught newcomers a shared set of organisms, techniques and standards of proof, so that a physicist, a chemist and a microbiologist could compare results from the first day. In that respect they resemble the wartime laboratories described in Part II of this book more than they resemble the private discussions in Berlin.

Dublin, February 1943

Erwin Schrödinger was one of the physicists who had made quantum mechanics. His wave equation of 1926 was its most widely used form, and he had shared the Nobel Prize in Physics with Dirac in 1933. That same year he gave up his chair in Berlin in protest against the new regime and went to Oxford. In 1936 he returned to Austria, to the University of Graz; after the annexation of Austria in 1938 he was dismissed and fled. In October 1939, at the invitation of Éamon de Valera, the Irish head of government, he arrived in Dublin to lead the School of The-

oretical Physics of a new Dublin Institute for Advanced Studies, which de Valera had modelled on the institute at Princeton.

The crystallographer Paul Ewald, a fellow refugee then teaching at Queen's University, Belfast, gave him a copy of the Three-Man Paper. In February 1943 Schrödinger gave a series of public lectures under the auspices of the Institute at Trinity College, Dublin, titled "What Is Life?" By his own account the audience numbered about four hundred and did not dwindle, although they had been warned that the lectures could not be called popular, even though they made almost no use of mathematics. The lectures were repeated to meet demand. De Valera attended, with members of his cabinet.[14] Cambridge University Press published them in 1944 as a small book of 91 pages.

The book's argument began with a puzzle that only a physicist would have framed in quite this way. The laws of physics and chemistry that govern ordinary matter, Schrödinger said, are *statistical*. The pressure of a gas, the rate of diffusion of a dye, the magnetism of a lump of iron are averages over enormous numbers of atoms behaving at random. Their precision comes from the numbers involved. If a process involves n independent particles, its typical random deviation is about $\sqrt{n}$, so the *relative* error is about $1/\sqrt{n}$: one part in a thousand for a million particles, one part in ten for a hundred. Schrödinger's name for the physicist's kind of law was *order from disorder*: regularity on the large scale emerging from chaos on the small.

An organism, he argued, must be large compared with atoms for exactly this reason, so that its workings are not swamped by fluctuations. Yet the hereditary material inside each cell was not large. Using the cytologists' estimates of chromosome size, he showed that a gene could contain at most a few million atoms; using the Three-Man Paper, he arrived at about a thousand. A structure of a thousand atoms ought, by the $\sqrt{n}$ rule, to be at the mercy of thermal agitation. Yet genes were copied faithfully for generations. His example was the protruding lower lip of the Habsburg dynasty, visible in portraits of family members painted in the sixteenth century and again in the nineteenth. The gene responsible had been kept at around 98 degrees Fahrenheit for centuries and had passed through many cell divisions without being disordered by heat. How?

The answer, Schrödinger said, was what he called Delbrück's model. Classical statistical physics could not explain the stability of genes; quantum mechanics could. In a molecule, atoms are held in discrete energy states, separated by thresholds, and the time a molecule waits for a thermal fluctuation large enough to cross a threshold rises exponentially with the ratio of threshold to thermal energy. In his own illustration, a threshold thirty times kT gives a waiting time of about a tenth of a second; fifty times kT, about sixteen months; sixty times kT, about thirty thousand years. Small changes in the threshold produce enormous changes in stability, which is why genes can be nearly, but not perfectly, permanent. Mutations were the rare quantum jumps between stable states.

From there Schrödinger made the two moves for which the book is remembered. The first concerned structure. A crystal, such as salt, gets its stability from the same quantum-mechanical bonds as a molecule, but it is *periodic*: the same small unit repeats, like the pattern on ordinary wallpaper, and so it carries very little specific information. A gene, or perhaps the whole chro-

mosome fibre, must be an *aperiodic crystal* or *aperiodic solid*: a structure with the stability of a crystal but without repetition, in which each group of atoms plays an individual part. He compared the difference to that between wallpaper and a masterpiece of embroidery. Schrödinger followed the geneticists of his day in supposing that the hereditary substance was probably a large protein molecule.

The second move concerned function. Schrödinger suggested that the pattern of the aperiodic solid amounted to a *code-script*, which specified the whole future development of the organism. To show how a small number of building blocks could specify a vast number of possibilities, he used the Morse code: dots and dashes in groups of up to four give thirty different signs, and five kinds of sign in groups of up to twenty-five give more than 3×10^{17}. The idea was not only that the chromosomes held a description to be read, but that they were at once the plan and the means of carrying it out: the architect's plan and the builder's craft in one, as he put it.

The last part of the book took up a separate question, of how living things maintain their order at all, given the second law of thermodynamics, which says that the entropy, or disorder, of an isolated system tends to increase. An organism, Schrödinger said, stays alive by continually drawing order from its environment; in a much-quoted sentence, "What an organism feeds upon is negative entropy." In a note to that chapter, he conceded that physicists would have preferred him to speak of *free energy*, and that he had avoided the term only because he thought lay readers would confuse it with energy. He ended with a principle he called *order from order*: in living things, unlike the physicist's gases, macroscopic order was produced from microscopic order, from a single aperiodic crystal at the centre of each cell. Living matter, while obeying the laws of physics so far established, was likely, he suggested, to involve other laws of physics, as yet unknown.

Readers

What Is Life? was widely read, widely reviewed and translated into several languages, and it had an influence out of all proportion to its length. It is often credited with turning a generation of physicists towards biology, and some of the people who later built molecular biology said that it had done so for them. The claims deserve some care, because the book has become the centre of a founding myth, and the details differ from person to person.

James Watson read it as an undergraduate at the University of Chicago, where he had enrolled at fifteen intending to study birds. He later recalled that the idea of life being carried on by means of an instruction book written in a secret code appealed to him, and that he decided the gene was where the important problems lay. He went on to graduate school at Indiana in 1947 as Luria's first doctoral student, working on phage, and met Delbrück in 1948.

Francis Crick, a physicist whose research had been interrupted by the war, spent it designing magnetic and acoustic mines for the Admiralty. He left in 1947 to study biology, spending two years at the Strangeways Laboratory in Cambridge before joining the Medical Research Council

unit in the Cavendish Laboratory in 1949. He read Schrödinger's book after the war, found its arguments flawed, and was nonetheless persuaded that a physicist could contribute to understanding life. On 12 August 1953, with the double helix published, he wrote to Schrödinger that he and Watson had both been influenced by his "little book", and that the term "aperiodic crystal" was going to prove a very apt one. In later years Crick, like others, faulted the book for neglecting chemistry.

Maurice Wilkins, a physicist who had worked on radar and then, in 1944–45, on uranium isotope separation for the Manhattan Project at Berkeley, read it at the end of the war, when he rejoined John Randall at St Andrews, and it was one reason for his move into biophysics. Seymour Benzer, who took his doctorate in solid-state physics at Purdue in 1947 with a thesis on germanium, read it as a graduate student, took the Cold Spring Harbor phage course in 1948, and joined Delbrück at Caltech as a postdoctoral fellow in 1949. He would later use phage to map the internal structure of a single gene in fine detail. Gunther Stent, who took the course with Benzer, became one of the group's chroniclers.[15] Several of these readers said that they might well have moved into biology anyway; the book gave a name and a respectability to a direction many were already considering.

The critics came later, and from among the people best qualified to judge. Hermann Muller, in a letter of 1960, said that whatever the book got right about the hereditary molecule had been published before 1944, and that Schrödinger's own contributions were the speculations that were wrong. In 1987, at the centenary of Schrödinger's birth, Linus Pauling, who had built the chemistry of the chemical bond on quantum mechanics, wrote that he had been disappointed by the book on first reading, and called its discussion of thermodynamics "vague and superficial". Max Perutz, the crystallographer who had spent his career on the structure of haemoglobin, was blunter. He wrote that "what was true in his book was not original", and that most of what was original was known not to be true even when it was written. He asked why Schrödinger had not simply called his aperiodic crystal a polymer, as chemists would have done, and pointed out that the apparent conflict between heredity and the statistical laws of physics had been resolved by chemistry, a science Schrödinger largely ignored. In a separate article that year, Perutz judged that the book's chief merit was to rescue the Three-Man Paper from obscurity.[16]

Both judgements can be true at once. The physics of the book was mostly Delbrück's, and its chemistry was thin. What Schrödinger added was a way of framing the problem: the gene as a stable physical object, the stability as a matter of quantum mechanics, the specificity as a matter of pattern, the pattern as a code. That framing did not solve anything. It told a certain kind of reader that the problem of heredity was solvable by the methods he already knew.

Outcomes and Legacy

The hereditary molecule. The gene did turn out to be an aperiodic solid, but not the one Schrödinger had in mind. In the same year that his book appeared, Oswald Avery, Colin MacLeod and Maclyn McCarty at the Rockefeller Institute in New York reported that the substance that transformed one strain of pneumococcus into another was deoxyribonucleic acid,

DNA, not protein. In 1952 Hershey and his assistant Martha Chase, using radioactive labels, showed that when a phage infects a bacterium it is mainly the phage's DNA, not its protein, that enters the cell. A year later Watson and Crick proposed the double helix, in which the sequence of four bases along each strand can be any sequence at all: an aperiodic crystal with a code-script. That story, and the work of Rosalind Franklin and Wilkins that made it possible, belongs to Chapter 7.

Phage and the new genetics. The Phage Group's methods and organisms became the experimental basis of much of early molecular genetics. Benzer mapped the fine structure of a gene in phage T4 in the 1950s, showing that mutations within one gene could be ordered along a line. Watson, Benzer, Stent and many others trained in the group's habits of quantitative argument. In 1969 Delbrück, Hershey and Luria shared the Nobel Prize in Physiology or Medicine "for their discoveries concerning the replication mechanism and the genetic structure of viruses". Timoféeff-Ressovsky and Zimmer, whose work had started the line, were not included; neither was Ellis.

The name and the patron. Weaver's term "molecular biology" outlasted his programme, and the Rockefeller Foundation's support for physicists, chemists and their instruments in biology shaped the field's first generation, at Caltech and in Europe. Historians disagree about how much credit the Foundation deserves and what it was trying to achieve. Lily Kay argued that its programme grew out of a broader "science of man" agenda that included the hope of rationalising and controlling human behaviour, and that it largely created the new biology at Caltech. Pnina Abir-Am offered a critical reappraisal of the Foundation's "policy". Both treat Weaver's money as a central fact of the field's origins rather than a background condition.

The information metaphor. Schrödinger's code-script was the first influential statement of the idea that heredity is a matter of stored instructions. After Claude Shannon's theory of communication appeared in 1948 (Chapter 6), the vocabulary of information, code and message spread quickly through biology, and it shaped the search for the genetic code in the 1950s and 1960s. The historian Lily Kay showed that molecular biologists did not generally speak of "information" until around 1950; before that they spoke of biological "specificity".[17]

Physicists in biology. The traffic that Delbrück and Schrödinger started has never stopped. Physicists brought X-ray crystallography, electron microscopy, statistical mechanics and later single-molecule techniques into biology; today biological physics and quantitative biology are established disciplines with their own departments, journals and courses. Rob Phillips of Caltech, writing for the book's seventy-fifth anniversary, argued that several of Schrödinger's themes, from fluctuations to the emergence of order from order, have become central to that field. The fluctuation test has had a long afterlife too: the Luria–Delbrück distribution is still used to estimate mutation rates, for example in studies of antibiotic resistance. The question it settled was reopened in 1988, when John Cairns and colleagues reported apparently directed mutation in starving bacteria. The long debate that followed uncovered ways in which stressed bacteria raise their mutation rates, but it did not establish that they can aim mutations at the genes that would help them.

The Costs of Crossing

The story of physicists in biology is usually told as a story of fertile trespass. It was that. It also shows the limits of the thesis of this book.

The idea that drew the border-crossers was wrong. Delbrück went into biology looking for a paradox, a point where physical explanation would fail and Bohr's complementarity would be needed. He never found it. In a 1954 letter to Bohr he said, in effect, that this search had been his hidden motive in biology from the start; in a 1949 lecture he had predicted that the paradoxes would appear only once the analysis of living cells had gone much further. The double helix was a blow to that hope, because it showed that replication, the very process Delbrück had thought might be beyond chemistry, was explained by chemistry, through the pairing of bases by hydrogen bonds. He turned in the 1950s to the light responses of the fungus *Phycomyces*, hoping that the way a few quanta of light could trigger a large response would show something new. It did not. Complementarity found no lasting use in biology, and the new laws of physics that Schrödinger had suggested were never needed.[18] That is an uncomfortable fact for any account of interdisciplinary discovery that credits the outsider's vision. The most productive physicist in early molecular biology was motivated by a mistaken expectation. What made him productive was not his philosophy but his standards: the insistence on simple systems, quantitative experiments and clear arguments.

The chemists were closer to the answer. The physicists' framing was general and elegant, but the problem was solved at the level of chemistry: of particular molecules, particular bonds and particular shapes. In 1940 Pauling and Delbrück published a short paper in *Science* attacking the physicist Pascual Jordan's proposal that identical molecules attract one another by a quantum-mechanical resonance, and argued instead that biological specificity depended on the *complementarity* of molecular shapes, like a die and a coin, adding that a molecule that could copy itself would need a structure in which complementarity and identity coincided.[19] That remark was nearer the double helix than anything in *What Is Life?*, and it came from a chemist's way of thinking, even though a physicist's name stood beside Pauling's on the paper. Schrödinger's book was less a guide than a recruiting poster, and the people it recruited had to learn the chemistry it left out.

The metaphor did work, and also harm. The code-script became the genetic code, and the language of information has been extraordinarily productive. But the metaphor has limits. Philosophers of biology have argued for decades about whether "information" in genetics means anything more precise than "causal specificity", and whether calling DNA a program or blueprint, rather than one cause among many in development, has encouraged a misleading genetic determinism. The idea that the organism is "written" in its genes, which began with Schrödinger's elegant pages, has to be argued with in every generation.

The darker context. The collaboration took place in Nazi Berlin, and its people paid very different prices. Timoféeff-Ressovsky chose to stay at the Buch institute in 1945 rather than move west. His elder son, Dmitri, had been arrested by the Gestapo in 1943 for anti-fascist activity and died in Mauthausen concentration camp in 1945. In September 1945 the Soviet secret po-

lice arrested Timoféeff-Ressovsky himself; in 1946 a Soviet military court sentenced him to ten years, as a defector who had refused to return to the Soviet Union. In Butyrka prison in Moscow he met Aleksandr Solzhenitsyn, who later described him in *The Gulag Archipelago*. Malnutrition in a labour camp in Kazakhstan damaged his eyesight, and he survived because the Soviet nuclear programme needed radiobiologists: from 1947 he worked at a secret laboratory at Sungul in the Urals. Zimmer, taken to the Soviet Union in 1945, worked at the same laboratory and returned to West Berlin in 1955. Timoféeff-Ressovsky was released in the 1955 amnesty but remained an unrehabilitated former prisoner, barred from travelling abroad, and died in Obninsk in 1981. In 1991 the Soviet prosecutor general found no legal basis for the treason charge, and he was formally rehabilitated in 1992. The Buch institute itself has its own history: from 1940 to 1945 its neuropathologists Julius Hallervorden and Hugo Spatz studied the brains of victims of the Nazi "euthanasia" killings, and the Max Planck Society buried the remaining specimens in 1990. Timoféeff-Ressovsky's genetics department was separate, and there is no evidence that he was involved. The geneticist Benno Müller-Hill, reviewing the record, concluded that he had sometimes posed as a supporter of the regime's race hygiene but in practice did nothing for it; others have testified that he protected people at risk, including two "half-Jewish" members of his staff. Delbrück built his career in America; Timoféeff-Ressovsky's was broken by a second dictatorship. Even Schrödinger's reputation has been revised: in 2022 Trinity College Dublin renamed its Schrödinger lecture theatre after reports that he had groomed and sexually abused young girls.[20] A history of border-crossing that tells only the intellectual story leaves out what the borders of the 1930s and 1940s actually meant.

Coda

The three men of 1935 met in a private house because the public institutions around them were being emptied. One of them crossed an ocean on a fellowship, found in a dish of bacteria the simple system he had been looking for, and taught its methods to a generation of physicists and chemists, who used them to show that the gene was a chemical. The other two were taken to the Soviet Union in 1945 and spent years in a closed laboratory in the Urals, one of them after a spell in a labour camp. The paradox that Bohr had promised did not appear, and the gene they measured with radiation turned out to be a molecule that a chemist could describe. Their question, how an object of a few thousand atoms can carry heredity faithfully through time, was the right one, and it was answered within twenty years of those discussions in Berlin.

Notes

[1]Delbrück's recollection is in Max Delbrück, interview by Carolyn Harding, Pasadena, July–September 1978, Oral History Project, California Institute of Technology Archives, https://resolver.caltech.edu/CaltechOH:OH_Delbruck_M. The lecture was published as Niels Bohr, "Light and Life," *Nature* 131 (1933): 421–23 and 457–59, after a Danish version in *Naturens Verden*.

[2]Thomas Hunt Morgan, "The Relation of Genetics to Physiology and Medicine," Nobel Lecture, 4

June 1934, in *Nobel Lectures, Physiology or Medicine 1922–1941* (Amsterdam: Elsevier, 1965). Morgan moved to the California Institute of Technology in 1928 to found its Division of Biology; see the Nobel Prize's account of his work at https://www.nobelprize.org/prizes/medicine/1933/morgan/article/. H. J. Muller, "Variation Due to Change in the Individual Gene," *American Naturalist* 56 (1922); Muller developed the argument in "The Gene as the Basis of Life," a lecture given in 1926 and published in *Proceedings of the International Congress of Plant Sciences* 1 (1929): 897–921. H. J. Muller, "Artificial Transmutation of the Gene," *Science* 66 (1927): 84–87. On the experiments and the 150-fold figure, see the Embryo Project Encyclopedia, "Hermann Joseph Muller's Study of X-rays as a Mutagen, (1926–1927)," https://embryo.asu.edu/pages/hermann-joseph-mullers-study-x-rays-mutagen-1926-1927.

[3]P. A. M. Dirac, "Quantum Mechanics of Many-Electron Systems," *Proceedings of the Royal Society of London A* 123 (1929): 714–33. The remark is often paraphrased; Dirac's point was that the remaining problems were mathematical and practical.

[4]William Hayes, "Max Ludwig Henning Delbrück," *Biographical Memoirs of the National Academy of Sciences* 62 (Washington, DC: National Academy Press, 1993); Delbrück's autobiographical notes for the Nobel Foundation, https://www.nobelprize.org/prizes/medicine/1969/delbruck/biographical/; and the entry in *Neue Deutsche Biographie*, https://www.deutsche-biographie.de/pnd120256568.html. Delbrück was a postdoctoral visitor with Bohr and Pauli, not their student. Daniel J. McKaughan, "The Influence of Niels Bohr on Max Delbrück: Revisiting the Hopes Inspired by 'Light and Life'," *Isis* 96, no. 4 (2005): 507–29.

[5]Hayes, "Max Ludwig Henning Delbrück," which gives both venues and Zimmer's recollection; Delbrück, interview by Harding. The Max Delbrück Center for Molecular Medicine notes that the private circles met while many Jewish colleagues were no longer allowed to work: "The Simplicity behind Complexity," https://www.mdc-berlin.de/news/news/simplicity-behind-complexity. On Zimmer, see the Max Delbrück Center for Molecular Medicine, "Karl Günter Zimmer," https://www.mdc-berlin.de/karl-guenther-zimmer. On Timoféeff-Ressovsky's early career, see Mark B. Adams and Zhores A. Medvedev's entry on him in the *Dictionary of Scientific Biography*, reproduced at https://www.encyclopedia.com/science/dictionaries-thesauruses-pictures-and-press-releases/timofeeff-ressovsky-nikolai-vladimirovich.

[6]N. W. Timoféeff-Ressovsky, K. G. Zimmer, and M. Delbrück, "Über die Natur der Genmutation und der Genstruktur," *Nachrichten von der Gesellschaft der Wissenschaften zu Göttingen, Mathematisch-Physikalische Klasse, Fachgruppe VI, Biologie*, n.s., 1, no. 13 (1935): 189–245. An English translation by Brandon Fogel, with essays, is in Phillip R. Sloan and Brandon Fogel, eds., *Creating a Physical Biology: The Three-Man Paper and Early Molecular Biology* (Chicago: University of Chicago Press, 2011). Timoféeff-Ressovsky, Zimmer, and Delbrück, "Über die Natur der Genmutation," sec. I, *Zusammenfassung*, where the corrected temperature coefficient for $10\,^{\circ}\mathrm{C}$ is given as about 5 and the spontaneous rate is said to follow the van 't Hoff rule.

[7]J. A. Crowther, "X-Rays and Living Matter," *Nature* 118 (1926): 86–88. On Dessauer's role, see S. Hazout et al., "Historical View of the Effects of Radiation on Cancer Cells," *Oncology Reviews* 19 (2025): 1527742. The roentgen was defined in 1928 by the charge freed in air; one roentgen corresponds to about 2.08×10^{9} ion pairs in 0.001293 grams of air (one cubic centimetre at standard temperature and pressure) and deposits about 0.0096 grays in soft tissue. The *Drosophila* rate of 4.36×10^{-8} mutations per rad per locus, for mature sperm, is from M. L. Alexander, "Genetic Damage at Specific Gene Loci in *Drosophila* with Betatron X-Rays," *Genetics* 81 (1975): 493–500; Alexander found conventional 250 kV X-rays somewhat more effective. The calculation in the primer is my illustration, not the 1935 authors' own.

[8]Quoted in Hayes, "Max Ludwig Henning Delbrück."

[9]Warren Weaver, "Molecular Biology: Origin of the Term," *Science* 170 (1970): 581–82; on Weaver's career, see the MacTutor biography, https://mathshistory.st-andrews.ac.uk/Biographies/Weaver/, and the Rockefeller Archive Center's account of the experimental biology programme, which it dates 1933–1951. Delbrück's habilitation without a teaching licence is recorded in *Neue Deutsche Biographie*; the official judgement on his political maturity and his own explanation are reported in the Embryo Project Encyclopedia, "Max Ludwig Henning Delbruck (1906–1981)," https://embryo.asu.edu/pages/max-ludwig-henning-delbruck-1906-1981.

[10]Hayes, "Max Ludwig Henning Delbrück," gives Ellis's and Delbrück's recollections of their first meeting. Recollections by early phage workers are collected in John Cairns, Gunther S. Stent, and James D. Watson, eds., *Phage and the Origins of Molecular Biology* (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory of Quantitative Biology, 1966). E. L. Ellis and M. Delbrück, "The Growth of Bacteriophage," *Journal of General Physiology* 22 (1939): 365–84.

[11]On Luria's early career, see the Salvador E. Luria Papers, "Profiles in Science," US National Library of Medicine, https://profiles.nlm.nih.gov/spotlight/ql/feature/biographical-overview; and his Nobel biography, https://www.nobelprize.org/prizes/medicine/1969/luria/biographical/. Most accounts place the 1940 meeting in Philadelphia; the National Library of Medicine gives the date as 30 December. Franklin W. Stahl, "Alfred Day Hershey," *Biographical Memoirs of the National Academy of Sciences* 80 (Washington, DC: National Academy Press, 2001).

[12]Luria's account is in S. E. Luria, "Mutations of Bacteria and of Bacteriophage," in Cairns, Stent, and Watson, eds., *Phage and the Origins of Molecular Biology*; he retold it in his autobiography, *A Slot Machine, a Broken Test Tube* (New York: Harper and Row, 1984). Luria's own account places the episode in January 1943; the National Library of Medicine's Luria Papers site places it in February. S. E. Luria and M. Delbrück, "Mutations of Bacteria from Virus Sensitivity to Virus Resistance," *Genetics* 28 (1943): 491–511. The figures in the primer are the paper's own: Experiment 16 in its Table 2 (individual cultures), Experiment 10a in its Table 1 (samples from one culture), and Experiment 23 in its Table 3 (the zero-class estimate). The individual counts for Experiment 16 are as transcribed by Steven M. Carr, Memorial University of Newfoundland, https://www.mun.ca/biology/scarr/smcLuria-Delbruck_results.html.

[13]Hayes, "Max Ludwig Henning Delbrück," sections on Vanderbilt and on Cold Spring Harbor. On the course's history, see also Cairns, Stent, and Watson, eds., *Phage and the Origins of Molecular Biology*, a collection of recollections prepared for Delbrück's sixtieth birthday.

[14]M. F. Perutz, "Erwin Schrödinger's *What Is Life?* and Molecular Biology," in C. W. Kilmister, ed., *Schrödinger: Centenary Celebration of a Polymath* (Cambridge: Cambridge University Press, 1987), 234–51, describes Ewald's role. Erwin Schrödinger, *What Is Life? The Physical Aspect of the Living Cell* (Cambridge: Cambridge University Press, 1944), whose opening chapter gives the audience as about four hundred. On de Valera's attendance, see Kevin O'Sullivan, "Erwin Schrödinger in Dublin: Physicist, Womaniser, Fugitive," *Irish Times*, 1 September 2018. Accounts differ on whether there were three lectures or four; the Dublin Institute for Advanced Studies' own history says each was repeated.

[15]On Crick's war work and career, see his Nobel biography, https://www.nobelprize.org/prizes/medicine/1962/crick/biographical/. The letter of 12 August 1953 is held by the Dublin Institute for Advanced Studies; its phrase is quoted in Philip Ball, "Schrödinger's Cat among Biology's Pigeons: 75 Years of *What Is Life?*," *Nature* 560 (2018): 548–50, and described in the Nobel Prize's "Perspectives: What Is Life?", https://www.nobelprize.org/prizes/medicine/1962/perspectives/, which also gives Watson's recollection. K. R. Dronamraju, "Erwin Schrödinger and the Origins of Molecular Biology," *Genetics* 153 (1999): 1071–76, lists Delbrück, Stent, Watson, Crick, Wilkins and Benzer among those who acknowledged a debt. On Wilkins, see King's College London Archives, "Maurice Wilkins (1916–2004)," https://kingscollections.org/exhibitions/archives/dna/key-individuals/wilkins; on Benzer

and Stent, the Cold Spring Harbor Laboratory DNA Learning Center, "Biography 27: Seymour Benzer," https://www.dnaftb.org/27/bio-2.html.

[16]Linus Pauling, "Schrödinger's Contribution to Chemistry and Biology," in Kilmister, ed., *Schrödinger*, 225–33; Perutz, "Erwin Schrödinger's *What Is Life?* and Molecular Biology," in the same volume; M. F. Perutz, "Physics and the Riddle of Life," *Nature* 326 (1987): 555–58. The Pauling and Perutz quotations follow Rob Phillips, "Schrödinger's *What Is Life?* at 75," *Cell Systems* 12, no. 6 (2021): 465–76. Muller's 1960 letter, to a journalist, is reported in secondary sources without a full citation; I have not seen it and give only its substance.

[17]Lily E. Kay, *The Molecular Vision of Life: Caltech, the Rockefeller Foundation, and the Rise of the New Biology* (New York: Oxford University Press, 1993); Pnina Abir-Am, "The Discourse of Physical Power and Biological Knowledge in the 1930s: A Reappraisal of the Rockefeller Foundation's 'Policy' in Molecular Biology," *Social Studies of Science* 12, no. 3 (1982): 341–82. Lily E. Kay, *Who Wrote the Book of Life? A History of the Genetic Code* (Stanford, CA: Stanford University Press, 2000). For the philosophical debate over the concept, see James Tabery, Monika Piotrowska, and Lindley Darden, "Molecular Biology," *Stanford Encyclopedia of Philosophy*, https://plato.stanford.edu/entries/molecular-biology/.

[18]Bernard S. Strauss, "A Physicist's Quest in Biology: Max Delbrück and 'Complementarity'," *Genetics* 206 (2017): 641–50; Max Delbrück, "A Physicist Looks at Biology," *Transactions of the Connecticut Academy of Arts and Sciences* 38 (1949): 173–90.

[19]Linus Pauling and Max Delbrück, "The Nature of the Intermolecular Forces Operative in Biological Processes," *Science* 92 (1940): 77–79.

[20]Timoféeff-Ressovsky's arrest, sentence and later life are summarised in *Neue Deutsche Biographie*, https://www.deutsche-biographie.de/sfz107912.html, and in the Great Russian Encyclopedia, which gives 1992 for his rehabilitation. On Zimmer's captivity, see the Max Delbrück Center, "Karl Günter Zimmer." Daniil Granin's documentary novel *Zubr* (1987) made his story widely known in the Soviet Union. Benno Müller-Hill, "Heroes and Villains," review of Daniil Granin, *Der Genetiker*, *Nature* 336 (1988): 721; Andrei G. Malenkov and Valery I. Ivanov, "Heroes and Villains," *Nature* 338 (1989): 612. The protection of two employees is recorded in the Max Delbrück Center's account of Zimmer. On the Buch brain collection, see the history of the Max Planck Institute for Brain Research, its successor. Michael Banks, "Schrödinger Lecture Theatre at Trinity College Dublin Renamed after Sexual-Abuse Reports," *Physics World*, 20 April 2022.

Further Reading

Erwin Schrödinger, *What Is Life? The Physical Aspect of the Living Cell* (Cambridge University Press, 1944; reprinted with *Mind and Matter* and autobiographical sketches, 1992). Short, clear and still worth reading in full; the chapters on Delbrück's model and on order and entropy are the core.

Phillip R. Sloan and Brandon Fogel, eds., *Creating a Physical Biology: The Three-Man Paper and Early Molecular Biology* (University of Chicago Press, 2011). The first English translation of the 1935 paper, with essays on its context and influence. The place to go for the details of target theory and Delbrück's model.

John Cairns, Gunther S. Stent, and James D. Watson, eds., *Phage and the Origins of Molecular Biology* (Cold Spring Harbor Laboratory, 1966; centennial edition, 2007). Recollections by members of the Phage Group, written for Delbrück's sixtieth birthday, including Luria's account of the slot machine. Affectionate and partisan, and an indispensable primary source.

Ernst Peter Fischer and Carol Lipson, *Thinking about Science: Max Delbrück and the Origins of Molecular Biology* (W. W. Norton, 1988). The standard biography, good on the Berlin years and on Delbrück's continuing interest in Bohr's ideas.

Horace Freeland Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology* (Simon & Schuster, 1979; expanded ed., Cold Spring Harbor Laboratory Press, 1996). The classic narrative history of molecular biology, based on interviews with most of its founders.

Lily E. Kay, *The Molecular Vision of Life: Caltech, the Rockefeller Foundation, and the Rise of the New Biology* (Oxford University Press, 1993). A critical history of Weaver's programme and its aims, which complicates the heroic version of the story.

Michel Morange, *A History of Molecular Biology*, trans. Matthew Cobb (Harvard University Press, 1998). A concise scholarly overview from the 1930s to the 1990s, careful on the roles of physicists and chemists.

Daniel J. McKaughan, "The Influence of Niels Bohr on Max Delbrück: Revisiting the Hopes Inspired by 'Light and Life'," *Isis* 96 (2005). The best short account of what Bohr actually argued and what Delbrück took from it.

Salvador E. Luria, *A Slot Machine, a Broken Test Tube: An Autobiography* (Harper and Row, 1984). Luria's own story, from Turin and Paris to Bloomington and beyond.

Part II

The Crucible of Crisis and the Post-War Boom (1939–1953)

Chapter 4

The Mansion of Misfits at Bletchley Park (1939–1945)

A Forest South of Warsaw

On 25 July 1939, a small party of British and French visitors was driven out of Warsaw to a patch of forest near the village of Pyry, a few miles to the south. Hidden among the trees, behind barbed wire, stood the concrete buildings and radio masts of the Polish General Staff's Cipher Bureau, the *Biuro Szyfrów*. The French delegation was led by Major Gustave Bertrand, head of the French intelligence service's cipher section, with Captain Henri Braquenié. The British sent three men: Commander Alastair Denniston, head of the Government Code and Cypher School; Dillwyn Knox, its senior cryptanalyst, a classical scholar who had spent years on the German Enigma cipher machine without breaking its military version; and a third man, long misidentified in print as the intelligence chief Stewart Menzies, who was in fact Commander Humphrey Sandwith of the Admiralty's interception and direction-finding service.[1]

Their hosts were the bureau's chief, Lieutenant Colonel Gwido Langer, Major Maksymilian Ciężki, head of its German section, and three young mathematicians: Marian Rejewski, Henryk Zygalski and Jerzy Różycki. What the Poles revealed surprised their guests. Since the winter of 1932–33, they had been reading German military Enigma traffic. They had worked out the wiring of the machine's rotors by mathematics, without ever seeing one, built working copies, and designed electromechanical devices, which they called *bomby*, to search for daily keys.

Knox had gone further on his own than anyone in Britain, but he had been stuck on one detail. Rejewski later recalled that Knox's first question was how the keys of the keyboard were connected to the machine's entry plate. The answer was disarmingly simple. In the commercial Enigma that Knox had studied, the connections followed the order of the German keyboard, QWERTZU. In the military machine, they followed the alphabet: A to the first contact, B to the second, and so on. Knox had apparently never tested so obvious a possibility.[2] Accounts of his mood during the visit differ; afterwards he sent the Poles a note of thanks. Each delegation was promised a Polish-built replica of the military Enigma. On 16 August Bertrand carried Britain's

to London and handed it to Stewart Menzies, then deputy head of the Secret Intelligence Service, at Victoria Station.

Five weeks after the meeting, Germany invaded Poland. In Britain the work the Poles had begun was taken up at a Victorian country house in Buckinghamshire, and grew there into one of the strangest intellectual enterprises of the war. It is often told as the story of one man. It was the work of thousands, under conditions that were very unusual.

Room 40 and the Professor Type

Britain's codebreakers had a tradition to draw on. In October 1914, a few weeks into the First World War, the Admiralty set up a small section to read intercepted German naval signals. Its head was Sir Alfred Ewing, the Admiralty's Director of Naval Education, an engineer and physicist best known for discovering magnetic hysteresis. In November the section moved into Room 40 of the Admiralty Old Building in Whitehall, and the room gave it its name. Ewing recruited people he could trust who knew German: schoolmasters from the naval colleges (Denniston, who had taught German at Osborne, was one), and men from the universities and publishing, among them the classicist Frank Adcock, the historian Frank Birch, the publisher Nigel de Grey, a translator of German theology named William Montgomery, and Dilly Knox. Room 40 is often described as a nest of classicists. It was more varied than that, and it was run by an engineer.

Its best-known success, in January 1917, was the Zimmermann telegram, Germany's proposal of an alliance with Mexico against the United States, whose release helped bring the United States into the war. In 1919 Room 40 and the War Office's codebreaking section, MI1b, were merged into a single peacetime body, the Government Code and Cypher School (GC&CS), which formally came into being on 1 November 1919 with Denniston as its operational head.[3]

Between the wars GC&CS was small, and worked mainly on other governments' diplomatic codes, still largely enciphered by hand. Its methods were those of the linguist and the puzzle-solver, and Knox was their best exponent. Born in 1884, educated at Eton and King's College, Cambridge, he had worked on the fragmentary papyrus texts of the Greek poet Herodas, whose edition he completed with Walter Headlam's notes in 1922. Restoring a damaged text and breaking a cipher both require building and testing hypotheses about missing material from a few fixed points. Knox is said to have bought a commercial Enigma in Vienna in 1925, and in April 1937 broke the version used by Franco's forces in the Spanish Civil War, using a method of paper strips he called "rodding." That version had no plugboard. The German military machine did, and it defeated him.

By 1938 Denniston could see that a war with Germany would bring a flood of machine-enciphered traffic that his staff could not handle. He wrote to the Foreign Office in November 1938 about recruiting suitable staff, and he sought what he called "men of the professor type." Through his contacts at the universities he drew up lists of people who agreed to join GC&CS if war came, rather than the armed forces. Peter Twinn, an Oxford mathematics graduate, joined early in 1939, the first mathematician GC&CS recruited, and was set to work on Enigma under

Knox. Alan Turing, a twenty-six-year-old fellow of King's College, Cambridge, began part-time work in 1938. Gordon Welchman, a Cambridge algebraic geometer, was recruited to one of the short training courses that Denniston organised.[4]

They needed somewhere to go. In 1938 Admiral Sir Hugh Sinclair, head of the Secret Intelligence Service and of GC&CS, bought Bletchley Park, an architecturally confused Victorian mansion with some fifty-eight acres, beside the junction of the main line from London to the north and the line between Oxford and Cambridge. In September 1938, at the height of the Munich crisis, a group from GC&CS and SIS arrived there for a trial run under the cover name "Captain Ridley's shooting party." On 15 August 1939 they came back for good.

The Science: How Enigma Worked

Enigma was a commercial invention before it was a military one. The German engineer Arthur Scherbius applied for a patent on a rotor cipher machine in February 1918; the German navy adopted a version in 1926 and the army in 1928. It looked like a portable typewriter in a wooden box, except that instead of printing it lit up letters. Pressing a key sent current through a chain of wiring and lit a lamp under one of twenty-six letters on a panel, which an operator wrote down. The receiver, with an identical machine set up the same way, typed the ciphertext and the lamps showed the plaintext.

The core of the machine was a set of three *rotors*, wheels each with twenty-six electrical contacts on each face, cross-wired inside so that each contact on one side was connected to a different contact on the other. A rotor by itself is a simple substitution: it turns A into, say, E. Beyond the third rotor sat a fixed *reflector*, which connected the twenty-six contacts in pairs and sent the current back through the three rotors by a different route. So each keystroke passed through seven substitutions: three rotors forwards, the reflector, and three rotors backwards.

What made the machine more than an elaborate substitution was that the rotors moved. Each time a key was pressed, the right-hand rotor turned one place before the current flowed, so the next letter was enciphered by a different wiring. Once in each revolution a notch on the right-hand rotor's ring made the middle rotor step; once in each of its revolutions the middle rotor made the left-hand rotor step, in the manner of a mileometer. The result was a *polyalphabetic* cipher: the same plaintext letter was enciphered differently almost every time it occurred, and a frequency count of the ciphertext showed nothing.

The reflector had two consequences that mattered enormously. The first was a convenience. The whole machine was symmetrical at any given position: if A enciphered to Q, then Q enciphered to A, so the same settings served to encipher and decipher. The second was a weakness. Because the current had to come back by a different path from the one it went in by, no letter could ever be enciphered as itself. It meant that if a codebreaker guessed that a certain word appeared somewhere in a message, any position where a letter of the guess lay over the same letter of the ciphertext could be ruled out at once.

The military machine added one more component, the *plugboard* (*Steckerbrett*), a panel at

the front with a socket for each letter. A cable plugged between two sockets swapped those two letters on the way into the rotors and again on the way out. With ten cables in place, as became usual during 1939, twenty of the twenty-six letters were swapped in pairs and six were left alone. The plugboard multiplied the number of settings enormously, and it disguised the rotor wiring that a codebreaker might otherwise deduce from traffic, which is why Knox's methods failed against the German machine.

To communicate, two operators had to set their machines identically. A printed key list, changed daily, specified the *wheel order* (which three rotors from a set, and in what order), the *ring settings* (the position of a lettered ring on each rotor relative to its wiring, which governed when the next rotor stepped), and the plugboard connections. Until September 1938 the key list also specified a *Grundstellung*, or ground setting: a starting position for the rotors. The operator set the rotors to the ground setting, chose his own three-letter *message key* (say, PDX), and typed it twice (PDXPDX), producing six enciphered letters that he sent at the start of the message as its *indicator*. He then turned his rotors to PDX and enciphered the message itself. The receiver reversed the process. The doubled key was a precaution against garbled transmission. It was also, as we will see, the Poles' way in.

Science Primer: How many ways to set an Enigma?

Count the settings of an army Enigma of 1939, with three rotors chosen from five and ten plugboard cables.

Wheel order. Any of the five rotors can go in the left-hand position, any of the remaining four in the middle and any of the remaining three on the right: $5 \times 4 \times 3 = 60$ orders.

Rotor positions. Each rotor can start at any of 26 positions: $26 \times 26 \times 26 = 17{,}576$.

Plugboard. The number of ways to choose 10 disjoint pairs from 26 letters is

$$\frac{26!}{6!\,10!\,2^{10}} = 150{,}738{,}274{,}937{,}250.$$

Here 26! ("26 factorial," $26 \times 25 \times \cdots \times 1$) counts every way of lining up the alphabet; read the first twenty letters off in pairs and leave the last six unplugged. We then divide by 6! because the order of the six unplugged letters does not matter, by 10! because the order of the ten pairs does not matter, and by 2^{10} because each pair can be written either way round.

Multiplying the three numbers gives

$$60 \times 17{,}576 \times 150{,}738{,}274{,}937{,}250 = 158{,}962{,}555{,}217{,}826{,}360{,}000,$$

or about 1.6×10^{20}. (The figure of 1.5×10^{20} that sometimes appears truncates this.) The navy's machines, which drew three rotors from eight, had $8 \times 7 \times 6 = 336$ wheel orders, and so about 8.9×10^{20} settings. The ring settings add a further factor, but much of their effect duplicates that of the starting positions, and most authors leave them out.

Two cautions. This is not a count of daily keys, since the starting positions changed with every message. And the size of the key space says little about the cipher's security. A machine trying a million settings a second would need some five million years to try them all, and nobody broke Enigma that way. The codebreakers broke it by finding properties of the machine and of its users that let them solve for the parts of the key separately: the plugboard's effect on one question, the rotors' on another.

The Science: The Mathematicians of Poznań

In 1929 the Polish Cipher Bureau arranged a secret course in cryptology for mathematics students at the University of Poznań, in the formerly German west of the country, where many students were fluent in German. Three of the students were later taken on by the bureau. Marian Rejewski, born in 1905 in Bydgoszcz, had studied mathematics at Poznań and spent a year at Göttingen studying actuarial statistics. Henryk Zygalski and Jerzy Różycki were his friends from the university. Rejewski joined the bureau's German section on 1 September 1932, and in the autumn he was given the problem of the military Enigma.

His method was to treat the machine as an algebraic object. Mathematicians call a rearrangement of the alphabet a *permutation*, and the theory of permutations, part of group theory, was standard university mathematics. Every Enigma setting is a permutation. Rejewski's insight was that the doubled message key exposed a structure in these permutations that the plugboard could not hide.

Consider the first and fourth letters of an indicator. Both are encipherments of the same letter of the message key, made at two machine positions three steps apart. Call the permutation the machine performs at the first position E_1 and at the fourth position E_4. If the operator's key began with the letter x, the first indicator letter is $E_1(x)$ and the fourth is $E_4(x)$. Because the machine is symmetrical, E_1 undoes itself, so whatever the first letter is, applying E_1 to it gives back x, and applying E_4 then gives the fourth letter. In other words, the combined permutation E_4E_1 (first E_1, then E_4) maps each indicator's first letter to its fourth letter. With enough indicators from one day (a busy network produced dozens), the codebreaker could write out this permutation completely without knowing any message key. The same went for letters two and five, and three and six.

Rejewski then looked at the *cycle structure* of these permutations. Follow a letter through E_4E_1, then follow where that goes, and so on: eventually the chain returns to its start, forming a cycle. The alphabet breaks up into cycles of various lengths, such as two cycles of 13 letters, or cycles of lengths 10, 10, 3 and 3. Two facts made this pattern a fingerprint. Because of the reflector, each E_i swaps letters in thirteen pairs with no letter left in place, and the product of two such permutations always has its cycles in matched pairs of equal length. More importantly, the plugboard does not change the cycle lengths at all. In algebraic terms the plugboard S enters as $E_i = SR_iS$, where R_i is the permutation of the rotors and reflector alone, so that $E_4E_1 = S(R_4R_1)S$. Rearranging a permutation's letters in this way (mathematicians call it *conjugation*)

relabels the letters in the cycles but leaves their lengths untouched. The cycle lengths depended only on the wheel order and the rotor positions, the part of the key the Poles could hope to catalogue, and not on the plugboard, which they could not.[5]

The cycles became the basis of the bureau's daily method. Its first breakthrough, though, was the rotor wiring itself, which Rejewski solved at the end of 1932 by setting up and solving equations in permutations. He had help. A German employee of the cipher office in Berlin, Hans-Thilo Schmidt, had been selling documents to French intelligence since 1931, and in December 1932 Bertrand's material gave Rejewski operating instructions and the daily keys for two months of that year. With the plugboard known for those days, his equations became tractable, though he still got inconsistent results until he guessed that the entry connections ran in alphabetical order, the guess Knox would fail to make. By the end of December the bureau was reading Enigma messages.

Rejewski designed a device, the *cyclometer*, to compute the cycle structure for every rotor position, and the team built a catalogue of the results for the six wheel orders then in use: $6 \times 17{,}576 = 105{,}456$ entries. In September 1938 the Germans let operators choose their own ground setting for each message, and the catalogue became useless. Zygalski responded with sets of large perforated sheets, punched at the positions that produced a particular pattern in the indicators; stacked on a light table, they let light through only at the correct setting. Rejewski designed the *bomba*, which drove sets of Enigma rotors through all 17,576 positions automatically, stopping when a pattern in the indicators appeared. Six were built, one for each wheel order.

Then, on 15 December 1938, the Germans issued two more rotors, so that operators chose three from five: sixty wheel orders instead of six. The Poles deduced the new wirings, but they would have needed ten times as many bomby and sheets, and the number of plugboard cables was also rising. It was in this situation that they decided to share everything with their prospective allies.

The Science: A Paper about Imaginary Machines

One more piece of mathematics belongs in this story, though not for the reason usually given. In 1935 Turing, newly elected a fellow of King's, attended lectures by the Cambridge topologist Max Newman on the foundations of mathematics, which described a problem posed by David Hilbert: whether there was a mechanical procedure that could decide, in a finite number of steps, whether any given statement of mathematical logic was provable. This was the *Entscheidungsproblem*, the "decision problem."

To answer it, Turing first had to say exactly what a mechanical procedure was. In "On Computable Numbers, with an Application to the Entscheidungsproblem," submitted to the London Mathematical Society on 28 May 1936, he imagined a machine that does what a clerk does when calculating with pencil and paper, stripped to essentials. It reads and writes symbols on a tape, one square at a time, moving left or right; at each moment it is in one of a finite number of

internal states, and a table of instructions says, for each state and symbol, what to write, which way to move and what state to enter next. Turing showed that a single *universal* machine could imitate any other, given its description on the tape, and that no machine could decide in general whether another would ever print a given symbol; it followed that the answer to Hilbert's question was no. Alonzo Church at Princeton had reached the same conclusion by a different route shortly before, and Turing went to Princeton to work with him, taking his doctorate there in 1938.[6]

The universal machine is now recognised as the abstract model of the stored-program computer. But it played no direct part in breaking Enigma; the machines Turing designed at Bletchley were special-purpose devices. What the paper shows is a habit of mind: Turing thought naturally about what a mechanism could and could not do, and was willing to treat logical inference as something a machine might carry out. That habit mattered more at Bletchley than the paper did.

Cribs, Loops and the Bombe

Turing reported to Bletchley Park on 4 September 1939, the day after Britain declared war. Within weeks he and the other mathematicians had concluded that copying the Polish bomba would not do. It depended on the doubled indicator, which the Germans might abandon at any moment (the army and air force dropped it on 1 May 1940), and on letters left unplugged, which were becoming scarce. Turing looked for a method that relied only on a guess at part of a message's plaintext. Bletchley called such a guess a *crib*.

Cribs came from the habits of German operators: predictable formalities, routine reports sent in the same words every day, and stock phrases such as *WETTERVORHERSAGE* (weather forecast). A cribster still had to guess where in the message the phrase lay. Here the reflector's weakness helped: since no letter could encipher to itself, the guessed phrase could be slid along the ciphertext and every position where any letter coincided with the letter beneath it discarded. With a long crib, most positions crashed and only a few remained.

Once a crib was placed, each pair of plaintext and ciphertext letters gave a link: at position 1, say, E enciphered to Q; at position 7, Q to R; at position 12, R to E. Drawn as a diagram, the links formed a network, which Bletchley called a *menu*, and the most useful menus contained closed loops, like E to Q to R to E. Each link passed through the plugboard on the way in and on the way out, and through the rotors at a particular position. If one knew the plugboard partner of E, one could follow its consequences around the loop and see whether one came back to where one started. If not, either the rotor position or the guess about E's partner was wrong. The beauty of a loop is that the unknown partners of Q and R cancel out of the consistency test; only E's partner and the rotor position matter.

Turing's machine, which took over the Polish name as the *bombe*, mechanised this test. It contained banks of rotating drums, each of which reproduced the wiring of an Enigma rotor; three drums in a column made one Enigma scrambler, and a standard bombe had thirty-six of

them. They were not thirty-six machines searching independently: they were wired together according to the menu, one scrambler for each link, offset by the position of its letter in the crib, so that the whole machine was a single electrical model of the crib's logical consequences at one trial rotor position. A voltage applied to one of twenty-six wires representing a hypothesis about E's plugboard partner flowed through the network, and every conclusion it implied lit up further wires. Turing's crucial idea was to feed every conclusion back in as a new hypothesis at once. A false hypothesis implies other false conclusions, which imply more, and at a wrong rotor position the current typically spread to all twenty-six wires: every possible partner for E led to a contradiction. At the right position, it did not. If the hypothesis was true, only one wire was live; if it was false, all but one were live, and the dead wire marked the correct partner. Either way, fewer than twenty-six live wires meant the machine had found a candidate, and a relay stopped the drums. The operators noted the position and the implied plugboard pair, and restarted; many stops were false, and each was tested on a modified British cipher machine to see whether it produced German. The bombe, then, did not test possibilities one after another in search of one free of contradiction. It tested all twenty-six hypotheses about one letter at once, at each rotor position, by letting contradictions propagate as electric current, and ran through the 17,576 positions of one wheel order in about twenty minutes.

Gordon Welchman made the decisive improvement. Born in Bristol in 1906 and a fellow of Sidney Sussex College, Cambridge, he had been set by Knox to study the external features of German traffic, and soon organised the section that broke army and air force Enigma, housed in a wooden building called Hut 6. Looking at Turing's design, Welchman noticed that it ignored a symmetry of the plugboard: if E is plugged to K, then K is plugged to E. He devised a grid of fixed connections, the *diagonal board*, that wired every such implication into the machine. A false hypothesis now generated contradictions far faster, so that menus with few loops, or none, became usable, and false stops fell sharply. Turing saw its value at once.[7]

The bombe had to be built, and here a third kind of expertise entered. The British Tabulating Machine Company of Letchworth made punched-card machinery under licence from IBM, and its chief engineer, Harold Keen, known as "Doc" from the bag of tools he carried, turned Turing's logical design into a cabinet of drums, brushes and relays about seven feet wide. The first bombe, named Victory, went into operation at Bletchley in mid-March 1940. The second, Agnus Dei, the first with Welchman's diagonal board, arrived on 8 August 1940. Victory was sent back to Letchworth to be fitted with one. By the end of the war the bombe section had 211 machines.

Before the bombes arrived, Hut 6 depended on the Polish methods. Bletchley made its own copies of Zygalski's sheets and sent a set to the Polish team, then working for the French near Paris, whom Turing visited in January 1940; the first wartime breaks of army and air force Enigma followed. The army and air force stopped doubling their message keys on 1 May 1940, which made the sheets useless. On 22 May, less than two weeks after the German offensive in the west began, David Rees of Hut 6 broke back into the main air force key, which Bletchley called Red, by exploiting a prediction about lazy operators made by one of Welchman's former students, John Herivel. Throughout the war much of Hut 6's daily work consisted of finding cribs and exploiting operators' bad habits, rather than of mathematics.

Knox, meanwhile, went his own way. With a small team of young women, among them Mavis Lever, a student of German from University College London, and Margaret Rock, he broke the Italian navy's Enigma, which had no plugboard, and the section's decrypts contributed to the British victory at Cape Matapan in March 1941. In the autumn of 1941 he broke the Enigma used by the Abwehr, German military intelligence, a different model with rewired rotors; the first decrypts were issued in December. He was already ill with cancer, and died on 27 February 1943.[8]

Hut 8 and the Naval Enigma

The navy's Enigma was the hardest. It drew its rotors from a set of eight, and from 1937 the navy used a more secure way of sending message keys. Its indicating procedure combined groups of letters taken from a printed book with a ground setting that was the same for every message on a given day, and disguised the result by a further encipherment using printed tables of letter pairs, called bigram tables. Turing took it on, by his own account, because nobody else was working on it and he could have it to himself. His section became Hut 8.

Turing's first great contribution to naval Enigma was statistical. Because all the day's indicators were enciphered from the same ground setting, two messages of the same day could be slid against each other until they were *in depth*: letter by letter, both enciphered by the same permutation. In that case, wherever the two plaintexts happened to have the same letter, the two ciphertexts would too, and since German text repeats letters more often than random text does, messages in depth would show more coincidences than messages slid by a wrong amount. Turing's procedure was to punch messages onto long strips of card, lay pairs over each other on a light table, and count the coincidences at each offset. The strips were printed in the town of Banbury, and the procedure became known as *Banburismus*. Its aim was to find which rotors were in the right-hand and middle positions, which, combined with the rules the Germans followed in choosing wheel orders, could cut the number the bombes had to test from 336 to between ten and twenty.

To decide which offsets were real, Turing needed to weigh many small pieces of evidence. He measured evidence by the logarithm of the factor by which it changed the odds, and called the unit a *ban*, after Banbury, with a tenth of it a *deciban*. The principle is Bayes's theorem; its routine use in this additive form was new.

Science Primer: Banburismus and the deciban

Bayes's theorem, in its simplest form, says that when evidence arrives, the odds in favour of a hypothesis are multiplied by a *Bayes factor*: the probability of that evidence if the hypothesis is true, divided by its probability if the hypothesis is false.

$$\text{odds after} = \text{odds before} \times \frac{P(\text{evidence} \mid \text{true})}{P(\text{evidence} \mid \text{false})}.$$

Taking logarithms turns multiplication into addition. Turing defined the *weight of evidence* as the logarithm to base 10 of the Bayes factor, measured in bans; in decibans it is

$$w = 10 \log_{10} \frac{P(\text{evidence} \mid \text{true})}{P(\text{evidence} \mid \text{false})}.$$

A factor of 10 is 10 decibans, a factor of 2 about 3 decibans. Independent pieces of evidence simply add their decibans.

Now apply this to two naval messages overlapped at a trial offset. Bletchley used the figures that, for messages truly in depth, two letters in the same column coincided about once in 17 places, because of the uneven letter frequencies of German naval text; for messages not in depth, about once in 26, as for random letters. A single coincidence is therefore worth

$$10 \log_{10} \frac{1/17}{1/26} \approx +1.8 \text{ decibans},$$

and each column *without* a coincidence is worth

$$10 \log_{10} \frac{16/17}{25/26} \approx -0.09 \text{ decibans}.$$

Suppose two messages overlap for 60 letters and show 7 coincidences. (By chance we would expect about 2.3; in depth, about 3.5.) The total weight is $7 \times 1.85 - 53 \times 0.093 \approx +8$ decibans, a Bayes factor of about 6. If, before counting, this offset had been one of many equally likely candidates, with odds of 1 to 20, it now stands at roughly 1 to 3: worth pursuing, but not proven. The real Banburists used refined tables that gave extra weight to repeated pairs and triples of letters, and combined scores across many pairs of messages before committing bombe time. (This worked example is my illustration, using Bletchley's two repeat rates.)

Turing's assistant I. J. Good later observed that a deciban, or half of one, was about the smallest change in the weight of evidence that a person could sense intuitively. The units were designed for people who had to make many quick judgements, by hand, all night.

The ban is sometimes said to have anticipated Claude Shannon's *bit* (Chapter 6). The resemblance should not be overstated. A ban measures the weight of evidence for a hypothesis, not the information in a message, and a base-10 logarithmic measure of information had been published by the Bell Labs engineer Ralph Hartley in 1928. Turing and Shannon did meet, over tea at Bell Laboratories during Turing's visit to the United States in early 1943, but they are not known to have discussed their secret work. Nor did Turing create sequential analysis, the method of deciding, observation by observation, whether enough evidence has accumulated. Abraham Wald and his colleagues at Columbia University's Statistical Research Group developed it during the war, publishing in 1945, and George Barnard's group in Britain did similar work. Good described Turing as one of its independent inventors, which is accurate and credit enough.[9]

Banburismus could not even begin until Hut 8 knew the bigram tables, and that is where

the *pinches* came in: captures of German cipher material at sea. A German patrol boat taken on its way to Narvik on 26 April 1940 gave six days of traffic and confirmed Turing's deductions about the indicator system. The decisive captures came in 1941. A commando raid on the Lofoten Islands on 4 March took the armed trawler *Krebs*, with the keys for February, from which Hut 8 rebuilt the bigram tables. Harry Hinsley, a Cambridge history undergraduate who had become Bletchley's expert on German naval traffic, reasoned that German weather ships stationed for weeks in the North Atlantic must carry future keys, probably locked in a safe that a crew abandoning ship might forget. The *München* was seized on 7 May with the keys for June, and the *Lauenburg* on 28 June with those for July. On 9 May, escorts of convoy OB 318 forced *U-110* to the surface, and a boarding party under Sub-Lieutenant David Balme took an intact machine, key tables and the bigram book. From June 1941 the home waters key, which Bletchley called Dolphin, was read almost continuously, usually with little delay, for the rest of the war.

The captures did not break naval Enigma; they supplied the starting material that the statistical and mechanical methods needed. The people who turned material into daily breaks included Joan Clarke, a Cambridge mathematician recruited by Welchman, the only woman among the Banburists and one of the best of them; and Jack Good, a twenty-four-year-old Cambridge mathematician, born Isidore Jacob Gudak, who had just finished a doctorate under A. S. Besicovitch and G. H. Hardy and joined Turing in May 1941. In March 1941 Hugh Alexander moved to Hut 8 from Hut 6. Born in Cork in 1909, he had read mathematics at King's College, Cambridge, taught at Winchester and become head of research at the John Lewis Partnership. He was also one of the strongest chess players in Britain, British champion in 1938 and again in 1956, and an International Master from 1950; he was never a grandmaster. He was, by general agreement, a far better administrator than Turing, and in November 1942, when Turing left for the United States, he formally took over the hut.

In October 1941 the strain of too much work and too few clerks came to a head. Turing, Welchman, Alexander and Stuart Milner-Barry wrote directly to Winston Churchill, over the heads of Denniston and his superiors, asking for clerks for Hut 8, typists for Hut 6 and Wrens for the bombes. Milner-Barry, a chess player of international standard who had been a stockbroker and then chess correspondent of *The Times*, carried the letter to Downing Street himself. It was dated 21 October. The next day Churchill sent a minute to his chief of staff, marked "Action this day," ordering that they be given "all they want on extreme priority."[10] Milner-Barry, it should be said, was a Hut 6 man, not a Hut 8 one; he led its crib room from 1940 and became head of Hut 6 in the autumn of 1943, when Welchman moved on to direct mechanisation for the whole of Bletchley.

Then, on 1 February 1942, the Atlantic U-boats switched to a machine with a fourth rotor, on a key Bletchley called Shark. With twenty-six times as many rotor positions, it was beyond the three-rotor bombes, and for more than ten months, through the period when the U-boats did their greatest damage, Hut 8 could not read it. The breach came from the eastern Mediterranean. On 30 October 1942 the destroyer HMS *Petard* forced *U-559* to the surface. Lieutenant Anthony Fasson and Able Seaman Colin Grazier boarded the sinking boat and passed documents out to a young canteen assistant, Tommy Brown, before it went down with them inside; both were awarded the George Cross posthumously. The papers included the current short

weather code book, which U-boats used to compress weather reports before enciphering them, and they reached Bletchley on 24 November. Because the four-rotor machine, at one setting of its extra rotor, behaved like a three-rotor one, the weather reports gave cribs the existing bombes could handle. On 13 December 1942 Bletchley sent the Admiralty the positions of more than a dozen U-boats from Shark decrypts. The Germans changed the weather book in March 1943, causing a short break; Hut 8 got back in within nine days. British four-rotor bombes came into service in June 1943 and American ones in August, and from September Shark was generally read within a day.[11]

Tunny

Enigma was a field cipher, operated by hand, one lamp at a time. For its highest-level communications the German army used something else: a cipher attachment for the teleprinter, built by the Lorenz company and known as the SZ40 and SZ42, which enciphered messages automatically as they were typed and sent them by radio. An experimental link began operating in June 1941. Bletchley called the family of German teleprinter ciphers Fish, and this one, the first to be studied, Tunny. By 1944 Tunny links connected the German army high command near Berlin with the commands of army groups across Europe. Some messages went out over Hitler's signature, but Tunny was not, as is sometimes implied, a private line between Hitler and his field marshals; it carried the operational and strategic traffic of the high command and its army groups.

A teleprinter represents each character as five binary pulses (Bletchley wrote dots and crosses; we will write 0 and 1). The Lorenz machine generated a stream of five-bit key characters and added them to the plaintext, pulse by pulse, in the arithmetic in which $1 + 1 = 0$. Adding the same key again removes it, so an identical machine at the receiving end recovered the plaintext. The weakness of any such cipher is the *depth*: if two messages are sent with the same key, adding the two ciphertexts cancels the key and leaves the sum of the two plaintexts, which a skilled cryptanalyst can sometimes tease apart.

On 30 August 1941 an operator on the link between Vienna and Athens sent a very long message twice, by most accounts because the receiving station had asked for a repeat. He used the same machine setting, as shown by the same twelve-letter indicator, but did not type quite the same text: one version was 3,976 characters long, the other about 500 longer. The two messages were in depth. John Tiltman, an army officer who had become one of Bletchley's best cryptanalysts of hand ciphers, worked on them for about ten days, guessing words in one text and seeing what they implied for the other, until he had recovered both plaintexts and, with them, 3,976 consecutive characters of the machine's key.[12]

Nobody at Bletchley had seen a Lorenz machine, and for months the key resisted analysis. Some three months later, by Tutte's recollection, with the key still unsolved, the head of the Research Section, Major G. W. Morgan, gave a copy to Bill Tutte. Born in Newmarket in 1917, the son of a gardener at a racing stable, Tutte had won a scholarship to Trinity College, Cambridge, taken a first in chemistry in 1938, begun research in physical chemistry and then

switched to mathematics. With three friends he had worked on the problem of dividing a square into smaller squares all of different sizes, solved by translating the geometry into the theory of electrical networks; the four also published jointly under the pseudonym Blanche Descartes. He was twenty-four.

Tutte did what the cryptography course had taught him. He wrote out the first pulse of each key character in rows of a fixed length, looking for vertical repeats that would reveal a period. A trial length of 575 showed nothing clear; he noticed repeats running diagonally instead, tried 574, saw more, and then reasoned that the true period might be a factor of 574, which is $2 \times 7 \times 41$. Written in rows of 41, the key showed a pattern full of repetitions. He inferred that the first pulse was generated partly by a wheel with 41 positions, and that another, irregularly moving component was superimposed on it. The whole Research Section joined in, and by January 1942 they had deduced the logical structure of the machine: twelve wheels, five of which (Bletchley called them chi wheels, with 41, 31, 29, 26 and 23 positions) moved one step with every character; five more (the psi wheels, with 43, 47, 51, 53 and 59) that moved together but only intermittently; and two motor wheels (61 and 37) that decided when the psi wheels moved. It was a reconstruction of a machine from a few thousand characters of its output, and it remains one of the great feats of cryptanalysis. It was also, as Tiltman's own account records, the work of Morgan's section as well as Tutte's.[13]

Knowing the structure was not the same as reading the traffic. For each message the codebreakers had to find the cam patterns on the wheels, which changed periodically, and the starting positions of all twelve wheels. In July 1942 a section under Ralph Tester, an accountant and German speaker who had worked for Unilever, was formed to do this by hand, using methods partly devised by Turing, who had briefly turned his attention to Tunny. The Testery depended on depths and on operators' mistakes, and as the Germans tightened their procedures these grew scarcer. In November 1942 Tutte found a statistical method that needed neither.

Science Primer: Tutte's statistical method

Write P for a plaintext character, χ for the contribution of the chi wheels and ψ' for that of the psi wheels (the prime marks that they did not always move). Each is five bits, and each pulse of the ciphertext Z is the sum

$$Z = P + \chi + \psi',$$

where $+$ means addition with $1 + 1 = 0$.

Tutte looked not at characters but at the *differences* between successive characters, written Δ: ΔZ is the sum of one character and the next. Differencing helps because the psi wheels often stood still between one character and the next, and when they did, $\Delta\psi' = 0$: they vanished from the difference. Adding the differences of the first two pulses gives

$$\Delta Z_1 + \Delta Z_2 = (\Delta P_1 + \Delta P_2) + (\Delta\chi_1 + \Delta\chi_2) + (\Delta\psi'_1 + \Delta\psi'_2).$$

The last bracket is 0 more often than not, because the psi wheels often stand still. The

first bracket is also 0 more often than not, because of regularities in German teleprinter text, such as doubled characters. When two biased quantities are added, the sum is still biased. So $\Delta Z_1 + \Delta Z_2$ agrees with $\Delta\chi_1 + \Delta\chi_2$ more often than half the time. Bletchley's measurements put the rate typically around 55 per cent, against 50 per cent for a wrong guess.

The test is therefore: for each possible pair of starting positions of the first two chi wheels ($41 \times 31 = 1{,}271$ pairs), generate $\Delta\chi_1 + \Delta\chi_2$, compare it with the ciphertext, and count the agreements. For a message of 4,000 characters, a wrong pair gives about 2,000 agreements, give or take about 32 (one standard deviation); the right pair gives about 2,200, some six standard deviations above. The right answer stands out. (These illustrative figures are my calculation.) Similar counts then set the other chi wheels, after which the psi and motor wheels could be found by hand. The method needed no depth and no crib. It did need very large amounts of counting, which is why it led to machines.

The Newmanry and Colossus

Max Newman, whose lectures had set Turing on the road to "On Computable Numbers," came to Bletchley in the late summer of 1942 and joined the Testery that autumn. He saw that Tutte's method could be mechanised, persuaded his superiors, and in December 1942 was given a small section of his own, the Newmanry, to do it. The first machine was built in a few months by engineers at the Post Office Research Station at Dollis Hill in north London, with high-speed electronic counters designed by C. E. Wynn-Williams of the Telecommunications Research Establishment, the radar laboratory at Malvern. It read two loops of punched tape, one carrying the ciphertext and one the wheel patterns, and counted the agreements. The first machines reached Bletchley in the spring of 1943 (the Newmanry's own history says April; some accounts say June). The Wrens who ran it named it after the cartoonist of preposterous contraptions, Heath Robinson. It worked, but the two tapes stretched, slipped out of synchronisation and broke at high speed.

Tommy Flowers had already helped Bletchley. Born in 1905 in Poplar, in London's East End, the son of a bricklayer, he had served an apprenticeship at the Royal Arsenal in Woolwich, taken an engineering degree at evening classes and joined the Post Office in 1926. Experiments with thermionic valves (vacuum tubes) in telephone switching had convinced him that the received wisdom, that valves were too unreliable to use in large numbers, was wrong: they failed mostly when switched on and off, and if left running they lasted a long time. In February 1941 his director, W. Gordon Radley, had sent him to Bletchley to help with an attachment for the bombes, and Turing recommended him to Newman. Flowers designed Heath Robinson's combining unit.

In February 1943 Flowers proposed something more radical: a machine that did away with the second tape altogether by generating the wheel patterns electronically, in rings of valves, so that only the ciphertext tape had to be read. It would need well over a thousand valves. By Flow-

ers's own account the proposal was received at Bletchley with considerable scepticism, chiefly about whether so many valves could work together reliably. Bletchley gave priority to more two-tape machines. Flowers and his Dollis Hill colleagues, with Radley's backing, went ahead anyway. Flowers later said that Bletchley was not interested until it saw the machine working. It is often added that Flowers paid for some of the components out of his own pocket. That claim rests on later recollection and is hard to check. What the record shows is that Colossus was built on the Post Office's initiative, with Post Office resources, ahead of any formal order.

A team of some fifty Dollis Hill engineers, among them Sidney Broadhurst, William Chandler and later Allen Coombs, built it in about eleven months, much of it from standard telephone components. The tape reader, designed by Arnold Lynch, used small vacuum photocells of a type originally developed for anti-aircraft proximity fuses, behind an optical system that projected the tape's holes onto them. The first machine was working at Dollis Hill by early December 1943, was taken apart and delivered to Bletchley on 18 January 1944, and attacked its first message on 5 February. Bletchley named it Colossus. It read the tape at 5,000 characters per second, generated the wheel patterns internally, applied a logical test that the operators set up on switches and plug panels, and counted the results. Flowers gave its valve count as about 1,500; other sources give 1,600. Early in 1944 he was asked for more machines, the first to be working by 1 June. The first Mark 2, with about 2,400 valves and five sets of circuits working in parallel on successive characters, so that it processed the equivalent of 25,000 characters a second, went into service on the morning of 1 June 1944, five days before the Normandy landings. By the end of the war in Europe ten Colossi were working at Bletchley and an eleventh was being assembled.[14]

Colossus was electronic, digital and programmable within its task, but it was not a stored-program computer and did not break Tunny by itself. It was used mainly to find wheel settings, and later also to help recover the cam patterns; the decryption itself was finished by hand, much of it in the Testery. At the end of the war the Newmanry had 26 cryptographers, 28 engineers and 273 Wrens. The cryptographers included Good, who had moved from Hut 8, and Donald Michie, a classics scholar who later became a pioneer of artificial intelligence.

The Factory

By January 1945 Bletchley Park and its outstations employed nearly nine thousand people. About three-quarters were women: on 31 December 1944, 6,760 of them, 4,086 in the women's services (the Women's Royal Naval Service, the Women's Auxiliary Air Force and the Auxiliary Territorial Service) and 2,674 civilians. The first eight Wrens arrived to work on the bombes on 24 March 1941. By the end of the war the bombe section had 1,676 Wrens on its strength and had trained nearly 3,000 over its life, most of them working eight-hour shifts around the clock in the huts at Bletchley and at outstations in Buckinghamshire and on the north-western edge of London, at Stanmore and Eastcote. The work was hot, noisy and monotonous. Colossus, too, was run by Wrens; by May 1945 the Newmanry alone had 273 of them. They did more than press buttons: they loaded the tapes, set up the wheel patterns and logical tests on the

switches, and ran the sequences of tests the cryptographers specified.

A few women did cryptanalytic work of the first rank, among them Clarke, Lever and Rock. The institution did not make it easy. Clarke was paid less than men doing the same work, and her promotion was arranged by classifying her as a linguist. She later recalled, with some amusement, a form on which her grade was linguist and her languages none.[15]

What did the place look like as an intellectual system? Not a single trading zone where every discipline met every other, but a chain of them, each with its own pidgin. Linguists and intelligence officers in Hut 3 and the naval section translated decrypts and judged what the Germans were likely to say, which fed cribs back to the huts. Mathematicians turned cribs into menus. Engineers at Letchworth and Dollis Hill turned logical designs into machines. Wrens ran the machines to procedures written for them.

Table 4.1: Some of the people of Bletchley Park and what they brought to it

Person or group	**Training before the war**	**Principal contribution**
Marian Rejewski, Henryk Zygalski, Jerzy Różycki	Mathematics (Poznań)	Reconstruction of Enigma's wiring; the cyclometer, bomba and perforated sheets (before Bletchley).
Dilly Knox	Classics and papyrology	Rodding; Spanish, Italian and Abwehr Enigma.
Alan Turing	Mathematical logic	Design of the bombe; Banburismus; early work on Tunny.
Gordon Welchman	Algebraic geometry	Organisation of Hut 6; the diagonal board.
Hugh Alexander	Mathematics; business research; chess	Banburismus; leadership of Hut 8 from 1942.
Stuart Milner-Barry	Classics and moral sciences; stockbroking; chess	Hut 6 crib room; head of Hut 6 from 1943.
Harold Keen and BTM	Punched-card engineering	Engineering and production of the bombes.
John Tiltman	Army officer; hand ciphers	Solution of the Tunny depth of August 1941.
Bill Tutte	Chemistry, then mathematics	Structure of the Lorenz machine; the statistical method.
Tommy Flowers and Dollis Hill	Telephone engineering	Design and construction of Colossus.
Wrens and other service women	Varied; Colossus operators were often chosen for mathematical aptitude	Operation of the bombes and Colossi.

The table's second column is a reminder that the codebreakers' disciplines were not always the ones they used. Alexander and Milner-Barry are often called Bletchley's "chess players," as if chess technique had transferred to cryptanalysis. There is no evidence that it did. What they brought was a facility for concentrated, rule-bound problem-solving that a mathematician or a classicist might equally have had.

The growth of the enterprise strained its management, and the letter to Churchill had bypassed Denniston. In February 1942, amid criticism of its administration, the organisation was divided. Commander Edward Travis, Denniston's deputy, took charge of the military work at Bletchley, and Denniston moved to offices in Berkeley Street in London to run the diplomatic and commercial sections, where he continued to direct successful work against those targets. It was, in effect, a demotion. He retired in 1945 on a smaller pension than he expected and taught French and Latin at a preparatory school. GCHQ's own historians have since judged that he was treated badly.[16]

Outcomes and Legacy

What Ultra did. Intelligence from high-grade decrypts was distributed under the codeword Ultra, and its effects are easier to describe in particular cases than in general. In the Atlantic, the reading of Dolphin from June 1941 let the Admiralty route convoys around known U-boat positions; Hinsley later put average monthly sinkings at about 280,000 tons before June 1941 and about 120,000 in the second half of the year, and attributed much of the fall to Ultra. The Shark blackout of 1942 coincided with the U-boats' most destructive year, though other causes, including the American unpreparedness after Pearl Harbor and the German navy's own codebreakers, who were reading the British convoy cipher for much of 1942 and early 1943, mattered as well. After Shark was broken, Ultra helped route convoys and direct hunting groups, but the defeat of the U-boats in May 1943, when more than forty were lost and Admiral Dönitz withdrew them from the North Atlantic, owed as much to long-range aircraft, escort carriers, radar and better-trained escort groups. Ralph Erskine, the leading historian of naval Enigma, has concluded that the U-boats would have been defeated without Ultra, but at a higher cost.

Before the Normandy landings, decrypts gave the German order of battle in the invasion area and, through Tunny, access to the communications between the German commander in the west, Field Marshal Gerd von Rundstedt, and Berlin. Abwehr decrypts let the Allies check that German intelligence believed the deception plan, which presented the landings as a feint before a larger invasion at the Pas de Calais by a fictitious army group. In later life Flowers recounted that a Colossus decrypt of an order from Hitler had been handed to Eisenhower on 5 June, prompting the decision to go. The story is attractive and uncorroborated. Eisenhower's decision to launch the invasion on 6 June was made in the early hours of 5 June on the strength of a weather forecast that predicted a brief break in the storms.[17]

Computing. After the war Newman became professor of mathematics at Manchester, obtained a grant of £35,000 from the Royal Society for a computing laboratory, and was joined there by the engineer F. C. Williams, appointed to the Manchester chair of electrical engineering, who brought Tom Kilburn with him from the Telecommunications Research Establishment. Their small experimental machine, the Baby, ran the first stored program on 21 June 1948. Newman did not design the machine, and how much Bletchley shaped Manchester is still argued over. Turing's design for an Automatic Computing Engine, presented to the National Physical Laboratory in February 1946, was one of the first complete designs for a stored-program com-

puter; frustrated by delays, he left for Manchester in 1948. His later work on morphogenesis appeared in Chapter 2, and the postwar meeting of computing, information theory and neurophysiology is the subject of Chapter 6. Flowers spent the rest of his career at the Post Office, where he worked on the random-number generator ERNIE for the Premium Bonds and on the experimental electronic telephone exchange at Highgate Wood, opened in 1962. He could not cite Colossus as evidence of what valves could do.

GCHQ and secrecy. GC&CS became the Government Communications Headquarters in 1946 and moved to Cheltenham in the early 1950s. Eight of the ten Colossi were dismantled after the war; two went to GCHQ and were dismantled around 1960, when the drawings were burned. Most of Bletchley's staff kept silent for thirty years and more. The first public accounts came from Bertrand's *Enigma*, published in Paris in 1973, and Frederick Winterbotham's *The Ultra Secret* in 1974, written from memory without access to documents and wrong in places. The official history of British intelligence in the war, of which Hinsley was principal author, appeared between 1979 and 1990. Photographs of Colossus were released in 1975, after the computer scientist Brian Randell had pressed for them; Flowers was allowed to publish a technical account in 1983; and the main postwar report on the Tunny work was declassified only in 2000.[18] A volunteer team led by Tony Sale, working from eight wartime photographs and fragments of circuit diagrams, built a working reconstruction of Colossus, first switched on in 1996. It runs in Block H at Bletchley, now The National Museum of Computing.

Turing. In January 1952 Turing reported a burglary at his house in Manchester, and in the course of the investigation told the police of his relationship with a young man. On 31 March 1952 he was convicted of gross indecency and given probation on condition that he accept hormone treatment with a synthetic oestrogen. His security clearance was withdrawn. He was found dead at his home on 8 June 1954, having died the day before of cyanide poisoning; the inquest recorded suicide, although some have argued since that the death may have been accidental. On 10 September 2009 the prime minister, Gordon Brown, issued an apology on behalf of the government for the way he had been treated. On 24 December 2013 Turing received a posthumous royal pardon, and legislation in 2017 extended pardons to thousands of other men convicted under the same laws. Since 2021 his portrait has been on the Bank of England's £50 note.

The others. Tutte took a doctorate at Cambridge and moved in 1948 to the University of Toronto, and later to Waterloo, where he became one of the founders of modern graph theory. Welchman moved to the United States in 1948; when he published *The Hut Six Story* in 1982, the first detailed account of the bombes in English, he lost his security clearances. Alexander became head of cryptanalysis at GCHQ. Rejewski, who escaped through Spain to Britain in 1943 and spent the rest of the war breaking German hand ciphers in a Polish army signals unit, never at Bletchley, returned to Poland in 1946, worked for two decades in office and sales posts in industry, and began to describe his work only in the late 1960s. Zygalski stayed in England and taught statistics. Różycki had died in January 1942 when a French passenger ship sank in the Mediterranean.

The Costs of Crossing

Bletchley Park is the most cited example in this book of disciplines brought together to solve a problem none could solve alone, and in its essentials the example holds. It also complicates the argument in at least four ways.

Secrecy erased the credit. The people who did the work could not claim it, and the gap was filled by those who had seen least of it. For thirty years the Polish contribution was unknown in the West, and after it became known, British accounts long minimised it; Rejewski spent his last years correcting them. Flowers watched American machines celebrated as the first electronic computers while Colossus remained a state secret, and his career never reflected what he had done. The women who were the majority of the workforce were not even an anonymous chorus; they were invisible, and many learned only decades later what the machines they had run had done. Interdisciplinary work spreads credit thinly at the best of times, because no single discipline's habits of attribution cover it. Secrecy made that worse.

The myth of the lone genius. Turing was a genius by any measure, and his treatment after the war was a disgrace. But the popular story, told most widely by the 2014 film *The Imitation Game*, in which Turing alone builds a machine that breaks Enigma against the opposition of a hostile Denniston, misrepresents nearly every element. The Poles had broken Enigma years earlier; the bombe was Turing's design improved by Welchman and engineered by Keen, and more than two hundred were built in Letchworth, none at Bletchley; Denniston backed the mathematicians; and Colossus, often supposed to have been built against Enigma, was built by Flowers against the Lorenz cipher, a different machine whose structure Tiltman, Tutte and the Research Section had worked out by hand. A related myth holds that the universal "Turing machine" of 1936 broke Enigma. It did not; the bombe was a special-purpose relay machine, and Colossus was not a universal machine either. Such stories teach that discovery is a matter of individual inspiration, which is close to the opposite of what happened at Bletchley.[19]

The counterfactual has been overclaimed. It is often said that Bletchley shortened the war by two years, or "by two to four years," as if this were an established finding. Its source is mainly Hinsley, Bletchley's former naval analyst and later its official historian, who argued in a lecture in Cambridge in October 1993 that without Ultra the U-boat war and the North African campaign would have lasted longer, the Normandy landings could not have taken place before 1946, and the war would have been something like two, perhaps three, possibly four years longer. Hinsley himself warned that such reasoning is dangerous unless used very carefully, and noted that the atomic bomb makes any estimate beyond 1945 speculative. Other historians, including John Keegan, have argued more generally that intelligence is rarely decisive in war, which is won by force, and the effect of Ultra cannot be isolated from radar, aircraft, industrial production and Soviet manpower. Eisenhower's letter of July 1945 to Menzies, thanking Bletchley for a "very decisive" contribution, is real; Churchill's much-quoted praise of the "geese that laid the golden eggs and never cackled" has never been traced to a source.[20] Ultra was immensely valuable. How valuable, in years, nobody knows.

It was not a model for peacetime science. Bletchley's mix of disciplines worked under con-

ditions no university or company can reproduce: a single overriding goal, a clear test of success (did the decrypt read as German?), the power to conscript talent and to override budgets with a prime minister's minute, and a workforce that could neither leave nor publish. It also had real frictions. Twinn later recalled that senior staff of the old GC&CS regarded mathematicians with suspicion; Frank Birch of the naval section complained in 1940 that Turing and Twinn were brilliant but impractical; Denniston, who had built the institution, was removed from it. And the compartmentalisation that made the system secure, by which each section knew only what it needed, is the opposite of the open exchange on which peacetime interdisciplinary science depends. The Radiation Laboratory (the "Rad Lab"), in the next chapter, faced the same tension in a different form. What carried over from Bletchley into peacetime was not its structure but its people, many of them forbidden to say where they had learned what they knew.

Coda

On the day the Poles shared their secret at Pyry, the British had one partial method against Enigma and no machine. Six years later Bletchley Park was reading a large share of the German armed forces' traffic, using more than two hundred bombes, ten electronic computers and some nine thousand people, most of whom never knew the whole of what they were part of. The ideas that made this possible came from permutation theory, from logic, from Bayesian statistics, from telephone engineering and from the close reading of texts. None of them would have been enough without the punched-card factory at Letchworth, the intercept operators who took down the signals, and the shift workers who ran the machines at three in the morning. When it was over, the machines were broken up, the papers burned, and the staff dispersed under the Official Secrets Act, most of them to say nothing about it for thirty years.

Notes

[1]GCHQ, "The Pyry Forest Meeting," https://www.gchq.gov.uk/information/the-pyry-forest-meeting, gives the dates as 25 and 26 July; other accounts give 24–25 July or 25–27 July, the variation arising mainly from whether the delegations' arrival in Warsaw and the talks in the city are counted. The identification of the third Briton is in Patrick Beesly, "Who Was the Third Man at Pyry?," in Brian J. Winkel, Cipher A. Deavours, David Kahn, and Louis Kruh, eds., *The German Enigma Cipher Machine: Beginnings, Success, and Ultimate Failure* (Boston: Artech House, 2005). The description of the site follows an article on the Polish history portal *Dzieje.pl*, https://dzieje.pl/podzielic-sie-tajemnica.

[2]Rejewski's recollection of Knox's question, and Knox's subsequent thank-you note to the Poles, are recounted in Gordon Welchman, "From Polish Bomba to British Bombe: The Birth of Ultra," *Intelligence and National Security* 1, no. 1 (1986): 71–110. Welchman suggests that Knox had independently reached many of the Polish ideas but had been stalled by this one assumption.

[3]On Room 40 and the formation of GC&CS, see Patrick Beesly, *Room 40: British Naval Intelligence, 1914–18* (London: Hamish Hamilton, 1982); and Joel Greenberg, *Alastair Denniston: Code-Breaking from Room 40 to Berkeley Street and the Birth of GCHQ* (Barnsley: Frontline Books, 2017). On Ewing, see the University of Edinburgh's biographical note, https://ourhistory.is.ed.ac.uk/index.php/Sir_Alfred_James_

Ewing_(1855-1935).

[4]GCHQ, "Denniston's Approach to the Growing Cryptanalytic Challenge," https://www.gchq.gov.uk/information/dennistons-approach-growing-cryptanalytic-challenge, which illustrates his letter of 25 November 1938; and "Denniston's Support for a Culture of Individualism and Ingenuity," https://www.gchq.gov.uk/information/dennistons-support-culture-individualism-and-ingenuity.

[5]Marian Rejewski, "How Polish Mathematicians Deciphered the Enigma," *Annals of the History of Computing* 3, no. 3 (1981): 213–34. Rejewski's paper is the source for the treatment of the plugboard as a conjugation that preserves cycle lengths. For an accessible modern explanation of the paired-cycle theorem, see Bill Casselman, "Marian Rejewski and the First Break into Enigma," Feature Column, American Mathematical Society, November 2009, https://www.ams.org/samplings/feature-column/fcarc-enigma.

[6]A. M. Turing, "On Computable Numbers, with an Application to the Entscheidungsproblem," *Proceedings of the London Mathematical Society*, 2nd ser., 42 (1936–37): 230–65. On Newman's lectures and the paper's origins, see Andrew Hodges, *Alan Turing: The Enigma* (London: Burnett Books, 1983).

[7]Frank Carter, "The Turing Bombe," *The Rutherford Journal*, https://www.rutherfordjournal.org/article030108.html, gives a clear technical account of menus, loops, simultaneous scanning and the diagonal board. Welchman's own account is in Gordon Welchman, *The Hut Six Story: Breaking the Enigma Codes* (New York: McGraw-Hill, 1982). For production figures, see the Turing–Welchman Bombe Rebuild Project's edited transcription of the end-of-war report of the bombe section, The National Archives, HW 3/146, https://bombe.org.uk/historical-background/. That report says the first bombe came into operation on 14 March 1940; other accounts give 18 March for its installation.

[8]Mavis Batey, *Dilly: The Man Who Broke Enigmas* (London: Dialogue, 2009); GCHQ, "Dilly Knox," https://www.gchq.gov.uk/person/dilly-knox, which dates the first decrypt on the Abwehr key, ISK1, to 25 December 1941. Sources differ over whether to date the break itself to October or December 1941.

[9]I. J. Good, "Studies in the History of Probability and Statistics XXXVII: A. M. Turing's Statistical Work in World War II," *Biometrika* 66, no. 2 (1979): 393–96; Abraham Wald, "Sequential Tests of Statistical Hypotheses," *Annals of Mathematical Statistics* 16, no. 2 (1945): 117–86; R. V. L. Hartley, "Transmission of Information," *Bell System Technical Journal* 7, no. 3 (1928): 535–63. The repeat rates of 1/17 and 1/26 are those given in standard accounts of Banburismus, drawn from Hugh Alexander's postwar *Cryptographic History of Work on the German Naval Enigma*, The National Archives, HW 25/1. Turing's reason for taking on the naval problem is reported in A. P. Mahon, *The History of Hut Eight, 1939–1945* (1945), The National Archives, HW 25/2.

[10]The letter and Churchill's minute are in The National Archives, HW 1/155; see "A Dramatic Plea for Churchill's Help," https://www.nationalarchives.gov.uk/explore-the-collection/stories/a-dramatic-plea-for-churchills-help/. On Alexander, see the biography in the MacTutor History of Mathematics archive, https://mathshistory.st-andrews.ac.uk/Biographies/Alexander_Hugh/.

[11]Ralph Erskine, "Naval Enigma: The Breaking of Heimisch and Triton," *Intelligence and National Security* 3, no. 1 (1988): 162–83; Erskine's summary, "Enigma: Allied Breaking of Naval Enigma," *uboat.net*, https://www.uboat.net/technical/enigma_breaking.htm, gives the dates for Shark used here.

[12]John H. Tiltman, "The 'Tunny' Machine and Its Solution," based on a lecture of October 1960 and released by the National Security Agency in 2007, https://www.cryptocellar.org/Lorenz/Tunny_Machine_Tiltman.pdf. Tiltman gives the date of interception as 30 August 1941; some secondary accounts give 31 August.

[13]W. T. Tutte, "FISH and I," lecture at the University of Waterloo, 1998, University of Waterloo Department of Combinatorics and Optimization research report CORR 98-39, https://uwaterloo.ca/combinatorics-and-optimization/sites/default/files/uploads/documents/corr98-39.pdf; Tiltman, "The 'Tunny' Machine," credits "Dr. Morgan and Mr. Tutte."

[14]T. H. Flowers, "The Design of Colossus," *Annals of the History of Computing* 5, no. 3 (1983): 239–52, which gives the 1,500 valves and describes the reception of the proposal; B. Jack Copeland, "Colossus: Its Origins and Originators," *IEEE Annals of the History of Computing* 26, no. 4 (2004): 38–45, which records Flowers's remark that Bletchley was not interested until it saw the machine working; and B. Jack Copeland, ed., *Colossus: The Secrets of Bletchley Park's Codebreaking Computers* (Oxford: Oxford University Press, 2006), for the dates of first operation. On Radley's support, see the profile of Flowers at the Crypto Museum, https://www.cryptomuseum.com/people/flowers/tommy.htm; on the photocells, Tony Sale's account at https://codesandciphers.org.uk/virtualbp/fish/colossus.htm.

[15]Figures for women at 31 December 1944 are from GCHQ, "Celebrating 100 Years of Women's Service in the UK Armed Forces," https://www.gchq.gov.uk/information/centenary-womens-service-uk-armed-forces. Bombe-section figures are from HW 3/146, as above. On the Colossus Wrens, see Allison Marsh, "The Hidden Figures behind Bletchley Park's Code-Breaking Colossus," *IEEE Spectrum*, 31 December 2019. Clarke's recollection is in Joan Murray (née Clarke), "Hut 8 and Naval Enigma, Part I," in F. H. Hinsley and Alan Stripp, eds., *Codebreakers: The Inside Story of Bletchley Park* (Oxford: Oxford University Press, 1993).

[16]GCHQ, "The End of Denniston's Career, and His Legacy," https://www.gchq.gov.uk/information/end-dennistons-career-and-his-legacy; Greenberg, *Alastair Denniston*.

[17]GCHQ, "D-Day: 75 Years On," https://www.gchq.gov.uk/information/d-day-75-years-on; Flowers's recollection is in his essay "D-Day at Bletchley Park," in Copeland, ed., *Colossus*. The American Battle Monuments Commission's account of Eisenhower's decision at Southwick House is at https://www.abmc.gov/video/ok-lets-go.

[18]F. W. Winterbotham, *The Ultra Secret* (London: Weidenfeld and Nicolson, 1974); Gustave Bertrand, *Enigma ou la plus grande énigme de la guerre 1939–1945* (Paris: Plon, 1973); F. H. Hinsley et al., *British Intelligence in the Second World War: Its Influence on Strategy and Operations*, vols. 1–3 (London: HMSO, 1979–88), whose volume 3, part 2 (1988) contains a revised account of the Polish, French and British contributions to the breaking of Enigma. Volume 4 (1990) is by Hinsley and C. A. G. Simkins, volume 5 (1990) by Michael Howard.

[19]On the film's departures from the record, see Christian Caryl, "A Poor Imitation of Alan Turing," *NYR Daily*, *New York Review of Books*, 19 December 2014, https://www.nybooks.com/online/2014/12/19/poor-imitation-alan-turing/. Dermot Turing, *X, Y & Z: The Real Story of How Enigma Was Broken* (Stroud: History Press, 2018), gives a balanced account of the Polish, French and British contributions.

[20]F. H. Hinsley, "The Influence of ULTRA in the Second World War," lecture to the Security Group, Computer Laboratory, University of Cambridge, 19 October 1993, transcript at https://www.cdpa.co.uk/UoP/HoC/Lectures/HoC_08e.PDF; a version appears as the introduction to Hinsley and Stripp, eds., *Codebreakers*. John Keegan, *Intelligence in War: Knowledge of the Enemy from Napoleon to Al-Qaeda* (London: Hutchinson, 2003). On the Churchill quotation, see Tim Mitchell, "Historical Musing: Geese and Golden Eggs," Friends of the Intelligence Corps Museum, 20 November 2016, https://friendsintelligencemuseum.org/?p=1237.

Further Reading

F. H. Hinsley and Alan Stripp, eds., *Codebreakers: The Inside Story of Bletchley Park* (Oxford University Press, 1993). Short memoirs by people who worked there, including Milner-Barry on Hut 6, Joan Murray (Clarke) on Hut 8 and Jack Good on Tunny, with Hinsley's assessment of Ultra's influence. The best single introduction to the place as its staff saw it.

Gordon Welchman, *The Hut Six Story: Breaking the Enigma Codes* (McGraw-Hill, 1982; revised edition, M&M Baldwin, 1997). The first detailed account of the bombe and of Hut 6's methods, by its founder. Technical in places and partisan in others; read it alongside his 1986 article "From Polish Bomba to British Bombe," in which he revised his account of the Polish contribution.

Marian Rejewski, "How Polish Mathematicians Deciphered the Enigma," *Annals of the History of Computing* 3 (1981). Rejewski's own explanation of the permutation-theory attack, with its mathematics. Demanding but rewarding.

Dermot Turing, *X, Y & Z: The Real Story of How Enigma Was Broken* (History Press, 2018). A readable account of the Polish, French and British collaboration before and after 1939, careful about who did what.

Andrew Hodges, *Alan Turing: The Enigma* (Burnett Books, 1983; centenary edition, Princeton University Press, 2012). The standard biography, excellent on Turing's mathematics and on his life and death, and more measured on Bletchley than the films it inspired.

B. Jack Copeland, ed., *Colossus: The Secrets of Bletchley Park's Codebreaking Computers* (Oxford University Press, 2006). Essays by Flowers, Coombs, Michie, Good and others who built and used Colossus, with Copeland's introductions. The fullest account of Tunny and the Newmanry.

Mavis Batey, *Dilly: The Man Who Broke Enigmas* (Dialogue, 2009). A biography of Knox by one of his team, good on the older, linguistic tradition of codebreaking and on the women of his section.

Ralph Erskine and Michael Smith, eds., *The Bletchley Park Codebreakers* (Biteback, 2011; first published as *Action This Day*, Bantam, 2001). Scholarly essays on naval Enigma, Tunny, the Abwehr and much else, by historians and veterans.

Joel Greenberg, *Alastair Denniston: Code-Breaking from Room 40 to Berkeley Street and the Birth of GCHQ* (Frontline Books, 2017). A corrective to the caricature of Denniston, drawing on family and GCHQ papers.

Online: GCHQ's history pages, `https://www.gchq.gov.uk/section/history`; Tony Sale's Codes and Ciphers site, `https://codesandciphers.org.uk`, with transcriptions of wartime reports; and The National Museum of Computing, `https://www.tnmoc.org`, home of the rebuilt Colossus.

Chapter 5

Building 20: The Rad Lab and the Pidgin of Innovation (1940–1945)

Magnetron Number 12

On 7 August 1940 a physicist from the Air Ministry's radar establishment picked one device out of a small batch of prototypes made by the General Electric Company at its research laboratories in Wembley, north-west London. Edward Bowen, known to everyone as Taffy, was a twenty-nine-year-old Welshman who had helped to build Britain's first airborne radar sets. The device he chose was small enough to hold in one hand: a block of copper with fins for air cooling. Its type was E1189, and its serial number 12. Bowen was taking it to America.

The journey that followed has become part of the folklore of the war, mostly through Bowen's own later account. He kept the device in a small black metal deed box, of the kind solicitors use for property documents, together with papers describing most of Britain's secret military technology. By his recollection he slept with it under his bed in a London hotel, strapped it to the roof of a taxi on the way to Euston station, nearly lost sight of it when an over-eager porter carried it off, and was given an army escort in Liverpool. At the end of August he sailed on the Canadian Pacific liner *Duchess of Richmond*, which reached Halifax, Nova Scotia, on 6 September. Most of the rest of the British Technical and Scientific Mission travelled with him: an army officer, a naval officer, the nuclear physicist John Cockcroft and a civil servant as secretary. Its leader, Sir Henry Tizard, scientific adviser to the Air Ministry, had gone ahead by flying boat in August with the mission's RAF member, to prepare the ground in Washington.[1]

The mission's purpose was a trade. Britain had ideas, prototypes and a year's experience of war, but its factories were stretched and under bombardment. The United States had industrial capacity, money and a large community of physicists, and was not at war. Tizard's instructions were to show the Americans almost everything, in the hope of getting production and research in return. The Americans, for their part, were unsure how much the British had to offer.

The magnetron settled the matter. On 19 September, in Washington, Bowen and Cockcroft showed it to members of a new committee of the National Defense Research Committee that was

charged with microwave work. On 29 September they discussed it at length at Tuxedo Park, the private laboratory of the committee's chairman, the investment banker and amateur physicist Alfred Loomis. On 6 October Bowen took it to the Bell Telephone Laboratories site at Whippany, New Jersey, where engineers connected it to a pulsed power supply and a magnet. It produced pulses of about fifteen kilowatts at a wavelength just under ten centimetres. The best American valves of the day could manage only a small fraction of that at such short wavelengths. When the Bell engineers X-rayed the device to see how to copy it, they found eight resonant cavities in the copper block. The drawings Bowen had brought showed six.

For a few anxious days nobody could explain the discrepancy. Bowen telephoned Eric Megaw, who led the magnetron work at GEC, and later recalled that Megaw seemed as puzzled as he was. Bowen came to believe that number 12 was an odd experimental variant that happened to be in the batch. Recent work in GEC's records suggests otherwise: Megaw had decided in July to try an eight-cavity design that would work in the weaker field of a permanent magnet, and number 12 was built to that design.[2] Either way, the NDRC contracted Bell to make thirty copies; the first few were built from November, and Western Electric made more in 1941.

James Phinney Baxter, the official historian of American wartime science, later wrote that the mission had carried "the most valuable cargo ever brought to our shores."[3] The phrase is often repeated. It overstates the role of a single object, since the mission also brought information on jet engines and much else, and opened the channels through which British work on the atomic bomb later reached the United States, but it captures how the Americans felt. Within weeks a new laboratory had been set up at the Massachusetts Institute of Technology to turn the magnetron into working radar. Within five years that laboratory employed nearly four thousand people and had designed a large share of the radar the Allies used. And from 1943 its largest single home was a three-storey wooden building on Vassar Street, put up as a temporary measure, that MIT would keep for more than half a century.

This chapter is about what happened inside that laboratory: how physicists who had spent the 1930s studying atomic nuclei learned to work with radio engineers whose ideas and vocabulary they barely shared, and what that collaboration produced, during the war and afterwards.

The Science: Seeing with Short Waves

Radar is simple in principle. A transmitter sends out a short, powerful pulse of radio waves. If the pulse strikes an object (an aircraft, a ship, a coastline) a tiny fraction of its energy is reflected back. A receiver picks up the echo, and the delay between pulse and echo gives the distance, because radio waves travel at the speed of light, about 300,000 kilometres per second. An echo that returns after one microsecond (a millionth of a second) comes from a target 150 metres away, since the pulse has to go there and back. An echo from 10 kilometres arrives after about 67 microseconds. If the antenna sends the pulse out as a narrow beam, the direction in which it is pointing when the echo returns gives the target's bearing.

Britain's first operational radar, the Chain Home system that guarded the east and south coasts during the Battle of Britain, worked at frequencies of 20 to 30 megahertz: wavelengths of 10 to 15 metres. Its transmitting aerials hung from steel towers 360 feet high. It could detect aircraft forming up over France, but it could not form a sharp beam; it found the direction of a target by comparing the signals received on crossed aerials, and its picture of the sky was coarse. That was acceptable for early warning. It was useless for the problem that dominated British radar research in 1940: finding a German bomber at night from the cockpit of a fighter.

The first airborne interception sets, which entered service in the summer and autumn of 1940, worked at about 200 megahertz, a wavelength of about 1.5 metres. Their aerials were spikes and dipoles mounted on the nose and wings. Because the transmitted energy spread out in all directions, much of it struck the ground, and the ground returned an enormous echo at a range equal to the aircraft's height. Nothing beyond that range could be seen. A fighter flying at 15,000 feet could not detect a bomber more than about three miles away, and a bomber that flew low could hide in the ground return altogether.[4]

The cure was a narrow beam, and a narrow beam from a small antenna requires a short wavelength. The reason is diffraction, which limits every telescope, microscope and antenna in the same way.

Science Primer: Wavelength, antenna size and the width of a beam

Any wave passing through an opening, or sent out by an antenna, spreads as it travels. The spreading is governed by a single ratio. For an antenna (or a mirror or lens) of width D, radiating waves of wavelength λ, the angular width of the beam is roughly

$$\theta \approx \frac{\lambda}{D},$$

where θ is measured in radians (one radian is about 57 degrees). The exact factor in front depends on the shape of the antenna and on how one defines the edge of the beam, but it is close to one. The same ratio sets the finest detail a telescope can resolve, which is why astronomers build large mirrors.

Suppose, for illustration, a dish 75 centimetres across. (When the British adapted a 10-centimetre set for Wellington patrol bombers in 1942–43, they cut its dish from 36 to 28 inches, about 71 centimetres, to fit the aircraft's nose.)

At $\lambda = 1.5$ metres, $\lambda / D = 1.5 / 0.75 = 2$ radians: more than 100 degrees. There is no beam worth the name.

At $\lambda = 10$ centimetres, $\lambda / D = 0.10 / 0.75 \approx 0.13$ radians, or about 7.6 degrees. At a range of 5 kilometres, the beam is about $0.133 \times 5{,}000 \approx 670$ metres wide. A pilot can point it at the sky ahead and keep it off the ground.

At $\lambda = 3$ centimetres, $\lambda / D = 0.03 / 0.75 = 0.04$ radians, about 2.3 degrees, and the beam at 5 kilometres is about 200 metres wide: narrow enough to separate two aircraft flying close together, or to draw a rough map of a town from the air.

Turn the calculation round. To make a 7.6-degree beam at Chain Home's wavelength of about 12 metres would need an antenna about 90 metres across. The physics of diffraction is why radar had to move to short waves, and why an airborne radar was impossible without a powerful source of centimetre waves.

Shorter wavelengths bring a second advantage. Wavelengths of a few centimetres are similar to or smaller than the details of a submarine's conning tower or a ship's superstructure, so these objects reflect them strongly. And a beam that does not spill onto the sea or the ground is not swamped by its echoes.

In 1939, nobody had a way of producing centimetre waves at useful power. Wavelengths of 10 centimetres correspond to a frequency of 3,000 megahertz (3 gigahertz): fifteen times the frequency of the airborne sets. The ordinary radio valve, the triode, amplifies by passing a stream of electrons from a hot cathode to an anode under the control of a grid. At such frequencies the electrons cannot cross the gap between the electrodes in the time it takes the field to reverse, and the valve stops working. Several devices could generate centimetre waves, including the klystron, invented at Stanford in 1937–38 by Russell and Sigurd Varian with the physicist William Hansen. None could yet produce the kilowatts of pulsed power that a radar needed to see an aircraft several miles away.

The Science: A Copper Block in a Magnet

The magnetron itself was not new. Albert Hull at General Electric in Schenectady had published his work on it in 1921: a cylindrical anode around a heated cathode, with a magnetic field running along the axis. Researchers in Germany, Czechoslovakia, Japan, the Soviet Union, France and Britain had experimented with variants through the 1920s and 1930s, and some had cut resonant structures into the anode. What none had done was produce a device that delivered high power at centimetre wavelengths with useful efficiency.

The breakthrough came from a group at the University of Birmingham led by the Australian physicist Mark Oliphant, set up at the end of 1939 to develop a high-power source of centimetre waves for airborne radar. Most of the group worked on improving the klystron. Two junior members, John Randall, who had spent years in industrial research on luminescent materials, and Harry Boot, a young research student, were given what seemed a side problem and chose to try the magnetron. Randall later said that the idea for the resonator had come to him from reading an English translation of Heinrich Hertz's *Electric Waves*, the collected papers in which Hertz had described his experiments of the 1880s, including the loop of wire with a small gap that he used to detect radio waves. A loop like Hertz's is a resonant circuit: the loop has inductance, the gap has capacitance, and the combination rings at one frequency. Randall's thought was to make a three-dimensional version, a cylindrical hole drilled in a block of copper and connected by a narrow slot to the space around the cathode, and to arrange several of them in a ring.

Boot and Randall bored six holes around a central chamber in a copper block, sealed the ends, placed the whole thing between the poles of a large electromagnet and connected it to a vacuum pump, since the device was not yet sealed. They first switched it on, on 21 February 1940. By later accounts, it produced so much power that it burned out the car headlamp bulbs they used as loads. Measured the next day, its wavelength was 9.8 centimetres and its continuous output about 400 watts, roughly a hundred times what anyone had obtained at that wavelength.[5] The figure of ten kilowatts often attached to the first device belongs to its successors. The work of turning a laboratory device into something that could fly fell to Megaw's team at GEC, who sealed the block, fitted an oxide-coated cathode of a type they had seen in a French magnetron brought over in May 1940, and designed it to work in a permanent magnet. The first GEC E1189 ran at the end of June. By August GEC had made a handful of the new eight-cavity type, and number 12 went to America.

How does a block of copper in a magnet produce microwaves? The mechanism takes some explaining, and in its details it is still the subject of computer simulation, but the essentials are these.

At the centre is a cathode, heated so that it gives off electrons, and held several thousand volts negative relative to the copper block around it, which is the anode. The electric field between them points radially, from the anode inward. On its own, it would pull the electrons straight out to the anode. But the magnet supplies a strong field along the axis of the tube, and a magnetic field pushes sideways on a moving charge. The electrons therefore do not travel straight out; they curve, and if the magnetic field is strong enough for the voltage, they curl back before reaching the anode and swirl around the cathode in the space between. Physicists call this arrangement *crossed fields*: electric and magnetic fields at right angles, which together make the electrons drift around the tube at a speed fixed by the ratio of the two.

The anode's inner face is not smooth. It is broken by the slots that lead into the cavities. Each cavity, like Hertz's loop, is a resonator, and as the cloud of electrons sweeps past, the cavities begin to ring. Their oscillating electric fields reach out through the slots into the space where the electrons are circling. At any instant, the field at some slots pushes the passing electrons forward and at others holds them back. Electrons that are held back give up energy to the field; with less energy they spiral outward and eventually strike the anode. Electrons that are pushed forward gain energy, curl back and strike the cathode. The process sorts the cloud: the electrons that survive are those that arrive at each slot at the right moment to be slowed, and so to hand energy over. They gather into bunches that extend outward from the cathode like the spokes of a wheel, and the spokes rotate in step with the oscillating pattern of fields around the ring of cavities. In the preferred mode of oscillation, neighbouring cavities ring in opposite phase, so a block with eight cavities carries four spokes. The energy fed into the cavities comes, in the end, from the high-voltage supply that drives the electrons, and a small loop or slot in one cavity draws the microwave power out into a coaxial line or waveguide.

Early magnetrons had a weakness: the ring of cavities could oscillate in more than one pattern, and the device sometimes jumped from one to another, changing its frequency. In 1941 (some accounts say 1942) another member of Oliphant's group, James Sayers, found a remedy:

connecting alternate segments of the anode with metal straps, which forced the cavities into the desired pattern. Strapping made magnetrons both more stable and more efficient, and it was adopted on both sides of the Atlantic.

The magnetron solved one problem and created several others. A ten-centimetre wave cannot be handled with the components of ordinary radio. At 3 gigahertz, a single cycle lasts a third of a nanosecond, in which time light travels just 10 centimetres. A wire a few centimetres long, which in a broadcast receiver is simply a connection, is now a substantial fraction of a wavelength: it has inductance, it radiates, and the current at one end is not the same as the current at the other. Currents flow only in a thin skin at the surface of conductors, so resistive losses rise. The assumption on which ordinary circuit theory rests, that a component is small compared with a wavelength and can be described by a single number for its resistance, inductance or capacitance, fails. Engineers call that assumption the *lumped-element* approximation, and at microwave frequencies the lumps dissolve into fields spread through space.

The solution was to stop using wires. A *waveguide* is a hollow metal pipe, usually rectangular in cross-section, down which electromagnetic waves travel by reflecting from the walls. Lord Rayleigh had shown theoretically in 1897 that waves could travel inside a conducting tube only in certain patterns, called modes, and only if the wavelength was short enough; George Southworth at Bell Laboratories and Wilmer Barrow at MIT demonstrated practical waveguides independently in the mid-1930s. For the simplest mode in a rectangular guide of width a, the condition is that the wavelength must be shorter than $2a$. A guide for 10-centimetre radar is therefore about 7 centimetres wide inside; a guide for 3-centimetre radar, about 2.3 centimetres. Waveguides carry microwave power with little loss, and they can be bent, twisted, split and joined. But to a radio engineer brought up on circuit diagrams, a network of brass pipes, with screws poking into them and thin metal plates soldered across them, looked more like plumbing than electronics. Every bend, junction and obstacle reflected part of the wave, and the only exact way to calculate how much was to solve Maxwell's equations, the four equations of electromagnetism, for the fields inside that particular piece of metal. That was a physicist's problem. The question of how to make it an engineer's problem is the subject of the second half of this chapter.

A Laboratory Named as a Disguise

The Microwave Committee that met Bowen had been set up in the summer of 1940 as one of the sections of the National Defense Research Committee, the body that Vannevar Bush, president of the Carnegie Institution of Washington and former vice-president of MIT, had persuaded President Roosevelt to create in June. Its chairman was Loomis, and its members included representatives of Bell Laboratories, General Electric, RCA, Westinghouse and Sperry, as well as the Berkeley physicist Ernest Lawrence, inventor of the cyclotron. The committee's first plan had been to farm out pieces of the problem to university and industrial groups. The magnetron, and the scale of the work it made possible, changed that. The committee would build a central laboratory, staffed largely by academic physicists, and work closely with industry.

The chain of decisions is worth getting straight, because it is often compressed into a sentence in which Bush and Loomis simply found the laboratory. Lawrence and Loomis looked for a director and settled on Lee DuBridge, a 39-year-old nuclear physicist who had built a cyclotron at the University of Rochester; Lawrence telephoned him on 15 October 1940, and he accepted the next day. MIT's president, Karl Compton, agreed on 17 October to house the laboratory. The NDRC approved the contract on 25 October, with initial funding of a little under half a million dollars. Bush, who as NDRC chairman stood above all of this, had been one of the founders of the company that became Raytheon, which would soon be a major producer of magnetrons. The new laboratory opened in November in borrowed space in MIT's main buildings. It was named the Radiation Laboratory, a choice made, according to the standard histories, so that outsiders would assume it was doing nuclear physics like Lawrence's laboratory at Berkeley, which bore the same name.[6]

Recruitment ran through the networks of prewar physics. At the end of October MIT hosted a conference on applied nuclear physics, sponsored by the American Institute of Physics, which drew several hundred physicists to Cambridge; Kenneth Bainbridge of Harvard, who chaired one of its sessions, was asked to find hotel rooms for those who were expected to stay on, and the conference served as a recruiting ground. The people who came were overwhelmingly nuclear physicists, for a reason that was partly sociological and partly technical. Builders of cyclotrons and other accelerators knew about high voltages, vacuum systems, radio-frequency oscillators and the art of making temperamental equipment work. They also knew each other. The laboratory's associate director, I. I. Rabi of Columbia, who would win a Nobel Prize in 1944 for his molecular-beam measurements of nuclear magnetic properties, brought his Columbia colleague Jerrold Zacharias and his former student Norman Ramsey. Luis Alvarez came from Berkeley, Edward Purcell from Harvard, Robert Dicke from Rochester. Rabi later compared the early selection of staff to choosing sides for a baseball team.

Drawing partly on British advice from the Tizard Mission, the Microwave Committee set three projects, which became the laboratory's first: an airborne interception radar for night fighters, a long-range navigation system, and a radar to aim anti-aircraft guns automatically. On 4 January 1941 an experimental 10-centimetre set on an MIT rooftop picked up reflections from buildings across the Charles River. In March the first airborne set flew in a Douglas B-18 bomber.

Systems, Factories and Allies

The Rad Lab grew faster than anyone had planned. It had a few dozen staff at the end of 1940 and more than a thousand by the end of 1942. Its peak came in August 1945, with 3,897 employees: 1,189 scientific and engineering staff, 1,301 other men and 1,407 other women.[7] It spread through MIT's existing buildings, then through temporary ones, and sent field teams to Britain, the Mediterranean and the Pacific. By the laboratory's own count it developed more than a hundred distinct radar systems, and it designed roughly half of all the radar the United States deployed during the war. Most were never famous. A few changed how the war was fought.

Table 5.1: Some Radiation Laboratory systems and what they did

System	Purpose	Notes
SCR-720 (AI Mk X in RAF service)	Airborne interception, 10 cm	Grew from the first project; production sets reached Britain from 1943.
SCR-584	Automatic tracking for anti-aircraft guns, 10 cm	First used in combat at Anzio, February 1944; used against V-1 flying bombs in 1944.
H2X ("Mickey")	Ground-mapping radar for bombing through cloud, 3 cm	Developed from the British H2S; first used against Wilhelmshaven, 3 November 1943.
LORAN	Long-range navigation by timed radio pulses	Not a microwave system; by 1945 its stations covered a large part of the earth's surface.
MEW	Microwave early warning	Used Alvarez's linear-array antenna; one was installed at Start Point in Devon in 1944.
GCA	Ground-controlled approach for landing in bad weather	Alvarez's system; controllers on the ground talked pilots down by voice.

The SCR-584 shows how the pieces fitted together. A team led by Ivan Getting and Lee Davenport designed a 10-centimetre radar that searched the sky until it found an aircraft, then locked on and followed it automatically by spinning its beam in a narrow cone around the target, feeding its range and bearing to an electrical gun director. Combined with the proximity fuze, which detonated a shell when it passed near its target, it transformed anti-aircraft gunnery. In the summer of 1944 the guns massed on the south coast of England against the V-1 flying bombs, equipped with American radars, directors and fuzes, went from destroying a small fraction of the bombs that crossed the gun belt to destroying a large majority of them by the end of August.[8]

The saying that radar "won the war" while the atomic bomb ended it is a slogan rather than a historical judgement, and the claim, sometimes made, that Rad Lab radar won the Battle of the Atlantic needs both narrowing and sharing. Centimetric radar on patrol aircraft did matter greatly in 1943: German U-boats carried a receiver, Metox, that warned them of the older 1.5-metre sets but could not detect the new 10-centimetre ones, and boats on the surface were caught without warning. But the decisive airborne set in the British campaign was ASV Mark III, a version of the British H2S built at the Telecommunications Research Establishment (TRE), which began operational patrols in March 1943. The defeat of the U-boats that spring also depended on long-range aircraft, escort carriers, better-trained escort groups, signals intelligence (Chapter 4) and the sheer number of ships the Allies could build.

None of this was done by physicists alone. The laboratory designed and built prototypes, but industry made the sets: Western Electric, the manufacturing arm of the Bell System, General Electric, Westinghouse, Philco and many others, working from the laboratory's drawings and often sending their own engineers to Cambridge to learn the designs. Magnetrons were the bottleneck. Bell Laboratories made the first copies, and Raytheon became the largest producer, largely through the work of Percy Spencer, a self-taught engineer who redesigned the device

for mass production by building the anode from laminated parts instead of machining it from a solid block. Raytheon's output rose, by the company's account, from seventeen magnetrons a day to 2,600.[9] Relations with the services were close and sometimes fraught; the laboratory's engineers often went into the field to install and repair equipment and to train the people who used it.

The relationship with Britain was the laboratory's founding condition and a continuing source of friction. TRE, at Malvern after May 1942, was the Rad Lab's British counterpart, and the two exchanged visitors, designs and complaints. H2X was an American 3-centimetre development of H2S; the airborne interception sets of both countries drew on a common stock of ideas. In October 1943 the NDRC formally approved a British Branch of the Radiation Laboratory, set up beside TRE in the grounds of Malvern College under, for most of its life, John Trump. It had about a hundred staff, most of them working at airfields rather than at Malvern, and it supported the American equipment that now served in Europe: H2X in bombers, LORAN chains, microwave early-warning sets that followed the armies across France, and SCR-584s used to direct fighter-bombers. According to its history, collaboration with TRE was less close than intended, each laboratory being absorbed in its own problems.

As the draft took men out of the laboratory, it recruited and trained women, not only as secretaries and clerks but as technicians, draughtswomen and machinists, and a few on the research staff; by 1945 women made up about 36 per cent of the workforce, and by the end of the war roughly as many held technical jobs as clerical ones. According to MIT's Black History Project, the Institute also increased its recruitment of Black staff for the laboratory and its other wartime units. The names of most of these people do not appear in the laboratory's publications. Some do, in prefaces and acknowledgements. The *Waveguide Handbook*, which we will come to shortly, records that most of its numerical computations were carried out under the direction of the mathematician A. E. Heins by a small team, and that one "Mrs. A. Marcus" did most of the work on its plots of the field patterns in waveguides. Behind the physicists' formulas lay a good deal of hand computation, done by people whose contribution was recorded, if at all, in a line of thanks.

Schwinger's Night Shift

Julian Schwinger came to the Rad Lab in 1943, aged twenty-five. He had grown up in New York, had published research papers while still a teenager, and had taken his doctorate at Columbia under Rabi; he was then teaching at Purdue. He became, by general agreement, the laboratory's leading theorist, although he was rarely seen. He worked through the night, arriving as others left and going home as they arrived, and he valued the privacy this gave him. He stayed at the Rad Lab rather than going to Los Alamos, for reasons he gave later as a moral objection to weapons work, a preference for the problems at hand, and a fear of being swallowed by a team.[10]

His problem was the one left at the end of the science section: what happens to a wave in a waveguide when it meets a discontinuity. A waveguide system is full of them: a thin metal plate

with a slot in it (an iris), a post or screw projecting into the guide, a sudden change of width, a junction where one guide branches into two or three, a coupling hole into a cavity. Each reflects part of the wave and passes the rest, and each stores some energy in the complicated fields that cling to it. Radar designers needed to know, for every such part, how much it reflected and with what phase, at every frequency of interest, and they needed to know it without building and measuring hundreds of variants.

Schwinger attacked the fields directly, with the classical mathematics of electromagnetism, not with the methods of quantum theory. His work on quantum field theory came after the war, and if anything the influence ran the other way. He reformulated each discontinuity problem as an *integral equation* for the field across the opening, built with Green's functions, which describe how a disturbance at one point in the guide produces fields at another. These equations could rarely be solved exactly. But Schwinger found *variational* expressions for the quantities that mattered: formulas with the useful property that an approximate guess at the field across the opening gives an answer whose error is much smaller than the error in the guess. With them, a rough estimate of the field could yield a reflection coefficient accurate to a few per cent.

What made the work historically interesting was the form in which he delivered the answers. He did not hand engineers the fields. He showed that, as far as anything happening at a distance from the discontinuity was concerned, the only thing that mattered was a small set of numbers, and that those numbers could be expressed as the values of components in an ordinary circuit. A thin iris across a guide behaved like an inductance or a capacitance connected across a transmission line, depending on its orientation; a junction behaved like a small network of such elements and transformers. The waveguide became a transmission line, the discontinuity became a lump, and the engineer was back on familiar ground.

This was the *equivalent circuit*. The idea was not Schwinger's alone, or new. Engineers had long described loudspeakers and transformers by circuits that reproduced their behaviour at the terminals without modelling what went on inside, and Sergei Schelkunoff at Bell Laboratories had argued in the 1930s for extending the impedance concept to electromagnetic waves generally. What the Rad Lab added was a systematic theory, and a body of calculated and measured results, for the particular structures that microwave engineers used. Schwinger supplied much of the theory. Nathan Marcuvitz, an electrical engineer from the Polytechnic Institute of Brooklyn who headed the laboratory's experimental group on these problems, developed accurate methods for measuring the circuit parameters of discontinuities, checked the theory against them and tabulated the results. David Saxon, Schwinger's closest colleague, Harold Levine and others, among them Hans Bethe, worked on particular cases. Marcuvitz's *Waveguide Handbook*, published in 1951 as volume 10 of the laboratory's series of technical books, gathered hundreds of discontinuities with their equivalent circuits and formulas, in a form an engineer could use with a slide rule. Its preface credits Schwinger with a dominant role in the work and his integral-equation formulation with pointing the way.[11]

Science Primer: A metal plate as a circuit element

Picture a rectangular waveguide carrying a wave towards a perfectly matched load, which absorbs everything that reaches it. Now solder a thin metal plate across the guide, leaving a gap in the middle: an *iris*. Part of the wave is reflected. How much?

The engineer's answer begins by treating the empty guide as a *transmission line*, like a long pair of wires, with a characteristic impedance Z_0. It is convenient to use the inverse of impedance, the *admittance* $Y = 1/Z$, and to measure everything relative to the line's own admittance $Y_0 = 1/Z_0$, so that a matched load has a normalised admittance of exactly 1.

Theory and measurement show that a thin iris whose edges run parallel to the electric field acts, at a distance, like an inductor connected across the line. Its effect is captured by one number, a normalised *susceptance* b (the imaginary part of an admittance), which depends on the width of the gap and on the frequency. A narrow gap gives a large b; a wide gap a small one. The line now ends in the matched load and the iris in parallel, and admittances in parallel add, so the total normalised admittance seen by the incoming wave is

$$y = 1 + jb,$$

where j is the engineer's symbol for $\sqrt{-1}$, marking a quantity that shifts phase rather than absorbing power.

The fraction of the wave's amplitude reflected, the *reflection coefficient* Γ, follows from a standard transmission-line formula:

$$\Gamma = \frac{1 - y}{1 + y} = \frac{-jb}{2 + jb}, \qquad |\Gamma|^2 = \frac{b^2}{4 + b^2}.$$

Here $|\Gamma|^2$ is the fraction of the incoming power that is reflected. If $b = 1$, then $|\Gamma|^2 = 1/5$: one fifth of the power bounces back. If $b = 2$, half of it does. If $b = 0$ (no iris), nothing is reflected.

Two consequences explain why engineers loved this. First, the hard physics, solving Maxwell's equations around the edges of the plate, is needed only once, to find b as a function of gap and frequency; after that, the plate is a circuit element like any other. Second, reflections can be cancelled by circuit reasoning. Place a second obstacle at the right distance along the guide, and its reflection can be made to arrive out of phase with the first, so that the two cancel. Radar engineers did this all the time, with irises and adjustable screws, to match magnetrons to waveguides and waveguides to antennas. The calculation of b was Schwinger's kind of problem; everything after it was the engineer's.

Schwinger drew a lesson from this work that went well beyond waveguides. In a lecture to engineering students in 1969 he recalled starting out naively by solving Maxwell's equations and soon learning better: the useful thing was to isolate the few quantities that the outside world could detect and to describe everything else as a black box. "Most of the information in Maxwell's equations is really superfluous," he told them.[12] When he turned after the war

to the problem of the infinities in quantum electrodynamics, the theory of electrons and light, he approached it in the same spirit: separate what can be observed (the measured mass and charge of the electron) from the inner structure that cannot, and organise the theory around the former. The work earned him a share of the 1965 Nobel Prize in Physics with Richard Feynman and Sin-Itiro Tomonaga. Schwinger himself, and later the historian Peter Galison, drew the line from the Rad Lab's equivalent circuits to that strategy.

Pidgins and Creoles

Galison, a historian of physics at Harvard, made the Rad Lab one of the central cases of his book *Image and Logic* (1997), a long study of how the instruments and working cultures of twentieth-century particle physics were made. One question the book asks is how groups with different training, vocabularies and standards of proof manage to work together at all. Philosophers of science, following Thomas Kuhn, had argued that people working in different paradigms in some sense cannot fully understand one another, because their key terms have different meanings. Yet theorists, experimenters and engineers do collaborate. Galison's answer borrowed a metaphor from anthropology and linguistics.

When two groups without a common language need to trade, they do not first learn each other's languages. They develop a *pidgin*: a reduced contact language, with a small vocabulary and simple grammar, adequate for the business at hand and not much else. Pidgins have arisen repeatedly around ports, plantations and trading posts. No one speaks a pidgin as a first language. If the contact persists, and especially if children grow up speaking it, a pidgin can expand into a *creole*: a full language with a complete grammar and vocabulary, able to express anything its speakers need, including poetry and argument about language itself. Tok Pisin, now one of the official languages of Papua New Guinea, began as a plantation pidgin and has native speakers today.

Galison called the places where such local languages develop *trading zones*. The important point about a trading zone is that the two parties need not agree about the meaning of what they exchange. They need only agree on the terms of exchange. A physicist could think of an equivalent circuit as a compressed solution of Maxwell's equations; an engineer could think of it as an addition to the familiar toolkit of radio; both could use the same diagram and the same tables of numbers, and their designs would work.

In Galison's account, the physicists and engineers who arrived at the Rad Lab in 1940 and 1941 could barely communicate. The physicists knew field theory and had no feel for the engineers' practical circuit algebra; the engineers distrusted physicists who solved boundary-value problems and could not say what a component would do in a circuit. What grew up between them, with the equivalent circuit at its centre, was something new. Summarising the book's argument, Galison put it in linguistic terms: the physicists supplied much of the vocabulary, the concepts of fields and modes and resonators, while the engineers supplied the grammar, the rules for combining components into working networks. By the end of the war this contact language had become a discipline of its own, which its practitioners called "microwave physics,"

neither Maxwellian electrodynamics as the physicists had known it nor radio engineering as the engineers had.[13] The Radiation Laboratory Series, written after the war, was in this sense the grammar book of a creole.

The trading zone is the book's third mechanism, and this is its original home. But Galison's picture is more specific than the general idea that mixing people produces ideas. It is not proximity that does the work, but the slow construction of a shared, limited language, organised around particular objects and techniques, which lets each side keep its own world-view while coordinating action with the other. That is a claim about language and practice, not about buildings. The building came later.

A Building for the Duration

By early 1943 the Rad Lab had outgrown every space MIT could give it. Its staff had spread through the main buildings and into an earlier temporary wooden structure, Building 22. Plans for a second building began in the spring. On 2 April 1943 the Boston architects McCreery and Theriault sent the laboratory three schemes, ranging from about 128,000 to 192,000 square feet; the design was complete by 1 May. Because steel was scarce, the building would have a frame of heavy timber, with wooden columns and girders on concrete footings, an exterior of grey asbestos-cement shingles, and interior partitions of wallboard. A wooden building of that size was not allowed under Cambridge's codes in that district, and on 5 May the city's Board of Appeal granted a variance. The estimated cost was a little over a million dollars. The building, numbered 20 in MIT's system, was ready for occupancy in December 1943, and parts of nine of the laboratory's divisions moved in.[14]

Its total floor area, including the bridges that connected it to its neighbours, was about 196,000 square feet: some four and a half acres, not the eighteen acres sometimes claimed, and less than the 250,000 square feet given in some later accounts. It had three storeys, a long spine parallel to Vassar Street, and wings lettered from A, of which the first three went up together. Rooms were numbered by wing, floor and room: the Tech Model Railroad Club's later home, for example, was 20E-214. An often-repeated story says that the building was designed in an afternoon. The archival record shows a month of design work, which by the standards of the time was fast enough.

The architect later explained that the city had allowed the building as a war measure, with a life of the duration of the war and six months thereafter. It is sometimes said that the building was designed to be torn down six months after the war. More precisely, its permission to exist was temporary; nobody seems to have planned its demolition, and MIT simply kept it. By the time the Rad Lab moved in, most of the laboratory's basic science had already been done, and the Rad Lab occupied many other buildings besides. The building is remembered as the laboratory's home because it was its largest one, and because it outlived it.

Outcomes and Legacy

The Radiation Laboratory closed on 31 December 1945. Its staff dispersed to universities and companies, but not before they had been asked to write down what they had learned. The result was the Radiation Laboratory Series, published by McGraw-Hill under the general editorship of Louis Ridenour between 1947 and 1953: twenty-seven technical volumes and an index, twenty-eight books in all, on everything from radar system engineering and magnetrons to servomechanisms, threshold signals in noise and the theory of computing linkages. For a generation the series was the standard reference of microwave engineering, and much of the vocabulary of electronics after the war was learned from it.

The physics of the war's leftovers. The Rad Lab's most striking legacy is in the research its people did once they returned to their universities, carrying wartime techniques and in many cases wartime equipment. In the autumn of 1945 Edward Purcell, who had led the laboratory's Fundamental Developments Group exploring new wavelengths, was still in Cambridge writing his share of the series with Henry Torrey and Robert Pound. Over lunch the three decided to look for the absorption of radio waves by atomic nuclei in an ordinary solid: the effect Rabi had measured in beams of isolated molecules. They borrowed a large magnet that had been used for cosmic-ray research at Harvard, built a resonant cavity and a sensitive receiver largely from leftover radar parts and wartime technique, and filled the cavity with paraffin wax, which is rich in hydrogen nuclei and transparent to radio waves. They found the resonance on 15 December 1945, at a magnet current higher than they had calculated, after they turned the magnet all the way up. Within weeks, at Stanford, Felix Bloch, William Hansen and Martin Packard independently observed the same phenomenon, which they called nuclear induction, in water. Bloch had spent part of the war working on radar countermeasures at Harvard's Radio Research Laboratory, and Hansen was one of the inventors of the klystron. Purcell and Bloch shared the Nobel Prize in Physics in 1952.[15] Nuclear magnetic resonance became the most important analytical tool in chemistry, and from the 1970s, through the work of Paul Lauterbur and Peter Mansfield, who shared the 2003 Nobel Prize in Physiology or Medicine, the basis of magnetic resonance imaging. The discovery is often dated to 1946, the year of publication; the experiment itself was done in December 1945, with the laboratory's techniques and some of its hardware.

Purcell's postwar career kept crossing borders. In 1951 he and his student Harold Ewen detected the radio emission of interstellar hydrogen at a wavelength of 21 centimetres, using a horn antenna of plywood lined with copper and receiver techniques from the war; the spectral line became one of radio astronomy's basic tools. A quarter of a century later he turned his physicist's eye on swimming bacteria, a story told in Chapter 8.

Robert Dicke, at the Rad Lab, had invented a way of measuring very faint microwave radiation by switching a receiver rapidly between the antenna and a reference source. In 1945 he and colleagues used the instrument to show that water vapour absorbs strongly near 1.25 centimetres (which explained why the laboratory's 1.25-centimetre radars had disappointed), and in passing reported an upper limit, of the order of 20 K, on any radiation from what they called cosmic matter.[16] Nineteen years later, at Princeton, Dicke's group was building a radiometer

of the same type to look for the faint afterglow of a hot early universe when Arno Penzias and Robert Wilson at Bell Laboratories, puzzling over an unexplained excess of noise of about 3.5 K in their antenna, found it first. The Dicke radiometer remains the basic design for instruments that measure faint microwave emission.

Luis Alvarez, back at Berkeley, built the first practical proton linear accelerator, a 40-foot copper tank in which protons were accelerated to about 32 million electron volts by a 200-megahertz field. The field was driven by oscillators that had begun life as surplus radar transmitters; it was the transmitters, not radar cavities, that the war supplied.[17] Charles Townes, who had worked on radar bombing systems at Bell Laboratories during the war, ran into the same water-vapour absorption that Dicke measured and turned it into a research programme in microwave spectroscopy. Working at the Columbia Radiation Laboratory, founded under Rabi in 1942 for wartime research on microwave tubes and kept going after the war with military funding, he conceived the maser in 1951 and built the first one with James Gordon and Herbert Zeiger in 1954. The laser followed. Townes was never at the MIT laboratory, but the maser grew from the same wartime microwave culture.

The incubator. The Rad Lab's Basic Research Division continued at MIT after the laboratory closed, and on 1 July 1946 it became the Research Laboratory of Electronics, MIT's first interdepartmental laboratory, under Julius Stratton. Its money came from a new Joint Services Electronics Program, in which the Army Signal Corps, the Navy and the Army Air Forces all took part. RLE took over much of Building 20, and the building began its second life as the home of whatever at MIT did not fit anywhere else. Jerrold Zacharias's group built one of the first practical caesium-beam atomic clocks there in the early 1950s, the forerunner of the first commercial one. Morris Halle, a phonologist who had come to MIT in 1951 to teach languages and do acoustic research on speech at RLE, recommended the hiring of Noam Chomsky in 1955. Chomsky was employed at RLE, in part on a project on mechanical translation led by Victor Yngve, which disappointed its leader by attracting linguists more interested in theory than in translation. *Syntactic Structures*, which grew out of Chomsky's lecture notes for MIT undergraduates and was published in The Hague in 1957, lists his affiliation as the Department of Modern Languages and RLE, and thanks the Army Signal Corps, the Air Force Office of Scientific Research and the Office of Naval Research, as well as the National Science Foundation and the Eastman Kodak Corporation, for support.[18] Linguistics at MIT grew up in Building 20, and Halle and Chomsky kept offices there for more than three decades.

In the same building Amar Bose, who completed his doctorate in electrical engineering in 1956, began research in physical acoustics and psychoacoustics, prompted partly by his disappointment with the loudspeakers he could buy; it led to the company he founded in 1964. Jerome Lettvin worked with Humberto Maturana, Warren McCulloch and Walter Pitts on the frog's visual system, published as "What the Frog's Eye Tells the Frog's Brain" in 1959; that work, and the world of cybernetics from which it came, belong to Chapter 6. The Tech Model Railroad Club, founded in 1946, occupied room 20E-214 from about 1948, and its members' delight in elaborate systems, and in clever ways around their rules, became one of the roots of what Steven Levy called the hacker ethic. Some of them moved on to MIT's computers, and the game *Spacewar!*, written in 1961–62 largely by club members and friends, ran on a PDP-1 in

Building 26, not in Building 20.[19]

The building was emptied in 1996–98. Its occupants held a farewell, called "The Magical Incubator," on 27 March 1998, and demolition began later that year. In its place MIT built the Ray and Maria Stata Center, designed by Frank Gehry and occupied from March 2004, whose tilted and colliding forms were meant in part to encourage the same chance meetings that Building 20 was remembered for. In 2007 MIT sued Gehry's firm and the builders over leaks, cracking and mould; the case was settled in 2010.

The template. The Rad Lab's most lasting legacy may have been institutional. It showed that a large laboratory, run by academic scientists, funded by government contract, working closely with industry and the military on a defined mission, could produce results at a pace no university department or company research laboratory had matched. Its veterans helped to run the laboratories that followed, among them MIT's Lincoln Laboratory, founded in 1951–52 for air defence, and they sat on the committees that shaped American science policy. The arrangement that Dwight Eisenhower would later call the military-industrial complex, with the universities as a third partner, took much of its form from the Rad Lab and Los Alamos. That legacy is not wholly a happy one.

The Costs of Crossing

The Rad Lab is a natural example for this book's argument: a problem that no single discipline could solve, solved by a coalition, with a well-documented account of how the coalition learned to talk. The story also complicates the argument in at least four ways.

The patron shaped the science. The money that made postwar American physics so rich came overwhelmingly from the armed services and the Atomic Energy Commission, and the Rad Lab was the model for how it flowed. In 1987 the historian Paul Forman argued that this patronage did more than pay for physics. Taking quantum electronics, the field of masers and lasers, as his main case, he argued that national-security funding redirected American physics towards problems and styles of work that served military ends, while physicists sustained the belief that they were following their own curiosity. Daniel Kevles replied that the integration of physics into the national-security state was real but came mostly after the Korean War, that most physicists embraced it knowingly, and that its effects on physics were on the whole positive.[20] The debate has not been settled, and need not be settled here. The point for this book is that a trading zone has terms of trade, and someone sets them. The language that physicists and engineers built at the Rad Lab was shaped by what the services wanted to buy, and the institutions that inherited it, RLE included, lived for decades on military contracts. Chomsky, whose politics later made him one of the Pentagon's sharpest critics, did his foundational work in a laboratory supported by all three services, as well as by civilian funders. Secrecy cost something too: much of the laboratory's work could not be published until after the war, and some of it never was.

The romance of the shed. Building 20 has become a parable about architecture. In *How*

Buildings Learn (1994), Stewart Brand made it the prime example of what he called Low Road buildings: cheap, ugly, disposable structures that occupants feel free to alter, and which for that reason keep finding new uses. He called it the most loved building at MIT. The idea has an older relative in Jane Jacobs's dictum, in *The Death and Life of Great American Cities* (1961), that "New ideas must use old buildings," although Jacobs was writing about the economics of cheap urban space, not about laboratories, and did not, as far as I can find, discuss Building 20. Its occupants' testimony about the building's freedom is consistent and sincere: they cut holes in walls for cables, took down partitions and bolted equipment to the roof without asking anyone. But how much of its productivity belonged to the building, and how much to the people, the money and the era? The building housed RLE, a laboratory with generous, flexible military funding and a mandate to cross departmental lines; it housed people whom MIT had chosen and who had nowhere else to go. Survivor bias does the rest: nobody tells stories about the dull projects in the shed next door. The research evidence on space and collaboration is real but narrower than the legend. Thomas Allen's studies of engineering laboratories in the 1960s and 1970s found that the frequency of technical communication between colleagues falls off steeply with the distance between their desks, dropping to a low, flat level beyond about 50 metres. Studies since then have found that collaborators in the same building tend to produce more highly cited papers, and that labs moved close together by an asbestos-removal programme at a Paris campus became more likely to collaborate. But open-plan offices, designed to promote encounters, have been found to reduce face-to-face interaction sharply, by about 70 per cent in one pair of studies, as people retreat into email.[21] Proximity seems to lower the cost of finding a collaborator; it does not by itself create the shared language that Galison describes. And the wartime work that produced that language had mostly been done before Building 20 existed.

The British disappear. In American popular memory, radar is often a Rad Lab story, and the magnetron an American device. The cavity magnetron was invented in Birmingham, engineered at Wembley and carried across the Atlantic by a British mission; H2S, ASV Mark III and the airborne interception sets that defended Britain in 1940–41 were British; and the first two years of the Rad Lab drew heavily on British experience, much of it transmitted by Bowen, who stayed in the United States and Canada after the mission left. Part of the imbalance is a matter of scale, since the United States built far more equipment, and part is a matter of who wrote the histories. The Radiation Laboratory Series was published openly and widely read; TRE's work stayed classified for longer, and its people, such as Bernard Lovell, wrote their own accounts decades later. Britain's financial need to trade its secrets for help also meant that much of the commercial value of its inventions, the magnetron above all, was realised in American factories.

The limits of the trading zone. Galison's metaphor is illuminating, and it has drawn fair criticism. One reviewer of *Image and Logic* found the pidgin-and-creole analogy overstretched. It is worth noticing that in a real pidgin, people with no common language must build a new one, whereas the physicists and engineers of the Rad Lab shared English, mathematics and a good deal of training. Harry Collins, Robert Evans and Michael Gorman have argued that the trading zone is now used for almost any interdisciplinary collaboration, and that Galison's inter-language is only one kind: collaborations can also be coerced rather than voluntary, and can leave the parties' cultures separate rather than blending them.[22] The Rad Lab was, in their

terms, partly an enforced zone: a wartime emergency in which a government conscripted talent, set the goal and paid the bills, and in which disagreements could be settled by a deadline. Those conditions explain some of its success, and they are not ones that a peacetime university can or should reproduce.

Coda

In 1939 there was no way to make a powerful beam of centimetre waves. By 1945 the Allies had thousands of microwave radars, in aircraft, on ships and at gun sites, built by a coalition of British inventors, American physicists, radio engineers, factory workers, technicians and human computers, many of the last two groups women whose names survive, if at all, in acknowledgements. What the physicists and engineers built between them was not only equipment but a way of talking: fields reduced to circuits, waveguides to transmission lines, a metal plate to a single number in a table. The wooden building most associated with them was put up after much of that language already existed, and outlived its purpose by half a century. Magnetron number 12 is in a museum in Ottawa. Its descendants are in most kitchens.

Notes

[1] E. G. Bowen, *Radar Days* (Bristol: Adam Hilger, 1987), is the source for Bowen's account of the journey. On the mission as a whole, see David Zimmerman, *Top Secret Exchange: The Tizard Mission and the Scientific War* (Montreal: McGill-Queen's University Press, 1996). Tizard's departure on 14 August is given in Roger Connor, "The Tizard Mission: 75 Years of Anglo-American Technical Alliance," Smithsonian National Air and Space Museum, 17 November 2015, https://airandspace.si.edu/stories/editorial/tizard-mission-%E2%80%93-75-years-anglo-american-technical-alliance; other accounts date his flight later in August. Ciardiello (next note) gives the date on which Bowen chose number 12.

[2] Emilio Ciardiello, "The Development of the British Cavity Magnetron and the Role of E. C. S. Megaw at GEC," https://www.ase-museoedelpro.org/a/The%20development%20of%20E1189_magnetron_revB.pdf, reconstructs the dates of the Bell tests and the X-ray from GEC and Bell records; he attributes the figure of 15 kW at Whippany to the accounts of Bowen, Conant and Phelps. Other sources give about 10 kW for the device, and some place the October demonstration at a General Electric laboratory in New Jersey rather than at Bell's. On the meetings of 19 and 28–29 September, see Zimmerman, *Top Secret Exchange*; and Jennet Conant, *Tuxedo Park: A Wall Street Tycoon and the Secret Palace of Science That Changed the Course of World War II* (New York: Simon & Schuster, 2002). Number 12 is now in the collection of Ingenium, the Canada Science and Technology Museum, in Ottawa.

[3] James Phinney Baxter III, *Scientists Against Time* (Boston: Little, Brown, 1946).

[4] On the wavelengths and limitations of Chain Home and of the airborne sets, see Louis Brown, *A Radar History of World War II: Technical and Military Imperatives* (Bristol: Institute of Physics Publishing, 1999). Technical details of Chain Home are summarised at https://www.radarpages.co.uk/mob/ch/chainhome2.htm.

[5] H. A. H. Boot and J. T. Randall, "Historical Notes on the Cavity Magnetron," *IEEE Transactions on Electron Devices* 23, no. 7 (1976). Randall's statement about Hertz's *Electric Waves* is in a 1984 let-

ter, reported in the Association of Radar and Microwave Museums' "Summary of Magnetron Development," https://www.armms.org/media/uploads/06_armms_nov12_rburman.pdf. For the date, power and wavelength, see also the IEEE Milestone "Development of the Cavity Magnetron, 1939–1941," https://ethw.org/Milestones:Development_of_the_Cavity_Magnetron,_1939-1941. The standard technical account of how magnetrons work, from the period, is George B. Collins, ed., *Microwave Magnetrons*, Radiation Laboratory Series 6 (New York: McGraw-Hill, 1948).

[6]Henry E. Guerlac, *Radar in World War II*, 2 vols., The History of Modern Physics 8 (New York: Tomash Publishers and American Institute of Physics, 1987), is the laboratory's official history, written during and just after the war and published decades later. Robert Buderi, *The Invention That Changed the World: How a Small Group of Radar Pioneers Won the Second World War and Launched a Technological Revolution* (New York: Simon & Schuster, 1996), is the best popular account. The dates of DuBridge's appointment are given in Buderi, *The Invention That Changed the World*, and Guerlac, *Radar in World War II*; on the committee's change of plan, see the oral history of Kenneth T. Bainbridge, IEEE History Center, https://ethw.org/Oral-History:Kenneth_T._Bainbridge.

[7]Guerlac, *Radar in World War II*. The laboratory's own commemorative volume, *Five Years at the Radiation Laboratory* (Cambridge, MA: Massachusetts Institute of Technology, 1946), presented to staff in September 1945, gives a contemporary picture of its organisation. Guerlac is also the source for the figures on women's employment given later in this section; on Black staff, see the MIT Black History Project, "Radiation Lab Group 36 Trainees, 1945," https://www.blackhistory.mit.edu/archive/radiation-lab-group-36-trainees-1945.

[8]On the SCR-584 at Anzio, see the American Physical Society's Historic Sites citation for the Radiation Laboratory, https://www.aps.org/programs/honors/history/historicsites/mit.cfm. On the V-1 campaign and the radar's role in it, see Buderi, *The Invention That Changed the World*; and Brown, *A Radar History of World War II*.

[9]National Inventors Hall of Fame, "Percy L. Spencer," https://www.invent.org/inductees/percy-l-spencer. Spencer later noticed that microwaves heated food, and Raytheon's microwave oven, the Radarange, followed.

[10]Kimball A. Milton, "In Appreciation: Julian Schwinger: From Nuclear Physics and Quantum Electrodynamics to Source Theory and Beyond," *Physics in Perspective* 9 (2007): 70–114, is the best short scientific biography and the source for Schwinger's habits and reasons. See also Jagdish Mehra and Kimball A. Milton, *Climbing the Mountain: The Scientific Biography of Julian Schwinger* (Oxford: Oxford University Press, 2000).

[11]N. Marcuvitz, *Waveguide Handbook*, Radiation Laboratory Series 10 (New York: McGraw-Hill, 1951), preface. Schwinger's lectures on the subject were published as Julian Schwinger and David S. Saxon, *Discontinuities in Waveguides: Notes on Lectures by Julian Schwinger* (New York: Gordon and Breach, 1968); a fuller collection is Kimball A. Milton and Julian Schwinger, *Electromagnetic Radiation: Variational Methods, Waveguides and Accelerators* (Berlin: Springer, 2006). The equivalent-circuit approach to microwave components generally is set out in C. G. Montgomery, R. H. Dicke and E. M. Purcell, *Principles of Microwave Circuits*, Radiation Laboratory Series 8 (New York: McGraw-Hill, 1948).

[12]Julian Schwinger, "Julian Schwinger's Approach to Particle Theory," Stanley H. Klosk Lecture, New York University School of Engineering Science, 1969, published in *Scientific Research*, 18 August 1969, as quoted in Milton, "Julian Schwinger."

[13]Peter Galison, *Image and Logic: A Material Culture of Microphysics* (Chicago: University of Chicago Press, 1997), especially the chapters "Laboratory War: Radar Philosophy and the Los Alamos Man" and "The Trading Zone: Coordinating Action and Belief." Galison's summary of the argument, including

the phrase "microwave physics," is in his "Author's Outline" in the review symposium on the book in *Metascience* 8 (1999): 356–60; the reviewers' criticisms and his "Author's Response," 393–404, follow in the same issue. See also Peter Galison, "Pragmatism at War," in Joan Ockman, ed., *The Pragmatist Imagination* (New York: Princeton Architectural Press, 2001), 148–55; and "Feynman's War: Modelling Weapons, Modelling Nature," *Studies in History and Philosophy of Modern Physics* 29, no. 3 (1998): 391–434.

[14]MIT Libraries, Institute Archives and Special Collections, "Celebrating Building 20: History," https://libraries.mit.edu/archives/mithistory/building20/history.html, which summarises the architects' correspondence, the variance and the costs. McCreery's phrase about the building's intended life is from a 1946 letter quoted there.

[15]E. M. Purcell, H. C. Torrey and R. V. Pound, "Resonance Absorption by Nuclear Magnetic Moments in a Solid," *Physical Review* 69, nos. 1–2 (1946): 37–38; F. Bloch, W. W. Hansen and Martin Packard, "Nuclear Induction," *Physical Review* 69, nos. 3–4 (1946): 127. The circumstances of the Harvard experiment are described in Harvard University Department of Physics, "The Discovery of NMR," 2019, https://www.physics.harvard.edu/sites/projects.iq.harvard.edu/files/physics/files/2019-nmr.pdf.

[16]R. H. Dicke, "The Measurement of Thermal Radiation at Microwave Frequencies," *Review of Scientific Instruments* 17, no. 7 (1946): 268–75; Robert H. Dicke, Robert Beringer, Robert L. Kyhl and A. B. Vane, "Atmospheric Absorption Measurements with a Microwave Radiometer," *Physical Review* 70, nos. 5–6 (1946): 340–48; A. A. Penzias and R. W. Wilson, "A Measurement of Excess Antenna Temperature at 4080 Mc/s," *Astrophysical Journal* 142 (1965): 419–21. Secondary accounts describe the 1946 limit variously; Dicke's later recollections give a lower figure for the 1.25-centimetre measurement.

[17]Smithsonian National Museum of American History, "Alvarez Proton Linear Accelerator," https://www.si.edu/object/nmah_700150.

[18]Noam Chomsky, *Syntactic Structures* (The Hague: Mouton, 1957), preface; W. John Hutchins, "Obituary: Victor H. Yngve," *Computational Linguistics* 38, no. 3 (2012): 461–67; "Institute Professor Emeritus Morris Halle, Innovative and Influential Linguist, Dies at 94," MIT News, 3 April 2018. Accounts differ over who was most responsible for Chomsky's appointment; Halle, Roman Jakobson, RLE's director Jerome Wiesner and Yngve himself are all credited in different sources. On Halle's and Chomsky's offices in Building 20, see MIT Libraries, "Celebrating Building 20."

[19]J. Y. Lettvin, H. R. Maturana, W. S. McCulloch and W. H. Pitts, "What the Frog's Eye Tells the Frog's Brain," *Proceedings of the IRE* 47, no. 11 (1959): 1940–51; Steven Levy, *Hackers: Heroes of the Computer Revolution* (Garden City, NY: Anchor Press/Doubleday, 1984). On the club's room, see MIT Libraries, "Celebrating Building 20." On *Spacewar!*, see J. M. Graetz, "The Origin of Spacewar," *Creative Computing* 7, no. 8 (August 1981), which places the PDP-1 next to the TX-0; that machine had moved with RLE to Building 26 by 1957.

[20]Paul Forman, "Behind Quantum Electronics: National Security as Basis for Physical Research in the United States, 1940–1960," *Historical Studies in the Physical and Biological Sciences* 18, no. 1 (1987): 149–229; Daniel J. Kevles, "Cold War and Hot Physics: Science, Security, and the American State, 1945–56," *Historical Studies in the Physical and Biological Sciences* 20, no. 2 (1990): 239–64. For a summary of the exchange, see Zuoyue Wang, "From Modern Physics to the Cold War and Beyond," *Historical Studies in the Natural Sciences* 50, nos. 1–2 (2020): 25–30.

[21]Stewart Brand, *How Buildings Learn: What Happens After They're Built* (New York: Viking, 1994); Jane Jacobs, *The Death and Life of Great American Cities* (New York: Random House, 1961); Thomas J. Allen, *Managing the Flow of Technology: Technology Transfer and the Dissemination of Technological Information within the R&D Organization* (Cambridge, MA: MIT Press, 1977); Thomas J. Allen and Gunter Henn, *The Organization and Architecture of Innovation: Managing the Flow of Technology* (Oxford: Butterworth-Heinemann,

2007); Kyungjoon Lee, John S. Brownstein, Richard G. Mills and Isaac S. Kohane, "Does Collocation Inform the Impact of Collaboration?," *PLoS ONE* 5, no. 12 (2010): e14279; Christian Catalini, "Microgeography and the Direction of Inventive Activity," *Management Science* 64, no. 9 (2018): 4348–64; Ethan S. Bernstein and Stephen Turban, "The Impact of the 'Open' Workspace on Human Collaboration," *Philosophical Transactions of the Royal Society B* 373, no. 1753 (2018): 20170239.

[22]H. M. Collins, Robert Evans and Mike Gorman, "Trading Zones and Interactional Expertise," *Studies in History and Philosophy of Science* 38, no. 4 (2007): 657–66. The criticism of the linguistic analogy is made in Jeff Hughes's contribution to the *Metascience* symposium on *Image and Logic*, *Metascience* 8 (1999): 379–87, at 382.

Further Reading

Robert Buderi, *The Invention That Changed the World: How a Small Group of Radar Pioneers Won the Second World War and Launched a Technological Revolution* (Simon & Schuster, 1996). The most readable history of the Rad Lab and its postwar consequences, based on many interviews. Its title is more triumphant than its content.

Henry E. Guerlac, *Radar in World War II*, 2 vols. (Tomash Publishers and American Institute of Physics, 1987). The laboratory's official history, exhaustive on organisation, projects and people. A reference work rather than a narrative.

E. G. Bowen, *Radar Days* (Adam Hilger, 1987). The Tizard Mission and early British airborne radar from the man who carried the magnetron. Lively and personal; best read alongside more documented accounts.

David Zimmerman, *Top Secret Exchange: The Tizard Mission and the Scientific War* (McGill-Queen's University Press, 1996). The diplomatic and scientific history of the mission, careful about what each side gave and got.

Louis Brown, *A Radar History of World War II: Technical and Military Imperatives* (Institute of Physics Publishing, 1999). A technical history covering all the combatants, useful for putting British and American work in proportion.

Peter Galison, *Image and Logic: A Material Culture of Microphysics* (University of Chicago Press, 1997). Long and demanding; the chapters on the Rad Lab and on the trading zone are the source of this chapter's central idea and can be read on their own.

Kimball A. Milton, "Julian Schwinger: From Nuclear Physics and Quantum Electrodynamics to Source Theory and Beyond," *Physics in Perspective* 9 (2007). A clear scientific biography by Schwinger's former student, good on the Rad Lab years and their influence on his later physics.

N. Marcuvitz, *Waveguide Handbook* (McGraw-Hill, 1951; reissued by the Institution of Electrical Engineers). For the technically minded: the equivalent-circuit pidgin in its finished form, still in use.

Stewart Brand, *How Buildings Learn: What Happens After They're Built* (Viking, 1994). The source of the Building 20 legend in its best-known form, and a thoughtful book about buildings in its own right.

Online: MIT Libraries, "Celebrating Building 20," `https://libraries.mit.edu/archives/mithistory/building20/`, with the building's history and occupants; and the IEEE History Center's milestone pages on the cavity magnetron and the Radiation Laboratory, `https://ethw.org`.

Chapter 6

The Macy Conferences and the Cybernetic Dream (1946–1953)

575 Park Avenue

On the morning of Friday 8 March 1946, about twenty people sat down together in a meeting room of the Beekman Hotel, at 575 Park Avenue in Manhattan. The war had been over for six months. Most of the people in the room had spent it on military work, some of it still secret, and few of them had met all the others. They included two mathematicians, Norbert Wiener of the Massachusetts Institute of Technology and John von Neumann of the Institute for Advanced Study in Princeton; an engineer, Julian Bigelow; four neurophysiologists, among them the Mexican Arturo Rosenblueth and the Spaniard Rafael Lorente de Nó; a psychiatrist who had become a neurophysiologist, Warren McCulloch of the University of Illinois, who was in the chair; McCulloch's young collaborator Walter Pitts, who had no degree at all; two anthropologists, Margaret Mead and her husband Gregory Bateson; a psychoanalyst, Lawrence Kubie; the social psychologist Kurt Lewin; the sociologist Paul Lazarsfeld; a statistician, Leonard Savage; psychologists, a philosopher and a few others. The Josiah Macy Jr. Foundation paid for their travel, their rooms and their meals.

The foundation's medical director, Frank Fremont-Smith, opened proceedings by telling the group that every meeting of this kind was an experiment: if the participants found it exciting enough, they would meet again. Then von Neumann described the new electronic digital computers, and Lorente de Nó described the neuron, treating it as a switching element. Over the two days Wiener and Rosenblueth explained how machines and animals could pursue goals by correcting their own errors, McCulloch showed how networks of idealised neurons could carry out logic, Bateson asked whether a machine could learn how to learn, and Kubie explained neurosis as a compulsion to repeat. When Kubie spoke of psychic energy, Wiener objected that what mattered in a nervous system was not energy but information. Attempts to record the meeting mechanically largely failed, and nothing of substance survives of what Lewin said; Mead kept her own notes in shorthand.[1]

The meeting's title was "Feedback Mechanisms and Circular Causal Systems in Biological and Social Systems." It was the first of ten conferences, held between 1946 and 1953, that are now known collectively as the Macy conferences on cybernetics, a word that did not yet exist. Their premise was that a few ideas worked out during the war, about control, communication and computation, applied equally to anti-aircraft guns, nervous systems, minds and societies. Some of that premise proved right, and changed several sciences. Some of it proved to be analogy, and it did not survive. This chapter is about both.

The Science: Feedback and Its Discontents

The central idea in that room was older than anyone in it. A machine that controls itself must measure the difference between what it is doing and what it is supposed to be doing, and use that difference to change what it does. Engineers call the measured difference the *error*, and the arrangement by which the error is fed back to the controller *feedback*. When the correction acts to reduce the error, as it must if the machine is to settle on its goal, the feedback is *negative*.

The classic example is the centrifugal governor of the steam engine, which James Watt adapted from millwrights' practice in the 1780s. Two heavy balls hang from arms on a spindle turned by the engine. As the engine speeds up the balls fly outward, and the arms, through a linkage, close the steam valve; as it slows they fall and open it. By the middle of the nineteenth century engineers had found that governors could misbehave. Instead of holding an engine steady, some made its speed swing up and down, a fault they called *hunting*. In 1868 James Clerk Maxwell, the physicist who unified electricity and magnetism, published a short paper in the *Proceedings of the Royal Society* called "On Governors." It begins plainly: a governor is "a part of a machine by means of which the velocity of the machine is kept nearly uniform." Maxwell wrote down linearised equations for the motion of the engine and its governor and showed that whether the motion settled or hunted depended on the roots of a polynomial built from the machine's constants: the system was stable only if every root had a negative real part. He solved the problem completely for the simplest cases and left the general one open. Edward Routh, a Cambridge mathematician, solved it in 1877.

The same problem returned in the telephone network. Long-distance lines needed amplifiers every few dozen miles, and the vacuum-tube amplifiers of the 1920s distorted the signals they amplified, by amounts that drifted as the tubes aged. On the morning of 2 August 1927, Harold Black, a young engineer at Bell Telephone Laboratories in New York, was crossing the Hudson on the Lackawanna ferry when he saw a solution, and sketched it on a blank page of his copy of the *New York Times*. Build an amplifier with far more gain than needed, and feed a fraction of its output back to its input, inverted. The amplifier then amplifies the difference between what it is producing and a scaled copy of what it should produce, and the overall gain depends almost entirely on the passive components in the feedback path, not on the temperamental tubes. Black's patent application met years of resistance from examiners, apparently because the idea ran against accepted theory; the patent was granted in December 1937. Meanwhile his colleagues found that feedback amplifiers sometimes burst into oscillation, singing

at a frequency of their own. Harry Nyquist, also in the Bell System, worked out the condition for stability in 1932, in a form engineers could read off a graph of the amplifier's response, and Hendrik Bode turned his result into a design method.[2]

Why should a mechanism designed to correct errors make them worse? The answer, in every one of these cases, is a combination of too much correction and too little time.

Science Primer: Gain, delay and oscillation

Imagine a controller that tries to bring some quantity x (a shaft's speed, a gun's bearing, a hand's position) to a goal g. It acts in discrete steps. At each step it measures the error, $x_n - g$, and moves x by a fixed fraction k of the error in the direction that reduces it:

$$x_{n+1} = x_n - k\,(x_n - g).$$

Here n counts the steps and k, the *gain*, says how hard the controller pushes. Writing $e_n = x_n - g$ for the error, the rule becomes simply

$$e_{n+1} = (1 - k)\,e_n.$$

Each step multiplies the error by $(1 - k)$. Start with an error of 10 units and try some gains:

- $k = 0.5$: the errors are 10, 5, 2.5, 1.25, ... A smooth, cautious approach.
- $k = 1$: 10, 0. The controller corrects exactly in one step.
- $k = 1.5$: 10, -5, 2.5, -1.25, ... It overshoots, then overshoots back, but each swing is smaller. A damped oscillation.
- $k = 2$: 10, -10, 10, -10, ... The swings never die away.
- $k = 2.5$: 10, -15, 22.5, -33.75, ... Each correction is bigger than the error it was meant to fix. The system runs away.

The error shrinks only if the multiplier $(1 - k)$ lies between -1 and 1: that is, if $0 < k < 2$. Above $k = 1$ the approach is oscillatory; above $k = 2$ the oscillation grows.

Now add a delay, which every real system has. Suppose the controller acts on the error it measured one step *earlier*: $e_{n+1} = e_n - k\,e_{n-1}$. Starting from errors of 10 and 10, a gain of 0.5 gives 10, 10, 5, 0, -2.5, -2.5, -1.25, 0, ...: it overshoots and swings, but settles. A gain of 1 gives 10, 10, 0, -10, -10, 0, 10, 10, ...: a steady oscillation. A gain of 1.2 gives swings that grow. (The size of the swings changes by a factor of $\sqrt{k}$ at every step, so the boundary is now $k = 1$.) The delay has halved the gain the system can tolerate.

This is the whole story of hunting governors and singing amplifiers in miniature. Feedback is safe only if the product of how hard you correct and how late you correct stays below a limit. Maxwell's roots, Nyquist's criterion and Bode's design rules are rigorous ways of finding that limit for continuous systems with many delays and lags. (These calculations are my illustration.)

The Science: Predicting an Aeroplane

Norbert Wiener came to anti-aircraft gunnery from a long way off. He was born in Columbia, Missouri, on 26 November 1894, the son of Leo Wiener, a philologist who became professor of Slavic languages at Harvard and who educated his son at home with a severity that the son later described, with mixed feelings, in his memoir *Ex-Prodigy*. Norbert graduated from Tufts College at fourteen and took a Harvard doctorate in 1913, at eighteen, with a dissertation in mathematical logic comparing Ernst Schröder's algebra of relations with that of Whitehead and Russell's *Principia Mathematica*. He went on to study with Bertrand Russell at Cambridge in 1913–14 and briefly with David Hilbert at Göttingen in 1914. After a restless few years, including wartime work computing ballistic tables at the Aberdeen Proving Ground, he joined the mathematics department of MIT in 1919 and stayed there for the rest of his career. His work of the 1920s gave a rigorous mathematical description of Brownian motion, the jittering of small particles in a fluid, which led him into the mathematics of random processes and of signals that fluctuate in time. He was short, stout and very short-sighted, and generations of MIT students remembered him walking the corridors reading, with one hand trailing along the wall to guide him.[3]

In September 1940, with the Battle of Britain at its height, Wiener wrote to Vannevar Bush, who ran the new National Defense Research Committee, offering his services. By November he had proposed a way of improving anti-aircraft fire, and on 1 December the NDRC's fire-control section, run by the mathematician Warren Weaver (the Rockefeller director of Chapter 3), gave MIT a contract for a "General Mathematical Theory of Prediction and Applications." In January 1941 Wiener took on Julian Bigelow, a twenty-seven-year-old electrical engineer trained at MIT who was also an amateur pilot.

The problem was this. A shell fired at a bomber flying several miles up takes ten or twenty seconds to arrive, and in that time the bomber may move a mile or more. The gun must be aimed at where the aircraft will be, not where it is. If the bomber flew straight and level, a simple extrapolation would do. But a pilot under fire weaves, and the radar or optical tracker that follows him adds errors of its own. Wiener's idea was to treat the aircraft's track as a statistical signal. A pilot cannot fly however he likes: his aeroplane has inertia, and so, under stress, does he. Wiener and Bigelow came to describe the pilot as behaving like a servomechanism, and to think of the gunner too as one more component in a loop of men and machines. If you knew, from many recorded tracks, how strongly an aircraft's position at one moment was correlated with its position a second or two or ten later, you could design the best possible predictor: a device that takes a weighted sum of the recent track and outputs a forecast, with the weights chosen to make the average squared error of the forecast as small as possible. The same mathematics also solves the problem of separating a signal from noise, which is why this kind of optimal linear predictor became known as the *Wiener filter*. The Soviet mathematician Andrey Kolmogorov had reached equivalent results for discrete sequences independently, in 1939–41.

Wiener wrote up the theory in a classified report dated 1 February 1942, *Extrapolation, Interpolation, and Smoothing of Stationary Time Series with Engineering Applications*. It was bound

in yellow covers, and the engineers who struggled with its mathematics called it the Yellow Peril. Meanwhile Wiener and Bigelow built an electrical predictor and tested it, first on tracks generated in the laboratory by a person steering a spot of light with a deliberately sluggish control stick, and in the summer of 1942 on real tracking data from Camp Davis in North Carolina. Watching a demonstration on 1 July 1942, George Stibitz of Bell Laboratories, one of Weaver's advisers, wrote in his diary that the statistical predictor "accomplishes miracles." But the miracle extended only a second or two into the future, and the gun needed ten or twenty. When Wiener compared his method with much simpler predictors designed by Bode at Bell Laboratories, on the same recorded tracks, the statistical method did about as well as the best of them, slightly better on one track and somewhat worse on another. Weaver concluded in late 1942 that it offered only a marginal advantage over Bode's far simpler design, and the NDRC ended the project in January 1943. Bigelow moved to a wartime statistical group at Columbia University; Wiener, who believed that a larger body of data would show his method's value, agreed that it could not be ready in time to matter.[4]

The anti-aircraft directors that went to war came from Bell Laboratories. The M9 gun director, an electrical analogue computer proposed by David Parkinson and Clarence Lovell in 1940, reached the army as a prototype in December 1941 and was combined in 1944 with the Radiation Laboratory's SCR-584 radar and the proximity fuze in the defence of southern England against the V-1 flying bombs (Chapter 5). Its prediction rested on simpler assumptions about the target's course, not on Wiener's statistics. At the end of the war three Bell Laboratories researchers, Ralph Blackman, Bode and a young man named Claude Shannon, wrote a report on data smoothing and prediction in fire control that built on Wiener's work but questioned some of its assumptions, and treated the problem as one of separating signal from noise in a communication system. Wiener's predictor never fired a shot. What survived of it was the theory, and a way of thinking: that a human operator and a machine could be described in the same terms, as parts of one loop.

Purpose Tremor

Wiener's closest scientific friend in the 1930s was a physiologist. Arturo Rosenblueth, born in Chihuahua in 1900 and trained in medicine in Berlin and Paris, had gone to Harvard Medical School in 1930 to work with Walter Cannon, whose studies of how the body keeps its temperature, blood sugar and acidity within narrow limits had given biology the word *homeostasis* and the book *The Wisdom of the Body* (1932). At Harvard, Rosenblueth ran a monthly dinner seminar on scientific method, held at a round table in Vanderbilt Hall, at which a speaker presented a paper and the others, mostly young scientists from many fields, attacked it. Wiener was a regular. In the introduction to *Cybernetics* he recalled that he and Rosenblueth had long shared the conviction that the most fruitful territory for science lay in the "no-man's land between the various established fields," and that it could only be explored by teams of specialists who each understood something of their neighbours' work. It is a fair statement of this book's thesis, made in 1948.

According to the account Wiener gave in that introduction, the anti-aircraft work led him and Bigelow to a general conclusion: feedback was essential not only to machines but to voluntary human action. When you reach for a pencil, you do not compute in advance the sequence of muscle contractions that will bring your hand to it. You start moving and correct continuously, guided mainly by the sense of the position of your own limbs, until the distance between hand and pencil is zero. Patients who lose that sense, as in the late stages of syphilis of the spinal cord, cannot make the correction and move clumsily. But the predictor work had taught Wiener and Bigelow that excessive feedback is as bad as too little. So they asked Rosenblueth whether there was a condition in which a patient trying to perform a voluntary act overshoots the target and goes into an uncontrollable oscillation. Rosenblueth, in Wiener's telling, answered at once that there was: it was called *purpose tremor*, and it was often associated with injury to the cerebellum. (Neurologists today usually call it intention tremor.) The three men took this as strong confirmation of their view.

The anecdote should be read for what it is: a retrospective account, by one participant, of an insight that probably formed more gradually. But the clinical picture is real, and the analogy is apt. In the language of the primer, a damaged cerebellum seems to leave the arm's control loop with the wrong balance of gain and delay.

Rosenblueth presented the group's ideas in public in May 1942, at a small meeting in New York on cerebral inhibition that Fremont-Smith had organised for the Macy Foundation. Its official subjects were hypnosis, introduced by the psychiatrist Milton Erickson, and the conditioned reflex, introduced by the physiologist Howard Liddell. Rosenblueth's talk on feedback and purpose made the strongest impression. McCulloch was there, and so were Bateson and Mead. Mead later recalled being so absorbed that she did not notice until the meeting was over that she had broken a tooth. The following year Rosenblueth, Wiener and Bigelow published "Behavior, Purpose and Teleology" in the journal *Philosophy of Science*.

The paper is short, and stranger than its reputation. It proposes a classification of behaviour by its outward form alone: active or passive; purposeful or random; and, within purposeful behaviour, guided by negative feedback or not, predictive or not. A frog snapping at a fly acts too fast to correct its aim in flight, so its behaviour is purposeful but not guided by feedback; a cat chasing a mouse runs towards where the mouse will be, which is predictive. A torpedo with a target-seeking mechanism, by the same definitions, behaves purposefully. The authors argued that "teleology," the explanation of behaviour by its goals, had been discredited because it seemed to require a future cause to act on the present, and that this was unnecessary: purposeful behaviour could be defined as behaviour controlled by negative feedback, which works entirely through the present error. Machines and organisms, they concluded, could be studied with the same categories. The cerebellar patients appear in a single sentence, as people whose hands swing back and forth when they try to lift a glass of water. Not everyone was persuaded. The philosopher Richard Taylor argued in 1950 that the authors' definition captured little of what the word "purpose" ordinarily means.[5]

Logic in the Nervous System

Warren McCulloch, who would chair every one of the Macy conferences, was born in Orange, New Jersey, in 1898. He studied philosophy and psychology at Yale, took a medical degree at Columbia in 1927, worked as a neurologist and in a psychiatric hospital, and in the 1930s did research on the organisation of the primate cortex at Yale. In 1941 he moved to the University of Illinois's Neuropsychiatric Institute in Chicago. He was a bearded, voluble man who wrote poetry, drank a good deal and kept open house, and he had long been preoccupied with a philosopher's question: what kind of logic a nervous system could embody.

In Chicago he acquired two young protégés. Jerome Lettvin was a medical student, born in 1920. Walter Pitts, born in Detroit on 23 April 1923, was something else entirely. He had left home in his teens, and by his late teens was living precariously around the University of Chicago, where he sat in on classes without enrolling and impressed the logician Rudolf Carnap and the mathematical biophysicist Nicolas Rashevsky. Several of the stories told about his youth, including that he had read *Principia Mathematica* in a public library at twelve and written to Russell about its errors, come from Lettvin's later recollections, and one of Pitts's biographers warns that embellishment has crept into them. What is certain is that by 1942 McCulloch had taken Pitts and Lettvin to live with his family in the Chicago suburb of Hinsdale, and that the evenings of talk there produced a paper.

"A Logical Calculus of the Ideas Immanent in Nervous Activity," by McCulloch and Pitts, appeared in Rashevsky's *Bulletin of Mathematical Biophysics* in 1943. Pitts was about nineteen when it was written. The paper took the physiology of the day, in which a neuron either fires or does not, and simplified it into an abstract unit. Its claim was that anything expressible in a certain formal logic could be computed by a network of such units, and conversely. Its logical language was taken from Carnap, its notation partly from *Principia*. With loops in the network the units could hold information over time; with the addition of something like a tape, the authors noted, such a network could compute whatever Alan Turing's abstract machine could (Chapter 4).

Science Primer: Threshold logic: the McCulloch–Pitts neuron

A McCulloch–Pitts unit has several input lines and one output. Time moves in discrete steps. At each step every line is either active (1) or silent (0). Some inputs are *excitatory*, some *inhibitory*. The unit has a *threshold*, a whole number θ. The rule is: at the next step the unit fires if, and only if, at least θ of its excitatory inputs are active and none of its inhibitory inputs is. (In the 1943 paper a single active inhibitory input vetoes firing absolutely.)

AND. Give a unit two excitatory inputs, a and b, and a threshold of 2. It fires only when both are active:

a	b	output
0	0	0
0	1	0
1	0	0
1	1	1

OR. The same unit with a threshold of 1 fires when either input, or both, is active.

NOT. Give a unit one excitatory input that is always active, and make a an inhibitory input, with a threshold of 1. When a is silent, the constant input fires the unit; when a is active, it vetoes firing. The output is the opposite of a.

Since AND, OR and NOT can be combined to build any logical function of any number of inputs, networks of these units can compute any such function. Feed a unit's output back to its own excitatory input and it keeps firing once started: a one-bit memory. Modern textbooks describe the same unit with numerical *weights*: each input is multiplied by a weight (negative for inhibition), the products are summed, and the unit fires if the sum reaches the threshold. Two inputs with weights of 1 and a threshold of 1.5 make AND; with a threshold of 0.5, OR.

One function a single unit cannot compute is "exclusive or" (fire if exactly one input is active), because no single threshold separates the cases (0,1) and (1,0) from (0,0) and (1,1). It needs two layers of units. That limitation, analysed at length by Marvin Minsky and Seymour Papert in 1969, would shape the history of neural networks.

Most neurophysiologists took little notice of the paper; its neurons were too simple to describe real ones, and it made no predictions they could test. Its first important reader was a mathematician. In the autumn of 1943 Lettvin brought Pitts to Wiener, who was so impressed that he took him on at MIT as a special student. Wiener introduced the paper to von Neumann, and when von Neumann wrote the *First Draft of a Report on the EDVAC* in June 1945, the document that set out the logical design of the stored-program computer, he described its circuits in a notation of idealised neurons. The only work the report cites is McCulloch and Pitts. The borrowing was a matter of notation rather than architecture, as the historians Thomas Haigh and Mark Priestley have pointed out, but it shows how quickly the abstraction travelled. A neuron had become a logic gate, and a logic gate could be described as a neuron.[6]

By the end of 1944 Wiener, von Neumann and Howard Aiken, builder of the Harvard Mark I calculator, were planning a meeting of engineers, mathematicians and neurophysiologists interested in what all three kinds of system had in common. It took place in Princeton in January 1945, and those present talked of forming a "Teleological Society."[7] The society never formally existed. Its programme was taken over by McCulloch, who persuaded Fremont-Smith to sponsor a series of meetings; Bateson, back from wartime service in South-East Asia, persuaded Fremont-Smith that social scientists should be included.

The Conferences

The Josiah Macy Jr. Foundation had been set up in 1930 by Kate Macy Ladd, in memory of her father, with an endowment to support medicine. Her letter of gift asked the foundation to concern itself with "fundamental aspects of health, of sickness, and of methods for the relief of suffering," and to prefer work that would integrate the medical sciences rather than divide them. Fremont-Smith, a Harvard-trained physician who had worked in neuropathology and who became its medical director in 1936, turned that preference into a method. Instead of funding projects, he convened small groups of specialists from several fields, around a shared problem, for two days of discussion rather than formal papers, and published the discussions afterwards. Between 1941 and 1960 the foundation held some 160 such conferences, on subjects across medicine and biology. The cybernetics series was the most mixed of them.

The format was not as wild as it has sometimes been described. Speakers prepared presentations, often coordinated in advance, but they were expected to be interrupted, and they were; the published transcripts are full of questions and objections in mid-presentation. A core group of about twenty attended regularly, with a few invited guests each time. Their title changed as the group's sense of itself did. The first meeting spoke of "Feedback Mechanisms and Circular Causal Systems"; the second, in October 1946, of "Teleological Mechanisms"; from the fourth the series used "Circular Causal and Feedback Mechanisms in Biological and Social Systems." Meanwhile, in the summer of 1947, Wiener and his colleagues had settled on a name for the whole field, from the Greek *kybernētēs*, a steersman, the root, by way of a Latin corruption, of the English word "governor." Wiener's book *Cybernetics: Or Control and Communication in the Animal and the Machine* appeared in 1948 in Paris and New York. It is dense with mathematics, but it sold well, went through several printings, and was reviewed in *Time*. At the sixth conference, in March 1949, the group adopted Wiener's term, and from the seventh the series was called "Cybernetics: Circular Causal and Feedback Mechanisms in Biological and Social Systems."[8]

Records of the first five conferences are fragmentary. At the sixth, Heinz von Foerster, a thirty-seven-year-old Viennese physicist who had arrived at the University of Illinois that year with a theory of memory, was invited as a guest and took on the editing of the proceedings; with Mead and the psychologist Hans-Lukas Teuber as assistant editors, he published edited transcripts of the last five meetings between 1950 and 1955. The transcripts make clear that the conferences were not a symposium of agreement. They were a sustained argument, and the arguments are the most interesting part.

The sharpest were between those who wanted mechanisms and those who offered interpretations. Kubie, a psychoanalyst, returned again and again to the problem of neurosis, and McCulloch, who had worked in psychiatric hospitals and was sceptical of psychoanalysis, criticised it openly at the sixth meeting. Pitts, decades younger than most of the others, questioned speakers with a rigour that some found exhilarating and others intimidating; when the group discussed whether to make the psychoanalyst Erik Erikson a permanent member after his paper of 1947, Pitts's view that he lacked rigour prevailed. The Gestalt psychologist Wolfgang Köhler, one of the most eminent psychologists in the world, was invited to explain his theory

Table 6.1: The ten Macy conferences on cybernetics. All but the last were held at the Beekman Hotel in New York

Conference and date	**Some guests or new members**	**Some topics and events**
1. 8–9 March 1946	(Founding core group)	Von Neumann on computers; Lorente de Nó on neurons; Wiener and Rosenblueth on feedback; Kubie on neurosis.
2. October 1946	Schneirla, Brosin, Marquis	Lewin on field theory; Schneirla on army ants.
3. March 1947	Erikson, Kluckhohn, Festinger	Lewin had died in February; Erikson's paper on child psychiatry poorly received.
4. 23–24 October 1947	Teuber	Köhler's Gestalt field theory, criticised by McCulloch and Pitts; long argument over analogue and digital.
5. Spring 1948	Jakobson, Lee, Morris, Bavelas	A session on language, organised by Mead and Bateson.
6. 24–25 March 1949	Von Foerster	"Cybernetics" adopted; von Foerster on memory; first transcripts published.
7. 23–24 March 1950	Shannon, Licklider	Shannon on the redundancy of printed English; Gerard warns against overstated claims.
8. 15–16 March 1951	MacKay, Richards, Shannon	Shannon's maze-solving machine; MacKay on information and meaning. Wiener and von Neumann no longer attend.
9. 20–21 March 1952	Ashby, Quastler, Wiesner	Ashby's homeostat; Bateson on humour and paradox.
10. 22–24 April 1953, Princeton	Grey Walter, Bar-Hillel, Shannon	Teuber objects to publishing the discussions; only papers are published.

that perception arises from electrical fields in the cortex. The cyberneticians had been waiting to hear him, and his talk led to a bad-tempered argument, with McCulloch and Pitts demanding neurological evidence that Köhler did not have. He did not come back. Heinrich Klüver, a psychologist and a founding member, later criticised both Köhler and McCulloch. And through several meetings the group returned, without resolution, to whether the nervous system was best described as digital, like the McCulloch–Pitts network, or analogue, like a chemical or electrical continuum. The neurophysiologist Ralph Gerard argued that much of it was analogue and warned his colleagues against claiming more than they knew.

The social scientists found the atmosphere difficult. Mead complained that the group invited guests from other fields without briefing them on its vocabulary and then grumbled when they did not keep up. Lazarsfeld drifted away; Lewin's death in February 1947 removed the social scientist most interested in formal models. The philosopher F. S. C. Northrop, the only professional philosopher among the founders, is said to have stayed largely silent after the first meeting. Wiener himself was sceptical of the social sciences' appetite for his ideas: he warned at a special meeting for social scientists in 1946 that they lacked the long runs of consistent statistical data on which his methods depended.

At the end of the last conference, in Princeton in April 1953, McCulloch summed up. The group's most notable agreement, he said, was that its members had learned to know one another better, and "to fight fair in our shirt sleeves."[9] After seven years, it was an honest assessment.

Information

Claude Shannon came to the seventh conference, in March 1950, as a guest, and he attended twice more. He was then thirty-three, a mathematician at Bell Laboratories who had written, as an MIT master's student in 1937, the thesis that showed how Boolean logic could describe telephone relay circuits. During the war he had worked on fire control, where he met Wiener's ideas from the other side, and on cryptography, where in a classified report of 1945 he had begun to measure the uncertainty in a message. He had met Alan Turing over tea at Bell Laboratories in 1943 (Chapter 4).

In July and October 1948 he published "A Mathematical Theory of Communication" in the *Bell System Technical Journal*. It set aside the question that most people would think central. "These semantic aspects of communication," Shannon wrote of meaning, "are irrelevant to the engineering problem." The engineer's problem is to reproduce at one point a message selected at another, and what matters about a message is that it was chosen from a set of possible messages. The more possibilities there were, and the more evenly likely they were, the more information the choice conveys. Shannon gave that idea a number, with a unit he called the *bit*, a word suggested by his Bell Labs colleague John Tukey, and used it to prove theorems about how much information any channel could carry and how far messages could be compressed. Ralph Hartley, also at Bell, had proposed a logarithmic measure of information in 1928. Shannon's measure generalised it to choices whose outcomes are not equally likely.[10]

Science Primer: Entropy: counting surprise in bits

Suppose a source produces one of several outcomes, with probabilities $p_1, p_2, \ldots$ that add up to 1. Shannon defined its *entropy*, the average information per outcome, as

$$H = -\sum_i p_i \log_2 p_i.$$

The logarithm to base 2 means that information is measured in bits: $\log_2 2 = 1$, $\log_2 4 = 2$, $\log_2 8 = 3$. The minus sign makes H positive, since logarithms of numbers less than 1 are negative. Each term $-\log_2 p_i$ measures the surprise of one outcome (rare outcomes are more surprising), and H averages the surprise over all outcomes.

A fair coin. Two outcomes, each with $p = \frac{1}{2}$. Then $H = -(\frac{1}{2}\log_2 \frac{1}{2} + \frac{1}{2}\log_2 \frac{1}{2}) = 1$ bit. One toss settles one yes-or-no question.

A biased coin. Heads with $p = 0.9$, tails with $p = 0.1$. Then $H = -(0.9\log_2 0.9 + 0.1\log_2 0.1) \approx 0.47$ bits. You can usually guess the result, so learning it tells you less. A coin that always lands heads has $H = 0$.

A fair die. Six equally likely faces: $H = \log_2 6 \approx 2.58$ bits. When all N outcomes are equally likely, $H = \log_2 N$, which is Hartley's measure.

Two dice, added. The sum runs from 2 to 12, but not evenly: 7 can be made six ways out of 36, 2 and 12 only one way each. Working through the eleven terms gives $H \approx 3.27$ bits, less than the $\log_2 11 \approx 3.46$ bits that eleven equally likely outcomes would carry. Unevenness reduces entropy.

Shannon's coding theorem says that H is the smallest average number of binary digits per outcome into which the source's output can be compressed. Twenty-six equally likely letters would need $\log_2 26 \approx 4.7$ bits each. English is far from even: letters have unequal frequencies and constrain one another. By asking people to guess the next letter of passages of text, Shannon estimated in 1951 that printed English carries only about one bit per letter, between roughly 0.6 and 1.3. That gap between 4.7 and about 1 is *redundancy*, and it is what lets you read a smudged page. Shannon spoke on it at the seventh Macy conference.

The formula has the same form as one in physics. In the statistical mechanics of Ludwig Boltzmann and J. Willard Gibbs, the thermodynamic entropy of a system that can be in states with probabilities p_i is $S = -k_B \sum_i p_i \ln p_i$, where k_B is Boltzmann's constant and ln is the natural logarithm. Shannon noted the resemblance. But his H is a property of a probability distribution over messages, measured in bits; S is a physical quantity, measured in joules per kelvin. Shannon's entropy is not a thermodynamic measure, and a telephone line has no temperature in his theory. The relation between the two, which runs through the physics of measurement and computation, was worked out by others over the following decades and is still debated.

Why "entropy"? A famous story says that John von Neumann suggested the word, telling

Shannon that the function already had that name in statistical mechanics and, more importantly, that nobody really knows what entropy is, so in a debate Shannon would always have the advantage. The story's source is the engineer Myron Tribus, who said that Shannon had told it to him during a visit to MIT in 1961; Tribus told it in print in the 1960s and again, more prominently, in 1971. When the engineer Robert Price put it to Shannon in an interview published in 1984, Shannon said he was quite sure it had not happened between von Neumann and himself; Price noted that Shannon had already used the word in his wartime cryptography report.[11] The anecdote is too good to disappear, and too thinly sourced to repeat as fact.

Shannon's paper and Wiener's book appeared in the same year and were often treated as halves of one theory, which annoyed both men's admirers. Shannon acknowledged in 1948 that communication theory was heavily indebted to Wiener for its basic philosophy, and cited the Yellow Peril as the first clear formulation of communication as a statistical problem. Wiener, in *Cybernetics*, treated information as a central concept of his new science and derived a version of the same measure. In later life Shannon said that he did not think Wiener had had much to do with information theory. The two theories are related but different: Wiener's concerned the estimation of a continuous signal in noise, Shannon's the coding of discrete messages for transmission, and engineers took up Shannon's.

Shannon was also a builder of ingenious machines, and at the eighth conference, in March 1951, he presented one. Theseus was a small model mouse that found its way through a maze of twenty-five squares whose walls could be rearranged. The mouse was moved by an electromagnet on a carriage beneath the floor; the intelligence lay in several dozen telephone relays under the maze. Exploring by trial and error, the mouse recorded at each square the direction in which it had last left; once it had found the goal, the relays held the path, and on its next run it went straight there. Change the maze and it explored again, keeping what was still valid. Whether such a machine could be said to learn, or to remember, was a question that became harder to wave away with the machine on the table.

The British psychiatrist W. Ross Ashby brought another machine to the ninth conference, in 1952. His homeostat, completed in March 1948 at Barnwood House, a psychiatric hospital in Gloucester, consisted of four interconnected units built partly from surplus RAF bomb-control equipment, each with a magnetised needle that swung in a trough of water. Each unit's output affected the others. When a needle strayed outside its limits, a switch changed the unit's connections at random, and the machine went on changing them until it found an arrangement that was stable. Ashby called this *ultrastability*, and argued that it was a model of how a brain adapts: not by being designed for each situation, but by trial and change until the essential variables are back within bounds. The popular press had already called it a synthetic brain. Its reception at the conference was mixed: some participants doubted that it modelled anything a brain actually did. Ashby's *Design for a Brain* was published the same year.[12] At the tenth conference the British neurophysiologist W. Grey Walter, builder of small battery-powered robot "tortoises" that steered towards light, was a guest. British cybernetics, built around machines like these and Ashby's, was in some ways more practical than the American kind.

The Anthropologists

Why were two anthropologists among the founders? Part of the answer is personal: Bateson and Mead had been at the 1942 meeting, and Bateson had lobbied for the social sciences to be included. Part is intellectual. Bateson had been thinking for a decade about systems that feed on their own output.

Gregory Bateson, born in 1904, was the son of the geneticist William Bateson, who had coined the word "genetics," and he had trained in biology before turning to anthropology. In the late 1920s and early 1930s he did fieldwork among the Iatmul of the Sepik River in New Guinea, and in *Naven* (1936) he tried to explain a ceremony in which Iatmul men and women dressed as the opposite sex. He introduced a term, *schismogenesis*, for a process of progressive differentiation in which each party's behaviour provokes more of the same from the other. In its *symmetrical* form, each party responds to the other's boasting, or arming, with more of its own; in its *complementary* form, one party's assertiveness elicits the other's submission, which elicits more assertiveness. Left alone, either process escalates until the relationship breaks. Bateson thought that rituals like naven might act to restrain it.

Read in the vocabulary of the primer, schismogenesis is runaway positive feedback, and naven is something like a corrective loop. Bateson saw this himself, after the fact. In 1971 he wrote that the writing of *Naven* had brought him to "the very edge of what later became cybernetics," and that what he had lacked was the concept of negative feedback. He recalled meeting McCulloch and Bigelow, full of talk about feedback, at the Macy meeting of 1942, and going to Fremont-Smith after the war to ask for a conference on the subject.[13] In the late 1930s he and Mead, who had married in 1936, did fieldwork together in Bali, making thousands of photographs and many hours of film, and in 1949 he published an essay on Balinese society called "Bali: The Value System of a Steady State." Its puzzle was why the schismogenic escalation he had seen among the Iatmul seemed absent in Bali. His answer was psychological and cultural rather than mechanical. He described how, as he and Mead had observed, Balinese mothers would stimulate a child towards a climax of excitement and then let their attention drift, so that the child learned not to expect cumulative interactions to build to a resolution; and he argued that Balinese values favoured a continuing, even level of activity over the pursuit of climax and the maximisation of any single goal. The essay is sometimes summarised as describing a "cultural thermostat," a negative-feedback mechanism that damps escalation. That is not quite its argument. It is about character formation and values, and Bateson framed it as a hypothesis, admitting that one part of it could not yet be documented.

Mead, already famous for *Coming of Age in Samoa* (1928), attended every one of the ten conferences, by Ronald Kline's account, took notes when no machine would, helped edit the transactions and kept the social scientists in the room. She was less interested in formal models than Bateson and more in the conferences as an experiment in communication across disciplines, which in a sense they were. In 1967 she gave the keynote address to the first meeting of the American Society for Cybernetics, urging its members to apply cybernetic thinking to their own society; von Foerster published it under the title "Cybernetics of Cybernetics."

Outcomes and Legacy

Cybernetics as a named field did not survive long in the United States. Its ideas did, scattered across disciplines that rarely acknowledge the common source. Tracing them requires care, because the conferences have been credited with almost everything.

Cognitive science. The psychologist George Miller dated the birth of cognitive science to 11 September 1956, the second day of a symposium on information theory at MIT, at which Allen Newell and Herbert Simon described a program that proved theorems in logic, Noam Chomsky presented the transformational grammar that would make him famous (and used information theory as a foil), and Miller himself spoke on the limits of short-term memory. Miller had been a behaviourist and had tried to apply Shannon's measure to psychology; by his own account he found it of limited help, and turned to Chomsky. The decline of behaviourism had several causes: the computer as a model of internal processes, Chomsky's linguistics, the work of Jean Piaget and Jerome Bruner, and a general impatience with theories that refused to talk about the mind. Cybernetics belongs on that list, as one source of the idea that internal states, goals and information processing were legitimate objects of scientific study. It did not "give birth" to the cognitive revolution, and several of the revolution's founders, Chomsky among them, owed little to it.

Artificial intelligence. In August 1955 John McCarthy, Marvin Minsky, Nathaniel Rochester and Shannon proposed a summer research project at Dartmouth College on "artificial intelligence"; it took place in the summer of 1956. McCarthy later wrote that one of his reasons for inventing the term was "to escape association with 'cybernetics'," and that he did not want either to accept Wiener as a guru or to have to argue with him.[14] The early AI programme built symbolic reasoning programs, not adaptive machines, and its leaders saw themselves as a new field. But the line from the McCulloch–Pitts paper, Shannon's work on chess-playing programs and his maze-solving machine, and von Neumann's late work on automata to Dartmouth is direct, and Minsky's own doctoral thesis was on neural networks.

The frog's eye. The collaboration between McCulloch, Pitts and Lettvin moved to MIT's Research Laboratory of Electronics in 1952 (Chapter 5), and in 1959 Lettvin, Humberto Maturana, McCulloch and Pitts published "What the Frog's Eye Tells the Frog's Brain." Recording from single fibres of the frog's optic nerve, they found cells that responded not to light as such but to specific features: edges, moving contrasts, dimming, and small dark convex objects moving in jerks: in effect, bug detectors. "The eye speaks to the brain in a language already highly organized and interpreted," they wrote. It was a founding paper of the study of feature detection in the visual system, and the processing it described, analogue, local and tailored to the animal's way of life, was a long way from the logical calculus of 1943.[15]

Neural networks. In 1958 Frank Rosenblatt, a psychologist at the Cornell Aeronautical Laboratory, published the *perceptron*, a network of threshold units like McCulloch and Pitts's but with adjustable connection weights that changed with experience, so that the network could learn to classify patterns. The "exclusive or" problem of the primer, and the difficulty of training networks with more than one layer, led to a long eclipse. The method that eventually solved

the training problem, back-propagation of errors, popularised in 1986, and the vast computing power of the twenty-first century produced the deep networks that now recognise images and generate text. In 2024 the Nobel Prize in Physics went to John Hopfield and Geoffrey Hinton for foundational discoveries that enable machine learning with artificial neural networks. Chapter 12 follows one application. The units in those networks still compute a weighted sum and pass it through a threshold, or a smooth version of one.

Control and estimation. Feedback control did not need cybernetics; it had Maxwell, Nyquist and Bode, and in wartime laboratories such as MIT's Servomechanisms Laboratory it became a discipline with its own textbooks. Wiener's filter became a standard tool of signal processing, and in 1960 Rudolf Kalman published a recursive method of estimation, suited to digital computers, that superseded it for many purposes and was used to navigate the Apollo spacecraft.[16] Most control engineers today would not call themselves cyberneticians; in Europe and the former Soviet Union, the word survives more readily in the names of departments.

Family therapy. In the early 1950s Bateson, then in California, began a research project on communication, based at the Veterans Administration hospital in Menlo Park, with Jay Haley, John Weakland and, from 1954, the psychiatrist Don Jackson. Their paper of 1956, "Toward a Theory of Schizophrenia," proposed that schizophrenia might arise in families whose members repeatedly put one another in a *double bind*: contradictory messages at different levels, with no permission to comment on the contradiction or to leave. In 1958–59 Jackson and colleagues founded the Mental Research Institute in Palo Alto, which became one of the centres of family therapy, an approach that treats the family rather than the individual as the system to be understood. Bateson's ideas were central to it, but he did not found it. As an explanation of the cause of schizophrenia, the double-bind hypothesis has not been supported; schizophrenia is now understood to have a large genetic component.[17]

Second-order cybernetics. Von Foerster founded the Biological Computer Laboratory at the University of Illinois on 1 January 1958, with support mainly from the US Air Force, the Navy and other federal agencies. Ashby joined it in 1961; Maturana and Francisco Varela, who later developed the theory of living systems as self-producing (*autopoietic*), visited from Chile. In the late 1960s and 1970s von Foerster argued for a "cybernetics of observing systems" as opposed to the cybernetics of observed systems: one that included the observer in what was observed. The laboratory closed in the mid-1970s, when military funding agencies began to require research with clear military applications. Second-order cybernetics influenced constructivist philosophy, family therapy and design theory more than the sciences.

The Soviet Union and Chile. In the Soviet Union, cybernetics went from heresy to orthodoxy in a decade. Articles from 1950 onwards attacked it as an American pseudoscience that reduced people to machines, and the *Short Philosophical Dictionary* of 1954 called it a reactionary pseudoscience. In 1955 the military engineer Anatoly Kitov and the mathematicians Sergei Sobolev and Alexey Lyapunov published "The Main Features of Cybernetics" in the leading philosophy journal, presenting it as a general science of control and information. In 1959 the Academy of Sciences set up a Council on Cybernetics under Admiral Aksel Berg, and in 1961 the council published a volume titled *Cybernetics in the Service of Communism*. For Soviet geneti-

cists still recovering from the Lysenko years, the vocabulary of information offered cover: a unit of hereditary information sounded less provocative than a gene. The most ambitious attempt to use cybernetics in government came in Chile. In 1971 Fernando Flores, a senior official of Salvador Allende's government, invited the British management cybernetician Stafford Beer to design a system for running the newly nationalised industries. Project Cybersyn linked factories to Santiago by telex, ran statistical software to flag problems, and built an operations room with swivel chairs and screens. The telex network helped the government keep supplies moving during a strike in October 1972. The project was incomplete when the military coup of 11 September 1973 ended it.[18]

The Costs of Crossing

The Macy conferences look like the ideal of this book: mathematicians, engineers, physiologists, psychiatrists and anthropologists in one room, finding the same structure in guns, nerves and societies. The story also shows the limits of that ideal, in at least four ways.

Analogy is not a result. The conferences were best at finding resemblances and worst at testing them. The resemblance between a hunting governor and a tremor was illuminating because both could be described by the same equations, and those equations made predictions. The resemblance between a feedback loop and a society's rituals, or between a nervous system and a digital computer, was often only a resemblance, and nobody in the room had the data to turn it into more. Wiener knew this; he warned the social scientists that they lacked the long, consistent series of observations his methods required. Shannon knew it too. In 1956 he wrote an editorial for the journal of his own field, titled "The Bandwagon," complaining that information theory had been "ballooned to an importance beyond its actual accomplishments," that people in psychology, economics and biology were using its words without its methods, and that whether a human being behaves like an ideal decoder is an experimental question, not a mathematical one.[19] The vocabulary of information, feedback and system spread through the social sciences in the 1950s and 1960s, in political science, in management and in the general systems movement, far faster than any demonstrated result. Some of what came of it was valuable; much of it renamed familiar ideas. Molecular biology adopted the language of codes and information, to great effect and with some confusion (Chapter 3). The movement's reputation suffered for its enthusiasts' claims, and when cybernetics faded in the United States in the 1960s, it was partly because its most visible products were analogies and its most productive researchers had moved into fields with other names.

People, not only ideas, broke the circle. In 1951 or 1952 (accounts differ), Wiener broke off all relations with McCulloch and everyone associated with him, including Pitts and Lettvin, just as McCulloch's group was moving to MIT to work alongside him. He never explained why. Flo Conway and Jim Siegelman, drawing on interviews with Wiener's daughters and with Lettvin, attribute the break to Wiener's wife, Margaret, who disliked McCulloch and his household and is said to have told her husband that their daughter Barbara had been seduced by members of McCulloch's circle while staying with them in Chicago some years before. Lettvin regarded

the accusation as false. The account rests largely on interviews conducted half a century later, and members of the wider Wiener family have disputed the biography's portrait of Margaret; it should be treated as the best available explanation, not as established fact. The effect is not in doubt. Wiener had been Pitts's mentor and protector, and by Lettvin's account the break devastated him. At some point afterwards (sources disagree about when) he destroyed his unfinished doctoral dissertation and years of notes, and he refused to complete the formalities for a degree. He drank heavily and experimented on himself with drugs. He went on working with Lettvin's group, and his name is on the frog's-eye paper, but he published little else. He died alone in a boarding house in Cambridge, Massachusetts, on 14 May 1969, of bleeding from oesophageal varices, a complication usually of cirrhosis of the liver. He was forty-six. McCulloch died that September.[20] The trading zone that the conferences created depended on a handful of personal relationships, and it was as fragile as they were.

The field was born of a weapon, and its founder turned against weapons. Cybernetics grew out of gunnery: the predictor, the M9, the fire-control reports in which Wiener, Bode and Shannon all worked out their ideas. Wiener's later stance makes this uncomfortable rather than simple. In the *Atlantic Monthly* for January 1947 he published an open letter, "A Scientist Rebels," refusing an aircraft company's request for one of his wartime reports. After Hiroshima and Nagasaki, he wrote, a scientist could no longer assume that giving information to whoever asked for it was innocent, and he did not intend to publish future work that could do damage "in the hands of irresponsible militarists."[21] That month he also cancelled a talk at a symposium on calculating machines because it was funded by the military, and he spent much of his remaining career warning about the social effects of automation. Others in the group took the opposite course: von Neumann became one of the most influential scientific advisers to the American military and the Atomic Energy Commission. The postwar sciences that grew from these conferences, computing, AI and control above all, were funded overwhelmingly by the armed services, as the Biological Computer Laboratory's fate shows. The terms of trade in this trading zone were set, as at the Rad Lab (Chapter 5), largely by the military.

The founder myth. Wiener is routinely called the father of cybernetics, and the conferences are often called the place where it was born. Both are half true. The mathematics of feedback was Maxwell's, Nyquist's and Bode's; the predictor that went to war was Bell's; the information theory that engineers used was Shannon's, who said Wiener had little to do with it; the theory of prediction had been reached independently by Kolmogorov; and the engineering of the predictor was Bigelow's, who went on to be chief engineer of von Neumann's computer at the Institute for Advanced Study. Pitts, who contributed perhaps the most original single idea, died in obscurity. The conferences themselves were less a birthplace than a meeting point, a place where results obtained elsewhere were compared, argued over and generalised, sometimes too far. That is not a small thing. But it is a different thing from discovery.

Coda

The ten conferences produced no theory on which all their members agreed, and few results that could not have been obtained without them. What they did was put a computer designer, a neuroanatomist, a psychoanalyst and an anthropologist in the same room, about once a year, long enough to discover what they did not understand about each other. The word they adopted has become a prefix for anything to do with computers, a use none of them intended. The ideas went their separate ways: into control engineering, into the visual cortex of a frog, into family therapy in Palo Alto, into an operations room in Santiago, and into networks of threshold units that, some eighty years after McCulloch and Pitts, learned to write.

Notes

[1]The date, venue, list of participants and order of the opening presentations are from Steve J. Heims, *The Cybernetics Group* (Cambridge, MA: MIT Press, 1991), which reconstructs the early meetings from participants' papers and Mead's notes. A conference-by-conference summary based on Heims and on Jean-Pierre Dupuy, *The Mechanization of the Mind: On the Origins of Cognitive Science* (Princeton: Princeton University Press, 2000), is maintained by the American Society for Cybernetics at `https://asc-cybernetics.org/foundations/history/MacySummary.htm`. Some secondary sources give 21–22 March 1946 for the first meeting; 8–9 March is the date given by Heims and the ASC summary.

[2]J. C. Maxwell, "On Governors," *Proceedings of the Royal Society of London* 16 (1868): 270–83. Wiener called it the first significant paper on feedback mechanisms: Norbert Wiener, *Cybernetics: Or Control and Communication in the Animal and the Machine* (Paris: Hermann; Cambridge, MA: Technology Press; New York: Wiley, 1948). Ronald Kline, "Harold Black and the Negative-Feedback Amplifier," *IEEE Control Systems* 13, no. 4 (August 1993): 82–84, gives the date and circumstances of Black's idea and the history of the patent; H. S. Black, "Stabilized Feedback Amplifiers," *Bell System Technical Journal* 13, no. 1 (1934); H. Nyquist, "Regeneration Theory," *Bell System Technical Journal* 11 (1932): 126–47. The best history of control engineering before cybernetics is David A. Mindell, *Between Human and Machine: Feedback, Control, and Computing before Cybernetics* (Baltimore: Johns Hopkins University Press, 2002).

[3]Biographical details from I. E. Segal, "Norbert Wiener, November 26, 1894–March 18, 1964," *Biographical Memoirs of the National Academy of Sciences* (1992); the title of the dissertation is "A Comparison between the Treatment of the Algebra of Relatives by Schroeder and That by Whitehead and Russell" (PhD diss., Harvard University, 1913). Wiener's own accounts are *Ex-Prodigy: My Childhood and Youth* (New York: Simon & Schuster, 1953) and *I Am a Mathematician: The Later Life of a Prodigy* (Garden City, NY: Doubleday, 1956). The hand on the wall is a recollection of former students; see "The Original Absent-Minded Professor," *MIT Technology Review*, 21 June 2011.

[4]The contract, the report and the termination are documented in David A. Mindell, Jérôme Segal and Slava Gerovitch, "From Communications Engineering to Communications Science: Cybernetics and Information Theory in the United States, France, and the Soviet Union," in Mark Walker, ed., *Science and Ideology: A Comparative History* (London: Routledge, 2003), 66–96. The demonstration, Stibitz's diary and the comparison with Bode's predictors are from Peter Galison, "The Ontology of the Enemy: Norbert Wiener and the Cybernetic Vision," *Critical Inquiry* 21, no. 1 (1994): 228–66. The report was published as Norbert Wiener, *Extrapolation, Interpolation, and Smoothing of Stationary Time Series, with Engineering Applications* (Cambridge, MA: Technology Press; New York: Wiley, 1949).

[5]Wiener, *Cybernetics*, introduction. The exchange with Rosenblueth is known only from this account, written several years later; Wiener does not claim to give the words of the conversation, and versions in which Wiener and Bigelow walk across to the medical school, or Rosenblueth reacts with astonishment, are later embroidery. On Rosenblueth, see Arturo Rosenblueth, Walter B. Cannon and the Harvard physiology department in the biographical sources collected by Heims, *The Cybernetics Group*. On the Cerebral Inhibition Meeting, held in New York in May 1942, see Heims, *The Cybernetics Group*, which quotes Mead's recollection. Some accounts date it 13–15 May. Arturo Rosenblueth, Norbert Wiener and Julian Bigelow, "Behavior, Purpose and Teleology," *Philosophy of Science* 10, no. 1 (1943): 18–24; Richard Taylor, "Comments on a Mechanistic Conception of Purposefulness," *Philosophy of Science* 17, no. 4 (1950): 310–17. Rosenblueth and Wiener replied in the same journal.

[6]Neil R. Smalheiser, "Walter Pitts," *Perspectives in Biology and Medicine* 43, no. 2 (2000): 217–26, gives Pitts's birth date and his living arrangements and cautions about the anecdotes. Amanda Gefter, "The Man Who Tried to Redeem the World with Logic," *Nautilus*, no. 21 (2015), is a vivid popular account that draws on Lettvin's recollections and on Flo Conway and Jim Siegelman's biography of Wiener. Warren S. McCulloch and Walter Pitts, "A Logical Calculus of the Ideas Immanent in Nervous Activity," *Bulletin of Mathematical Biophysics* 5 (1943): 115–33; Thomas Haigh and Mark Priestley, "Von Neumann Thought Turing's Universal Machine Was 'Simple and Neat.' But That Didn't Tell Him How to Design a Computer," *Communications of the ACM* 63, no. 1 (2020): 26–32. Pitts's arrival at MIT in the autumn of 1943 is from Wiener's introduction to *Cybernetics*.

[7]Haigh and Priestley, "Von Neumann Thought," date the meeting to January 1945 from the participants' correspondence; a study of Wiener's papers by Mai Sugimoto (in Japanese, Kyoto University, 2008) also places it in January 1945. Wiener himself, in *Cybernetics*, placed it in the late winter of 1943–44, and some later accounts follow him.

[8]The foundation's own history, published in 2012, quotes the letter of gift of 24 April 1930: `https://macyfoundation.org/assets/img/macy-history-book--final-2012.pdf`. Fremont-Smith's role and the format of the conference programme are described in Heims, *The Cybernetics Group*. Titles and the adoption of the new name are from the ASC summary and from Ronald R. Kline, *The Cybernetics Moment: Or Why We Call Our Age the Information Age* (Baltimore: Johns Hopkins University Press, 2015), which gives the first title in a slightly different form ("... in Biology and the Social Sciences"). Wiener dates the word to the summer of 1947 and explains its derivation in *Cybernetics*.

[9]Heinz von Foerster, Margaret Mead and Hans Lukas Teuber, eds., *Cybernetics: Circular Causal and Feedback Mechanisms in Biological and Social Systems*, Transactions of the Sixth to Tenth Conferences, 5 vols. (New York: Josiah Macy Jr. Foundation, 1950–55). All five volumes, with surviving material from the earlier meetings, are reprinted in Claus Pias, ed., *Cybernetics: The Macy Conferences 1946–1953. The Complete Transactions* (Zurich: Diaphanes, 2016). The disputes are summarised in the ASC summary and discussed in Heims, *The Cybernetics Group*, which has a chapter on Köhler's visit, and in Kline, *The Cybernetics Moment*, which describes Erikson's rejection, Mead's complaint about the treatment of guests and Wiener's warning to the social scientists. McCulloch's summary appears in the *Transactions of the Tenth Conference* (1955); see also Pias, ed., *The Complete Transactions*.

[10]C. E. Shannon, "A Mathematical Theory of Communication," *Bell System Technical Journal* 27 (1948): 379–423, 623–56; republished with an introductory essay by Warren Weaver as Claude E. Shannon and Warren Weaver, *The Mathematical Theory of Communication* (Urbana: University of Illinois Press, 1949). The estimate for English is from C. E. Shannon, "Prediction and Entropy of Printed English," *Bell System Technical Journal* 30, no. 1 (1951): 50–64. For his life, see Jimmy Soni and Rob Goodman, *A Mind at Play: How Claude Shannon Invented the Information Age* (New York: Simon & Schuster, 2017).

[11]Myron Tribus and Edward C. McIrvine, "Energy and Information," *Scientific American* 225, no. 3

(September 1971): 179–88; Robert Price, "A Conversation with Claude Shannon: One Man's Approach to Problem Solving," *IEEE Communications Magazine* 22, no. 5 (May 1984): 123–26.

[12]Claude E. Shannon, "Presentation of a Maze-Solving Machine," in von Foerster, Mead and Teuber, eds., *Transactions of the Eighth Conference* (1952), reprinted in N. J. A. Sloane and A. D. Wyner, eds., *Claude Elwood Shannon: Collected Papers* (New York: IEEE Press, 1993). The original machine is in the MIT Museum. W. Ross Ashby, *Design for a Brain* (London: Chapman & Hall, 1952). On the homeostat's construction and reception, see Andrew Pickering, *The Cybernetic Brain: Sketches of Another Future* (Chicago: University of Chicago Press, 2010), which also covers Grey Walter, Bateson and Stafford Beer.

[13]Gregory Bateson, "Culture Contact and Schismogenesis," *Man* 35 (1935): 178–83; Bateson, *Naven: A Survey of the Problems Suggested by a Composite Picture of the Culture of a New Guinea Tribe Drawn from Three Points of View* (Cambridge: Cambridge University Press, 1936; 2nd ed., Stanford, CA: Stanford University Press, 1958). Gregory Bateson, foreword to *Steps to an Ecology of Mind* (San Francisco: Chandler, 1972). The collection also reprints "Bali: The Value System of a Steady State," first published in Meyer Fortes, ed., *Social Structure: Studies Presented to A. R. Radcliffe-Brown* (Oxford: Clarendon Press, 1949).

[14]George A. Miller, "The Cognitive Revolution: A Historical Perspective," *Trends in Cognitive Sciences* 7, no. 3 (2003): 141–44. John McCarthy, review (1988) of Brian Bloomfield, ed., *The Question of Artificial Intelligence* (London: Croom Helm, 1987), https://www-formal.stanford.edu/jmc/reviews/bloomfield/bloomfield.html. The Dartmouth proposal is dated 31 August 1955.

[15]J. Y. Lettvin, H. R. Maturana, W. S. McCulloch and W. H. Pitts, "What the Frog's Eye Tells the Frog's Brain," *Proceedings of the IRE* 47, no. 11 (1959): 1940–51.

[16]F. Rosenblatt, "The Perceptron: A Probabilistic Model for Information Storage and Organization in the Brain," *Psychological Review* 65, no. 6 (1958): 386–408; Marvin Minsky and Seymour Papert, *Perceptrons: An Introduction to Computational Geometry* (Cambridge, MA: MIT Press, 1969). R. E. Kalman, "A New Approach to Linear Filtering and Prediction Problems," *Journal of Basic Engineering* 82, no. 1 (1960): 35–45.

[17]Gregory Bateson, Don D. Jackson, Jay Haley and John Weakland, "Toward a Theory of Schizophrenia," *Behavioral Science* 1, no. 4 (1956): 251–64. For a sympathetic review that nonetheless concludes the causal claim remains unestablished, see Matthijs Koopmans, "Schizophrenia and the Family: Double Bind Theory Revisited" (1997), https://goertzel.org/dynapsyc/1997/Koopmans.html.

[18]Slava Gerovitch, *From Newspeak to Cyberspeak: A History of Soviet Cybernetics* (Cambridge, MA: MIT Press, 2002); S. L. Sobolev, A. I. Kitov and A. A. Lyapunov, "Osnovnye cherty kibernetiki" [The Main Features of Cybernetics], *Voprosy filosofii*, no. 4 (1955): 136–48; Mindell, Segal and Gerovitch, "From Communications Engineering." Eden Medina, *Cybernetic Revolutionaries: Technology and Politics in Allende's Chile* (Cambridge, MA: MIT Press, 2011).

[19]Claude E. Shannon, "The Bandwagon," *IRE Transactions on Information Theory* 2, no. 1 (1956): 3.

[20]Flo Conway and Jim Siegelman, *Dark Hero of the Information Age: In Search of Norbert Wiener, the Father of Cybernetics* (New York: Basic Books, 2005). For criticism of its portrait of Margaret Wiener, see the letter of Hope Franklin O'Neill, Wiener's niece, in "Knowing Norbert Wiener," *New York Review of Books*, 22 September 2005. Smalheiser, "Walter Pitts"; Gefter, "The Man Who Tried to Redeem the World with Logic." Lettvin's own recollections are in James A. Anderson and Edward Rosenfeld, eds., *Talking Nets: An Oral History of Neural Networks* (Cambridge, MA: MIT Press, 1998).

[21]Norbert Wiener, "A Scientist Rebels," *Atlantic Monthly*, January 1947. Wiener elaborated his concerns about automation and control in *The Human Use of Human Beings: Cybernetics and Society* (Boston: Houghton Mifflin, 1950).

Further Reading

Steve J. Heims, *The Cybernetics Group* (MIT Press, 1991). The standard history of the conferences, reconstructed from participants' papers and Mead's notes; strongest on the social scientists and on the arguments. Now available open access.

Ronald R. Kline, *The Cybernetics Moment: Or Why We Call Our Age the Information Age* (Johns Hopkins University Press, 2015). A careful history of how cybernetics and information theory spread and then separated, good on the conferences' internal politics and on why cybernetics faded in the United States.

Norbert Wiener, *Cybernetics: Or Control and Communication in the Animal and the Machine* (Technology Press and Wiley, 1948; 2nd ed., MIT Press, 1961). The introduction, which tells the story of the predictor and the tremor, is readable by anyone; the rest is mathematics.

Peter Galison, "The Ontology of the Enemy: Norbert Wiener and the Cybernetic Vision," *Critical Inquiry* 21 (1994). An influential and critical essay arguing that cybernetics carried the logic of the anti-aircraft predictor into its picture of human beings.

David A. Mindell, *Between Human and Machine: Feedback, Control, and Computing before Cybernetics* (Johns Hopkins University Press, 2002). A corrective to Wiener-centred accounts, showing how much of the engineering had been done before 1946.

Flo Conway and Jim Siegelman, *Dark Hero of the Information Age: In Search of Norbert Wiener, the Father of Cybernetics* (Basic Books, 2005). A biography based on extensive interviews, the main source for the break with McCulloch; its account of Wiener's family has been disputed.

Jimmy Soni and Rob Goodman, *A Mind at Play: How Claude Shannon Invented the Information Age* (Simon & Schuster, 2017). A lively biography of Shannon, including Theseus and his machines.

Andrew Pickering, *The Cybernetic Brain: Sketches of Another Future* (University of Chicago Press, 2010). On the British cyberneticians, Grey Walter, Ashby, Beer and Pask, and on Bateson; sympathetic to cybernetics as a way of thinking rather than a technology.

Eden Medina, *Cybernetic Revolutionaries: Technology and Politics in Allende's Chile* (MIT Press, 2011). The history of Project Cybersyn, from Beer's design to the coup.

Claus Pias, ed., *Cybernetics: The Macy Conferences 1946–1953. The Complete Transactions* (Diaphanes, 2016). The transcripts themselves, for readers who want to hear the arguments as they happened.

Chapter 7

The Secret of Photo 51 (1951–1953)

Ninety-Two Per Cent

On Friday 2 May 1952, in the Biophysics Unit of King's College London, on the Strand, Raymond Gosling set a camera running on a fibre of DNA. The fibre was a fraction of a millimetre thick, drawn out of a viscous gel of the sodium salt of DNA from calf thymus, and it hung in the path of a narrow beam of X-rays inside a small sealed chamber. A steady stream of hydrogen flowed through the chamber, displacing the air, which would otherwise have scattered the X-rays and fogged the film. Before it entered the camera, the hydrogen had been bubbled through a saturated solution of a salt chosen to hold the humidity inside at a fixed value, in this case about 92 per cent. At that humidity the fibre took up water, swelled, and lengthened, and its molecules settled into the form that Gosling's supervisor, Rosalind Franklin, had named structure B.

The camera ran for a total of sixty-two hours. The film was developed on Tuesday 6 May. It was the fifty-first in the series, and it was given that number in Franklin's notebook.[1] What it showed was a pattern of short dark smudges arranged in a cross, like an X drawn in dashes, with a pair of heavy dark arcs at the top and bottom. To someone who knew how to read it, the cross said "helix". The spacing of its smudges said how long each turn of the helix was, and the arcs said how far apart the stacked units inside it lay.

Franklin knew how to read it. But she did not, at that moment, think it was the most important thing she had. Her attention was on the drier, more crystalline structure A, whose sharper photographs promised, through a long and rigorous calculation, an answer that would not depend on guesswork. Photograph 51 was put aside. Eight months later, at the end of January 1953, it was in the hands of Maurice Wilkins, the physicist who had started the unit's work on DNA, who showed it to a visitor from Cambridge named James Watson. Watson later wrote that his mouth fell open and his pulse began to race.

Photograph 51 has since become one of the most reproduced scientific images of the twentieth century, and the emblem of an argument about credit that has lasted for seventy years. This chapter is about how the structure of DNA was found, by people trained in physics, physical chemistry, crystallography, genetics and biochemistry, working in two laboratories fifty miles

apart that cooperated, competed and misunderstood each other in roughly equal measure. It is also about what the famous photograph did and did not tell them.

The Science: A Boring Molecule

DNA had been known for more than eighty years before anyone thought it interesting. By the 1930s chemists, above all Phoebus Levene at the Rockefeller Institute in New York, had established what it was made of. Its basic unit, which Levene called a *nucleotide*, has three parts: a phosphate group, a sugar, and a flat ring-shaped molecule called a base. In DNA the sugar is deoxyribose, which Levene identified in 1929. The nucleotides are joined into long chains through their phosphates, each phosphate linking the sugar of one nucleotide to the sugar of the next, so that the chain has a regular sugar–phosphate backbone with a base hanging off every sugar. There are four bases. Two, adenine (A) and guanine (G), are *purines*, with a double ring. The other two, thymine (T) and cytosine (C), are *pyrimidines*, with a single ring.

Levene also proposed, on the basis of analyses that suggested roughly equal amounts of the four bases, that DNA was built from a repeating set of four nucleotides, one of each kind. This *tetranucleotide hypothesis* was never a precise structural claim, but it shaped how a generation thought about the substance. A polymer that repeated the same four units over and over could carry no more information than a strip of wallpaper. Proteins, by contrast, were built from twenty kinds of amino acid in sequences that seemed to vary without limit, and they did nearly everything else in the cell. It was natural to assume that genes were made of protein, and that DNA, which was always found alongside protein in chromosomes, was some kind of scaffold.

Two kinds of evidence broke that assumption. The first, biological, is part of the background to this chapter rather than its subject. As we saw in Chapter 3, Oswald Avery, Colin MacLeod and Maclyn McCarty reported in 1944 that the substance capable of transforming one strain of pneumococcus into another was DNA; and in 1952 Alfred Hershey and Martha Chase showed that it was chiefly the DNA of a bacteriophage, not its protein coat, that entered the bacterium it infected.[2] Neither of these results convinced everybody. Avery's critics argued that a trace of protein might have contaminated his preparations, and Hershey and Chase were themselves cautious about what their experiment proved.

The second kind of evidence was chemical, and it struck at the tetranucleotide hypothesis directly. Erwin Chargaff, born in 1905 in Czernowitz, then in Austria-Hungary, had come to Columbia University in New York in 1935. After the war he applied two new techniques to DNA: paper chromatography, which separates the bases by how far they travel up a strip of filter paper in a solvent, and ultraviolet spectrophotometry, which measures how much of each base is present by how strongly it absorbs ultraviolet light of particular wavelengths. In a review published in 1950 he summarised the results of several years' work.[3] The proportions of the four bases were not equal, and they differed from one species to another. DNA, in other words, was not a monotonous repeat. But within that variety there was a curious regularity. The amount of adenine was always close to the amount of thymine, and the amount of guanine close to the amount of cytosine. Figures usually quoted from his work on human DNA are about 31 per

cent adenine and 29 per cent thymine, and about 20 per cent each of guanine and cytosine. The ratios were not exactly one, and Chargaff, a careful analyst, did not claim that they were. He noted the regularity but did not say what it meant. Nobody else did either, for three years.

There was one more piece of evidence, and it came from physics. In 1938 William Astbury and Florence Bell at the University of Leeds had taken X-ray photographs of DNA fibres. Their pictures were blurred, because their samples were mixtures of different forms, but they showed a strong reflection corresponding to a spacing of about 3.4 ångströms along the fibre (an ångström, written Å, is a ten-millionth of a millimetre, roughly the diameter of an atom). Astbury interpreted it as the distance between flat bases stacked on top of one another, like a pile of pennies.[4] He was right about the stacking. What held the pile together, how the chains ran, and how many of them there were, remained unknown. Finding out would require a better way of reading X-ray photographs, and better photographs to read.

The Science: Reading Shadows

Visible light cannot show the arrangement of atoms in a molecule, because its wavelength, around five thousand ångströms, is thousands of times longer than the distances between atoms. X-rays have wavelengths of about one ångström, which is the right scale. But there is no lens that can focus X-rays into an image. What can be done instead is to shine a beam of them through a sample and record the way they are scattered. Each atom scatters a little of the beam in all directions. Where the sample is regular, so that the same arrangement of atoms repeats many times, the scattered waves from all the repeats add up in some directions and cancel in others. The film records a pattern of spots or smudges where the waves have reinforced one another.

The rule that governs this was worked out in 1912 by William Lawrence Bragg, then a twenty-two-year-old research student at Cambridge, and it is usually written as

$$n\lambda = 2d \sin\theta.$$

Here λ is the wavelength of the X-rays; d is the spacing between repeating planes of atoms in the sample; θ is the angle at which the beam strikes those planes; and n is a whole number. The equation says that waves reflected from successive planes reinforce one another only when the extra distance travelled by the deeper wave, $2d \sin\theta$, is a whole number of wavelengths. The practical consequence is an inverse relationship: *small spacings in the sample produce spots far from the centre of the film, and large spacings produce spots close to it*. Bragg shared the Nobel Prize in Physics with his father in 1915 for founding X-ray crystallography on this principle. In 1952 he was Cavendish Professor of Physics at Cambridge, and the head of the laboratory in which the structure of DNA would be built.

Science Primer: Bragg's law and the spacings in Photo 51

Suppose X-rays from a copper target, the usual source in crystallography laboratories of the period, with wavelength $\lambda = 1.54$ Å. The strong arcs at the top and bottom of Photo 51 correspond to a repeat of $d = 3.4$ Å along the fibre. Bragg's law with $n = 1$ gives

$$\sin\theta = \frac{\lambda}{2d} = \frac{1.54}{6.8} \approx 0.226, \qquad \theta \approx 13^\circ.$$

The scattered beam is deflected by twice that angle, about 26°, from the direct beam. On a flat film 5 cm from the fibre (an illustrative distance), the arcs would fall about $5 \tan 26^\circ \approx 2.5$ cm from the centre.

Now take the longer repeat, the length of one complete turn of the helix, which Franklin measured as 34 Å. Ten times the spacing means about one-tenth of the angle:

$$\sin\theta = \frac{1.54}{68} \approx 0.023, \qquad 2\theta \approx 2.6^\circ,$$

which on the same film would put the first layer line only about 2 mm from the centre. In a fibre photograph these long repeats appear as horizontal rows of smudges, the *layer lines*, stacked at equal intervals above and below the centre. In Photo 51 the strong 3.4 Å arcs lie on the tenth layer line. Counting the rows gives the number of stacked units in one turn: $34/3.4 = 10$.

The width of the molecule can be estimated in a similar way, from the spacing between neighbouring molecules packed side by side in the fibre, which appears along the horizontal axis of the pattern. Franklin's measurements on the drier, crystalline form gave molecules roughly 20 Å across. Notice what this arithmetic does *not* supply: it says how far apart things are, but not what the things are. Converting distances into atoms requires a model.

A fibre is not a crystal. In a crystal, molecules are packed in a regular three-dimensional lattice, and the X-ray pattern consists of sharp, separate spots that can in principle be measured one by one and used to reconstruct the arrangement of atoms. In a DNA fibre, long molecules lie roughly parallel to the fibre's axis but are rotated at random about it. The pattern is correspondingly poorer: it is the average of the patterns from every orientation around the axis, and it contains far less information. What it does preserve is the repeat *along* the axis, which is why fibre photographs show layer lines.

What would a helix look like? The answer was worked out in Cambridge late in 1951 by William Cochran, Francis Crick and the Glasgow crystallographer Vladimir Vand, and published, first as a short letter by Cochran and Crick in February 1952 and in full that September.[5] At King's, the physicist Alexander Stokes had reached the same result independently; according to his colleague Herbert Wilson he worked it out on the train home after Wilkins asked him the question, and arrived the next day with a sketch that the laboratory nicknamed "Waves at Bessel-on-Sea". He never published it.

The name refers to the mathematical functions that appear in the answer, *Bessel functions*. They had turned up in the work of Daniel Bernoulli and Leonhard Euler in the eighteenth century; the astronomer Friedrich Bessel studied them systematically in 1824, and they bear his name. They describe, among many other things, the ripples on the surface of a drum, and they arise whenever waves interact with something that has circular symmetry. A Bessel function $J_n(x)$ is a wave-like curve that oscillates with slowly decreasing height. For every order except the zeroth it starts at zero and rises to a first peak; J_0 instead starts at its peak value of 1. Its subscript n, the *order*, controls where that first peak comes: the higher the order, the further out the first peak lies. J_0 is largest at zero, J_1 first peaks near $x = 1.8$, J_2 near 3.1, J_3 near 4.2, and so on, roughly one unit further out for each step in order.

The Cochran–Crick–Vand result says that a helix with pitch P (the length of one turn) and radius r scatters X-rays only onto layer lines spaced at intervals of $1/P$ in what crystallographers call reciprocal space, and that the strength of scattering on the n-th layer line, at horizontal distance R from the centre of the pattern, follows the Bessel function $J_n(2\pi Rr)$. Because the first peak of J_n moves outward as n increases, the brightest smudge on each successive layer line lies a little further from the vertical axis than the one below it. Joined up, the first peaks on the lower layer lines form two diagonal lines, one going up to the right and one up to the left. That is the X. Its angle depends on the ratio of the pitch to the radius, so from the angle and the layer-line spacing one can estimate the radius. For B-DNA the answer is that most of the scattering matter lies about 10 Å from the axis: on the outside of the molecule, where the heavy phosphate groups were thought to be.

There is a further detail in Photo 51 that the simple theory of one helix does not explain. The fourth layer line is missing, or very nearly so: the dashes of the X run up through layers 1, 2 and 3, then skip a row, and resume at layer 5. Something was cancelling the scattering at that level. One way to do it is to have two helices of the same pitch, wound round the same axis but displaced from each other along it. If the second helix is shifted by a fraction f of a turn, its contribution on layer line n is out of step with the first by $2\pi nf$, and the two cancel when that is an odd multiple of π. With $f = 3/8$, layer line 4 is exactly cancelled. Franklin and Gosling made this connection themselves: their paper of April 1953 attributed the absence of the fourth layer line to a second chain displaced by about three-eighths of the helix period.[6] The arrangement also produces the two unequal grooves that wind round every picture of the double helix.

It is worth being clear about what the photograph could not tell anyone. It could not say how many chains there were; that had to come from the density of the fibre and the size of the unit cell. It could not say which way the chains ran, whether the helix turned to the right or to the left, or where the bases were. Above all, it could not say how the bases on one chain related to those on another, which turned out to be the heart of the matter. Photo 51 was a powerful constraint on any model. It was not a model.

A Chemist of Disordered Things

Rosalind Franklin was born in London on 25 July 1920 into a prosperous Jewish family, and was educated at St Paul's Girls' School and at Newnham College, Cambridge, where she read chemistry in the Natural Sciences Tripos, graduating in 1941. She spent a year in the Cambridge laboratory of the physical chemist Ronald Norrish and then, in 1942, joined the British Coal Utilisation Research Association as an assistant research officer. The work was war work: coal was Britain's chief fuel. Franklin studied how coals and the carbons made from them changed their porosity as they were heated, and the research became her Cambridge doctorate, awarded in 1945.[7]

In February 1947 she went to Paris, to the Laboratoire Central des Services Chimiques de l'État, a government chemical laboratory, to work under the crystallographer Jacques Mering. Mering specialised in the X-ray study of materials that are neither crystalline nor fully disordered, such as clays and carbons, and Franklin learned there the techniques that would make her reputation. Using X-ray diffraction, she showed that carbons fall into two classes: *graphitising* carbons, which turn into crystalline graphite when heated to around 3000 °C, and *non-graphitising* carbons, which never do, however hot they are made, and she related the difference to the way small crystalline regions in the material are cross-linked. It was work of lasting value, and it taught her to extract structural information from blurred, imperfect diffraction patterns: exactly the skill that DNA fibres would demand. She valued the collegial culture of the Paris laboratory, made lasting friendships there, and left reluctantly.

She came back to London on a three-year Turner and Newall fellowship to work in the Biophysics Unit that John Randall had built at King's College London with money from the Medical Research Council. Randall was a physicist who had co-invented the cavity magnetron at Birmingham in 1940 (Chapter 5 told what that device made possible), and after the war he set out to apply physical methods to biology. His unit was large, well funded and, for its time, unusually open to women, with what the college's own history calls a relatively high number of women scientists. Franklin had been hired to study proteins in solution. In a letter of 4 December 1950, Randall changed her project. She was to work instead on the X-ray structure of DNA fibres, and, as far as the experimental X-ray effort was concerned, there would for the moment be only herself and a graduate student, Raymond Gosling.[8] She started in January 1951.

The trouble was that the DNA work already belonged, in his own mind, to someone else. Maurice Wilkins was born in Pongaroa, New Zealand, on 15 December 1916, read physics at St John's College, Cambridge, and took his doctorate under Randall at Birmingham, on electrons trapped in phosphorescent solids. During the war he worked on radar and then, as Chapter 3 recounted, on the separation of uranium isotopes at Berkeley for the Manhattan Project, an experience that left him wary of the uses of physics. He followed Randall to St Andrews and then to King's in 1946. In 1950 he obtained an exceptionally pure sample of DNA from the Swiss chemist Rudolf Signer, who had brought it to a meeting in London, and with Gosling he drew it into fibres and took X-ray photographs with an old apparatus that had been used to study ram sperm. Gosling later called the moment when the first sharp spots appeared in the developing dish a true eureka moment. In May 1951 Wilkins showed one of these photographs at a meeting

at the zoological station in Naples, where a young American in the audience saw it.

Randall did not tell Wilkins the terms of his letter to Franklin, and he did not tell Franklin that Wilkins thought of her as joining his project. Wilkins, away when she arrived, returned to find that she regarded the DNA fibres, the new equipment and Gosling as hers. Franklin, for her part, met a man who seemed to expect her to work as his assistant on a problem she had been told was her own. By July 1951 relations were so bad that, after Wilkins presented some of his results, Franklin told him to go back to his microscopes. Historians have given the blame different weights. Robert Olby argued that personalities alone did not explain it, and that Randall's mismanagement was a large part of the problem; Wilkins's own account, published in 2003, is candid about his share. The two never worked well together, and they rarely talked about their results.[9]

Franklin's first contribution was experimental, and decisive. Earlier workers had photographed DNA in whatever humidity their laboratory happened to have, and had obtained patterns that were blurred mixtures. Franklin equipped her camera so that the humidity around the fibre could be held steady for the hours or days an exposure took, using the stream of hydrogen bubbled through salt solutions described at the start of this chapter. With Gosling she found that DNA exists in two distinct forms. At about 75 per cent humidity the fibres gave a sharp, detailed pattern of many spots, from a well-ordered arrangement she called structure A (it was the form Wilkins had shown at Naples). When the humidity was raised to about 92 per cent the fibres took up more water, grew about a quarter longer, and gave the simpler, more diffuse pattern she called structure B. The change was reversible. Earlier photographs, including Astbury's, had been mixtures of the two, which was why no one had been able to interpret them.

The discovery also told her something structural. The phosphate groups in DNA are strongly attracted to water. If DNA could soak up so much water and swell so readily, the phosphates were probably on the outside of the molecule, where water could reach them. In a colloquium at King's in November 1951 she said so, and suggested that the molecule was probably a helix, perhaps with two or three chains. Her surviving notes for the talk record evidence for a spiral structure, and give the crystallographic symmetry of structure A and an estimate of its density.[10] In the audience, by his own later admission taking no notes, was the young American from Naples.

The Cavendish

James Watson had come to Cambridge in October 1951 with no training in crystallography at all. Chapter 3 followed him from the University of Chicago, where he had enrolled at fifteen with a passion for birds, to Indiana; he took his doctorate there in 1950, under Salvador Luria, on the effect of X-rays on bacteriophage multiplication. A fellowship then took him to Copenhagen to work on the biochemistry of viral DNA, which by his own account failed to hold his interest. At the Naples meeting in May 1951 he saw Wilkins's photograph of crystalline DNA and concluded, by his own account, that if genes could crystallise they must have a regular structure that could

be solved. With Luria's help he arranged to move to the Cavendish Laboratory, nominally to work on proteins with John Kendrew. He was twenty-three.

The Cavendish group he joined was small. It was officially the Medical Research Council Unit for Research on the Molecular Structure of Biological Systems, established in 1947 and led by Max Perutz, the Viennese-born chemist who had arrived in Cambridge in 1936 and had spent the years since trying to solve the structure of haemoglobin. Kendrew was working on the smaller protein myoglobin. Over them presided Bragg, who had taken the Cavendish chair in 1938 and who saw the protein work as a way of keeping Britain at the front of the science he had founded. The group's methods were those of classical crystallography: measure the intensities of thousands of spots from protein crystals, and work slowly, with mechanical calculators and later the university's early computer, towards a map of where the atoms were. Neither protein was solved until 1957–60.

Sharing Watson's room was Francis Crick, who at thirty-five was still a graduate student. Crick had read physics at University College London, spent the war designing magnetic and acoustic mines for the Admiralty, and moved to biology in 1947, as Chapter 3 described, joining the MRC unit in 1949. He became a research student again at Gonville and Caius College in 1950, and his thesis, submitted in July 1953, was titled "Polypeptides and Proteins: X-Ray Studies". He talked loudly and constantly, laughed louder, and had a habit, not always welcome, of finding the flaws in other people's arguments. But Crick was the best theoretician in the building, and his work with Cochran on the diffraction of helices had made him one of the few people in the world who could look at a fibre photograph and see a helix in it.

Watson and Crick's starting point was a recent humiliation. In 1950 Bragg, Kendrew and Perutz had published a long paper on the possible ways in which a protein chain might coil. They had considered many models and settled on none, and in doing so had allowed the peptide group, the link between amino acids, to bend and twist in ways that the American chemist Linus Pauling believed it could not. They had also assumed, without good reason, that each turn of a helix must contain a whole number of amino acids. In the spring of 1951 Pauling, with Robert Corey and Herman Branson at the California Institute of Technology, published the *alpha helix*: a coil with about 3.6 amino acids per turn, held together by hydrogen bonds between each amino acid and the fourth one along. Pauling had found it, by his own later account, while confined to bed with a cold in Oxford in the spring of 1948, by drawing a protein chain on a sheet of paper with the bond lengths and angles he believed correct, and folding the paper until the hydrogen bonds lined up.[11] Perutz, testing the prediction, found the reflection it required in a horsehair and in his own haemoglobin films, and called it the most thrilling discovery of his life.

The lesson that Watson and Crick drew was methodological. Pauling had not solved the alpha helix by calculating backwards from X-ray data, which for a fibre could not be done unambiguously. He had used what he knew from chemistry, the precise lengths and angles of chemical bonds learned from small molecules, to restrict the possibilities to a handful, and had then built the candidates and checked them against the few X-ray features available. If that worked for proteins, perhaps it would work for DNA. The method had a name in the trade, model building, and to classical crystallographers it was a little disreputable: a way of guessing,

rather than determining, a structure. That difference of philosophy between the two laboratories would matter more than any personal antagonism.

The pairing of Watson and Crick was itself a crossing of borders, of a kind this book calls a trading zone. Watson knew genetics and phage biology, and wanted, above all, to understand how genes replicated; he could not calculate a Fourier transform and knew little chemistry. Crick knew diffraction theory, physics and enough chemistry to argue with chemists, and was less interested than Watson in the details of genetics. Each was, by the standards of the other's field, an amateur. They talked incessantly, so much that, by most accounts, they were moved into a room of their own so as not to disturb anyone else.

A Model with No Water

After Franklin's colloquium in November 1951, Watson went back to Cambridge and described what he remembered of it to Crick. Within about a week they had built a model. It had three chains twisted round one another, with the sugar–phosphate backbones in the centre and the bases pointing outwards. Since the phosphates carry negative charges that would repel one another, the model needed something positive to hold the core together, and they chose magnesium ions, although, as a later account put it, there was no evidence that DNA contained any such ions.[12] They invited the King's group to see it, and Wilkins and Franklin came up from London with colleagues.

Franklin's objections were quick and specific. The model contained far too little water; by Watson's own later account, DNA took up about ten times as much as he had allowed. Positive ions in a wet fibre would be surrounded by water and could not bind the phosphates together in the way the model required. And the phosphates belonged on the outside. Watson, it emerged, had misunderstood a crystallographic point in her talk, confusing the water content of a whole repeating unit of the crystal with that of a smaller part of it. Asked where the water was, Watson and Crick had to admit that there was hardly any.

The consequences were administrative. Bragg, embarrassed that two members of his unit had trespassed on a problem that another MRC laboratory was pursuing, and with nothing to show for it, ordered them to stop working on DNA; it is usually said that he and Randall agreed that the problem should be left to King's. Watson later recalled that the jigs for making model components were handed over to King's, where nobody used them. Letters between Crick and Wilkins that came to light only in 2010 show that the two men privately regretted the episode. Wilkins wrote one formal letter, which their superiors could see, asking Crick to stay away from DNA, and a second, private one telling him how "bloody browned off" he was about the whole business. Crick replied two days later that even if they had kicked him in the pants, it had been between friends.

The moratorium was never complete. Watson was assigned to work on the structure of tobacco mosaic virus, and Crick returned to his thesis. But they went on thinking. In the summer of 1952 Crick asked a young mathematician, John Griffith, to calculate which bases might attract

one another. Griffith's rough calculation suggested that adenine might pair with thymine and guanine with cytosine. Crick did not at first see the significance, and later said that he had not then known Chargaff's results.

That summer Chargaff himself came to Cambridge and met Watson and Crick. Neither side enjoyed the meeting. Chargaff, a cultivated man with a sharp tongue and a deep knowledge of nucleic acid chemistry, found two young men who, as he put it later, wanted to fit DNA into a helix "unencumbered by any knowledge of the chemistry involved".[13] Chargaff told them of the one-to-one ratios. Crick, by his own account, could not at first remember which bases Griffith had paired and had to check; when he did, he realised that Griffith's pairs would produce exactly those ratios. It was a clue. Nobody yet knew how to fit it into a structure.

At King's, meanwhile, Franklin was making slow, rigorous progress on structure A, and it led her temporarily away from the helix. Rather than guessing a structure and testing it, she wanted to derive one from the data. Her chosen tool was the *Patterson function*, a mathematical transform of the measured intensities that produces a map, not of the atoms themselves, but of all the vectors between pairs of atoms. For a small molecule a Patterson map can be decoded; for something as large as DNA, it is a thicket. It required long calculations, and it took most of 1952. In the spring of that year, too, one A-form fibre gave a pattern that suggested the molecules were not round in cross-section, which seemed to rule out a helix. Crick, when he heard, told her it was probably an accident to be dismissed. She did not dismiss it. On 18 July 1952 Franklin and Gosling circulated a mock funeral card, edged in black, announcing the death of the DNA helix (crystalline) after a protracted illness, and naming Wilkins as the speaker at its memorial.[14] The joke was precise. It concerned structure A only, and Gosling later said that Franklin had never seriously doubted that the B form, at least, was helical. But her public scepticism persuaded Wilkins, and it later became the basis for the claim that she was anti-helical by temperament, which was not true.

Pauling, for his part, was barely involved. He had asked Wilkins for copies of the King's photographs in 1951 and had been politely refused. In 1952 the State Department refused to renew his passport, because of his left-wing political activity, and he missed a meeting at the Royal Society in London on 1 May 1952 that had been organised to discuss his protein work, at which he was to have been the first speaker. It has often been suggested that, had he come, he would have visited King's and seen the new photographs. That may be true, but it is speculation. What is certain is that he worked on DNA with the blurred photographs of Astbury and Bell, which were mixtures of the A and B forms, and that he did not take the problem very seriously until late in 1952.

Six Weeks in 1953

Pauling and Corey sent their paper, "A Proposed Structure for the Nucleic Acids", to the *Proceedings of the National Academy of Sciences* on 31 December 1952. It proposed three chains wound round each other with the phosphates in the centre, and it admitted that the structure was extraordinarily tight. A copy reached Cambridge in late January 1953 through Pauling's son Peter,

who had joined Kendrew's group as a research student that autumn and had become friendly with Watson and Crick. Watson read it with dread and then with disbelief. The model was much like their own failed attempt. Worse, to hold the phosphates together in the centre, Pauling had given each of them a hydrogen atom, so that they carried no charge. But at the acidity of a living cell the phosphate groups of DNA lose those hydrogen atoms; that is why the substance is called an acid. As Watson later put it in *The Double Helix*, Pauling's nucleic acid was in a sense not an acid at all.[15] The greatest chemist of the age had made an error that a student would be marked down for. Watson and Crick reckoned that Pauling would see it within weeks and return to the problem. Bragg, who had been beaten to the alpha helix by Pauling and did not intend to be beaten again, lifted his ban on DNA work.

On Friday 30 January 1953, Watson went to King's with a copy of the Pauling manuscript. He first called on Franklin, and by his own account tried to lecture her on helices; the conversation ended in a row. Wilkins, who had his own grievances against her, then took Watson into his office and showed him a print of Photograph 51. Gosling had given it to Wilkins earlier in the month, as Franklin prepared to leave King's for Birkbeck College and Gosling's supervision passed to Wilkins.[16] Franklin did not know that Watson had seen it. Watson recognised the X, and on the train back to Cambridge, by his account, he sketched what he remembered of it on the margin of his newspaper. He came back convinced, among other things, that the molecule had two chains, though his reasoning (that important biological things come in pairs) was not crystallographic.

The second piece of King's data that reached Cambridge was more important, and it came by a more bureaucratic route. In December 1952 the Medical Research Council's Biophysics Research Committee had visited Randall's unit, and Randall had circulated to its members a report on the unit's work, including a page from Franklin summarising her results on structure A: the dimensions of its unit cell, its density, and its crystallographic symmetry. One of the committee's members was Max Perutz. In the second week of February 1953, Perutz gave his copy to Crick. He later maintained that the report was not confidential, and it was not marked as such; but nobody asked Franklin whether her unpublished results could be used.[17]

The detail that mattered was a phrase that would have meant little to anyone outside crystallography: the space group of structure A was, in the report's words, face-centred monoclinic: in modern notation, C2. To Crick, it meant a great deal.

Science Primer: What C2 told Crick

A crystal's *space group* is a list of the symmetry operations that leave its arrangement of molecules unchanged. In the space group C2 ("C" for a particular way of centring the unit cell, "2" for its symmetry), the key operation is a *two-fold rotation axis*: turn the whole arrangement through 180° about that axis and it looks the same.

In a DNA fibre that axis lies at right angles to the length of the molecule. Picture a molecule standing vertically, and rotate it half a turn about a horizontal axis through its middle, so that it ends up upside down. If the molecule is to look the same afterwards, every feature

at the top must be matched by an identical feature at the bottom, pointing the other way.

A single DNA chain has a direction, because the sugar–phosphate links are not symmetrical: each phosphate joins one end of a sugar (chemists call it the 5′ carbon) to the other end of the next sugar (the 3′ carbon). Turn one chain upside down and its direction reverses, so a single chain can never satisfy the symmetry. But two chains running in *opposite* directions can: turned upside down, each chain takes the place of the other. The two-fold axis therefore implies that the chains come in pairs, and that the partners are *antiparallel*. With Franklin's density, which allowed room for two chains but hardly three, the conclusion was a double helix with chains running in opposite directions.

Crick saw this quickly partly because, by Watson's later account, he had been working on haemoglobin crystals with the same symmetry, whose molecules also come in upside-down pairs. Franklin had the same information and recorded the space group herself, but she did not at first draw the inference; Klug later suggested that she regretted it.

Franklin, by now packing to leave, was closing in from her own direction. Her notebooks show that on 10 February 1953 she returned to the question of how many chains structure B contained, and that by 24 February she had concluded that both forms had two chains. According to Klug, her analysis of the Patterson map of structure A had also pointed to chains running in opposite directions, though her March draft did not yet say so. She knew Chargaff's ratios, and in her notes she favoured the keto forms, the correct ones, for at least three of the four bases. What she did not have was the idea of specific pairing.[18]

In Cambridge, Watson was trying to fit the bases inside a two-chain helix, and failing. He first tried pairing like with like, adenine with adenine and so on, which would allow any sequence on one chain to be matched by the same sequence on the other. The pairs were of different sizes and the backbone buckled. They also depended on hydrogen atoms that, it turned out, were in the wrong places. Watson had taken the structures of the bases from a standard monograph, James Davidson's *The Biochemistry of the Nucleic Acids*, which drew guanine and thymine in what chemists call the *enol* form. Sharing the office was Jerry Donohue, an American structural chemist who had taken his doctorate under Pauling at Caltech in 1947 and was spending part of 1952–53 at the Cavendish on a Guggenheim fellowship, a stay of about six months. Donohue told Watson that the textbook forms were little more than guesses, and that the evidence from crystal structures of related molecules favoured the *keto* forms.

Science Primer: Tautomers and the shape of a base pair

Some molecules can exist in two forms that differ only in where one hydrogen atom sits. Such forms are called *tautomers*. In guanine and thymine, a carbon atom of the ring is attached to an oxygen. In the *keto* form the oxygen is double-bonded to the carbon (C=O) and the hydrogen sits on a neighbouring nitrogen of the ring (N–H). In the *enol* form the hydrogen has moved onto the oxygen (C–O–H), and the nitrogen has lost it. Adenine and cytosine have an analogous pair of forms, *amino* and *imino*, involving an NH_2 group.

The difference matters because hydrogen bonds join a hydrogen atom attached to a nitrogen or oxygen (a *donor*) to a nitrogen or oxygen that has no hydrogen but a pair of spare electrons (an *acceptor*). Moving one hydrogen turns a donor into an acceptor and vice versa, and so changes which partners a base can bond to. In their usual keto and amino forms, adenine presents to its neighbour a donor and an acceptor that match an acceptor and a donor on thymine; guanine presents a pattern that matches cytosine. Adenine cannot bond properly to cytosine, nor guanine to thymine.

The result that struck Watson was geometric. Each allowed pair joins one large two-ringed purine to one small single-ringed pyrimidine, so both pairs have the same overall length. More precisely, the distance between the two points where the bases attach to their sugars is nearly the same in both, about 10.5 to 11 Å, and the bonds to the sugars make nearly the same angles. So an A–T pair and a G–C pair are interchangeable rungs: either can be fitted between the two backbones, the right way round or flipped, without changing the backbone's shape. That is why any sequence of bases can be accommodated along a chain, and why the sequence on one chain fixes the sequence on the other. Watson and Crick drew the G–C pair with two hydrogen bonds; in 1956 Pauling and Corey showed that it has three, which only strengthens the case.

On the morning of Saturday 28 February 1953, using cardboard cut-outs of the bases in their keto forms, Watson found that adenine paired with thymine and guanine with cytosine had the same shape. The pairing explained Chargaff's ratios at once: every A on one chain faced a T on the other, so the totals had to match. And it fitted the antiparallel chains that Crick had derived from C2. According to Watson's account, Crick announced at lunch in the Eagle, the pub near the Cavendish, that they had found the secret of life. The story comes from Watson; Crick told his wife that evening, more modestly, that they seemed to have made a big discovery.

What followed took a week. Using metal plates cut to the shapes of the bases by the Cavendish workshop, and rods and clamps for the backbone, they built a model taller than a man, adjusting it until every bond length and angle was chemically acceptable and every distance between atoms was large enough. It had two right-handed helical chains running in opposite directions, ten base pairs per turn, a rise of 3.4 Å per base pair, a pitch of 34 Å, and the phosphates on the outside at a radius of about 10 Å. The figures came from King's: the 34 Å and 3.4 Å from the B-form photograph, the dimensions from Franklin's report. The pairing came from Cambridge. Wilkins came to see the model in mid-March and was convinced at once. News of it reached King's officially on 18 March. Franklin, who had moved to Birkbeck on 14 March, had dated her own draft paper on the B form 17 March; it contained much of the evidence for a two-chain helix with the phosphates outside, though not the pairing or the opposite directions.[19] Early in April Pauling, on his way to a conference in Brussels, saw the model in Cambridge and accepted that it was right.

Three Papers in One Issue

It was agreed between the two laboratories that King's and the Cavendish should publish together. On 25 April 1953 *Nature* printed three papers in succession. The first, by Watson and Crick, received on 2 April, was just over a page long, with one diagram drawn by Crick's wife, the artist Odile Crick. It began by suggesting a structure for the salt of DNA, briskly dismissed the Pauling–Corey and Fraser models, described the two antiparallel chains and the pairing of the bases, and ended with a sentence now famous for its understatement: that it had not escaped the authors' notice that the specific pairing immediately suggested a possible copying mechanism for the genetic material. It acknowledged Donohue's advice, and said that the authors had been stimulated by knowing, in general terms, the unpublished results and ideas of Wilkins, Franklin and their colleagues at King's.[20]

The second paper, by Wilkins, Stokes and Herbert Wilson, showed that DNA in intact biological material, such as sperm heads, gave X-ray patterns like those of extracted fibres, and discussed them in terms of helical diffraction theory. The third, by Franklin and Gosling, reproduced Photograph 51 and set out their evidence that the B form was a helix, with the phosphate groups on the outside at a radius of about 10 Å, ten nucleotides per turn and a pitch of 34 Å, and that it probably had two chains. It ended by noting that these conclusions were consistent with the model in the preceding communication. Placed third, the paper read as confirmation of someone else's idea. It was in fact largely written before Franklin had heard of the model.

Five weeks later, on 30 May, Watson and Crick published a second, more speculative paper on the genetic implications.[21] If the two chains separated, each could serve as a template for a new partner, and two identical molecules would result. The sequence of bases was presumably the code that carried genetic information. And mutations might arise when a base occasionally slipped into one of its rare tautomeric forms at the moment of copying and so paired with the wrong partner, which Donohue's correction had suddenly made thinkable. The tautomer theory of mutation was widely taught for decades on little direct evidence; it was not observed directly until the 2010s. The genetic paper was the one that mattered to biologists, and it was the one that showed most clearly why the structure was important: it was not merely a shape but a mechanism.

The immediate reaction was respectful rather than ecstatic. The structure was a model, not a determination: it agreed with the fibre photographs but could not be proved from them, and in 1953 there was no direct evidence for base pairing or for the proposed mode of replication. Crick and Watson set out the case more fully in the *Proceedings of the Royal Society* in 1954, in a paper that also acknowledged that, without the King's data, the formulation of their structure would have been "most unlikely, if not impossible".[22] The double helix was not confirmed in atomic detail until around 1980, when single crystals of short synthetic DNA molecules could at last be solved by the methods Franklin had preferred.

Table 7.1: Who brought what to the double helix

Person	**Training**	**Contribution**
Rosalind Franklin	Physical chemistry; X-ray study of disordered carbons	Humidity-controlled camera; A and B forms; phosphates outside; unit cell, density and C2 symmetry; Photo 51 (with Gosling); two-chain helix in her own analysis
Raymond Gosling	Physics; hospital physics	First sharp DNA photographs (with Wilkins, 1950); operated the camera for Photo 51
Maurice Wilkins	Physics (luminescence, isotope separation)	Started the King's DNA programme; obtained Signer's DNA; B-form studies of biological material
Alexander Stokes	Physics (diffraction by imperfect crystals)	Unpublished helical diffraction theory at King's
Erwin Chargaff	Biochemistry	Base ratios: A $\approx$ T and G $\approx$ C, composition varies by species
Francis Crick	Physics; protein crystallography	Helical diffraction theory (with Cochran and Vand); antiparallel chains from C2; stereochemistry of the model
James Watson	Zoology; phage genetics	Biological question of replication; base pairing
Jerry Donohue	Structural chemistry (Pauling's student)	Correct keto forms of the bases
Linus Pauling	Physical chemistry; X-ray crystallography	Model-building method, from the alpha helix; a wrong triple helix that spurred the final effort

Outcomes and Legacy

Replication. The copying mechanism that Watson and Crick suggested made a definite prediction: after one round of replication, each new double helix should contain one old chain and one new. In 1958 Matthew Meselson and Franklin Stahl at Caltech tested it. They grew bacteria for many generations on a medium containing heavy nitrogen, nitrogen-15, so that their DNA was denser than normal, then transferred them to ordinary nitrogen and extracted DNA after each generation. Spun at high speed in a solution of caesium chloride, which forms a density gradient in which each kind of DNA settles at its own level, the DNA after one generation formed a single band of intermediate density. After two generations there were two bands, one intermediate and one light. It was exactly the pattern the model predicted.[23]

The code. If the sequence of bases specified proteins, how? In a lecture in September 1957, published in 1958, Crick set out two principles that guided the next decade: the *sequence hypothesis*, that the order of bases in DNA encodes the order of amino acids in a protein; and what he called the *central dogma*, that information can pass from nucleic acid to protein but not back from protein to nucleic acid. In 1961 Crick, Leslie Barnett, Sydney Brenner and Richard Watts-Tobin used mutations in bacteriophage that added or removed single bases to show that the code is read in groups of three. In the same year Marshall Nirenberg and Heinrich Matthaei at the National Institutes of Health found that an artificial RNA made only of uracil, the RNA counterpart of thymine, directed cells' machinery to make a protein chain consisting only of the amino acid phenylalanine: the first word of the code. Har Gobind Khorana at the University of Wisconsin synthesised RNAs of defined repeating sequence that helped complete the dictionary by 1966. Nirenberg, Khorana and Robert Holley, who determined the structure of a transfer RNA, shared the Nobel Prize in 1968.[24] The search for the code was itself a story of physicists, chemists and biologists borrowing each other's tools, and of a good deal of elegant theory, some of it by the physicist George Gamow, that turned out to be wrong.

The prizes. In 1962 Crick, Watson and Wilkins shared the Nobel Prize in Physiology or Medicine for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material. In the same year Perutz and Kendrew won the Nobel Prize in Chemistry for the first protein structures. Franklin had died four years earlier. Before 1974 a person who died after being nominated could still receive a Nobel Prize, as Dag Hammarskjöld did in 1961; but as far as the Nobel nomination archive shows, Franklin was never nominated, and so she was not eligible; whether she would have shared the prize had she lived is unknowable, though it is hard to see how she could have been fairly left out.

Franklin's later work. At Birkbeck, in the department of the crystallographer J. D. Bernal, Franklin turned to the structure of viruses, and in five years she produced work of the highest quality. With a small group that included Aaron Klug, Kenneth Holmes, John Finch and the visiting American Donald Caspar, she showed that tobacco mosaic virus is a hollow tube built from identical protein units arranged in a helix, with its RNA wound in a helical groove among them. She began work on the poliovirus. In the summer of 1956, on a visit to the United States, she fell ill; in September surgery found ovarian cancer. She went on working through periods of remission, and died on 16 April 1958, aged thirty-seven. Klug continued the virus work,

and in 1982 he received the Nobel Prize in Chemistry for developing crystallographic electron microscopy and for determining the structures of complexes of nucleic acids and proteins. He did more than anyone to establish her scientific reputation, and his 1968 article in *Nature*, based on her notebooks, remains the starting point for any account of her DNA work.

The book. In 1968 Watson published *The Double Helix*, a vivid, funny, indiscreet account written from the point of view of his younger self. Harvard University Press withdrew from publishing it after Crick and Wilkins objected, and it appeared from Atheneum in New York and Weidenfeld and Nicolson in London. It became a best-seller, and its portrait of "Rosy", a sullen, unfeminine, combative assistant who could not interpret her own data, became for many readers the only picture of Franklin they had. The book's epilogue conceded that Watson's early impressions of her, scientific and personal, had often been wrong. It did little to undo the effect. The corrective histories followed: Anne Sayre's *Rosalind Franklin and DNA* (1975), written by a friend in direct reply; Robert Olby's *The Path to the Double Helix* (1974) and Horace Freeland Judson's *The Eighth Day of Creation* (1979), which reconstructed the science from documents and interviews; and Brenda Maddox's biography (2002), which drew on Franklin's letters to produce the fullest portrait of her as a person.

The reassessment. In April 2023, for the seventieth anniversary of the papers, the historians Matthew Cobb and Nathaniel Comfort published an essay in *Nature*, "What Rosalind Franklin Truly Contributed to the Discovery of DNA's Structure", based on documents in Franklin's archive at Churchill College, Cambridge.[25] One was an unpublished news story written for *Time* magazine by a London journalist, Joan Bruce, in consultation with Franklin. It described the discovery as the joint work of two teams, one at King's gathering the X-ray evidence and one at Cambridge building the model. Another was a letter of January 1953 from Pauline Cowan, a researcher at King's, inviting Crick to a talk by Franklin and Gosling and remarking that Perutz probably already knew more than the speakers would say. Cobb and Comfort read these as evidence that Franklin knew her results were circulating and was not troubled by it, and they argued that Watson's story of a single revelatory glimpse of Photo 51 was a literary device; the MRC report, not the photograph, had done more to confirm the structure. Their conclusion was that Franklin had been an equal member of a quartet that solved the double helix. Not everyone agreed. The historian Howard Markel, who had recently published a book arguing that Franklin was the victim of a theft, told the Associated Press that he remained convinced she had been wronged. Others, such as the philosopher of science Gregory Morgan, suggested that casting her either as a wronged heroine or as a willing collaborator was a false choice, and that the truth was more nuanced.

Gosling. Raymond Gosling finished his doctorate in 1954 with Franklin's help, after she had left King's, and spent his career in medical physics, latterly as professor of physics applied to medicine at Guy's Hospital Medical School, where he worked on ultrasound for assessing blood vessels. He died in 2015. He took the photograph that made Franklin famous and was named on one of the three papers, yet he is rarely mentioned in popular accounts. He seems not to have minded; when asked, he spoke of Randall's early bet on DNA and of the collaborative nature of the work.

Everything after. The double helix explained how genetic information could be stored, copied and occasionally changed, and it made the gene a chemical object that could in principle be read. Reading it took another quarter of a century, until the sequencing methods of Frederick Sanger and of Allan Maxam and Walter Gilbert in 1977, and the industrialisation of sequencing that Chapter 11 describes. Every technique of modern molecular biology, from the polymerase chain reaction to gene editing, depends on the pairing rules that Watson worked out with cardboard on a Saturday morning in 1953.

The Costs of Crossing

The discovery of the double helix is perhaps the most famous example of what this book calls a trading zone: physicists, a physical chemist, a geneticist and a biochemist, each holding part of the answer. It is also a case in which the trading was unequal, the terms were unclear, and the story told afterwards distorted what happened.

Credit and consent. Was Franklin's data stolen? The facts are less dramatic than the word and less comfortable than its denial. Watson saw Photo 51 without her knowledge, and Crick used her unpublished measurements from the MRC report without asking her. Neither the 1953 paper nor the 1954 paper said where the crucial symmetry information had come from; Klug later observed, mildly, that saying so would not have diminished their achievement. On the other hand, the report was not confidential; the information in it was hers but had been written for circulation; and Cobb and Comfort's documents suggest that she knew it had reached Cambridge and minded less than later writers on her behalf. She remained on friendly terms with Crick; in the autumn of 1956, recovering from surgery, she stayed with him and his wife in Cambridge. The fairest summary may be that the norms of the time allowed what happened, and that those norms were inadequate. They let senior men pass a junior colleague's data to her competitors through a committee, without asking her, and they let the competitors publish first with a vague acknowledgement. In a private letter of 1961, Crick wrote that the data that had really helped them had been obtained mainly by Franklin. That was true, and it was said in a letter, not in print.

Two methods, both reasonable. The usual account presents Franklin as a cautious experimentalist who could have solved the structure had she been bolder, and Watson and Crick as the imaginative model-builders who saw what she could not. This is unfair to her method. Model building had worked for the alpha helix, but it had also produced, in the hands of the most skilled model-builder alive, Pauling's inside-out triple helix, and in Cambridge's hands an earlier triple helix that a few questions destroyed. Franklin's insistence on extracting as much as possible from the data before guessing was the standard of her discipline, and it was what eventually confirmed the structure in atomic detail. Her mistake about structure A was a real one, but it was the kind of mistake a careful scientist makes when the data are ambiguous. By the end of February 1953 her own route had brought her to two chains, phosphates outside and a helix of the right dimensions; what she lacked was the pairing, which came from chemistry and from Watson's focus on replication. Klug judged that she was one and a half to two steps away.

The border-crossers succeeded by combining both approaches, which neither group alone was positioned to do.

Gender, class and the culture of King's. Franklin was a woman, a Jew, upper middle class, Cambridge-educated and fresh from a Parisian laboratory, in an Anglican college in which some of the social life was segregated by sex. How much these facts explain is disputed, and the most often repeated story needs care. Anne Sayre wrote that women at King's were excluded from the comfortable dining room in which male staff lunched. Maddox and Elkin found that the MRC unit's staff, including Franklin, usually ate together in a mixed dining room, and that Randall lunched with them. What Gosling recalled to Elkin was narrower and more telling: women were not allowed upstairs for coffee after lunch in the smoking room, a natural place for informal scientific conversation.[26] Randall's unit employed an unusual number of women scientists, and Franklin's quarrel with Wilkins had more to do with a badly defined job and two incompatible temperaments than with any policy. Yet the way she was described afterwards, above all in *The Double Helix*, which dwelt on her clothes and appearance, was plainly shaped by her sex; and the assumption that she must have needed men to interpret her own photograph is one that would hardly have been made about a man. The question is not whether sexism existed at King's, but which specific claims about it are true.

The race and its narrators. The phrase "the race for the double helix" comes largely from *The Double Helix*, and it shaped everything written afterwards. There was competition, and Pauling's involvement in early 1953 sharpened it. But King's and Cambridge were funded by the same council, shared data more than either admitted, and published together by arrangement. Pauling, the supposed rival, was barely in the race and lost through a chemical error rather than a lack of data. Casting the story as a race made it exciting and made it a story about winners. It also gave enormous authority to one participant's memory. Watson's later public statements showed the cost of that authority. In an interview published in the *Sunday Times* on 14 October 2007 he suggested that people of African descent were less intelligent than Europeans; Cold Spring Harbor Laboratory, which he had led for decades, suspended him from his administrative duties within days, and he retired soon afterwards. When he repeated the views in a television documentary in 2019, the laboratory revoked his honorary titles. Chargaff's bitterness is a smaller version of the same lesson. His ratios were one of the keys to the structure; he was not included in the prize, wrote to scientists around the world about it, and spent the rest of his life attacking the molecular biology that the double helix had launched, which, in a quip often attributed to him, he called the practice of biochemistry without a licence. His experimental work deserved better than either his exclusion or his later reputation as a crank. Stories about border-crossing tend to remember the people who crossed, and to forget the people whose ground they crossed onto.

Coda

Photograph 51 now hangs on the walls of classrooms all over the world, usually with a caption that gives it a single author and a single meaning. It had two people at the camera, and it

meant different things to the people who saw it. To Franklin in May 1952 it was a good picture of the less interesting form of DNA. To Watson in January 1953 it was confirmation of a helix he already believed in. To Crick it was a set of distances to be checked against a model. The structure itself came from somewhere else: from a page of a committee report, a symmetry symbol, a chemist's correction of a textbook, and a set of cardboard shapes moved around a desk. The photograph has become the symbol of the discovery because a picture is easier to show than a space group. Franklin, who distrusted pictures that had not been measured, might have found that the strangest part of the story.

James Watson died on 6 November 2025, aged ninety-seven. He was the last of the four people at the centre of this chapter: Franklin had died in 1958, and Crick and Wilkins in 2004.

Notes

[1]The dates (camera set up on Friday 2 May 1952, film developed on Tuesday 6 May) and the sixty-two-hour exposure from Franklin's laboratory notebook are given by King's College London, "The Story behind Photograph 51," https://www.kcl.ac.uk/the-story-behind-photograph-51. Some accounts date the photograph to 2 May and some to 6 May; both refer to the same exposure. Gosling, who operated the camera, later said that he had taken it as well. On the hydrogen atmosphere and the use of saturated salt solutions to fix the humidity, see Rosalind E. Franklin and R. G. Gosling, "The Structure of Sodium Thymonucleate Fibres. I. The Influence of Water Content," *Acta Crystallographica* 6 (1953): 673–77, which gives about 92 per cent relative humidity for structure B and about 75 per cent for structure A.

[2]Oswald T. Avery, Colin M. MacLeod, and Maclyn McCarty, "Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types," *Journal of Experimental Medicine* 79 (1944): 137–58; A. D. Hershey and Martha Chase, "Independent Functions of Viral Protein and Nucleic Acid in Growth of Bacteriophage," *Journal of General Physiology* 36 (1952): 39–56. Hershey and Chase separated phage coats from infected bacteria in a Waring blender, a laboratory version of the kitchen appliance; they were careful to say that their experiment did not prove that only DNA entered the cell.

[3]Erwin Chargaff, "Chemical Specificity of Nucleic Acids and Mechanism of Their Enzymatic Degradation," *Experientia* 6 (1950): 201–9. For human DNA see also E. Chargaff, S. Zamenhof, and C. Green, "Composition of Human Desoxypentose Nucleic Acid," *Nature* 165 (1950): 756–57.

[4]W. T. Astbury and Florence O. Bell, "X-Ray Study of Thymonucleic Acid," *Nature* 141 (1938): 747–48. On the purification of DNA and the tetranucleotide hypothesis, see Robert Olby, *The Path to the Double Helix* (London: Macmillan, 1974); and Michel Morange, *A History of Molecular Biology*, trans. Matthew Cobb (Cambridge, MA: Harvard University Press, 1998).

[5]W. Cochran and F. H. C. Crick, "Evidence for the Pauling–Corey α-Helix in Synthetic Polypeptides," *Nature* 169 (1952): 234–35; W. Cochran, F. H. C. Crick, and V. Vand, "The Structure of Synthetic Polypeptides. I. The Transform of Atoms on a Helix," *Acta Crystallographica* 5 (1952): 581–86. On Stokes's unpublished derivation, see Herbert R. Wilson, "Alexander Rawson Stokes," *Physics Today* 57, no. 1 (January 2004), https://physicstoday.aip.org/obituaries/alexander-rawson-stokes; and King's College London Archives, "Alexander Stokes," https://kingscollections.org/exhibitions/archives/dna/key-individuals/stokes.

[6]Aaron Klug, "The Discovery of the DNA Double Helix," *Journal of Molecular Biology* 335 (2004): 3–26, describes Franklin's draft of 17 March 1953 and its placing of the two chains 13 Å, or three-eighths of the

pitch, apart along the axis; the published version is Franklin and Gosling, "Molecular Configuration in Sodium Thymonucleate," *Nature* 171 (1953): 740–41. Klug's article is the most authoritative technical reconstruction of what each group knew and when.

[7]The biographical details in this section are from Brenda Maddox, *Rosalind Franklin: The Dark Lady of DNA* (London: HarperCollins, 2002); the US National Library of Medicine's "Rosalind Franklin Papers," Profiles in Science, https://profiles.nlm.nih.gov/spotlight/kr; and Elspeth F. Garman, "Rosalind Franklin 1920–1958," *Acta Crystallographica D* 76 (2020): 698–701.

[8]J. T. Randall to Rosalind Franklin, 4 December 1950, Rosalind Franklin Papers, Churchill Archives Centre, Cambridge, reproduced at https://profiles.nlm.nih.gov/spotlight/kr/catalog/nlm:nlmuid-101584586X1-doc. On Wilkins not being told, see Olby, *The Path to the Double Helix*, and Maddox, *Rosalind Franklin*. King's College London's archives say that the unit had a "relatively high number of women scientists" for the time.

[9]Maurice Wilkins, *The Third Man of the Double Helix: The Autobiography of Maurice Wilkins* (Oxford: Oxford University Press, 2003). The phrase about microscopes is reported by the National Library of Medicine, "The DNA Riddle: King's College, London, 1951–1953," https://profiles.nlm.nih.gov/spotlight/kr/feature/dna; Olby's judgement is in his review of Maddox, "Rosy Revised," *London Review of Books* 25, no. 6 (20 March 2003).

[10]Franklin's notes for the November 1951 colloquium are in the Rosalind Franklin Papers, Churchill Archives Centre, Cambridge. They are analysed in Klug, "The Discovery of the DNA Double Helix," and in Klug's earlier article, "Rosalind Franklin and the Discovery of the Structure of DNA," *Nature* 219 (1968): 808–10.

[11]On the 1950 paper and Pauling's objections, see Oregon State University Libraries Special Collections, "Linus Pauling and the Structure of Proteins: A Documentary History," https://scarc.library.oregonstate.edu/coll/pauling/proteins/; Pauling's recollection of the Oxford episode is in a 1973 filmed interview reproduced in the companion site "Linus Pauling and the Race for DNA," https://scarc.library.oregonstate.edu/coll/pauling/dna/. The alpha helix was published as Linus Pauling, Robert B. Corey, and H. R. Branson, "The Structure of Proteins: Two Hydrogen-Bonded Helical Configurations of the Polypeptide Chain," *Proceedings of the National Academy of Sciences* 37 (1951): 205–11.

[12]The Oregon State documentary history notes that Watson and Crick considered magnesium or calcium ions and that there was no good evidence for them: "Linus Pauling and the Race for DNA," narrative pages 9–10, https://scarc.library.oregonstate.edu/coll/pauling/dna/narrative/page9.html. Klug, "The Discovery of the DNA Double Helix," attributes the error over water content to Watson's confusion between the unit cell and the asymmetric unit. The Crick–Wilkins letters, found in 2010 among the papers of Sydney Brenner, are described in "New Letters Illuminate the Story behind DNA's Discovery," *PBS NewsHour*, 2010, https://www.pbs.org/newshour/science/new-letters-illuminate-the-story-behind-dnas-discovery.

[13]Erwin Chargaff, *Heraclitean Fire: Sketches from a Life before Nature* (New York: Rockefeller University Press, 1978). A description of a letter in the Crick Papers at the Wellcome Library dates the meeting to July 1952. Crick's recollection of the Griffith calculation and of hearing Chargaff's rules is in a filmed interview of 1973 reproduced in "Linus Pauling and the Race for DNA," https://scarc.library.oregonstate.edu/coll/pauling/dna/video/1973v.3-chargaff.html.

[14]The card is described in Science History Institute, "The Day the Helix Was Pronounced Dead," https://www.sciencehistory.org/collections/blog/the-day-the-helix-was-pronounced-dead/. Gosling's later recollection that Franklin never wholeheartedly believed the structure was other than helical is quoted there.

[15]Linus Pauling and Robert B. Corey, "A Proposed Structure for the Nucleic Acids," *Proceedings of the National Academy of Sciences* 39 (1953): 84–97, submitted 31 December 1952. Watson's remark is in *The Double Helix*. Peter Pauling's own reaction, in a letter to his parents of 3 February 1953, is quoted in "Linus Pauling and the Race for DNA," narrative page 24, https://scarc.library.oregonstate.edu/coll/pauling/dna/narrative/page24.html.

[16]Garman, "Rosalind Franklin 1920–1958," and the King's College London account cited above, give the circumstances in which Wilkins held the photograph. Watson's account of the day is in James D. Watson, *The Double Helix: A Personal Account of the Discovery of the Structure of DNA* (New York: Atheneum, 1968); a version with extensive scholarly annotations is *The Annotated and Illustrated Double Helix*, ed. Alexander Gann and Jan Witkowski (New York: Simon & Schuster, 2012).

[17]Max Perutz described the report and the circumstances in which he passed it on in M. F. Perutz, "DNA Helix," *Science* 164, no. 3887 (27 June 1969): 1537–39, replying to criticism from Erwin Chargaff and others after the publication of *The Double Helix*. Garman dates the handover to 9 February 1953; Klug, "The Discovery of the DNA Double Helix," to the second week of February.

[18]Klug, "The Discovery of the DNA Double Helix," gives the notebook entries of 10, 23 and 24 February 1953. Lynne Osman Elkin, "Rosalind Franklin and the Double Helix," *Physics Today* 56, no. 3 (2003), reproduces notebook entries showing that Franklin knew Chargaff's ratios and favoured the keto forms of the bases.

[19]The dates of Wilkins's visit, the arrival of the news at King's and Franklin's move are from Maddox, *Rosalind Franklin*, and Klug, "The Discovery of the DNA Double Helix." The model's metal plates partly survive and were used in a reconstruction now at the Science Museum, London (object 1977-310).

[20]J. D. Watson and F. H. C. Crick, "Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid," *Nature* 171 (1953): 737–38; M. H. F. Wilkins, A. R. Stokes, and H. R. Wilson, "Molecular Structure of Deoxypentose Nucleic Acids," *Nature* 171 (1953): 738–40; Rosalind E. Franklin and R. G. Gosling, "Molecular Configuration in Sodium Thymonucleate," *Nature* 171 (1953): 740–41. The order of the names Watson and Crick is said to have been decided by the toss of a coin.

[21]J. D. Watson and F. H. C. Crick, "Genetical Implications of the Structure of Deoxyribonucleic Acid," *Nature* 171 (1953): 964–67.

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Anne Sayre, *Rosalind Franklin and DNA* (W. W. Norton, 1975). A friend's reply to Watson, passionate and partisan; important for how the debate about Franklin began.

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Part III

Scales, Systems, and Invisible Worlds (1951–2000s)

Chapter 8

Life at Low Reynolds Number (1950s–1977)

A Tank of Corn Syrup

On 17 and 18 October 1974 the Massachusetts Institute of Technology held a symposium for Victor Weisskopf, the theoretical physicist who had led CERN in the early 1960s and who had formally retired from MIT at the end of July. Many of the world's leading scientists came to Cambridge, Massachusetts, for it, six Nobel laureates among them. The contributors to the published proceedings were what one would expect for a man of Weisskopf's standing: Hans Bethe, Murray Gell-Mann, Tsung-Dao Lee, Wolfgang Panofsky, Julian Schwinger, Stanislaw Ulam and others, among them Max Delbrück, the physicist turned biologist whom we met in Chapter 3.

One of the talks was about bacteria. Its speaker was Edward Purcell of Harvard, sixty-two years old, who had shared the Nobel Prize in Physics in 1952 for the discovery of nuclear magnetic resonance, the story told in Chapter 5. Purcell began by admitting that he would not have had the nerve to give such a talk on any other occasion, and that it was a story he had been saving up to tell "Viki," as Weisskopf's friends called him. It was not about nuclei or radio astronomy. It was about how things the size of a bacterium move through water, and why their world is so unlike ours that almost every intuition we have about swimming is wrong there.

He had one demonstration. He had set up a tall tank of corn syrup, about five thousand times as viscous as water, and turned an overhead projector on its side so that the audience could see what happened inside. In the syrup a helical model sank, and as it sank it turned, like a screw: in such a fluid, pushing a corkscrew along makes it rotate, just as rotating it makes it move. Purcell had chosen corn syrup rather than glycerine, he explained, because it was cheaper and quite uniform.

He also told a story about a model that he had not brought. Years before, he had heard Sir Geoffrey Taylor, the Cambridge fluid dynamicist, give a lecture at the National Academy of Sciences. At some point Taylor had pulled from his pocket a working model of a microscopic swimmer: a cylindrical body with a helical tail, driven by a twisted rubber band inside the

body, which he had tested in a tank of glycerine. The body carried a keel. Taylor, as Purcell remembered it, had admitted to being embarrassed that he had not thought to fit the keel in the first place.

Purcell's talk was published in 1976 in the proceedings of the symposium, *Physics and Our World*, and reprinted in the *American Journal of Physics* in January 1977 under the title he had given it, "Life at Low Reynolds Number."[1] It is a short, informal paper, with hand-drawn figures and asides about the energy budgets of bacteria. It has become one of the most widely read papers in the physics of living things, and one of the few that physicists pass to each other for pleasure. It gave a field that had existed for a quarter of a century its best-known phrase, and it marked the point at which three lines of work, which had grown up in different places for different reasons, finally met.

The first was a body of fluid mechanics, begun by Taylor in 1951, that asked how anything could swim when it was too small to coast. The second was cell biology's slow discovery of the molecular engines inside sperm tails and cilia. The third, and the one that brought Purcell to the subject, was the work of a younger Harvard colleague, Howard Berg, who had trained in atomic physics and built a microscope that could follow a single bacterium as it swam. This chapter is about how those three lines came together, and about what the physics did, and did not, explain about life at the scale of a micrometre.

The Science: Inertia and Treacle

Everything a swimmer does is governed by the equations of motion of the fluid around it. They were first written down for viscous fluids by the French engineer Claude-Louis Navier, whose memoir was read to the Académie des Sciences in 1822, and derived on firmer ground by George Gabriel Stokes at Cambridge in 1845. They are now called the Navier–Stokes equations. Their mathematics is formidable, but what they say can be put in words. Follow a small parcel of fluid. Its mass times its acceleration (the rate at which it is speeding up, slowing down or changing direction) must equal the sum of the forces on it. There are two that matter here. One is pressure: the fluid is pushed from regions of high pressure towards regions of low. The other is viscosity, the internal friction of the fluid: a parcel moving faster than its neighbours is dragged back by them, and a slower one is dragged along. The left-hand side of the equation, mass times acceleration, is the *inertia* of the fluid: its tendency to keep doing what it was doing. The viscous term on the right is what makes it stop.

Which side wins depends on the circumstances, and a single number decides it. Stokes himself recognised in 1851, in a long paper on how the air around a swinging pendulum slows it down, that viscous flows of different sizes and speeds behave alike if a certain combination of size, speed and viscosity is the same. In the same paper he worked out the drag on a small sphere moving slowly through a viscous fluid: the force is $6\pi\mu a U$, where μ is the viscosity, a the radius of the sphere and U its speed. This is Stokes's law, and it is the starting point of everything in this chapter.

The number became famous through an experiment. In 1883 Osborne Reynolds, the first professor of engineering at Owens College in Manchester, published an investigation of what he called the circumstances which determine whether the motion of water shall be "direct or sinuous." He ran water from a large tank through horizontal glass tubes of three sizes, from a quarter of an inch to an inch across, with a bell-shaped mouth to avoid disturbing the flow as it entered, and he introduced a thin filament of coloured water at the centre of the mouth. When the flow was slow, the coloured streak ran down the tube as a straight thread, as though drawn with a ruler. As he increased the speed, there came a point at which the thread suddenly wavered, broke up into eddies, and filled the tube with colour. The flow had become turbulent. Reynolds found that the change came at the same value of the combination $\rho v D / \mu$, where ρ is the density of the water, v its speed, D the diameter of the tube and μ the viscosity, whatever the size of the tube. For pipes, the critical value is around two thousand. The German physicist Arnold Sommerfeld proposed in 1908 that the quantity be called the Reynolds number, though his suggestion was largely forgotten; the name spread a few years later through the work of Ludwig Prandtl and his student Heinrich Blasius. It is a minor case of a familiar pattern in which a discovery is named after the person who made it famous rather than the one who first wrote it down.[2]

In general form, for any body of size L moving at speed v through a fluid of density ρ and viscosity μ,

$$Re = \frac{\rho v L}{\mu}.$$

The Reynolds number is a ratio. Roughly, the top line measures the inertial forces in the flow (how much momentum the moving fluid carries) and the bottom line the viscous forces (how strongly the fluid's internal friction resists being sheared). Because it has no units, it means the same thing at every scale: two flows with the same Reynolds number and the same geometry look alike, whether one is a ship and the other a model in a test tank. That is why engineers test model aircraft in wind tunnels, and it is why Purcell could stand in for a bacterium by putting a model several centimetres long into a fluid five thousand times thicker than water.

Chapter 2 followed D'Arcy Thompson's argument that as an animal shrinks, forces that act on surfaces, such as surface tension, come to dominate forces that act on volume, such as gravity. Something similar happens with inertia and viscosity, but here the governing quantity is not just size but size times speed, and small things are usually slow as well as small. Table 8.1 gives some examples, worked out for water, which has a density of 1,000 kilograms per cubic metre and a viscosity of about 0.001 pascal-seconds.

The range is more than ten powers of ten. At the top, inertia rules. A swimmer who stops kicking glides for a body length or more; a fish flicks its tail and coasts. Swimming at high Reynolds number works by throwing water backwards: the swimmer gives momentum to the water, and the water gives an equal and opposite momentum to the swimmer. At the bottom of the table there is no momentum to speak of. A bacterium does not throw water anywhere. It is in the position of a person who, in Purcell's image, has been put into a swimming pool full of molasses and forbidden to move any part of the body faster than about a centimetre a minute. If such a person could cover a few metres in a couple of weeks, Purcell said, he would qualify

Table 8.1: Reynolds numbers of some swimmers in water (illustrative sizes and speeds; $Re = \rho v L/\mu$ with $\rho = 1{,}000\ \mathrm{kg\,m^{-3}}$, $\mu = 0.001\ \mathrm{Pa\,s}$)

Swimmer	Length	Speed	Reynolds number
Human swimmer	2 m	1 m/s	2×10^{6}
Goldfish	10 cm	20 cm/s	2×10^{4}
Small guppy	1 cm	1 cm/s	10^{2}
*Parameciu*m	100 μm	1 mm/s	10^{-1}
Human sperm cell	50 μm	50–200 μm/s	10^{-3}–10^{-2}
E. coli (body)	2 μm	30 μm/s	6×10^{-5}

as a low-Reynolds-number swimmer.[3]

Science Primer: How far does a bacterium coast?

Purcell's most quoted illustration asks what happens if a bacterium swimming at 30 micrometres per second suddenly stops driving itself. How far does it coast?

A rough answer comes from comparing the cell's momentum with the drag that destroys it. Treat the cell as a sphere of radius $a = 1\ \mu\mathrm{m}$ (10^{-6} m) with the density of water. Its mass is

$$m = \tfrac{4}{3}\pi a^{3}\rho \approx 4 \times 10^{-15}\ \mathrm{kg}.$$

Stokes's law says the drag at speed v is $6\pi\mu a v$, which is proportional to the speed. A force proportional to speed slows a body exponentially, with a characteristic time

$$\tau = \frac{m}{6\pi\mu a} = \frac{2\rho a^{2}}{9\mu} \approx \frac{2 \times 1000 \times 10^{-12}}{9 \times 10^{-3}} \approx 2 \times 10^{-7}\ \mathrm{s},$$

a fifth of a microsecond. In that time, at 30 micrometres per second, it travels

$$v\tau \approx (3 \times 10^{-5}) \times (2 \times 10^{-7}) \approx 7 \times 10^{-12}\ \mathrm{m},$$

less than a tenth of an ångström. Purcell, using slightly different numbers, gave a coasting distance of about 0.1 ångström and a stopping time of about 0.6 microseconds. Either way, the bacterium stops within a distance about a tenth of the width of a hydrogen atom, in well under a microsecond.

The same arithmetic run for a person gives the opposite answer. For a swimmer moving at 1 metre per second the viscous estimate makes no sense at all: the water's resistance comes mainly from the momentum the swimmer throws into the wake, and a swimmer who stops kicking glides on for something like a body length. The point of the exercise is the ratio. For the sphere above, the coasting distance divided by the cell's diameter works out at the Reynolds number (based on that diameter) divided by eighteen. With a diameter of 2 micrometres and a speed of 30 micrometres per second, as in Table 8.1, $Re \approx 6 \times 10^{-5}$, and the cell coasts about three-millionths of its own length. The past has no influence on what a bacterium does next: its motion at any instant is fixed entirely by

the forces acting on it at that instant.

The Science: A World Without Momentum

When the Reynolds number is very small, the inertial side of the Navier–Stokes equations can be dropped altogether. What is left are the Stokes equations, which say that at every point in the fluid the push of pressure is exactly balanced by viscous friction. In symbols, $\nabla p = \mu \nabla^2 \mathbf{u}$, where p is the pressure, $\mathbf{u}$ the velocity of the fluid, and the symbols ∇ and ∇^2 stand for the rates at which these quantities change from place to place. The details matter less than two properties of the result, which together explain why microscopic swimming is so strange.

The first is that the Stokes equations are *linear*. If you double the speed of every moving surface, every velocity in the fluid doubles and every force doubles; if you superimpose two flows, the result is a flow. The Navier–Stokes equations are not linear (the inertial term contains the velocity multiplied by itself), and that is why turbulence, eddies and wakes exist. At low Reynolds number there are no wakes, no eddies, no turbulence, and no mixing by stirring.

The second property is that the Stokes equations contain no time. Nothing in them refers to how fast things happen, only to where the boundaries are and how fast they are moving at that instant. Reverse the motion of every boundary and the flow reverses exactly. Run it slowly or quickly and the fluid follows the same sequence of configurations. This is called *kinematic reversibility*, and it can be demonstrated with a striking simplicity. Fill the narrow gap between two concentric cylinders with a very viscous liquid and inject a small blob of dye. Turn the inner cylinder several times: the blob is drawn out into a thin sheet that winds around the gap until it seems to have been thoroughly mixed. Now turn the cylinder back by exactly the same number of turns. The sheet unwinds, and the blob reassembles itself almost exactly where it started, blurred only slightly at the edges by molecular diffusion.

The demonstration is usually credited to Taylor, who performed it in a film called *Low-Reynolds-Number Flows*, first issued in 1966 for the National Committee for Fluid Mechanics Films, a series of teaching films organised from MIT by the engineer Ascher Shapiro. In the same film Taylor showed swimming models, among them one that moved briskly in water but went nowhere in a viscous liquid, and one with a helical tail that made slow but steady progress. The unmixing apparatus was not his invention. The chemical engineer L. E. Scriven pointed out in 2007 that the film recreated, without acknowledgement, a demonstration that John P. Heller, a physicist at the Mobil research laboratories in Dallas, had described in the *American Journal of Physics* in 1960.[4] The film made it famous; generations of students have now watched a mixed fluid unmix itself.

Purcell drew the consequence for swimming. If the flow depends only on the sequence of shapes a swimmer passes through, and not on the speed at which it passes through them, then a swimmer that changes shape and then changes back by the same route must end up where it began.

Science Primer: The scallop theorem

A scallop swims by clapping its shell. It opens slowly, drawing water in, then snaps shut, driving a jet of water out past the hinge, and moves in the opposite direction. At the Reynolds number of a real scallop (several thousand or more), the trick works because the fast closing and the slow opening are different: the jet carries momentum, the shell coasts, and the slow reopening does not undo the gain.

Now imagine a microscopic scallop with a single hinge, in a fluid where the Stokes equations hold. It has one way to change its shape, the angle of its hinge, so every stroke must consist of opening and closing along the same path. Suppose that opening the shell moves the scallop a small distance Δx in some direction. Because the flow depends only on the shapes and not on time, closing the shell retraces the opening in reverse, whatever its speed, and must move the scallop back by exactly Δx. After one full cycle the net displacement is

$$\Delta x - \Delta x = 0.$$

Clap fast and open slowly, or the reverse: it makes no difference.

The general statement is now called the *scallop theorem*: in a Newtonian fluid (one whose viscosity does not depend on how fast it is sheared), with no inertia, a single body that changes shape in a *reciprocal* way (a sequence of shapes that looks the same when run backwards, like a film of a door opening and closing) cannot achieve any net displacement. Purcell called it "the theorem that got the scallop."

There are several ways out, and each one corresponds to something real.

- *Use two or more degrees of freedom.* Purcell imagined a swimmer made of three rigid links joined by two hinges, which could flap them in a sequence (first hinge, second hinge, first hinge back, second hinge back) that traces a loop in the space of its possible shapes. A loop is not reciprocal; played backwards it runs the other way round. Such a swimmer moves.
- *Propagate a wave.* A wave travelling along a flexible tail, from base to tip, is not reciprocal either: played backwards it runs from tip to base. Sperm and many other cells swim this way.
- *Rotate.* A turning corkscrew is the simplest non-reciprocal motion of all: run the film backwards and it turns the other way.
- *Change the fluid.* If the fluid's viscosity depends on how fast it is sheared, as in mucus and many biological fluids, fast and slow strokes no longer cancel. In 2014 a team at the Max Planck Institute for Intelligent Systems in Stuttgart built a single-hinged "micro-scallop" that, by opening and closing at different speeds, did swim in such fluids.

Purcell's argument was simple enough to fit on a transparency, and it has been generalised

many times since, most elegantly by the physicists Alfred Shapere and Frank Wilczek, who showed in 1989 that the net motion produced by a cycle of shape changes can be computed as a geometrical property of the loop the swimmer traces in its space of shapes.[5]

Why, then, does a waving tail or a turning corkscrew push a cell forward? The answer lies in a fact about long, thin objects at low Reynolds number. Drag a thin rod sideways through a viscous fluid and it meets about twice the resistance that it meets when dragged lengthways at the same speed. (For an infinitely thin rod the ratio tends to two; for real filaments of finite thickness it is somewhat less. Purcell found about 1.5 for his model propellers.)

This *drag anisotropy* is what turns sideways motion into thrust. Picture one short, straight piece of a flagellum, tilted at an angle to the direction in which the cell is swimming, and suppose the flagellum's wave or rotation is carrying that piece sideways. Split its velocity into two parts, one along the piece's length and one across it. The fluid resists the across-length part about twice as strongly as the along-length part, so the total drag on the piece does not point straight back against its motion; it is tilted, and part of it points along the axis of the cell. Add up the contributions from every piece of the tail and the sideways components cancel over a full wave, while the along-axis components add up to a net push. If drag were the same in every direction, as it is for a sphere, the push would vanish. A rotating helix works the same way: each piece of the helix sweeps sideways in a circle, and because it is tilted to that motion, each one pushes a little along the axis.

That is all there is to the propulsion of sperm and bacteria, at the level of principle. The rest, as the next sections show, was a matter of getting the numbers right and finding out what the cells actually do.

The Cambridge Swimmers

Geoffrey Ingram Taylor was born in St John's Wood, London, on 7 March 1886. His mother was a daughter of the mathematician George Boole, and when the boy was eleven he was introduced at a Christmas lecture to Lord Kelvin, who told him that he had known his grandfather. He went to Trinity College, Cambridge, and stayed in Cambridge for most of the rest of his life. In 1913 he sailed as meteorologist on the *Scotia*, chartered after the *Titanic* disaster to observe ice in the North Atlantic, and the measurements of temperature, pressure and humidity he made from it became the basis of his early theory of turbulent mixing in the atmosphere. In the First World War he went to the Royal Aircraft Factory at Farnborough, learned to fly (he took a pilot's certificate in 1915), studied the stability of parachutes and made parachute jumps himself. In 1923 the Royal Society made him a research professor, which freed him from teaching, a task he disliked and was not good at, for the rest of his career.

He was a lifelong small-boat sailor. In the 1930s he designed a new kind of anchor, the CQR, which held better for its weight than earlier designs and became popular among yachtsmen; in later life he and his wife sailed a 19-ton cutter to Shetland, Norway and the Lofoten Islands. In the Second World War he worked on blast waves and underwater explosions, and in 1944–45 he

was at Los Alamos as a member of the British mission to the Manhattan Project. He was among the observers at the Trinity test in New Mexico on 16 July 1945. In 1950 he published, in the *Proceedings of the Royal Society*, the theory of the blast wave from a very intense explosion that he had worked out for the British government in 1941, together with an analysis of photographs of the Trinity fireball. They came from a declassified motion-picture record of the test, issued in 1947 by the physicist Julian Mack, with clearer prints sent by Norris Bradbury, the director of Los Alamos, and others lent by the Ministry of Supply. From the photographs alone, with their time stamps and scale bars, he estimated the energy of the explosion as around 17 kilotons of TNT, close to the figure of about 20 kilotons that was then still secret.

That calculation, which extracted a secret number from pictures that were no longer secret, is a good example of Taylor's style. He was not a builder of grand theories. He looked for problems where a clear physical picture, a little mathematics and a simple experiment would give a definite answer, and he found them everywhere: in the atmosphere, in the spreading of oil on water, in the instability of a heavy fluid lying on a light one, in the way a drop of liquid is pulled into a point by an electric field. Swimming cells were one more such problem.

The question came to him from a zoologist. Victor Rothschild, who had succeeded his uncle as the third Baron Rothschild in 1937, was a Cambridge zoologist who had spent the war in MI5 working on counter-sabotage (he received the George Medal in 1944, for work that included dismantling bombs) and returned to the Department of Zoology to study fertilisation. In the late 1940s he was working on the physiology of sea-urchin spermatozoa and on methods of assessing the activity of bull semen for artificial insemination. Among the things that he and earlier observers had noticed was that sperm swimming close together and side by side tend to beat their tails in step. Rothschild's conversations with Taylor set Taylor thinking about whether a sperm cell swims like a fish, and why neighbouring tails might synchronise.[6] (It is sometimes said that Rothschild was studying how bull sperm swim. His main experimental work in these years was on sea urchins, though he also worked on bull semen.)

Taylor's paper, "Analysis of the Swimming of Microscopic Organisms," appeared in the *Proceedings of the Royal Society* in 1951. He began by stripping the problem down to its simplest form. Forget the head and the finite length of the tail. Imagine instead an infinite flat sheet, lying in a viscous fluid, along which a wave of small sideways ripples travels, as a wave travels along a flicked rope. Could such a sheet move itself, using viscous forces alone, with no inertia at all?

It could, and Taylor calculated how fast. If the ripples have amplitude b (the height of a crest above the mean position) and wavelength λ, and the wave travels along the sheet at speed c, the sheet moves in the direction opposite to the wave at a speed

$$U = \frac{2\pi^2 b^2}{\lambda^2}\, c.$$

This is a small-amplitude result, but it is instructive. The speed does not depend on the viscosity at all: thicker fluid makes swimming harder work, but not slower. It depends on the square of the amplitude, so that a wave half as high gives a quarter of the speed. And for plausible shapes

it is a respectable fraction of the wave speed. If the amplitude is one-tenth of the wavelength, U is about a fifth of c. Charles Brokaw, photographing sperm at Caltech in the 1960s, measured bending waves travelling down the tail at about a millimetre per second and sperm swimming at 150 to 200 micrometres per second, a ratio of the same order.

The second half of the paper took up Rothschild's observation. Taylor placed two waving sheets side by side and calculated the energy dissipated in the fluid between them. When the two waves were in phase, crest beside crest, the dissipation was much lower than when they were out of phase; and when they were slightly out of step, the viscous stresses between them tended to pull the two wave trains into phase. He argued that this might be why sperm swimming side by side beat in unison. The argument was suggestive rather than complete: it compared the energy dissipated by different arrangements but did not show how two sheets would actually move into step. When Gwynn Elfring and Eric Lauga worked out the dynamics in 2009, they found that waves of Taylor's purely sinusoidal form do not lock their phases at all; locking requires a waveform that is asymmetric from front to back, as real flagellar waves are. In a second paper, in 1952, Taylor extended the analysis from flat sheets to thin cylindrical tails, which are closer to a real flagellum.

Then, characteristically, he built a model. It had a cylindrical head and a tail made of a helix of metal wire sheathed in rubber tubing, which was anchored to the head, and a wound rubber band inside the head drove the tail. In a tank of glycerine, according to the fluid dynamicist Herbert Huppert's account, the model swam at a speed that agreed with Taylor's theory.[7] Taylor also made a mechanical fish that flapped its tail. It swam happily in water and, in a viscous syrup in which its Reynolds number matched that of a microbe, it went nowhere. A box of these models was found at the Cavendish Laboratory more than half a century later, and replicas are now used in teaching.

Taylor's analysis was a proof of principle, and its idealisations were obvious: an infinite sheet, waves of small amplitude, no head. The next step was taken by a zoologist and an applied mathematician. James Gray, professor of zoology at Cambridge from 1937, had been studying how animals move since the 1920s, from the beating of cilia (his book *Ciliary Movement* appeared in 1928) to the swimming of fish. Gray had photographs of the sperm of a sea urchin, which showed that the tail's bending waves were roughly sinusoidal. G. J. Hancock, a mathematician, had meanwhile extended Taylor's analysis in 1953 to waves of realistic amplitude on a thin filament.

In 1955 Gray and Hancock published a joint paper in the *Journal of Experimental Biology* that turned the problem into one a biologist could compute. They divided the tail into short pieces, treated each as a slender rod, and gave it two drag coefficients, one for motion along its length and one for motion across it, with the across-length coefficient roughly twice the other. The total thrust was the sum of the drag on all the pieces. This approach, now called *resistive force theory*, ignores the way the flow around one part of the tail affects the flow around another, and it is only an approximation. But it gave formulas that could be checked against photographs. When Gray and Hancock fed in the waveform from Gray's pictures, added the drag of the head, and calculated how fast the sperm should swim, they obtained a speed almost exactly equal to the

one Gray had measured.[8]

The agreement was partly fortunate (the drag coefficients they used were later revised), but the method survived. Resistive force theory became the standard tool of biologists who studied sperm and flagella, and in rough form it remains the first thing taught to students of the subject. In the terms of this book it was a piece of methodological smuggling in the most practical sense: a technique from the hydrodynamics of slender bodies, put into a form that could be applied with a ruler and a photograph.

Engines and Equations

Through the 1950s and 1960s the subject grew slowly, in a few places, and mostly among people who were trained in one discipline and working in another.

Charles Brokaw had been a graduate student in Gray's department in Cambridge from 1955 to 1958 and then moved to the California Institute of Technology, where he became the leading student of how sperm tails actually bend. In 1963, using a new flash illuminator built at Caltech, he photographed sperm tails with better resolution than Gray had managed, and found that their waves were not sine waves at all. They consisted of circular arcs of nearly constant curvature joined by straight stretches, and the bends were created at the base and travelled down the tail. The question Brokaw spent much of his career on was what made the bends, and how they were coordinated along a tail of molecular machinery. He later used computer simulations to explore how such bending could arise. A Caltech colleague in engineering, Theodore Wu, who had come to the problem in 1960 by way of Taylor's and Lighthill's work, analysed the swimming of flexible plates.

James Lighthill brought the subject its most powerful mathematician. Born in Paris in 1924, he had made his reputation in aerodynamics and acoustics; his 1952 theory of the sound generated by turbulent flow founded the science of jet noise. From 1959 to 1964 he directed the Royal Aircraft Establishment at Farnborough, the successor of the factory where Taylor had learned to fly, and when he moved to Imperial College as a Royal Society research professor in 1964 he turned much of his attention to animals. For more than fifteen years he wrote on the swimming of fish, the flight of birds and insects and the swimming of micro-organisms, and he collected the work in a book whose title named the subject: *Mathematical Biofluiddynamics*, published by the Society for Industrial and Applied Mathematics in 1975. His John von Neumann Lecture of that year, published in 1976 as "Flagellar Hydrodynamics," refined the drag coefficients of resistive force theory and became a standard reference. He was Lucasian Professor at Cambridge from 1969 to 1979. A strong swimmer all his life, he died in July 1998, aged seventy-four, when a heart valve failed near the end of an attempt to swim around the Channel Island of Sark, a swim he had first completed in 1973.

It would be too much to say that Lighthill, Brokaw and Wu founded the field: Taylor had done that in 1951, and Gray and Hancock had given it its working method. But by the early 1970s there was a recognisable community. In July 1974, three months before Purcell's talk,

about 250 people met at Caltech for a symposium on swimming and flying in nature, organised by Wu, Brokaw and the engineer Christopher Brennen, which brought together zoologists, physiologists, applied mathematicians and engineers in a single programme running from bacteria to birds.[9] It was, in the language of this book, a trading zone in the literal sense: a place built for the purpose, where people who did not share a training could exchange problems for methods.

Meanwhile biologists had found the engine. Ian Gibbons, born in Rye, Sussex, in 1931, had read physics at King's College, Cambridge, before taking a doctorate there in electron microscopy, and he had gone to Harvard to run a new electron microscopy laboratory in the biology department. Studying the cilia of the single-celled *Tetrahymena*, he began in 1963 to pick apart a protein that split ATP, the cell's common fuel. By 1965 he and Arthur Rowe had purified it, shown that it formed the small "arms" visible in electron micrographs on the nine pairs of microtubules that run along every cilium and every sperm tail around a central pair (the "nine plus two" arrangement), and named it *dynein*, from the dyne, the old unit of force; the name was suggested, by his own account, by his wife Barbara one evening at home.

How dynein made a cilium bend was a separate question. One possibility was that the microtubules themselves contracted on one side, as muscle contracts. Another, proposed by Peter Satir from electron micrographs in 1965 and 1968, was that the microtubules kept their length and slid past one another, so that a bend arose wherever sliding was resisted. In 1971 Gibbons, who had moved to the University of Hawaii in 1967, and his graduate student Keith Summers settled it. They stripped the membranes from sea-urchin sperm tails, digested the remaining machinery briefly with the enzyme trypsin to cut the links that normally hold the microtubules together, and added ATP. Under the microscope the tails telescoped apart, the microtubule doublets sliding actively past one another until the structure had disintegrated into separate strands.[10] In an intact tail, sliding is resisted at the base and by elastic links, so it turns into bending. The bending waves that Taylor had treated as a given, and that Gray and Brokaw had photographed, are produced by thousands of dynein molecules walking along microtubules, switched on and off in sequence along the tail.

This was the eukaryotic half of the story: sperm, cilia and the flagella of algae and protozoa all use the same axoneme, and all swim by propagating bending waves along a flexible tail, breaking the scallop theorem in the second of the ways listed in the primer. Bacteria, which are far smaller and have no microtubules or dynein, do something entirely different. Finding out what took a physicist.

The Bacterium That Turns

Howard Berg was born in Iowa City in 1934, the son of a biochemist at the University of Iowa. He went to Caltech intending to study electrical engineering, switched to chemistry, graduated in 1956, enrolled at Harvard Medical School, decided it was a mistake, and returned to basic science. He took his doctorate in chemical physics at Harvard in 1964 with Norman Ramsey, working on the hydrogen maser, the atomic clock that Ramsey and his students had invented.

(Berg had first approached Purcell in 1961 about joining his group; Purcell, by Berg's recollection, said that he had no graduate students and could not think of anything for one to do.) As a Junior Fellow of Harvard's Society of Fellows Berg began a long collaboration with Purcell, starting with a technique for separating large molecules by sedimentation, published in 1967, which they hoped would be useful in biology and which was not.

Berg's turn to bacteria came through a conversation with Max Delbrück, who had wanted to study the behaviour of microorganisms but not with *E. coli*, because, as Berg's colleagues later put it, he did not know how to "tame" bacteria. Bacteria were known to swim towards some chemicals and away from others, a behaviour called chemotaxis, first studied in the 1880s by the German biologists Theodor Engelmann and Wilhelm Pfeffer. What nobody could do was watch what an individual bacterium did as it swam. A cell a micrometre across swimming at thirty micrometres a second leaves the field of view of a high-power microscope in a few seconds, and leaves its narrow plane of focus faster still.

Berg's solution came straight from the physics laboratory. He built a microscope that followed a single bacterium automatically in three dimensions. Optical sensors registered when the cell drifted off centre, and the error signal was fed back to move the sample chamber so as to bring the cell back to the middle. The record of how the chamber had been moved was a record of the cell's path, sampled about a dozen times a second. It is the kind of feedback servo that atomic physicists build to lock a laser or a maser to a resonance, applied to a germ. Berg described the instrument in the *Review of Scientific Instruments* in 1971, by which time he had moved, after a sabbatical in Julius Adler's laboratory in Wisconsin, to the new department of molecular, cellular and developmental biology at the University of Colorado in Boulder.[11]

The tracks, published by Berg and Douglas Brown in *Nature* in 1972, showed that *E. coli* does not swim smoothly. It swims in nearly straight *runs* lasting on average about a second, interrupted by brief episodes, lasting about a tenth of a second, in which it jiggles about and sets off again in a new, more or less random direction. Berg and Brown called these episodes *twiddles*; the name that stuck was *tumbles*. A cell's path is a random walk. In a chemical gradient the walk is biased, and the tracks showed how. When a cell happened to be swimming up a gradient of an attractant, towards more food, its runs lasted longer. When it swam down the gradient, its runs were not much shorter than in a uniform solution. The bacterium does not steer. It simply postpones changing its mind when things are getting better. Berg liked to sum up the strategy in human terms: when life is getting better, make the most of it; when it is getting worse, don't fret.

That raised the question of how the runs and tumbles were produced. An *E. coli* cell carries several flagella, each a thin helical filament some micrometres long, too thin to see in an ordinary light microscope, attached at points around the cell body. Microbiologists had generally assumed that bacterial flagella, like the tails of sperm, propagated waves along their length.

In 1973 Berg and Robert Anderson argued, in a short paper in *Nature*, that this was wrong: bacteria swim by rotating their flagellar filaments. Each filament is a rigid helix, joined by a flexible coupling called the hook to a motor in the cell wall that turns it, like a propeller on a shaft. Their evidence was indirect: for instance, antibodies that cross-linked neighbouring filaments

stopped cells swimming, which was hard to understand unless the filaments in a bundle had to turn freely past one another. But the conclusion was clear and it made a prediction.

Michael Silverman and Melvin Simon, at the University of California, San Diego, tested it within months. If a flagellum was turned by a motor at its base, then fixing the flagellum to a glass slide should make the motor turn the cell instead. They used antibodies to stick cells to the glass by their flagellar hooks or the stubs of their filaments, and the cells spun, first one way, then the other. A paper from Julius Adler's laboratory in Wisconsin, published beside theirs in May 1974, used the same trick to make the connection to behaviour: anticlockwise rotation (as seen looking along the filament towards the cell) corresponded to smooth swimming, clockwise rotation to tumbling, and attractants and repellents shifted the balance between the two. When all of a cell's motors turn anticlockwise, the helical filaments, nudged together by the flow they generate, wrap into a single bundle behind the cell and drive it forward. When one or more motors reverse, the bundle flies apart and the cell tumbles.

It was the first true rotary motor known in biology. The motor is about 45 nanometres across, and in a swimming cell it turns its filament at around a hundred revolutions a second. What drives it was settled over the next three years. Adler's group showed in 1974 that the motor did not run directly on ATP, and in 1977 Michael Manson, working with Berg and the microbiologist Franklin Harold, showed that cells of a *Streptococcus* whose energy supply had been cut off could be set swimming again by an electrical voltage or by a difference in acidity across their membrane. Either component of the *proton-motive force*, the tendency of protons to flow back into a cell that has pumped them out, will drive the motor.[12] Some bacteria use sodium ions instead. Here, too, the physical picture borrowed from a familiar machine: the motor is a turbine, turned by a current of ions flowing downhill through it.

The cell's ability to reverse that motor was the other half of chemotaxis, and it was the half that biochemists and geneticists explained. Adler, a biochemist by training who had been inspired by Engelmann's and Pfeffer's papers, began working on chemotaxis soon after arriving at the University of Wisconsin in 1960. His group isolated mutants that could not perform chemotaxis, showed in 1969 that *E. coli* has dedicated receptors for attractants, independent of the machinery that takes them in, and devised an assay that counted the bacteria swimming into a fine capillary tube filled with attractant. Robert Macnab and Daniel Koshland at Berkeley answered a question that tracking alone could not. A cell is so small that the difference in concentration between its front and back is tiny; does it compare concentrations across its body, or over time? In 1972 they took *Salmonella* cells and, by rapid mixing, changed the concentration of attractant all at once, with no gradient in space at all. A sudden rise suppressed tumbling for a while; a sudden fall increased it. The cells were comparing the present with the recent past.[13] Later work in Berg's laboratory measured the memory directly: a tethered cell weighs the last second or so positively and the three seconds before that negatively, and responds to the difference.

Why a Bacterium Swims

Purcell came to all this through Berg. The two had kept talking after their sedimentation work, and at some point they watched together some films, made by the microbiologist Norbert Pfennig, of experiments that Engelmann had done in the 1880s. Purcell's first question, Berg remembered, was how anything so small could swim in a straight line at all. Berg described his own part in what followed as that of the "straight man."

The questions that interested Purcell were the ones a physicist would ask: not what molecules were involved, but what the laws of physics allowed. In his Weisskopf talk he asked one of them in its starkest form. Why does a bacterium swim? The obvious answer is that it is looking for food. But food reaches a cell by diffusion, the random thermal wandering of molecules, and at this scale diffusion is very fast. Perhaps, he suggested, the bacterium swims in order to stir the water around it and so bring more food within reach, as a person might stir sugar into tea.

He showed that it does not. A stationary cell of radius a that absorbs every molecule of a nutrient that touches it collects them at a rate $4\pi Dac$, where c is the concentration of the nutrient far away and D its diffusion coefficient, which for a small molecule such as a sugar in water is around 10^{-9} square metres per second. Swimming, or stirring, can only increase this by bringing fresh fluid to the cell faster than diffusion already does. Purcell defined a "stirring number," the ratio of the rate at which flow carries molecules across a distance ℓ to the rate at which diffusion does, and found that for a bacterium it is about one-hundredth. To increase its food supply by even ten per cent, he calculated, a bacterium would have to swim at about 700 micrometres per second, about twenty times faster than it actually does. In their formal paper on the subject, published in 1977, Berg and Purcell estimated that swimming at thirty micrometres per second raises a cell's uptake of a small molecule by about two and a half per cent. The cell carries its own neighbourhood of water along with it, and the food comes in by diffusion regardless.

What swimming does do is change the neighbourhood. A bacterium cannot improve its supply where it is; it can only go somewhere better. Purcell put the conclusion as a matter of grazing: the bacterium does not graze, it moves to find greener pastures. And to find them it has to outrun diffusion, because a move too short to do that tells it nothing about the world that diffusion was not already telling it.

Science Primer: Outrunning diffusion

Diffusion and swimming carry things over distance in different ways, and the difference explains the length of a bacterium's runs.

A molecule wandering at random does not travel a distance L in a time proportional to L. Its typical displacement grows only as the square root of time, so the time it takes to diffuse a distance L is roughly

$$t_{\text{diff}} \approx \frac{L^2}{D},$$

where D is the diffusion coefficient. (The exact numerical factor depends on the geometry; it does not affect the argument.) A swimmer moving steadily at speed v covers the same distance in

$$t_{\text{swim}} = \frac{L}{v}.$$

For short distances diffusion wins, because L^2 is small; for long distances swimming wins. The two times are equal at the *crossover length*

$$L^* = \frac{D}{v}.$$

Put in numbers for *E. coli*, swimming at $v = 30$ micrometres per second (3×10^{-5} m/s). For a small nutrient molecule, $D \approx 10^{-9}$ m^2/s (Purcell's round figure; glucose in water is about 6×10^{-10} m^2/s). Then

$$L^* = \frac{10^{-9}}{3 \times 10^{-5}} \approx 3 \times 10^{-5}\ \text{m} = 30\ \mu\text{m}$$

for Purcell's value, and about 20 micrometres for glucose.

Over one micrometre, the size of the cell, diffusion takes about $(10^{-6})^2/10^{-9} = 10^{-3}$ seconds, a millisecond, while swimming takes about 30 milliseconds: the molecules are thirty times faster than the cell. Over a millimetre, diffusion takes about 10^3 seconds, a quarter of an hour, while swimming takes about 30 seconds.

So a bacterium that wants to sample a part of its surroundings that is genuinely different from where it is now must swim further than a few tens of micrometres; any shorter, and the molecules it is trying to measure will have diffused there first. A run of about a second, at thirty micrometres a second, is about thirty micrometres long: just past the crossover. Purcell noted, tentatively, that this is about what swimming bacteria do. The same scale sets a limit on what the cell can learn. During a run it counts molecules arriving at its receptors, and because those arrivals are random, the count is noisy. Berg and Purcell showed that the precision of any such measurement improves only as the square root of the time spent counting, and that *E. coli*, with runs of about a second and a memory of a few seconds, comes close to the best that physics allows.

"Physics of Chemoreception," Berg and Purcell's paper in the *Biophysical Journal*, worked out the theory properly.[14] It asked how accurately a cell could measure the concentration of a chemical in a given time, and how it should arrange its receptors to do so. One of its results surprised biologists. A cell does not need to cover its surface with receptors to capture nearly all the molecules it could possibly capture. Because a molecule that diffuses up to a cell and misses one receptor is likely to wander around and hit another, a few thousand receptors, each about a nanometre in radius and together covering less than a thousandth of the surface, collect half as many molecules as a perfectly absorbing cell would. The rest of the surface is free for other jobs. The paper also showed why, for a swimming bacterium, comparing concentrations over time is the better strategy than comparing them across its length: by moving, the cell distorts the

concentration around its own body far more than the real gradient does. The time comparison found by Macnab and Koshland was not just what bacteria happened to do. It was what the physics favoured. Berg and Purcell shared the American Physical Society's Biological Physics Prize (now the Max Delbrück Prize) for the work in 1984.

Outcomes and Legacy

A field with a name. Purcell's lecture did not found the physics of microscopic swimming, but it gave it a shared vocabulary and a set of thought experiments that every newcomer could absorb in an afternoon: the swimmer in molasses, the coasting distance, the scallop, the stirring number. In 2011 the fluid dynamicist Eric Lauga described it as the most cited paper in the field. The scallop theorem in particular became a standard tool, and a whole literature now studies how nature and engineers evade it, with flexible tails, with several swimmers interacting, with inertia at intermediate scales and with non-Newtonian fluids.

Active matter. In the 1990s and 2000s physicists began to study large numbers of swimmers rather than one. A dense suspension of bacteria behaves like a strange fluid: it develops swirls and jets far larger than any cell, and its effective viscosity can fall below that of the water it is in. Such systems, whose parts each consume energy to move themselves, became a branch of statistical physics known as *active matter*, which now runs from bacterial suspensions to flocks of birds and the protein filaments inside cells. Its starting point is the low-Reynolds-number hydrodynamics of a single swimmer.

Artificial swimmers. The first microscopic artificial swimmer that actually worked was reported in 2005 by Rémi Dreyfus, Jérôme Bibette and colleagues in Paris, with Howard Stone at Harvard. It was a chain of magnetic colloidal particles, linked by strands of DNA and attached to a red blood cell, and an oscillating magnetic field made the chain beat like a flexible tail. It looked like a sperm cell, though it moved in the opposite direction, towards its tail. Helical magnetic propellers, turned by rotating fields in the manner of a bacterial flagellum, followed a few years later. The hope that such devices will carry drugs through the body has produced a large literature and many animal experiments; in November 2025 a team at ETH Zurich reported a system that steered drug-carrying magnetic microcapsules through the blood vessels of pigs, aiming at the clots that cause strokes, and said it hoped to begin trials in people. None is yet in clinical use.

Microfluidics. The same physics governs the tiny channels of "lab-on-a-chip" devices, which have become standard in biology and medicine since the 1990s. In a channel a few tens of micrometres wide, flows are smooth and reversible, and two streams can run side by side without mixing except by diffusion. That is useful for some purposes and a nuisance for others; one well-known solution, published in 2002 by Abraham Stroock, Howard Stone, George Whitesides and colleagues, uses grooves in the floor of the channel to fold the fluid over on itself repeatedly, so that diffusion has only short distances to cover.[15] The stirring number that told Purcell why a bacterium does not stir tells an engineer why a microchannel will not mix.

Inside the motor. The bacterial flagellar motor has become one of the most intensively studied machines in biology. It is built from some forty kinds of protein in *E. coli*, and electron cryo-microscopy has now revealed much of its structure at near-atomic resolution. In 2020 two groups, one of which included Berg, reported the structure of the stator units that convert the flow of ions into torque: each consists of a ring of five copies of one protein, MotA, around two copies of another, MotB, an arrangement that suggests that the ring itself turns as protons pass through it, like a small gear driving the large rotor.[16] Berg kept working on the motor until his death in December 2021, at the age of eighty-seven.

Sperm. The physics of sperm swimming, which began with Rothschild's observations, has become a practical subject in reproductive medicine. Rothschild himself reported in 1963 that bull sperm in a drop of suspension gathered near the glass surfaces. Hydrodynamic calculations and simulations since the 2000s have shown that swimming cells, sperm and bacteria alike, are drawn towards walls by the flows they create, and this has been proposed as part of the explanation of how sperm find their way along the surfaces of the female reproductive tract.[17]

Credit. The history of the subject is usually told through Taylor and Purcell, two eminent physicists who made brief, brilliant visits to biology. The people who did most of the sustained work are less well known outside it: Gray, who supplied the photographs and the questions; Hancock, whose analysis underlies resistive force theory; Brokaw, who spent four decades on the sperm tail; Gibbons and his wife Barbara, whose work on dynein was recognised with the American Society for Cell Biology's highest award in 1994; and Adler, Koshland and the geneticists who worked out the signalling network. Purcell's lecture names Taylor, Berg, and Silverman and Simon, but not Gray, Hancock, Lighthill or Brokaw. Berg later recalled that Purcell was not much interested in what the literature said about a problem; he wanted to think it through for himself. It made for a memorable lecture, and a partial history.

The Costs of Crossing

The physics of low Reynolds number is a clean example of the book's second mechanism, structural isomorphism: the recognition that a sperm cell, a bacterium and a corkscrew in syrup obey the same equations. The story also shows where that kind of recognition runs out.

The idealised swimmer. Taylor's sheet was infinite; Purcell's scallop swam in an unbounded fluid with no walls; resistive force theory treats each piece of a flagellum as though the others were not there. Real microbes live in a much messier world. Most bacteria in nature are near surfaces, and near a surface the physics changes. *E. coli* swimming close to a glass slide does not run in straight lines but in circles a few tens of micrometres across, clockwise when seen from above the surface, because the cell body and the flagellar bundle turn in opposite directions and the wall drags on them unequally; it is also drawn towards the wall and held there. Many swimmers live not in water but in mucus, which is elastic as well as viscous, so that the scallop theorem no longer holds and the speed of a stroke matters again. *Helicobacter pylori*, which colonises the human stomach, was long imagined to corkscrew its way through the gastric mucus. A study in 2009 found instead that it secretes an enzyme that raises the local

pH and turns the mucus from a gel into a liquid it can swim through.[18] The physicist's model told biologists what was possible; it could not tell them what the organism actually did.

The theory waited for the biology. Taylor's analysis appeared in 1951, and Gray and Hancock's working method in 1955. Yet the most basic fact about bacterial swimming, that the flagellum rotates, was not established until 1973–74, and it was established not by hydrodynamics but by a tracking instrument and antibody experiments. The theory had been perfectly able to describe a rotating helix (Taylor's own models had helical tails); it simply had no way to decide whether bacteria used one. Nor did the physics suggest that bacteria should run and tumble. Both discoveries needed the habits of an experimental physicist, but applied to watching cells rather than to writing equations about them. For two decades, the mathematics was ahead of the observations it needed, and most biologists had little reason to read it.

A metaphor taken literally. The bacterial flagellum was described from the start in the language of engineering: motor, rotor, stator, bushing, drive shaft, propeller. The words were apt, and they helped to make the discovery vivid. They also made it available for other uses. In *Darwin's Black Box* (1996) the biochemist Michael Behe presented the flagellum as an "irreducibly complex" machine, one that could not work if any part were removed and so could not, he argued, have evolved by gradual steps. The flagellum became the emblem of the intelligent design movement, and it was argued over in court in 2005 in *Kitzmiller v. Dover Area School District*, in which a federal judge in Pennsylvania, John E. Jones III, ruled on 20 December that teaching intelligent design in a public school biology class was unconstitutional. The biologist Kenneth Miller testified that a subset of the flagellum's proteins forms a working system of its own, the type III secretion system that some bacteria use to inject proteins into host cells. Later work has complicated that argument without helping Behe's. Mark Pallen and Nicholas Matzke pointed out in 2006 that there is no single "bacterial flagellum": flagella differ widely among bacteria, are driven by protons in some species and sodium in others, and only about half of the forty or so proteins in the *E. coli* flagellum seem to be universally needed. A phylogenetic study in 2012 concluded that the secretion system evolved from the flagellum rather than the other way round.[19] The episode is a reminder that a metaphor carried from one field into another brings its connotations with it. An outboard motor has a designer. A rotary protein complex that evolved from other protein complexes does not, and calling it a motor does not change that.

What the physics could not explain. Berg and Purcell showed that *E. coli* senses its chemical environment almost as well as physics allows, and why it must compare over time rather than across its body. They did not, and could not, say how it does so. The machinery turned out to be a network of proteins that adds and removes methyl groups from the receptors, adjusting their sensitivity so that the cell responds to changes rather than to absolute levels, and it was found by genetics and biochemistry, in Adler's and Koshland's laboratories and many others. Physics came back in the 1990s, when theorists such as Naama Barkai and Stanislas Leibler showed why this kind of network adapts reliably even when the amounts of its proteins vary.[20] But the sequence is telling. Physics set the limits and asked the questions; the answers came from the people who could take the cell apart.

Coda

Purcell ended his lecture with Osborne Reynolds. Besides his famous number and his work on lubrication, Reynolds had published in 1903 a strange book, *The Sub-Mechanics of the Universe*, which tried to build the world out of tiny interacting grains. Purcell said that Reynolds would not have found that work incongruous beside a talk on bacteria, and that he was sure Weisskopf would not either. It was a joke about the breadth of physics, and a modest one. The physics of a swimming bacterium is not deep in the way that particle physics is deep. It is a matter of dropping one term from an equation that had been known for a century and a half, and following the consequences carefully. What made it productive was that a few people on each side of the border bothered to do so: a fluid dynamicist with a box of rubber-band models, a zoologist with a camera, a cell biologist with a bottle of trypsin, and an atomic physicist who built a machine to follow one germ through a drop of water.

Notes

[1]E. M. Purcell, "Life at Low Reynolds Number," in *Physics and Our World: A Symposium in Honor of Victor F. Weisskopf*, AIP Conference Proceedings 28 (New York: American Institute of Physics, 1976): 49–64; reprinted in *American Journal of Physics* 45, no. 1 (1977): 3–11. The reprint was received by the journal in June 1976; the talk itself belongs to the symposium of 17–18 October 1974. Weisskopf's retirement date and the symposium are described in "Weisskopf Dies at 93; Was Protégé of Physicist Niels Bohr," *MIT News*, 24 April 2002, https://news.mit.edu/2002/weisskopf-0424. Some accounts date the lecture to 1976 or describe it as Purcell's retirement lecture; neither is correct.

[2]G. G. Stokes, "On the Effect of the Internal Friction of Fluids on the Motion of Pendulums," *Transactions of the Cambridge Philosophical Society* 9, part 2 (1851): 8–106; Osborne Reynolds, "An Experimental Investigation of the Circumstances Which Determine Whether the Motion of Water Shall Be Direct or Sinuous, and of the Law of Resistance in Parallel Channels," *Philosophical Transactions of the Royal Society of London* 174 (1883): 935–82. The history, including Sommerfeld's naming of the number at the International Congress of Mathematicians in Rome in 1908 and its later adoption by Prandtl and Blasius, is in N. Rott, "Note on the History of the Reynolds Number," *Annual Review of Fluid Mechanics* 22 (1990): 1–12.

[3]Purcell, "Life at Low Reynolds Number." Purcell's own round figures for a swimming man (about 10^4) and a goldfish or guppy (about 10^2) are loose; with the sizes in Table 8.1 a human swimmer comes out nearer 10^6. Values for *Paramecium*, human sperm and *E. coli* follow Eric Lauga and Thomas R. Powers, "The Hydrodynamics of Swimming Microorganisms," *Reports on Progress in Physics* 72, no. 9 (2009): 096601.

[4]G. I. Taylor, *Low-Reynolds-Number Flows* (16 mm film, National Committee for Fluid Mechanics Films, 1966; videorecording 1985), available with its film notes through MIT, https://web.mit.edu/hml/ncfmf.html. The film notes were published in 1967, and some sources date the film to that year or to the 1985 video release; J. P. Heller, "An Unmixing Demonstration," *American Journal of Physics* 28 (1960): 348; L. E. Scriven, "Windows and Credit in Irreversibility," letter, *Physics Today* 60, no. 8 (August 2007): 14.

[5]Purcell, "Life at Low Reynolds Number." The name "scallop theorem" came into general use later; see Eric Lauga, "Life around the Scallop Theorem," *Soft Matter* 7 (2011): 3060–65. Alfred Shapere and Frank Wilczek, "Geometry of Self-Propulsion at Low Reynolds Number," *Journal of Fluid Mechanics* 198

(1989): 557–85. The micro-scallop is Tian Qiu et al., "Swimming by Reciprocal Motion at Low Reynolds Number," *Nature Communications* 5 (2014): 5119.

[6]On Taylor's life, see G. K. Batchelor, *The Life and Legacy of G. I. Taylor* (Cambridge: Cambridge University Press, 1996); the MacTutor biography, https://mathshistory.st-andrews.ac.uk/Biographies/Taylor_Geoffrey/; and, for his presence at Trinity, the Atomic Heritage Foundation profile, https://ahf.nuclearmuseum.org/ahf/profile/geoffrey-taylor/. The blast-wave papers are G. I. Taylor, "The Formation of a Blast Wave by a Very Intense Explosion," parts I and II, *Proceedings of the Royal Society of London A* 201 (1950): 159–74 and 175–86; part II names its photographic sources as J. E. Mack's report MDDC 221 (1947), prints from Bradbury, and photographs lent by the Ministry of Supply. Taylor's preferred value was 16.8 kilotons. It is often said that he worked from photographs printed in *Life* magazine; his paper does not say so. Rothschild's role is described in Herbert E. Huppert, "G. I. Taylor and His Influence," *Nature* 322 (1986): 500; and in Otti Croze and François Peaudecerf, "G. I. Taylor and the Physics of Swimming," *CavMag* (Cavendish Laboratory), no. 15 (February 2016). Rothschild's own papers of the period include "Measurement of Sperm Activity before Artificial Insemination," *Nature* 163 (1949): 358–59. On Rothschild's career, see the biography published by the Department of Zoology, University of Cambridge, https://www.zoo.cam.ac.uk/alumni/biographies-of-zoologists/victor-rothschild-1910-1990.

[7]G. I. Taylor, "Analysis of the Swimming of Microscopic Organisms," *Proceedings of the Royal Society of London A* 209 (1951): 447–61. On phase locking, see Gwynn J. Elfring and Eric Lauga, "Hydrodynamic Phase Locking of Swimming Microorganisms," *Physical Review Letters* 103 (2009): 088101. Brokaw's figures are from Charles J. Brokaw, "The Movement of Spermatozoa," *Engineering and Science* (California Institute of Technology), February 1967. Huppert, "G. I. Taylor and His Influence"; Purcell, "Life at Low Reynolds Number," which describes the rubber sheath and the keel. G. I. Taylor, "The Action of Waving Cylindrical Tails in Propelling Microscopic Organisms," *Proceedings of the Royal Society of London A* 211 (1952): 225–39. A box of Taylor's models, including a mechanical fish and helical swimmers, was rediscovered in the Cavendish Laboratory in the 2010s; Croze and Peaudecerf, "G. I. Taylor and the Physics of Swimming."

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Chapter 9

The Iridium Layer: The Detective Story of the K-T Boundary (1977–1991)

A Centimetre of Clay

Gubbio is a medieval hill town in Umbria, in the Apennines about 160 kilometres north of Rome. A short way beyond its northern gate the road to the basilica on Monte Ingino climbs into a narrow gorge, the Gola del Bottaccione, beneath a fourteenth-century aqueduct that still runs along the mountainside. The walls of the gorge are limestone, pink and white, laid down in thin beds that were once the floor of a deep sea. The pink rock is the *scaglia rossa*, roughly "red flake", named for the way it splits into slabs. In the gorge it is about four hundred metres thick, and it records something like fifty million years of slow accumulation on the sea bed. Most of it is made of the shells of single-celled organisms, foraminifera, too small to see clearly without a lens.

At one level in the gorge the rock changes character. In the limestone below, a hand lens shows a crowd of foraminifera, some as large as grains of sand. In the limestone above, the shells are few and tiny. Between the two lies a layer of clay about a centimetre thick, in which there are no fossils at all. Geologists working in Umbria had known since the 1960s that this was the end of the Cretaceous period: the same horizon that, in rocks laid down on land in North America, marks the last of the dinosaurs.

In the summer of 1977 Walter Alvarez, a thirty-six-year-old geologist at Columbia University's Lamont–Doherty Geological Observatory, collected samples of the boundary clay from the limestone sections around Gubbio. With him was another geologist, Terry Engelder, who later remembered being one of the first two people to touch the samples. Later that year Walter took up a post at the University of California, Berkeley, where his father, the physicist Luis Alvarez, had spent most of his career. In October the samples went to Frank Asaro, a nuclear chemist at the Lawrence Berkeley Laboratory on the hill above the campus. For months nothing came back. Then, in June 1978, according to Walter's later account, his father telephoned. Asaro had results, and they did not make sense.[1]

The question they had asked was modest: how long had that centimetre of clay taken to settle? The answer turned into the claim that the world of the dinosaurs had ended not over millions of years but in a geological instant, when a body from space several kilometres across struck the Earth. It took a geologist, a physicist, two nuclear chemists, a Dutch micropalaeontologist, a mineralogist at the US Geological Survey, two oil-company scientists, a Canadian graduate student and many others fourteen years to turn that claim into a crater. Along the way it unsettled one of the oldest principles of the Earth sciences and started one of the most bitter scientific arguments of the late twentieth century.

The Science: A Slow Earth

To see why a centimetre of clay mattered so much, we have to go back a century and a half, to a fight about how the Earth works.

In 1830 Charles Lyell, a Scot who had practised briefly as a lawyer before turning to geology, published the first volume of *Principles of Geology*. The second followed in 1832 and the third in 1833. The subtitle stated the programme: the book was an attempt to explain the former changes of the Earth's surface "by reference to causes now in operation". Lyell was restating, with far more evidence and far better prose, an argument made in Edinburgh in the 1780s by James Hutton, who had concluded that in the rock record he could find "no vestige of a beginning, no prospect of an end". The past, on this view, was to be explained by the same slow processes that could be watched today: rivers cutting valleys, mud settling on the sea floor, coastlines rising and sinking by a few inches in a lifetime. Given enough time, they could do everything. The young Charles Darwin was given the first volume by Captain Robert FitzRoy at the start of the voyage of the *Beagle* in December 1831, and had the second sent out to meet him at Montevideo, where he collected it in November 1832.

Lyell's opponents are usually remembered as biblical literalists, but the most formidable of them were not simply that. In 1796 the French anatomist Georges Cuvier compared the bones of mammoths with those of living elephants and showed that they belonged to different species, which settled a long argument about whether extinction happened at all. Cuvier went on to describe a sequence of vanished faunas, each ended by what he called a revolution of the globe, and in the preliminary discourse to his great work on fossil bones (1812) he argued that the most recent of these upheavals had been sudden and not very long ago; he pointed to the flood stories of many ancient peoples as possible human memories of it. In England William Buckland of Oxford argued in *Reliquiae Diluvianae* (1823) that cave deposits and gravels were the work of a recent universal flood, and Adam Sedgwick at Cambridge agreed. These were careful field geologists reasoning from evidence, and when the evidence turned against them some changed their minds: Sedgwick publicly abandoned the flood theory in his farewell address as president of the Geological Society of London on 18 February 1831.

The labels that have stuck to the two sides were coined by William Whewell, whom we met in the Introduction inventing the word "scientist". Reviewing Lyell's second volume in the *Quarterly Review* in 1832, he divided geologists into "Uniformitarians" and "Catastrophists".

The uniformitarians won, and in winning they turned a method into an identity. Stephen Jay Gould later pointed out, in a paper of 1965 and at length in *Time's Arrow, Time's Cycle* (1987), that Lyell's "uniformity" bundled together quite different claims. Two of them, that the laws of nature are the same everywhere and always, and that we should explain the past by processes we know, are assumptions that every science makes. The other two, that geological processes have always run at much the same rate and that the Earth's condition has not changed in any particular direction, are claims about the world, which might be true or false. Lyell's rhetoric, and the textbooks that followed him, merged all four, so that doubting the slowness of the past felt like doubting the possibility of geology itself.

The merger had real virtues. It forced geologists to look for causes they could observe, and it gave them the immense spans of time that Darwin's theory would need. But by the twentieth century gradualism had become something closer to a professional reflex. Darwin had written it into evolution, and palaeontologists inherited it twice over. When a group of fossils vanished abruptly from a sequence of rocks, the first explanation to reach for was a gap in the record: erosion had removed some of the rock, or the rock had stopped forming for a while. Sudden global catastrophes were the stuff of popular books, not of journals.

The end of the Cretaceous, about sixty-six million years ago, was hard to explain by any means. The non-avian dinosaurs, the flying pterosaurs, the great marine reptiles, the coiled ammonites and a large share of the plankton disappeared at or near the same level in the rocks. By the 1970s the literature contained dozens of explanations, most of them gradual: changing climates, retreating shallow seas, competition from mammals. A few authors had suggested a collision with a comet or asteroid, among them the sponge specialist Max de Laubenfels in 1956, and in 1971 the Canadian palaeontologist Dale Russell and the physicist Wallace Tucker proposed that radiation from a nearby supernova had done the damage. None of these ideas came with evidence that could test it. They were stories, and most specialists treated them as such.

A note on names. Throughout the period this chapter covers, the horizon at Gubbio was called the Cretaceous–Tertiary boundary, abbreviated K-T; the K comes from *Kreide*, German for chalk. "Tertiary" was a survival of an eighteenth-century scheme that once also had a Primary and a Secondary. It was left out of the time scales approved by the International Union of Geological Sciences from 1989, and in 2005 the International Commission on Stratigraphy recommended that it no longer be used as a formal unit; the period after the Cretaceous is now the Palaeogene, and the boundary is the Cretaceous–Palaeogene or K-Pg boundary.[2] This chapter keeps K-T for the history, because that is what the people in it called it, and uses K-Pg for present-day science.

The Science: Reading Time in Rock

Walter Alvarez was in Gubbio because of two techniques for telling the time in rocks, and the story depends on both.

The first is *biostratigraphy*, the dating of rocks by the fossils in them. Species appear and disappear in a fixed order, so a rock containing a particular combination of species can be placed in that order wherever it is found. The best clocks are organisms that were abundant, widespread and quick to evolve, and few groups meet those requirements better than the planktonic foraminifera. These are single-celled protists that drift in the upper ocean and build tiny chambered shells of calcium carbonate. When they die the shells sink, and over millions of years they pile up as the deep-sea oozes that become limestones like the scaglia. Because the shells are so small, they can be studied in thin slices of rock under the microscope, and a single hand specimen may hold thousands.

The Gubbio section had been worked out in this way by two micropalaeontologists, Hans Peter Luterbacher and the Italian Isabella Premoli Silva, who published a preliminary revision of the Gubbio succession in 1962 and a full study of the Cretaceous–Tertiary boundary in the central Apennines in 1964. They were among the first to identify planktonic foraminifera reliably in thin sections of hard limestone rather than in loose sediment washed out of soft rock. Just above the boundary they described a new, tiny species and named it *Globigerina eugubina*, from *Eugubium*, the Latin name of Gubbio. Below the boundary the limestone is full of large, ornate Cretaceous species; above it are a few very small ones, some new and some that may be survivors. Popular accounts often say that a single species survived. The specialists' version is less tidy. Most Cretaceous planktonic species disappear at the boundary, but how many crossed it, whether one, a handful or more, has been argued over for forty years, partly because survivors and reworked older shells are hard to tell apart.

The second technique is *magnetostratigraphy*. Some minerals in sediments, especially tiny grains of iron oxide, settle with their magnetisation aligned to the Earth's magnetic field, like compass needles frozen in place. The field reverses its polarity at irregular intervals, so that north and south swap, and a pile of sediments records the sequence of reversals as alternating bands of "normal" and "reversed" rock. The same pattern was known from the magnetic stripes on the ocean floor, recorded by basalt cooling at the mid-ocean ridges. But the ocean floor could not easily give the stripes ages; that needed a section where the reversals could be tied to fossils.

Walter Alvarez and William Lowrie, a Scottish palaeomagnetist at Lamont, did not come to Umbria looking for reversals. They came in the early 1970s to measure the direction of magnetisation in the scaglia, to test whether the Italian peninsula had behaved as a separate microplate. The rocks proved too deformed to answer that question cleanly. Instead they found that the scaglia preserved a long, clean record of reversals that matched the ocean-floor pattern, and Premoli Silva's foraminifera could date it. Premoli Silva also taught them to recognise the boundary layer in the field. With Michael Arthur, Alfred Fischer, Giovanni Napoleone and William Roggenthen, they published the result in 1977 and proposed Gubbio as the type section for the reversal time scale of the Late Cretaceous and Palaeocene.[3] The boundary fell inside a reversed interval, later labelled chron 29R.

This mattered later in two ways. It meant that the boundary at Gubbio sat in one of the best-dated sections of marine rock in the world. And it gave the team an independent check on how fast the limestone had accumulated. If the centimetre of clay represented a long pause, the

magnetic record ought to show it.

The Science: An Element from Space

The tracer that answered Walter's question was a metal most people never encounter: iridium, a dense, silvery member of the platinum group, along with ruthenium, rhodium, palladium, osmium and platinum.

These elements are *siderophile*, "iron-loving". When the young Earth was hot enough for its iron to melt and sink to form the core, the platinum-group metals dissolved preferentially in the molten iron and went down with it. The rocky mantle left behind kept only a small fraction of its original share; for ruthenium, for example, the mantle holds around 5 parts per billion against about 700 in the most primitive meteorites. The crust, made from the mantle by further melting, is poorer still. The best estimate for iridium in the upper continental crust is about 0.02 parts per billion. The carbonaceous chondrites, primitive meteorites whose composition is close to that of the Sun, contain about 470 parts per billion: some twenty thousand times as much.[4] Most meteorites have never been through the sorting that stripped the Earth's surface of these metals.

That contrast makes iridium a sensitive marker of extraterrestrial material. A sediment made of ordinary crustal debris has almost none. Add a small amount of meteoritic dust and the dust supplies nearly all the iridium. The difficulty was measurement. At a fraction of a part per billion, the iridium in a gram of limestone amounts to about a ten-billionth of a gram, far below what ordinary chemical analysis could detect in the 1970s. The method that could do it came from nuclear physics.

Science Primer: Neutron activation analysis

The idea of neutron activation analysis is to make the atoms you are looking for announce themselves.

A powdered sample is placed in a nuclear reactor, where it is bathed in slow ("thermal") neutrons. A neutron has no charge, so it can approach a nucleus without being repelled, and some nuclei capture it. The result is a heavier isotope of the same element, often radioactive. It decays with its own *half-life*, the time in which half of a population of such nuclei decays, and the decay usually leaves the new nucleus in an excited state that emits *gamma rays* of precisely defined energies. Those energies are a fingerprint: no two isotopes share the same set.

Natural iridium consists of two stable isotopes, iridium-191 (37.3 per cent) and iridium-193 (62.7 per cent). Iridium-191 is unusually good at capturing slow neutrons. Its *cross-section*, the effective target area it presents to a neutron, is about 954 barns, where a barn is 10^{-24} cm^2; that is large by nuclear standards. Capture turns it into iridium-192, which has a half-life of 73.8 days and emits gamma rays chiefly at 316.5 and 468.1 kiloelectronvolts

(keV), in about 83 and 48 of every 100 decays respectively.

How many decays would a trace of iridium give? Take one gram of rock containing 0.1 parts per billion of iridium. That is 10^{-10} g, or about 3×10^{11} atoms, of which about 1.2×10^{11} are iridium-191. In a research reactor of the size Berkeley had, a one-megawatt TRIGA, the flux of thermal neutrons in the core is of the order of $\phi = 10^{13}$ neutrons per square centimetre per second. The rate of captures is the number of target atoms times the cross-section times the flux:

$$R = N\sigma\phi \approx (1.2 \times 10^{11}) \times (9.5 \times 10^{-22}\,\mathrm{cm}^2) \times (10^{13}\,\mathrm{cm}^{-2}\,\mathrm{s}^{-1}) \approx 1{,}100 \text{ per second.}$$

Eight hours of irradiation (about 29,000 seconds) therefore makes about 3×10^7 atoms of iridium-192. The *activity*, the number of decays per second, is the number of radioactive atoms times $\ln 2$ divided by the half-life; with a half-life of 6.4×10^6 seconds, that comes to about 3.5 decays per second.

That is a tiny signal, but it is a signal made of individual events, each of which can be counted. Suppose the sample is left for forty days, so that shorter-lived activity from more abundant elements dies away; sodium-24, for example, made from the sodium in every rock, has a half-life of only 15 hours and would otherwise swamp the spectrum. The iridium-192 has lost about a third of its activity, leaving about 2.4 decays per second, of which about 1.2 emit a 468 keV gamma ray. If the detector catches one of those in every fifty (an illustrative efficiency), a sixteen-hour count records more than a thousand of them, enough to stand clearly above the background. The 1980 paper illustrated a real measurement of this kind: a gamma-ray spectrum around 468 keV from a count of 980 minutes, begun 39.8 days after irradiation.

The method's strength is that it counts atoms one decay at a time, and identifies them twice over, by the energy of their gamma rays and by the rate at which those rays fade. Its weaknesses are interference from other isotopes with nearby gamma lines, and contamination. At these levels a speck of platinum jewellery on a technician's hand can ruin a sample.[5]

Father and Son

Walter Alvarez was born in Berkeley in October 1940. He studied geology at Carleton College in Minnesota and took his doctorate at Princeton in 1967 under Harry Hess, one of the architects of sea-floor spreading. He then spent three years as an exploration geologist for American Overseas Petroleum, in The Hague and then in Libya, where his time ended with Colonel Qaddafi's revolution. A fellowship took him to Rome, and in 1971 he joined Lamont as a research associate. He spoke Italian, and his work on the tectonics of the Mediterranean and on the Umbrian limestones made him almost as much an Italian geologist as an American one.

His father was a different kind of scientist. Luis Walter Alvarez, born in San Francisco in 1911, took his doctorate in physics at Chicago under Arthur Compton and moved to Ernest

Lawrence's laboratory at Berkeley. As Chapter 5 mentioned, he worked at the MIT Radiation Laboratory; he joined it in November 1940 and devised the ground-controlled approach system by which radar operators talked aircraft down through cloud. From 1944 he was at Los Alamos, where he led the development of the exploding-bridgewire detonators that fired the charges around the plutonium core of the implosion bomb with the necessary simultaneity. On 6 August 1945 he flew as a scientific observer in *The Great Artiste*, alongside the *Enola Gay*, to measure the blast over Hiroshima; on the way back he wrote a letter to his four-year-old son Walter, to be read when he was older, about what he had seen. After the war he built the proton linear accelerator described in Chapter 5, and in the 1950s and 1960s led the group whose liquid-hydrogen bubble chambers, and automated analysis of millions of photographs, revealed a large number of short-lived particles. They won him the Nobel Prize in Physics in 1968. He had a restless appetite for problems outside his field: he proposed using cosmic-ray muons to look for hidden chambers in the Second Pyramid at Giza (there were none in the part surveyed), and he analysed the film of President Kennedy's assassination. In 1977 he was nearly sixty-six and close to retirement, but far from inactive.

Walter brought him the question of the clay. As the son later told it, Luis first suggested measuring beryllium-10, a radioactive isotope made by cosmic rays in the atmosphere, which falls to the ground at a roughly steady rate. Count it in the clay, correct for decay, and you would know how long the layer had taken to collect. Luis put Walter in touch with Richard Muller, a Berkeley physicist who could attempt the measurement. Then they learned that the published half-life of beryllium-10 was wrong. The true value was shorter, and after sixty-five million years too little would be left to measure.

Luis's second idea was iridium. Meteoritic dust rains on the Earth all the time. If it fell at a steady rate, the iridium it carried would accumulate in proportion to the time the clay took to form. A layer laid down over hundreds of thousands of years would hold a measurable excess; a layer dumped in a few years would hold almost none. Either way the answer would date the clay. Luis later called it a geological timer, and the logic, as we will see, can be turned around.

Neither Alvarez could make the measurement. Frank Asaro could. Born in 1927 in Escondido, California, the son of an avocado farmer, he had taken his doctorate in nuclear chemistry at Berkeley under Isadore Perlman, head of the laboratory's chemistry division, and worked with him for some fourteen years on the structure of heavy nuclei. Perlman and Asaro then turned neutron activation into a precise tool for archaeology: by measuring dozens of trace elements in a potsherd they could identify the clay it was made from and trace it to its source. Their 1969 paper on pottery analysis became the field's most cited reference. Asaro's group traced the stone of the Colossi of Memnon to quarries near Cairo, and in 1977 he and Helen Michel, a nuclear chemist born in 1932, showed that "Drake's Plate of Brass", supposedly left in California by Francis Drake in 1579, was a modern fake.[6] The iridium measurement drew on everything they had built: irradiation facilities, high-resolution gamma-ray spectrometry, standards, and a habit of measuring many elements at once and asking what the pattern meant. It also drew on patience. Analysing iridium at these levels was slow, and the equipment was not always working.

Thirty Times Too Much

The result that Asaro showed the Alvarezes in June 1978 was not the faint signal of slow accumulation. By Walter's account they had expected something of the order of 0.1 parts per billion. The clay held about 3 parts per billion, some thirty times more, and later analyses, corrected for iridium lost in the chemical preparation, gave around 9. The excess was confined to the clay and fell away above and below it. Whatever had happened, it was not a steady trickle of dust.

The clay might simply be peculiar, the Umbrian sea floor somehow concentrating iridium from seawater. The test was to look elsewhere, and Walter found a candidate in the geological literature: the cliffs of Stevns Klint, about fifty kilometres south of Copenhagen, where the boundary is a dark, sulphurous layer known as the *fiskeler*, the fish clay, finely laminated because nothing lived on the sea floor to churn it. Its iridium stood at about 160 times the background, against about 30 at Gubbio. A third section, at Woodside Creek in New Zealand, studied with Dale Russell, the palaeontologist of the supernova hypothesis, was enriched about twenty times.

Three sites, in both hemispheres, all enriched at the same horizon: the event had been global. Luis later recalled Asaro saying that he had tried out a new theory on him once or twice a week for six weeks. The first serious candidate was Russell and Tucker's supernova. An exploding star nearby would shower the solar system with freshly made heavy elements, iridium among them, and also with plutonium-244, which has a half-life of about eighty million years. Any plutonium-244 left from the formation of the solar system had long since decayed away, so finding it in the clay would be strong evidence of a recent stellar explosion. Asaro and Michel separated plutonium chemically from batches of 25 and 50 grams of clay, irradiated it in the campus reactor and looked for its signature. According to Walter's later account, the first run seemed to show plutonium, and for a while the supernova looked confirmed; on repetition the signal vanished, and the first result was put down to contamination. The repeated measurement could have detected a tenth of the amount a supernova should have left, and found none. The ratio of the two iridium isotopes in the clay, moreover, matched ordinary solar-system iridium to within a fraction of a per cent. The iridium had come from within the solar system.[7]

Luis tried and discarded other ideas: the solar system passing through a cloud of gas, a flare-up of the Sun, material from Jupiter. The idea that survived was suggested by a Berkeley astronomer, Christopher McKee: an asteroid. From the numbers of asteroids crossing the Earth's orbit, Eugene Shoemaker of the US Geological Survey and George Wetherill had estimated that about seven were bigger than ten kilometres across, and that one of that size should hit the Earth about once every hundred million years. A large impact was not a fantasy; it should have happened several times in the history of animal life.

How could an impact kill on a global scale? Luis found an answer in a historical eruption. When Krakatoa exploded on 26 and 27 August 1883 it threw out about eighteen cubic kilometres of rock, of which about four reached the stratosphere, and the fine dust produced vivid sunsets around the world for two years or more. An impact large enough to account for the iridium would throw up vastly more: enough, the team argued, to darken the sky for years, stop photosynthesis and collapse the food chains of land and sea. The same Krakatoa figures

let them estimate the size of the body.

Science Primer: The dust clock, run backwards

Luis's iridium timer can be worked through with modern numbers, and then reversed to estimate the size of the impactor.

The timer. The best-known direct measurement of the cosmic dust falling on the Earth, made by Stanley Love and Donald Brownlee from the microscopic craters left on panels of a long-exposure satellite, gave about 40,000 tonnes a year. (Estimates vary widely, and several recent ones are lower, but the order of magnitude is what matters.) Spread over the Earth's surface of $5.1 \times 10^{18}\,\mathrm{cm}^2$, that is

$$\frac{4 \times 10^{10}\,\mathrm{g\,yr}^{-1}}{5.1 \times 10^{18}\,\mathrm{cm}^2} \approx 8 \times 10^{-9}\,\mathrm{g\,cm}^{-2}\,\mathrm{yr}^{-1}.$$

If the dust has the composition of a carbonaceous chondrite, about 4.7×10^{-7} of it by mass is iridium, so the iridium rain is about $4 \times 10^{-15}\,\mathrm{g}$ on each square centimetre every year.

The Berkeley team measured the total iridium in the Gubbio boundary layer, its *surface density* s, as about $8 \times 10^{-9}\,\mathrm{g}$ per square centimetre. Dividing,

$$\frac{8 \times 10^{-9}}{4 \times 10^{-15}} \approx 2 \times 10^{6}\ \text{years}.$$

If dust alone supplied the iridium, the centimetre of clay must represent about two million years in which almost nothing else accumulated. Yet the magnetic stratigraphy showed no sign of so long a halt. The clock gave an impossible answer, which meant that its assumption, a steady supply, was wrong.

Run backwards. Suppose instead that the iridium arrived all at once and was spread evenly over the globe. Then the total delivered is sA, where A is the Earth's area: about $4 \times 10^{10}\,\mathrm{g}$, roughly forty thousand tonnes of iridium. If the body had the iridium content of a carbonaceous chondrite, taken in the 1980 paper as $f = 5 \times 10^{-7}$, the mass that reached the stratosphere and settled out was

$$M_{\mathrm{dust}} = \frac{sA}{f} \approx \frac{4 \times 10^{10}\,\mathrm{g}}{5 \times 10^{-7}} \approx 8 \times 10^{16}\,\mathrm{g}.$$

(The paper, with slightly different inputs, gives $7.4 \times 10^{16}\,\mathrm{g}$.) Only part of the material thrown out by a large explosion goes into the stratosphere; at Krakatoa the fraction was about four parts in eighteen, or 0.22. Dividing the paper's figure by 0.22 gives an impactor mass of about $3.4 \times 10^{17}\,\mathrm{g}$. At an assumed density of $2.2\,\mathrm{g\,cm}^{-3}$ that is a sphere 6.6 km across. The Danish clay held about ten times as much iridium per square centimetre; since mass grows as the cube of diameter, ten times the mass means $10^{1/3} \approx 2.2$ times the diameter, about 14 km.

The team made three other estimates, from the frequency of large impacts, from the total

mass of the boundary clay, and from the darkness needed to stop photosynthesis, and all were consistent. Their published answer was a diameter of 10 ± 4 km. The calculation is crude: it assumes that the fallout was even, that the Krakatoa fraction scales up, and that the body was chondritic. Its value lay in turning a puzzle about time into a prediction about size, and therefore about the crater that ought to exist.[8]

The Berkeley group presented its results at a meeting of the American Geophysical Union in Washington in May 1979, and the laboratory's magazine carried an account that autumn. Newspapers picked up the story. The full argument went to *Science*.

Caravaca

The Berkeley team was not alone. In south-eastern Spain, near the town of Caravaca, a gully called the Barranco del Gredero exposes another continuous marine section across the boundary, and since 1975 a young Dutch micropalaeontologist at the University of Amsterdam, Jan Smit, had been studying it. His question was why the planktonic foraminifera had died, and the section answered part of it. The extinction was, in his phrase, "sharp as a knife", with no gradual decline beneath it. In 1977 he had about a hundred samples analysed by neutron activation, which showed anomalous nickel, chromium, cobalt, arsenic and antimony at the boundary but, at first, no iridium.

Smit visited Gubbio in 1978. In 1979 he read a report of the Berkeley result in *New Scientist*, and it occurred to him that a large meteorite impact was a real possibility. He sent Caravaca samples to Jan Hertogen, a Belgian geochemist who had recently returned from a postdoctoral post with Edward Anders in Chicago, a centre of meteorite chemistry, and who could measure the platinum-group elements. Hertogen quickly found the iridium that the earlier analyses had missed, along with osmium. By Walter's account, the two men's long friendship began at a symposium on Cretaceous–Tertiary boundary events in Copenhagen in 1979. Smit and Hertogen's paper, "An Extraterrestrial Event at the Cretaceous–Tertiary Boundary", was received by *Nature* on 23 January 1980 and published on 22 May, suggesting that a large meteorite impact could have supplied the anomalous elements. Smit, by his own account, was not yet ready to abandon the supernova, and he found it hard at first to see how a single impact could have global effects; it was the Berkeley team's darkness scenario that convinced him.

"Extraterrestrial Cause for the Cretaceous–Tertiary Extinction" by Luis Alvarez, Walter Alvarez, Frank Asaro and Helen Michel appeared in *Science* on 6 June 1980, two weeks after Smit and Hertogen. It ran to fourteen pages, long for that journal, and it read like a physicist's paper: a sequence of hypotheses, each tested against numbers and kept or discarded. It presented the three iridium anomalies, ruled out a terrestrial source and a supernova, and estimated the impactor at 10 ± 4 km across. It suggested that such a body would enter the atmosphere at about 25 km per second with a kinetic energy equivalent to about 10^8 megatons of TNT, and that, from estimates by the Canadian geologist Richard Grieve, it would leave a crater about 200 km in di-

ameter. It noted that there was about a two-thirds chance that the body had fallen in the ocean. And it proposed a kill mechanism: dust in the stratosphere turning day into night for several years, after which the sky would clear relatively quickly.

The paper is often remembered as having proved its case. It did not, and it did not claim to. It established a global iridium anomaly, made a strong argument that the anomaly was extraterrestrial, and drew from it a hypothesis that made predictions. Other impact debris should be found in the boundary layer. The extinctions should coincide with it exactly, everywhere. And somewhere there should be a crater, about two hundred kilometres across and sixty-five million years old.

The first of those predictions began to be met within a year. In 1981 Smit and Gerard Klaver reported small spherules in the Caravaca boundary clay, which they interpreted as droplets that had solidified from a melt. Their first identification of the spherules' mineral as an original high-temperature feldspar was revised in 1983, when Alessandro Montanari, an Italian geologist working with Walter at Berkeley, and his colleagues showed that such spheroids were impact droplets of basaltic composition that had been altered after they settled.[9] The droplets were evidence of melting, but they were not yet evidence that only an impact could explain.

The Long Argument

Different disciplines received the hypothesis differently, and the differences show what each counted as evidence.

Planetary scientists were the most receptive. The Apollo and Mariner missions had shown the Moon, Mercury and Mars to be covered in craters, and Eugene Shoemaker had spent two decades showing that Meteor Crater in Arizona was the scar of an impact rather than a volcanic vent. To someone who had looked at the Moon, a large impact on the Earth within the last hundred million years was not an extraordinary claim; it was close to an expectation.

The first big meeting was held at Snowbird, a ski resort above Salt Lake City, from 19 to 22 October 1981, under the title "Large Body Impacts and Terrestrial Evolution". It brought astronomers, geochemists, geologists and palaeontologists into one room, and its proceedings, edited by the Caltech geologist Leon Silver and the planetary scientist Peter Schultz, became a landmark volume. By then iridium anomalies had been found at many more marine sites and, crucially, in rocks laid down on land in New Mexico, at the level where several Cretaceous pollen species disappear. That ruled out any explanation peculiar to seawater.

The vertebrate palaeontologists were the most sceptical, and their objections were not foolish. The dinosaur record was sparse. In the best-studied sequences in Montana the highest dinosaur bone lay some metres below the boundary, which seemed to suggest that the dinosaurs had gone before the iridium arrived. Some groups appeared to have declined over millions of years, and many survived, including crocodiles, turtles, birds and most groups of mammals, in ways that years of darkness did not obviously explain. Two palaeontologists, Philip Signor and Jere Lipps, answered the first objection in the Snowbird volume. Because fossils are rare, the last one found

of any species will almost always lie below the level at which the species actually died out, and the rarer the fossil, the bigger the gap. A sudden extinction will therefore look gradual in the rocks. The effect now bears their names, and it turned an argument about dinosaurs into an argument about sampling.

A second line of opposition came from geologists who accepted the iridium but not the impact. Charles Officer and Charles Drake of Dartmouth College argued that the boundary events had been spread over a long interval and that volcanism could supply the iridium; Kilauea in Hawaii was found in the 1980s to emit iridium in its gases. Their candidate was the Deccan Traps of western India, a pile of basalt lavas more than a kilometre thick, which had erupted at about the right time. The geologist Dewey McLean had proposed in 1978 that the gases from these eruptions had caused the extinction. The volcanists' case had real strength. The eruptions were enormous, they were close to the boundary in age, and nobody had a crater.[10]

Luis Alvarez did not argue in the manner geologists were used to. He treated the debate as a contest between data and opinion. In *Physics Today* in 1987 he wrote that the volcanic theory did neither of the things a theory must do, and that Officer and Drake had made a serious scientific error. He was blunter in conversation. Interviewed by the *New York Times* in January 1988, he disparaged palaeontologists as poor scientists, "more like stamp collectors". In the same article he dismissed McLean as a weak scientist who was no longer invited to conferences. The *Times* headline described a debate that had taken an unusually rancorous turn, and the rancour was not all on one side.[11] Luis Alvarez died on 1 September 1988, aged seventy-seven. He did not live to see the crater.

Shocked Quartz

Iridium showed that something extraterrestrial had arrived; it did not show how. What was needed was a physical fingerprint of a violent impact, and it came from a mineral.

Quartz is one of the commonest minerals in the continental crust. When a shock wave passes through a quartz crystal at pressures of roughly ten to thirty gigapascals, a hundred thousand to three hundred thousand times atmospheric pressure, it leaves sets of extremely thin, parallel planes of disordered or glassy material, aligned with particular directions in the crystal lattice. Under a microscope a grain may show several sets crossing each other. Geologists call them *planar deformation features*. They were recognised as a mark of impact in the 1960s, and true examples have never been found in quartz from any setting other than an impact. Volcanic explosions are violent, but they act on molten or partly molten rock at modest pressures. The deep crust reaches one to three gigapascals, slowly. An impact applies tens of gigapascals to solid rock in a fraction of a second.

In 1984 Bruce Bohor, a mineralogist at the US Geological Survey, with Eugene Foord, Peter Modreski and Don Triplehorn, reported quartz grains with multiple sets of planar features in the iridium-rich boundary claystone of a non-marine sequence in eastern Montana. Luis later recalled seeing something like a shock wave pass through the Earth sciences community when

Bohor announced it. In 1987 Bohor and his colleagues reported shocked quartz from boundary clays at five sites in Europe, in a core from the north-central Pacific and in New Zealand. Abundant shocked quartz implied that the target had included continental rock, which is rich in quartz, and not only the basaltic floor of the deep ocean.[12] The volcanists replied that some eruptions might produce similar features, and the argument over what counted as a genuine planar deformation feature ran on for years. For most specialists in shock metamorphism, though, the question was settled.

Science Primer: The energy of a ten-kilometre asteroid

How much energy does a body ten kilometres across carry? Kinetic energy, the energy of motion, is $E = \frac{1}{2}mv^2$, where m is the mass and v the speed.

Mass. A sphere of diameter 10 km has radius $r = 5{,}000$ m and volume $\frac{4}{3}\pi r^3 \approx 5.2 \times 10^{11}$ m^3. Its density is uncertain. Ordinary crustal rock is about 2,600–2,700 kg m^{-3}, and recent computer simulations of the Chicxulub impact give the impactor a density in that range. Carbonaceous chondrites, which the impactor appears to have resembled, are often porous and lighter; the 1980 paper assumed 2,200 kg m^{-3}. Taking 2,600 kg m^{-3},

$$m \approx 2{,}600 \times 5.2 \times 10^{11} \approx 1.4 \times 10^{15} \text{ kg},$$

or about 1.4 million million tonnes.

Speed. Anything falling onto the Earth from an orbit around the Sun arrives at no less than the Earth's escape velocity, about 11 km s^{-1}; modellers of Chicxulub usually adopt about 20 km s^{-1}, and the 1980 paper assumed 25. At 20 km s^{-1} the body would cross the dense lower atmosphere in about a second.

Energy. With $v = 2 \times 10^4$ m s^{-1},

$$E = \tfrac{1}{2} \times (1.4 \times 10^{15} \text{ kg}) \times (2 \times 10^4 \text{ m s}^{-1})^2 \approx 2.8 \times 10^{23} \text{ J}.$$

A megaton of TNT is defined as 4.184×10^{15} J, so this is about 7×10^7 megatons: seventy million megatons. With the 1980 paper's assumptions (density 2,200 kg m^{-3}, speed 25 km s^{-1}) it comes to about 3.6×10^{23} J, or 9×10^7 megatons, which the paper rounded to 10^8. The Hiroshima bomb released about 15 kilotons, or 6×10^{13} J. The impact released several billion times as much.

A more revealing comparison is per kilogram. The impactor carried $\frac{1}{2}v^2 = 2 \times 10^8$ J in each kilogram, about fifty times the chemical energy of a kilogram of TNT. On contact the shock pressures reached hundreds of gigapascals, enough to vaporise the impactor, melt and vaporise a great volume of the target, and throw shocked and melted rock out of the atmosphere on paths that carried it round the globe. The numbers are uncertain; published estimates of the energy run from about 10^{23} J upwards by an order of magnitude or more. Every estimate in that range puts the event far beyond any eruption in recorded history.[13]

The Crater Nobody Was Looking For

The crater had in fact been found before the *Science* paper was published, by people looking for oil.

In 1978 Glen Penfield, a young American geophysicist with Western Geophysical of Houston, a contractor flying an airborne magnetic survey of the Gulf of Mexico for Pemex, Mexico's national oil company, was checking data flown along lines off the north coast of the Yucatán peninsula. As the survey worked south towards the coast, weak magnetic anomalies grew stronger and resolved into part of a ring. Combined with a gravity map of the land made years earlier, the ring closed into a "bullseye" about 180 kilometres across, half on land and half under the sea, centred near the village of Chicxulub Pueblo and buried about a kilometre deep under younger limestone. Penfield, by his own later account, took it for an impact crater and said so in his report to Pemex in August 1978, where the idea was received with good-natured laughter. Pemex had drilled exploratory wells in the area in the 1950s and 1960s, and its geologists had classified the glassy rock at the bottom of them as volcanic.

Penfield and the Pemex geologist Antonio Camargo were allowed to present the structure at the annual meeting of the Society of Exploration Geophysicists in Los Angeles in 1981, provided they gave away no company data; by Penfield's account the title of their talk left out the word "crater". About twenty people heard it. According to one account, Penfield also wrote to Walter Alvarez about the structure, but nothing came of it at the time. Carlos Byars, a science writer for the *Houston Chronicle* who had worked for Western Geophysical when Penfield made his find, put the story on his paper's front page in December 1981, suggesting a link with the dinosaurs. It made little impression. There were reasons beyond bad luck. The data belonged to Pemex. The cores from the old wells were reported to have been lost in a warehouse fire. And oil geophysicists and the people arguing about extinctions went to different meetings and read different journals.

Meanwhile the impact community was searching, and the evidence slowly narrowed towards the Gulf of Mexico and the Caribbean. In 1988 Joanne Bourgeois and colleagues described a sandstone bed at the boundary by the Brazos River in Texas as the deposit of a tsunami, and Smit and others later found thick, chaotic boundary beds in north-eastern Mexico, such as at Arroyo el Mimbral, which they also attributed to giant waves; the interpretation was disputed for years.

The person who drew these threads together was Alan Hildebrand, a Canadian graduate student in planetary science at the University of Arizona, working with the geochemist William Boynton. Hildebrand noticed a report of tektites in boundary rocks on Haiti and went to look. In southern Haiti the boundary layer was about half a metre thick, some twenty-five times thicker than at any site then known. In 1990 Hildebrand and Boynton argued in *Science* that the impact had happened within about a thousand kilometres of Haiti, and pointed to a possible buried structure in the Colombian Basin, off South America.

At a conference in 1990 Byars told Hildebrand about Penfield's structure. Hildebrand called Penfield, and together they went looking for rock from the old Pemex wells. A few samples had

escaped the fire because they had been sent elsewhere; one lot had been sitting at the University of New Orleans since 1965. In breccia from the wells Hildebrand found shocked quartz, and the glassy "andesite" looked like impact melt: crust melted by the impact and frozen in the crater. In 1991, after *Nature* had rejected the paper, Hildebrand, Penfield, David Kring, Mark Pilkington, Camargo, Stein Jacobsen and Boynton published "Chicxulub Crater: A Possible Cretaceous/Tertiary Boundary Impact Crater on the Yucatán Peninsula, Mexico" in *Geology*. They named it after the village, and, drawing on Jacobsen's isotopic analyses at Harvard, showed that the andesitic glass from the crater resembled, chemically and isotopically, the tektites of the boundary layer.[14]

The Haitian glass made the connection. In 1991 Haraldur Sigurdsson and colleagues argued in *Nature* that it had formed by the melting of continental crust and of carbonate sediments, and Glen Izett of the US Geological Survey, with Brent Dalrymple and Lawrence Snee, dated it by the argon–argon method to 64.5 ± 0.1 million years, indistinguishable from the boundary itself. In 1992 two groups dated the melt rock from inside the crater. Carl Swisher and colleagues, Walter Alvarez and Smit among them, obtained 64.98 ± 0.05 million years from glassy melt rock recovered by the Chicxulub-1 well at a depth of about 1,390 metres, statistically identical to the Haitian glass. Virgil Sharpton and colleagues found 65.2 ± 0.4 million years, elevated iridium in the melt and a reversed magnetisation consistent with chron 29R, the interval that holds the boundary at Gubbio.[15] Fourteen years after Asaro's measurement, the prediction of 1980 had been met: a crater of about the right size and the right age, in continental rock, near the sites where the debris was thickest.

Outcomes and Legacy

Consensus, of a kind. In March 2010 a review in *Science* by Peter Schulte and forty colleagues, from palaeontology, sedimentology, geochemistry, geophysics and planetary science, concluded that the Chicxulub impact had triggered the mass extinction: the boundary layer was a single ejecta-rich layer, traceable around the world and tied chemically to Chicxulub, and its timing matched the onset of the extinctions. Twenty-nine scientists replied in the same journal that the extinctions had multiple causes, among them volcanism, falling sea levels and climate change, while agreeing that the impact had played some part. The dating has continued to tighten. In 2013 Paul Renne and colleagues at the Berkeley Geochronology Center dated the boundary in Montana, and the Haitian tektites, to about 66.04 million years, with an uncertainty of about 43,000 years once all sources of error are included, and found the impact and the extinction synchronous within about 32,000 years.

Inside the crater. In April and May 2016 the joint International Ocean Discovery Program and International Continental Scientific Drilling Program Expedition 364, led by Joanna Morgan of Imperial College London and Sean Gulick of the University of Texas, drilled from a lift-boat into the crater's peak ring, a circle of hills inside the larger crater, buried beneath the sea floor off the port of Progreso. They recovered core to 1,335 metres below the sea floor. The peak ring turned out to be granite from deep in the crust, shattered, shocked and lifted kilometres within

Table 9.1: Who contributed what to the K-T impact case, 1962–1992

Discipline	**People**	**Contribution**
Micropalaeontology	Isabella Premoli Silva, Hans Peter Luterbacher; Jan Smit	Foraminiferal zonation of the Gubbio boundary (1962–64); abrupt plankton extinction at Caravaca.
Palaeomagnetism	Walter Alvarez, William Lowrie and colleagues	Gubbio reversal sequence dated by foraminifera (1977); steady sedimentation across the boundary.
Experimental physics	Luis Alvarez	The iridium "timer"; elimination of alternatives; size estimate from the Krakatoa analogy.
Nuclear analytical chemistry	Frank Asaro, Helen Michel; Jan Hertogen	Neutron activation measurements of iridium and the plutonium-244 test; iridium and osmium at Caravaca.
Mineralogy and petrology	Bruce Bohor and USGS colleagues; Smit, Montanari	Shocked quartz (1984, 1987); impact spherules (1981–83).
Sedimentology	Joanne Bourgeois and colleagues; Smit	Possible tsunami deposits around the Gulf of Mexico.
Exploration geophysics	Glen Penfield, Antonio Camargo (Pemex)	Magnetic and gravity ring at Chicxulub (1978; presented 1981).
Planetary science and geochemistry	Alan Hildebrand, William Boynton, David Kring, Stein Jacobsen	Haitian ejecta; identification of Chicxulub as the crater (1990–91).
Geochronology	Glen Izett, Carl Swisher, Virgil Sharpton and colleagues	Argon–argon ages of tektites and crater melt rock (1991–92).

minutes of the impact, a direct test of computer models of how large craters form. Above it lay about 130 metres of melt rock and breccia deposited on the first day of the Palaeogene, as the sea rushed back into the crater, and then charcoal from fires on land. Sulphur-bearing rocks, common in the surrounding sediments, were scarce in the core, consistent with their having been vaporised.

The kill mechanism. Here the Berkeley paper was right in outline and wrong in detail. The emphasis has shifted from dust to a combination of agents: sulphate aerosols from the vaporised gypsum and anhydrite of the target, soot from fires ignited by debris re-entering the atmosphere, and, according to a 2023 modelling study, very fine silicate dust after all. A 2022 review concluded that the Earth was dark and cold for perhaps a decade, though whether the worst lasted months or more than ten years is uncertain. The impactor itself has been identified more closely. A 2024 study of ruthenium isotopes in the boundary clay concluded that it was a carbonaceous-type asteroid, formed in the outer solar system beyond Jupiter.[16]

Nuclear winter. The impact hypothesis had a consequence far from palaeontology. James Pollack and Brian Toon, atmospheric scientists who had studied how dust storms cool the atmosphere of Mars, published with colleagues a model of the impact dust cloud in *Science* early in 1983. With Richard Turco, Thomas Ackerman and Carl Sagan, they then applied the same kind of model to the smoke and dust of a nuclear war. Their paper of December 1983, known from the authors' initials as TTAPS, concluded that a large nuclear exchange could bring months of subfreezing temperatures to the northern hemisphere. Its details were heavily criticised, and estimates of the severity have swung both ways since, but "nuclear winter" entered arms-control debate, and its scientific lineage ran straight back to the K-T boundary.[17]

Planetary defence. If an asteroid had done it once, it could do it again. In 1992 a report commissioned by the US Congress proposed the Spaceguard Survey, a name borrowed from Arthur C. Clarke's 1973 novel *Rendezvous with Rama*, to find the near-Earth asteroids more than a kilometre across. The collision of the fragments of Comet Shoemaker–Levy 9 with Jupiter in July 1994 gave the idea public urgency. NASA was directed to find ninety per cent of the kilometre-sized objects, a goal met somewhat late, and in 2005 Congress extended the target to objects down to 140 metres. On 26 September 2022 NASA's Double Asteroid Redirection Test (DART) spacecraft deliberately struck Dimorphos, a small moon of the asteroid Didymos, and shortened its orbit of 11 hours 55 minutes by about 32 minutes: the first demonstration that a spacecraft could change the path of an asteroid. As this chapter was written, in October 2026, the European Space Agency's Hera spacecraft was approaching Didymos to examine the results, with its rendezvous manoeuvres due to begin that month, and NASA was preparing NEO Surveyor, an infrared space telescope designed to find most of the remaining hazardous asteroids.[18]

Mass extinctions as a subject. Before 1980 mass extinctions were a minor topic, treated as puzzles about particular groups. The impact debate turned them into a field. In 1982 Raup and his Chicago colleague John Sepkoski identified, in a database of marine families, the five great mass extinctions that are now textbook material, and the search for impact signatures at the other four began. It has largely failed. No other major extinction has been convincingly tied to

an impact, and the leading explanation for the largest, at the end of the Permian, is the eruption of the Siberian Traps. The K-Pg extinction now looks like the exception, not the rule.

Catastrophism rehabilitated. The deepest change was conceptual. Geologists came to accept that rare, violent events can dominate the record, and that "the present is the key to the past" is a method, not a guarantee about rates. The British stratigrapher Derek Ager had argued since the 1970s that the stratigraphic record was episodic, made of long gaps punctuated by rare events, and his last book, *The New Catastrophism*, appeared in 1993, the year he died. The new catastrophism is not Cuvier's. It keeps the uniformity of natural law and drops the uniformity of rate: floods, eruptions, megatsunamis and impacts are ordinary physics, and the questions are only how big and how often. Gould's distinction between the two kinds of uniformity proved to be the one the profession needed.

Tanis. The most dramatic recent claim about the boundary is also among the most contested. In 2019 Robert DePalma and colleagues including Smit and Walter Alvarez described a site in the Hell Creek Formation of North Dakota, which DePalma had named Tanis. They interpreted it as a river deposit overwhelmed, shortly after the impact, by a surge of water set in motion by seismic waves, burying fish with impact spherules lodged in their gills. A magazine article published at the same time described dinosaur remains and other finds that were not in the peer-reviewed paper, which drew public criticism from other palaeontologists. In 2022 a separate team led by Melanie During published evidence from Tanis fish bones that the impact happened in the northern spring; later that year During raised allegations that DePalma had fabricated data in a 2021 paper making a similar claim. A University of Manchester investigation concluded in December 2023 that he had not fabricated data, but that several instances of poor practice in managing and presenting the isotope data together amounted to research misconduct; in 2025 the university reported that repeated analyses supported the original conclusions. Tanis may prove to be one of the most remarkable boundary sites known, but its significance will be clear only when more of its material has been described and checked by others.[19]

The Costs of Crossing

The K-T story is usually told as a triumph of interdisciplinary science, and it is one. It also shows how crossing borders can go wrong, and how the telling of a cross-border success can distort what happened.

Contempt as a method. Luis Alvarez's bluntness was part of what moved the hypothesis forward: he would not let a weak objection stand. But his remarks about palaeontologists did lasting damage. They turned a disagreement about evidence into a contest of status between disciplines, and made it harder for palaeontologists to concede a point without seeming to concede that physicists were the real scientists. Many of the palaeontologists' objections were reasonable, and some were right. The record of land animals was genuinely patchy; the pattern of survivors genuinely needed explaining; and the simple dust mechanism of 1980 has been substantially revised. The Signor–Lipps effect, the most useful single tool for reading the record of a sudden extinction, came from palaeontologists. A border-crosser who treats the people on the other

side as stamp collectors is not trading but annexing, and he loses what they know.

The volcanoes did not go away. The Deccan Traps remain a live question. Improved dating in 2015 showed that the main phase of eruption began a few hundred thousand years before the boundary and continued after it, and Paul Renne, Mark Richards and colleagues at Berkeley proposed that the seismic shaking from the impact intensified the eruptions. In 2019 two teams published new chronologies in the same issue of *Science*. Blair Schoene's group at Princeton, dating zircons by uranium–lead, found pulses of very rapid eruption, one beginning tens of thousands of years before the impact; Courtney Sprain and colleagues, using argon–argon dating, found that about three-quarters of the lava erupted after the boundary. The two chronologies disagree in important respects, and both left room for the eruptions to have contributed to the crisis. A 2020 study led by Pincelli Hull, comparing models of the carbon cycle with temperature records, found that most of the volcanic outgassing happened well before the impact and that only the impact coincided with the extinction, and a 2024 study of fossil peats found a volcanic cold snap about thirty thousand years before the boundary, from which temperatures had recovered by the time the asteroid struck.[20] Most specialists now treat the impact as the principal cause of the extinction and the volcanism as a stress on ecosystems before it and possibly a drag on their recovery afterwards. Gerta Keller of Princeton, the most persistent critic, has argued for decades that Chicxulub predates the extinction and that Deccan volcanism was the main cause. Hers is a minority view. But the volcanists were right that the Deccan eruptions mattered, and a history that treats them simply as the losers misrepresents the state of the science.

The overreach. Success breeds ambition. In 1984 Raup and Sepkoski published an analysis suggesting that mass extinctions had recurred about every 26 million years. If an impact caused one extinction, perhaps impacts caused all of them, on a schedule. Within months, two groups proposed in *Nature* that the Sun had a faint companion star on a long orbit, which every 26 million years disturbed the cloud of comets at the edge of the solar system and sent a shower of them inward. One of the authors was Richard Muller, the physicist who had been asked to measure the beryllium-10; his group named the star Nemesis. No such star has been found. An infrared survey of the whole sky, analysed in 2014, ruled out anything as large as Saturn out to ten thousand times the Earth's distance from the Sun, and the periodicity itself has been disputed ever since.[21] The episode shows the momentum of an idea that has crossed one border successfully: a physical mechanism, demonstrated once, was stretched over a pattern that the palaeontological data could barely support.

What the data owners kept. Chicxulub was recognised in 1978 and announced, after a fashion, in 1981, a decade before the impact community took it up. Nobody behaved badly. Oil companies own their surveys and have good commercial reasons to keep them, and Pemex allowed Penfield and Camargo to speak only on condition that they gave away no company data. But the episode shows a border that this book's argument tends to overlook. The exchange between academic science and industry is real, and much of what is known about the Earth's crust came from it, but its traffic is governed by property. Owned knowledge crosses borders only when its owners allow it, and at Chicxulub the crossing waited on a newspaper reporter and a graduate student.

The physicist sweeps in. The popular version of this story has a Nobel laureate in physics arriving in a sleepy field, applying the rigour of his discipline and solving a problem that had baffled the specialists. Almost every part of that is misleading. The question was a geologist's, and the samples came from a section that micropalaeontologists and palaeomagnetists had spent fifteen years turning into a precise clock. The measurement was made by two nuclear chemists whose method had been honed on archaeological pottery. A Dutch micropalaeontologist found the same anomaly independently, and Walter Alvarez has written that he has long thought of him as its co-discoverer, though Smit himself has credited the Berkeley group with finding it first. The decisive mineral evidence came from the US Geological Survey, the crater from oil-industry geophysicists, and its identification from a Canadian graduate student who had followed the debris to Haiti. Luis Alvarez's contributions, the iridium idea, the ruthless testing of alternatives and the size estimate, were real and important. But a story that names only the two Alvarezes, or only the elder, leaves Asaro, Michel, Premoli Silva, Lowrie, Smit, Hertogen, Bohor, Penfield, Camargo and Hildebrand in the footnotes.

Coda

The Bottaccione gorge is now a place of pilgrimage for geologists. The holes drilled in the 1970s for magnetic samples are still visible in the rock, along with marks drawn on the limestone by later researchers. Gubbio made Walter Alvarez an honorary citizen in 1994.

What made the discovery possible was a chain of borrowings, each of which made sense only after the one before. Micropalaeontologists made the section a clock. Palaeomagnetists used the clock to date the reversals, and showed in passing that the limestone had accumulated steadily. A physicist suggested measuring a metal from space to time the clay. Chemists who had learned to measure trace elements in Mediterranean pottery measured it. The answer was wrong for the question that had been asked, and right for a much larger one. The rest was fourteen years of finding out whether it was true.

Notes

[1] Walter Alvarez, *T. rex and the Crater of Doom* (Princeton, NJ: Princeton University Press, 1997), is the main source for the chronology of the sampling, the delivery of samples to Asaro and the call in June 1978; Sean B. Carroll's account, "The Day the Mesozoic Died," *Nautilus*, 2016 (adapted from his *Into the Jungle*, 2008), puts the call about nine months after the samples were handed over. On the 1977 fieldwork, see Terry Engelder, "Field Work in Italy, 1977," `https://personal.ems.psu.edu/~jte2/story/dino.html`; and Eldridge Moores, citation for the Penrose Medal to Walter Alvarez, Geological Society of America, 2002. The description of the gorge follows Terri Cook, "Travels in Geology: Gubbio, Italy: A Geologist's Mecca," *Earth*, 21 September 2016.

[2] William Whewell, review of Lyell, *Principles of Geology*, vol. 2, *Quarterly Review* 47 (1832): 103–32; see M. Romano, "Reviewing the Term Uniformitarianism in Modern Earth Sciences," *Earth-Science Reviews* 148 (2015): 65–76. On the publication of Lyell's three volumes and Darwin's copies, see Gordon Chancellor, "Charles Lyell's *Principles of Geology*," Darwin Online, `https://darwin-online.org.uk`. On

the earlier extinction hypotheses: M. W. de Laubenfels, "Dinosaur Extinctions: One More Hypothesis," *Journal of Paleontology* 30, no. 1 (1956): 207–18; D. Russell and W. Tucker, "Supernovae and the Extinction of the Dinosaurs," *Nature* 229 (1971): 553–54. On the fate of the Tertiary, see Robert Knox et al., "Tertiary: Survival of the Fittest?," *Geoscientist*, August 2010, which argues for its reinstatement and notes its continued informal use.

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[4]K. Lodders, H. Palme and H.-P. Gail, "Abundances of the Elements in the Solar System," in *Landolt-Börnstein, New Series VI/4B* (Berlin: Springer, 2009), give 469 ppb for CI chondrites; J.-W. Park et al., "Platinum Group Element Abundances in the Upper Continental Crust Revisited," *Geochimica et Cosmochimica Acta* 93 (2012): 63–76, give 0.022 ppb for the upper crust. The ruthenium figures are from the GERM Reservoir Database, `https://earthref.org`. Luis Alvarez put the crustal figure at one ten-thousandth of the meteoritic one.

[5]Nuclear data: half-life and gamma intensities for iridium-192 from the Laboratoire National Henri Becquerel, *Table de Radionucléides*: ^{192}Ir; the thermal capture cross-section of iridium-191 (954 ± 10 barns) from the National Nuclear Data Center evaluation for $A = 192$, `https://www.nndc.bnl.gov`. The Berkeley Research Reactor, a 1-megawatt TRIGA Mark III, operated from 1966 to 1987; the flux figure is typical of such reactors. The worked numbers are my calculation. The counting details are from Fig. 4 of Alvarez et al. (1980); the platinum-ring contamination is described in H. V. Michel et al., "Abundance Profiles of Iridium and Other Elements near the Cretaceous-Tertiary Boundary in Hole 516F of DSDP Leg 72," Lawrence Berkeley Laboratory report LBL-14181 (1982).

[6]Luis W. Alvarez, *Alvarez: Adventures of a Physicist* (New York: Basic Books, 1987). The letter to Walter is in the Luis W. Alvarez Papers at the National Archives at San Francisco. Walter's career is from his curriculum vitae, Accademia Nazionale dei Lincei, `https://lincei.it`; Moores, Penrose citation; and Walter Alvarez's response to it, in which he describes himself as Hess's graduate student. On the beryllium-10 and iridium ideas: Alvarez, *Crater of Doom*; Carroll, "The Day the Mesozoic Died"; Luis W. Alvarez, "Mass Extinctions Caused by Large Bolide Impacts," *Physics Today* 40, no. 7 (1987): 24–33. The University of California Museum of Paleontology's case study, "Asteroids and Dinosaurs: Unexpected Twists and an Unfinished Story," `https://undsci.berkeley.edu`, gives the same sequence. On Asaro and Michel: "Frank Asaro, Nuclear Chemist Who Contributed to Dinosaur Extinction Theory and Archaeological Studies, Passes Away," Lawrence Berkeley National Laboratory, June 2014, `https://eta.lbl.gov/news/article/57850/frank-asaro-nuclear-chemist-who`; I. Perlman and F. Asaro, "Pottery Analysis by Neutron Activation," *Archaeometry* 11 (1969): 21–38.

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[9]J. Smit and J. Hertogen, "An Extraterrestrial Event at the Cretaceous-Tertiary Boundary," *Nature* 285 (1980): 198–200; J. Smit, "A Flashback on the Dawn of the Meteorite Impact/Extinction Theory," *Acta Palaeontologica Polonica* 57, no. 4 (2012): 677–79. The *Nature* paper gives Hertogen's address as Leuven; Smit's recollection places the analyses at Ghent. On the meeting in Copenhagen and Smit as co-discoverer, Alvarez, *Crater of Doom*; Walter Alvarez's response to the Penrose citation (2002) says he had long regarded Smit as the co-discoverer of the iridium anomaly. Smit's 2012 memoir credits the Berkeley group with finding the anomaly first. Smit recalled the *New Scientist* item as a report of the American Geophysical Union's fall meeting of 1978; the 1980 *Science* paper cites a presentation at the Union's meeting of May 1979. On the spherules: J. Smit and G. Klaver, "Sanidine Spherules at the Cretaceous-Tertiary Boundary Indicate a Large Impact Event," *Nature* 292 (1981): 47–49; A. Montanari et al., "Spheroids at the Cretaceous-Tertiary Boundary Are Altered Impact Droplets of Basaltic Composition," *Geology* 11 (1983): 668–71.

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Further Reading

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Luis W. Alvarez, Walter Alvarez, Frank Asaro and Helen V. Michel, "Extraterrestrial Cause for the Cretaceous-Tertiary Extinction," *Science* 208 (1980): 1095–1108. The original paper: long but readable, and a model of hypothesis-testing on the page.

James Lawrence Powell, *Night Comes to the Cretaceous: Dinosaur Extinction and the Transformation of Modern Geology* (W. H. Freeman, 1998). A geologist's history of the debate, strong on the evidence and on the sociology of the argument; reviewers found it partisan towards the impact side.

William Glen, ed., *The Mass-Extinction Debates: How Science Works in a Crisis* (Stanford University Press, 1994). Essays by participants and historians from both sides, assembled while the argument was still hot.

Luis W. Alvarez, *Alvarez: Adventures of a Physicist* (Basic Books, 1987). The elder Alvarez's memoir, covering radar, Los Alamos, the bubble chamber, the pyramids and the asteroid, in his own forthright voice.

David M. Raup, *The Nemesis Affair: A Story of the Death of Dinosaurs and the Ways of Science* (Norton, 1986). A palaeontologist's candid account of the periodicity hypothesis and of how scientists behave when an exciting idea is in the air.

Jan Smit, "A Flashback on the Dawn of the Meteorite Impact/Extinction Theory," *Acta Palaeontologica Polonica* 57 (2012): 677–79. A short, open-access memoir by Smit, with the view from Caravaca.

Peter Schulte et al., "The Chicxulub Asteroid Impact and Mass Extinction at the Cretaceous-Paleogene Boundary," *Science* 327 (2010): 1214–18. The consensus review; read it alongside the replies it provoked.

Joanna V. Morgan, Timothy J. Bralower, Julia Brugger and Kai Wünnemann, "The Chicxulub Impact and Its Environmental Consequences," *Nature Reviews Earth & Environment* 3 (2022): 338–54. The best current technical summary of the impact, the crater and the kill mechanisms.

Glen Penfield, "Unlikely Impact," *AAPG Explorer*, December 2019, https://explorer.aapg.org/story/articleid/55293. The discovery of the crater, as remembered by the geophysicist who found it.

Chapter 10

The Monastery in the Desert: The Santa Fe Institute (1984–2000s)

A Boardroom in Santa Fe

On Friday 5 October 1984, a couple of dozen men gathered in a slightly dark room in Santa Fe, New Mexico, its walls hung with Native American artefacts. The room was the boardroom of the School of American Research, an institute for anthropology and archaeology, lent for the occasion by its president, the archaeologist Douglas Schwartz. Most of the men were in their sixties, and several were veterans of the weapons laboratory at Los Alamos, some thirty-five miles away on its mesa. Among those who took part in that autumn's meetings were four Nobel laureates. The youngest by far was a twenty-five-year-old physicist turned computer scientist from the Institute for Advanced Study, Stephen Wolfram.

The meeting was run by George Cowan, a chemist who had spent most of his career at Los Alamos. Its purpose was to decide what a new institute, which did not yet have a building, a staff or much money, should be for. It had been incorporated that spring under the name of the Rio Grande Institute. Murray Gell-Mann, the Caltech physicist who had named the quark, opened with a description of what he called "emerging syntheses": subjects growing up in the gaps between disciplines that could not be pursued inside any one of them. Over two days, and at a second workshop in November, the speakers ranged from the evolution of human behaviour to the foundations of mathematics, and from the dynamics of proteins to the theory of computation.

On the Saturday afternoon, by his later recollection, Wolfram asked what the group would do if it raised a few million dollars rather than the hundreds of millions its founders seemed to imagine. Cowan asked him what he would suggest. Wolfram proposed that the institute concentrate on what he called complex systems theory, and was asked to give a more formal presentation later that day.[1] It is a recollection written thirty-five years later, and should not be read as the moment the institute's purpose was fixed. Gell-Mann, for his part, remembered noticing that the talks kept returning to the same themes: simplicity and complexity, evolution,

learning and adaptation. Out of those themes came the phrase that the institute made its own, *complex adaptive systems*.

What followed over the next fifteen years was an experiment in institution-building as much as in science. The Santa Fe Institute (SFI) would have no departments, no students of its own and no tenure. It would bring economists into the same kitchen as physicists, put a field ecologist at the same blackboard as a particle theorist, and look for laws that held for cells, markets and cities alike. It produced some of the most widely cited ideas of the late twentieth century, and some of the most widely criticised. In the Santa Fe story the successes and the overreaches were often the same ideas seen from different distances.

The Science: More Is Different

The founders were reacting against a way of doing science that had been extraordinarily successful. Since the seventeenth century the dominant strategy of physics had been to explain a whole by its parts: to find the laws obeyed by the smallest constituents and to treat everything larger as, in principle, a consequence. By the 1970s the strategy had produced the quantum theory of the atom, the chemistry that followed from it, and a molecular biology that explained heredity by the pairing of bases (Chapter 7). Particle physics was assembling the Standard Model, in which Gell-Mann's quarks played a central part. If anyone had the right to believe that understanding the parts meant understanding everything, it was the people in that boardroom.

The most influential dissent had come from inside physics. In 1967, at the University of California in La Jolla, the condensed-matter theorist Philip Anderson of Bell Telephone Laboratories gave a Regents' Lecture that he expanded into a four-page essay in *Science* in August 1972. It was called "More Is Different."

Anderson did not reject reductionism. He accepted that everything, living things included, obeys the same fundamental laws. What he rejected was its converse, which he called the *constructionist* hypothesis: the assumption that because everything can be reduced to fundamental laws, it can be rebuilt from them. That hypothesis, he argued, broke down in the face of the twin difficulties of scale and complexity. At each level of organisation, large collections of simpler things show properties that the simpler things do not have, and that are better described by new concepts than by old ones. He arranged the sciences in a rough hierarchy (particle physics, many-body physics, chemistry, molecular biology, cell biology, physiology, psychology, the social sciences) in which the entities of each level obey the laws of the level below, and insisted that each level needs its own research and its own ideas: "psychology is not applied biology, nor is biology applied chemistry."

His central example was *broken symmetry*. The laws of physics do not distinguish between left and right, or between one direction in space and another. Yet a crystal picks out particular directions, a magnet points one way, and the sugars made by living things are all of one handedness. In each case the system as a whole settles into a state less symmetrical than the laws governing its parts, and the properties that matter (rigidity, magnetism, superconductivity)

belong to that collective state, not to any atom. Anderson's Nobel Prize, shared in 1977 with Nevill Mott and John Van Vleck, was for theoretical work on the electronic structure of magnetic and disordered systems. In 1975, with the British physicist Sam Edwards, he had begun the theory of *spin glasses*, magnetic alloys in which the atomic magnets freeze into a disordered arrangement with an enormous number of nearly equivalent states. Spin glasses began as a curiosity. By the 1980s they had become a source of mathematical ideas for any system with many competing parts and a rugged landscape of possible states, from proteins to neural networks.

"More Is Different" gave the word *emergence* a respectable home in physics, and it gave the Santa Fe founders a licence. If chemistry was not applied physics, perhaps there were principles of collective behaviour, discoverable by theory and computation, that cut across the sciences sideways rather than from the bottom up. The idea was not new. In 1948 Warren Weaver, who had run the American fire-control research programme described in Chapter 6, wrote that science had mastered problems of simplicity (a few variables, as in planetary motion) and problems of disorganised complexity (billions of variables, handled by statistics, as in a gas), but had barely begun on problems of *organised* complexity, in which many variables interact in structured ways, as in a living cell or an economy.[2] The cyberneticians of Chapter 6 had attacked such problems with the vocabulary of feedback and information. The Santa Fe founders had what the cyberneticians lacked: fast computers, and decades of statistical physics.

The Science: Complex and Adaptive

What, then, is a complex adaptive system? The institute never settled on a single definition, and some of its members thought that a strength. But the working idea, as Gell-Mann and the computer scientist John Holland described it in books of the mid-1990s, had four parts.

First, the system consists of many agents (cells, organisms, firms, traders, neurons) that interact, mostly locally. Second, there is no central controller: the behaviour of the whole arises from the interactions. Third, the agents adapt. Each carries some internal model or rule for how to act (Gell-Mann called it a *schema*), and the rules change with experience, by learning, competition or natural selection. Fourth, because every agent is adapting to the others, the environment each one faces is made largely of the other agents, and it changes as they change. Such a system need never settle into equilibrium.

A gas is many interacting parts with no central controller, but its molecules do not learn. An immune system, an ecosystem or a stock market is made of parts that do. The Santa Fe programme was to find out whether systems of the second kind, studied by separate disciplines with separate vocabularies, shared mathematical structure: whether, in this book's terms, there was a structural isomorphism to be found across biology, economics and the social sciences. Three ideas became the institute's signatures: *positive feedback*, by which small differences are amplified, so that history matters; *self-organisation*, by which order appears without design; and *scaling*, by which quantities change in regular, mathematically simple ways as systems grow. The rest of this chapter follows each in turn, with the people who carried them across disciplinary borders and the critics who checked what had been carried.

The Founders

George Cowan was born in Worcester, Massachusetts, on 15 February 1920. After graduating from Worcester Polytechnic Institute in 1941 he was drawn into the American atomic project, first on the cyclotron at Princeton under Eugene Wigner and then, from 1942, at Enrico Fermi's Metallurgical Laboratory in Chicago, where he machined graphite and cast uranium metal for the first reactors. He spent thirty-nine years at Los Alamos, as director of chemistry, associate director for research and senior laboratory fellow. He was also, unusually for a scientist, a founder and chairman of the Los Alamos National Bank, which later lent the new institute a measure of financial credibility. In 1982 he joined President Reagan's White House Science Council, and by his own account the experience convinced him that science needed a more integrated approach than its fragmented disciplines could offer.

He found allies among senior colleagues. The people usually counted as the institute's founders were Cowan; Gell-Mann; David Pines, a condensed-matter physicist at the University of Illinois; and five Los Alamos scientists: the astrophysicist Stirling Colgate, the computing pioneer Nicholas Metropolis, the nuclear physicist Herbert Anderson, Peter Carruthers, who headed the laboratory's theoretical division, and the particle theorist Richard Slansky. Some of them had lived through the most successful interdisciplinary project in the history of science, at Los Alamos in 1943–45, and had spent the decades since watching science divide itself back into specialities. Metropolis wanted the institute to concentrate on computing; others thought that too narrow. Gell-Mann pressed for a grand synthesis, and the word the group settled on, *complexity*, had the advantage of being loose enough to hold everyone's ambitions. Cowan became president and Gell-Mann chairman of the board. The founders deliberately placed the institute away from the great universities, partly to escape what Gell-Mann called the pressure of received ideas and partly to be near the computers at Los Alamos.[3]

The name was a problem of a different kind. The founders had wanted to call the place the Santa Fe Institute, but the name was already held by an organisation that helped people with drug and alcohol addiction. They incorporated as the Rio Grande Institute in March 1984, and took the Santa Fe name after the other organisation closed. For more than two years the institute had no premises of its own. In February 1987, with money beginning to arrive from the MacArthur Foundation, the National Science Foundation, the Department of Energy and others, its small staff moved into a former convent on Canyon Road, a street of studios and galleries on the east side of town, rented from the Catholic Church. The old chapel was used for workshops. Within days the building was full.

The institute's monastic reputation comes from the convent, and the institute has embraced it, describing itself on its website as a monastery in the mountains. The reality was more practical. Gell-Mann recalled that the institute stayed in the convent until it outgrew the building and the Church wanted it back, then spent some years in what he described as essentially a dental suite. In 1994 it moved to the hillside property on Hyde Park Road that is still its main campus, built around the adobe house of Patrick J. Hurley, Herbert Hoover's Secretary of War.

What made the institute distinctive was its structure. It had no departments and awarded no

degrees. It was designed as a visiting institution: a handful of resident researchers on fixed-term appointments, a much larger external faculty who held posts elsewhere and came for weeks or months, a steady stream of workshops, and postdoctoral fellows whose job was to talk to everyone. In 1997 *Nature* counted about six resident faculty and thirty visitors on site at any one time. In 1997 three of the six resident professors, Gell-Mann, Kauffman and Arthur, held five-year contracts due to expire in 1998. There was no tenure, and an outside review panel advised in 1997 against letting long appointments become tenure in all but name.[4] It had resident faculty, then, but none of them permanent. The arrangement kept ideas and people moving. It also meant that the institute's identity rested heavily on a few charismatic figures.

Economists in the Convent

The institute's first sustained research programme came not from physics or biology but from a bank. In the 1970s Citicorp, the largest bank in the United States, had lent heavily to Latin American governments, and when Mexico announced in 1982 that it could not meet its payments the bank was exposed to a debt crisis its economic models had not anticipated. Its chairman, John Reed, had become sceptical of conventional economic forecasting. In Philip Anderson's account, the connection with Santa Fe began with a conversation, arranged by the economist Carl Kaysen, between Reed and Robert McCormick Adams, the archaeologist who was then Secretary of the Smithsonian Institution. Reed came to Santa Fe for a one-day trial workshop at which he set out his concerns. Citicorp agreed to fund a programme, and Kenneth Arrow of Stanford, who had shared the economics Nobel in 1972 for work on general equilibrium and welfare, was asked with Anderson to organise a larger meeting of economists and natural scientists.[5]

The meeting took place at the convent in September 1987, under the title "Evolutionary Paths of the Global Economy." Arrow brought economists, among them Larry Summers, Thomas Sargent, William (Buz) Brock and a Stanford colleague with an unusual background, W. Brian Arthur. Anderson and Pines brought scientists: John Holland from Michigan, Stuart Kauffman, the mathematical physicist David Ruelle, and the physicists Richard Palmer and Doyne Farmer. Arthur remembered it as lasting about ten days. The proceedings were published in 1988 as *The Economy as an Evolving Complex System*; by one historian's count, of their twenty-one contributors twelve came from physics departments and six from economics.

What happened in the room has been retold many times, and the retelling has grown. The most popular version has one of the physicists, usually Anderson, exclaiming that the economists were using the equilibrium physics of a century before. I have not found any such remark in the proceedings or in the participants' own published accounts, and it is best treated as a later paraphrase of the meeting's mood.

What is well attested is that the two groups brought very different habits of thought. Neoclassical economics, from Léon Walras in the 1870s onwards, was built around *equilibrium*: a state in which supply equals demand in every market and no one has an incentive to change what they are doing. Arrow and Gérard Debreu had proved in the 1950s that such equilibria exist under certain conditions and have attractive properties. To keep the mathematics tractable, the

theory typically assumed rational, well-informed agents, given technologies and preferences, and *diminishing returns*, so that any departure from equilibrium set up forces pushing the economy back. In the 1970s the rational expectations school, of which Sargent was a leader, added the assumption that agents' forecasts are on average correct. Physicists who studied systems far from equilibrium found these assumptions strong. Arthur recalled that it was a question from Kauffman, about what economics would look like if it were done out of equilibrium, that set the direction of what followed.

The programme began in the autumn of 1988. Holland could not leave Ann Arbor, so Arthur, on sabbatical from Stanford, became its first director. When the group asked the funders what they wanted, Arrow relayed the answer: anything, provided it went to the foundations of economics and was not conventional. For about a month, by Arthur's account, the group met in the convent's kitchen in the late mornings to work out what that meant.[6]

The Man from Belfast

William Brian Arthur was born in Belfast on 31 July 1945. He took a degree in electrical engineering at Queen's University Belfast in 1966, a master's in operational research at Lancaster, another in mathematics at Michigan, and a doctorate in operations research at the University of California, Berkeley, in 1973, along with a master's in economics. From 1978 to 1982 he worked in a theoretical group at the International Institute for Applied Systems Analysis (IIASA) at Laxenburg, outside Vienna, a research centre founded during détente to bring together scientists from East and West. In 1983, at thirty-seven, he became Morrison Professor of Economics and Population Studies at Stanford, then the youngest holder of an endowed chair there.

Arthur's own account of where his central idea came from is that, as an engineer, he became interested in reading about the discovery of the structure of DNA, molecular biology and enzyme reactions, and followed the trail back into physics: laser theory, thermodynamics, enzyme kinetics. What struck him was that all these subjects contained processes that reinforce themselves, so that a small initial advantage grows rather than shrinks. He asked what economics would look like if the same were true of markets.[7]

The economic idea is easy to state. Most textbook markets show diminishing returns: the more of something is produced, the harder it becomes to produce more, because the best land, the richest ore and the easiest oil are used first. Diminishing returns act as negative feedback. If one firm gets ahead, rising costs slow it down, and the market settles to a predictable sharing-out. Some products work the other way. The more people use a technology, the more valuable it becomes to the next user, through compatibility, shared know-how or networks of suppliers. And the more of a high-technology product a firm makes, the cheaper each unit becomes, because the cost lies in the design rather than the copies. This is *increasing returns*, and it acts as positive feedback.

Economists had long known that increasing returns existed; Alfred Marshall discussed them in the 1890s. The difficulty was that they wrecked the mathematics of equilibrium. With positive

feedback there may be many possible equilibria, and nothing in the standard theory says which one the economy will reach. Arthur's contribution was to treat the outcome as the result of a random process unfolding in time. With two Soviet probabilists at IIASA, Yuri Ermoliev and Yuri Kaniovski, he proved theorems about a generalisation of a classic problem in probability theory, the *Pólya urn*, published in the Soviet journal *Kibernetika* in 1983. It was probability theory of this kind, not the physics of spin glasses, as is sometimes said, that underpinned his economics.

Science Primer: The Pólya urn and lock-in

An urn contains one red ball and one blue ball. Draw a ball at random, then put it back together with another ball of the same colour. Repeat. This is the Pólya urn, named after the mathematician George Pólya, who studied it in the 1920s.

Each draw makes the drawn colour more likely next time: positive feedback. The chance of drawing red three times running is

$$\frac{1}{2} \times \frac{2}{3} \times \frac{3}{4} = \frac{1}{4},$$

after which the urn holds four red balls and one blue, and red is drawn four times in five. The famous result is that the proportion of red balls settles down to a limit, but the limit is itself random: in this simplest urn, every proportion between 0 and 1 is equally likely. Ten computer runs of a thousand draws each might end with red shares of 0.64, 0.97, 0.44, 0.50, 0.36, 0.75, 0.89, 0.83, 0.38 and 0.61. Each run settles; no two settle in the same place. The accidents of the first few draws decide the outcome.

Arthur's 1989 model of competing technologies sharpened this into *lock-in*. Two technologies, A and B, are adopted one customer at a time. Half the customers (call them R-types) value A at 1.0 and B at 0.75; the other half (S-types) prefer B by the same margin. Every previous adopter of a technology adds 0.1 to its value for everyone who comes later, a network benefit. Write d for the number of A adopters minus the number of B adopters. An R-type switches to B only if B's network advantage outweighs his preference, that is, if $0.1 \times (-d) > 0.25$, which means B must lead by three or more. The same holds the other way round for S-types.

So while d stays between -2 and $+2$, each customer follows his own taste, and d moves up or down by one at random, like a coin-tossing game. But the first time either technology gets three ahead, every later customer of both types chooses it. The market is locked in, and half the customers are using the technology they would not have chosen. The lead behaves like a gambler's fortune between two absorbing barriers, and a standard calculation shows that lock-in arrives on average after only nine customers. In 200,000 simulated markets, about two in three had locked in by the ninth customer, and each technology won almost exactly half the time.

The outcome is *unpredictable* in advance, even with full knowledge of preferences; *inflexible* afterwards, since no small subsidy will shift it; and *potentially inefficient*, since the market

could lock into A even if B were slightly better in the long run. (The numbers are my illustration of Arthur's model, not his own.)

Arthur's paper "Competing Technologies, Increasing Returns, and Lock-In by Historical Events" was completed in 1983. By his account it was turned down for six years. It appeared in the *Economic Journal* in March 1989.[8] The examples used in it and in Arthur's later popular writing became famous: the QWERTY keyboard, whose persistence the economic historian Paul David had analysed in 1985, the triumph of VHS over Betamax, and the dominance of light-water reactors in nuclear power. With a popular version in *Scientific American* in February 1990, it became one of the founding documents of what came to be called complexity economics, and the centre of a legend to which we will return.

Machines That Learn to Trade

John Holland was the most important presence in the economics programme who was not an economist. Born in Fort Wayne, Indiana, in 1929, he studied physics at MIT and took a doctorate at Michigan in 1959, in what is often described as the university's first doctorate in computer science. His book *Adaptation in Natural and Artificial Systems* (1975) introduced *genetic algorithms*: programs that solve problems by maintaining a population of candidate solutions, encoded as strings of symbols, and improving them by selection, recombination and mutation, as natural selection improves organisms. He also developed *classifier systems*, in which an agent holds a large set of if–then rules, each with a strength that rises when the rule leads to reward and falls when it does not, and new rules are bred from successful old ones. A classifier system is a learner that never stops learning.

Holland's methods gave the economists a way to model agents who were neither perfectly rational nor merely random, but who learned from experience. Arthur put the point in a short paper of 1994 built around El Farol, a bar on Canyon Road with Irish music on Thursday nights. Suppose a hundred people would like to go, but the evening is enjoyable only if fewer than sixty turn up. Each must decide independently, using past attendance. There is no forecast that everyone can share: if everyone predicts a quiet night, everyone goes, and the prediction fails. Arthur showed that if each agent holds a set of rules of thumb and uses whichever has recently worked best, attendance fluctuates around sixty indefinitely, without settling. The "El Farol problem," and the *minority game* that physicists later abstracted from it, became standard examples in what came to be called agent-based modelling.

The most ambitious application was the *Santa Fe artificial stock market*, developed from about 1989 by Arthur, Holland, the finance economist Blake LeBaron, Richard Palmer and Paul Tayler. Inside the computer, a population of artificial investors trades a single stock, which pays a randomly fluctuating dividend, and a risk-free bond. Each investor holds forecasting rules of the classifier type: if the price has risen for several periods and is above its moving average, predict this; if the price is low relative to the dividend, predict that. The investors trade on their

forecasts, a market-maker sets the price, and every so often a genetic algorithm replaces each investor's worst rules with new ones bred from the best.[9]

The results depended on how fast the investors learned. When the genetic algorithm ran rarely, they converged on the forecasts that standard theory predicts, and the market behaved like a textbook efficient market. When it ran often, the market never settled: investors kept discovering rules that exploited the other investors' rules, and the others kept adapting. In this "complex" regime the artificial market developed features that real markets show and the efficient-market model struggles to explain: rules resembling the technical trading that professionals use, bubbles and crashes, clustered periods of high and low volatility, and price changes with more extreme values than a bell curve allows ("fat tails").

It is sometimes said that the artificial market replaced the rational agents of neoclassical theory and gave birth to agent-based economics and econophysics. The truth is more modest. The model contained the standard theory as a special case, the slow-learning regime, and showed how departures from it could arise when learning was fast. It was one of several early agent-based markets. And, as we will see, later work found that some of its most striking results depended on a technical detail of the code.

Order for Free

Stuart Kauffman arrived at his networks by way of philosophy and medicine. Born in Sacramento in 1939, he studied at Dartmouth and, as a Marshall Scholar, at Oxford, before taking a medical degree at the University of California, San Francisco, in 1968. In the 1960s he became interested in a question that the new molecular biology had made urgent. In 1961 François Jacob and Jacques Monod had shown that genes in bacteria switch one another on and off. A human cell contains many thousands of genes, and each cell type (liver cell, neuron, skin cell) has a different pattern of genes switched on. How could a vast network of mutual switching produce a small number of stable, reproducible patterns, rather than chaos?

Kauffman's answer was to model the network rather than any particular gene. He represented each gene as a switch that is either on (1) or off (0), wired to receive inputs from K others chosen at random. Each switch obeys a randomly chosen logical rule (a *Boolean* function, after the nineteenth-century logician George Boole) that sets its next state from the current states of its inputs, and all switches update together in time steps. There is no design in such a network, and no selection. Kauffman asked what random networks of this kind typically do. In the late 1960s he worked with Warren McCulloch's group at MIT's Research Laboratory of Electronics, where networks of logical switches were the natural language (Chapter 6), and he published his results in 1969.

Science Primer: A gene network you can run by hand

Take three genes, A, B and C, each either on (1) or off (0). Each gene's next state is set by the other two:

- A turns on only if B *and* C are both on;
- B turns on if A *or* C (or both) is on;
- C turns on only if A *and* B are both on.

This is a network with $N = 3$ genes and $K = 2$ inputs per gene. It has $2^3 = 8$ possible states. Writing each state as ABC and following it forward one step:

$$\begin{array}{llll} 000 \to 000 & 001 \to 010 & 010 \to 000 & 011 \to 110 \\ 100 \to 010 & 101 \to 010 & 110 \to 011 & 111 \to 111 \end{array}$$

Because the network is deterministic and has finitely many states, every starting point must eventually repeat itself. The states it ends up cycling through are called *attractors*. This network has three. The state 000 is a fixed point: everything off stays off. So is 111. And 011 and 110 alternate for ever, a cycle of length two. The set of states that flows into an attractor is its *basin*: five states (000, 001, 010, 100, 101) end at 000, two (011, 110) are already on the cycle, and only 111 itself leads to 111.

Kauffman proposed that attractors correspond to cell types: stable, self-maintaining patterns of gene activity, few in number among a vast number of possible states. Basins measure stability. Flip any one gene in 111 and the network leaves it for good, to the cycle or to 000. Flip one gene in 000 and the network returns to 000 within two steps. In this toy, "everything off" is robust and "everything on" is fragile.

Real networks are too large to tabulate: N genes give 2^N states, more than the number of atoms in the universe once N passes about 270. So Kauffman simulated many randomly wired networks and measured their typical behaviour. (The example network is my own.)

What Kauffman found was a sharp difference between networks with many inputs per gene and networks with few. With many inputs, the networks were what is now called *chaotic*: a change in a single gene propagated widely, nearby trajectories diverged, and cycles were astronomically long. With two inputs, the networks were orderly, settling quickly into short cycles, and there were few of them. In his simulations, the number of attractors and their typical length both grew roughly as the square root of N. Kauffman called this "order for free": order arising not from natural selection but from the statistics of random networks, and available for selection to work with.

The physics of this transition was clarified in 1986, when the French physicists Bernard Derrida and Yves Pomeau showed, with an approximation borrowed from the statistical mechanics of disordered systems, that $K = 2$ is a critical value. For random networks with unbiased rules, a perturbation dies out on average when K is less than 2 and spreads when K is greater than 2.

At exactly $K = 2$, a single changed gene changes on average one other gene: the network sits on the boundary between a frozen phase and a chaotic one. Chaos therefore begins as soon as K exceeds 2, and networks with $K = 1$ are simply ordered.[10]

Kauffman then made the leap that gave the work its fame and its vulnerability. If attractors are cell types, and their number grows as the square root of the number of genes, then an organism's number of cell types should grow as the square root of its gene count. On this reasoning a network of 100,000 genes, a common estimate of the human gene count before the genome was sequenced, would have roughly three hundred attractors, and humans have about 285 cell types by histological criteria.[11] He developed these ideas, with models of rugged fitness landscapes borrowed from spin-glass physics and a theory of the origin of life through self-reproducing sets of molecules, in *The Origins of Order* (1993), a long and technical book, and for a general audience in *At Home in the Universe* (1995). He received a MacArthur fellowship in 1987, spent much of the following decade at Santa Fe, and in 1996 co-founded a consultancy, the BiosGroup, to apply complexity methods to business.

The idea was a genuine crossing: a physician's question about cell types, answered with a logician's switches and a physicist's statistics. Whether the answer was right is a different question.

The Edge of Chaos

The second famous idea of the Santa Fe orbit in these years came from computer science. Christopher Langton reached the subject by an unusual road. A conscientious objector during the Vietnam War, he did his alternative service as an orderly at Massachusetts General Hospital in Boston. Later, working as a programmer, he spent late nights running John Conway's Game of Life, a grid of cells that switch on and off according to the states of their neighbours and can produce patterns that move, grow and reproduce. A hang-gliding crash on Grandfather Mountain in North Carolina broke some thirty-five of his bones and kept him on his back for months. He went on to study at the University of Arizona and then at Michigan, building on John von Neumann's work on self-reproducing automata, and designed a self-reproducing pattern far simpler than von Neumann's.

In September 1987, the same month as the economics meeting in the convent, Langton organised at Los Alamos the first workshop on what he named *artificial life*: the study of life by synthesising lifelike behaviour in computers and other media, rather than by analysing the living things that happen to exist. About 160 people came, from biology, physics, computer science, philosophy and computer animation. The Center for Nonlinear Studies at Los Alamos, the Santa Fe Institute and Apple Computer sponsored it.[12] Langton later joined the institute.

His best-known technical idea concerned cellular automata like the Game of Life. He defined a single number, λ, for any automaton's rule: roughly, the fraction of local situations in which the rule turns a cell on. At λ near zero almost everything dies out; at high λ the patterns become random-looking noise. Langton found that as λ increased, automata passed from or-

dered to chaotic behaviour, and that the rules with the longest transients and the most intricate, long-lived structures clustered near the transition. Because computation requires both storing information (which order provides) and transmitting it (which needs some disorder), he argued that the capacity to compute should be greatest near this boundary. His paper of 1990 was titled "Computation at the Edge of Chaos."

The physicist Norman Packard, a member of the Santa Cruz group that had helped found chaos theory in the 1970s, had already tested a version of the idea. In a paper of 1988 titled "Adaptation toward the Edge of Chaos," he used a genetic algorithm to evolve cellular automata for a simple computational task, deciding whether a random starting pattern contained more ones than zeros, and reported that the evolved rules clustered near the critical values of λ. Evolution, it seemed, pushed computing systems towards the edge. The phrase is often credited to Langton and Packard jointly; it appears in the titles of their papers of 1990 and 1988, and who first used it in conversation is not clear from the published record.

The "edge of chaos" had everything a slogan needs. It connected Langton's automata, Kauffman's $K = 2$ networks, which also sat on a boundary between order and chaos, and the idea, then fashionable among physicists, that many natural systems organise themselves towards critical points. It suggested a general law: that evolution drives adaptive systems to the boundary between rigidity and turmoil, where they are most flexible and capable. Kauffman made the suggestion explicitly. It travelled quickly into popular books and management literature, and Mitchell Waldrop's history of the institute, published in 1992, took a version of it for its subtitle.

In 1993 three researchers associated with the institute tested it. Melanie Mitchell, a computer scientist trained at Michigan, with the physicist James Crutchfield and Peter Hraber, repeated Packard's experiment. Their evolved automata did not cluster near the critical values of λ. They clustered near $\lambda = 1/2$, for a reason that had nothing to do with chaos: the task was symmetric between ones and zeros, so a rule that performed it well had to treat them symmetrically, which forces λ towards a half. Packard's clustering, they concluded, came from the workings of his genetic algorithm, not from any computational advantage at the edge of chaos. They did not rule out a link between computation and phase transitions, but found no evidence for the one that had been claimed.[13] The paper, first issued in the institute's own working-paper series, is one of the more admirable documents in its history.

The Fire of Life

The third signature idea, and the one with the most quantitative bite, began with an old observation about animals. Chapter 2 described how Galileo and D'Arcy Thompson used the square–cube law to show that large animals cannot be small animals magnified. The same geometry suggested a law of metabolism. An animal at rest burns food to keep warm and loses heat through its skin. If heat loss limits metabolism, metabolic rate should scale with surface area and so, for animals of the same shape, with body mass to the power two-thirds. In 1883 the German physiologist Max Rubner showed, in respiration experiments on dogs of different sizes, that metabolic rate per unit of surface area was roughly constant: the "surface law."

In 1932 Max Kleiber, a Swiss-born animal scientist at the University of California's agricultural campus at Davis, compiled measurements for thirteen groups of animals, from ring doves and rats to steers. Metabolic rate rose more steeply with body size than the surface law allowed, and Kleiber proposed that the right measure of metabolic body size was mass to the three-quarters power. In 1947, with more data, his least-squares fit gave an exponent of 0.756; he recommended rounding it to 3/4, partly because it could then be calculated without logarithms.[14] Related "quarter-power" laws turned up elsewhere: heart rate and breathing rate fall roughly as mass to the minus one-quarter, and lifespan and time to maturity grow roughly as mass to the one-quarter. Why should biology prefer quarters, when geometry suggested thirds?

Science Primer: Mouse and elephant

Kleiber's 1947 rule of thumb for resting mammals is

$$B \approx 70\, M^{3/4},$$

where B is the basal metabolic rate in kilocalories per day and M is body mass in kilograms. Compare a 25-gram mouse ($M = 0.025$) with a 4,000-kilogram elephant. The elephant is 160,000 times heavier.

If metabolism grew in proportion to mass, the elephant would need 160,000 times as much food as the mouse. If it grew with surface area, as $M^{2/3}$, the ratio would be $160{,}000^{2/3} \approx 2{,}900$. Kleiber's law gives

$$160{,}000^{3/4} = 8{,}000.$$

The formula predicts about 4.4 kilocalories a day for the mouse (about a fifth of a watt) and about 35,000 for the elephant (about 1.7 kilowatts). Per kilogram, the mouse burns $160{,}000^{1/4} = 20$ times as fast as the elephant.

The same factor of twenty appears in the heart. If heart rate scales as $M^{-1/4}$, the mouse's heart should beat twenty times as fast as the elephant's. Typical figures are about 550 beats a minute for a mouse and about 30 for an elephant, a ratio of about eighteen. If lifespan scales as $M^{1/4}$, the two effects cancel, and the number of heartbeats in a lifetime should be roughly the same for all mammals. A compilation published in 1997 put the average, excluding humans, at about 730 million, with a wide scatter; humans, with their long modern lives, are well above it. Popular accounts often round the figure up to one or one and a half billion. It is a striking regularity, but a loose one: the scatter is almost as large as the average.[15]

In the mid-1990s James Brown, an ecologist at the University of New Mexico in Albuquerque, best known for his work on desert rodents and on the large-scale patterns of animal distribution, wanted a physicist's help with scaling. A mutual acquaintance in Santa Fe suggested Geoffrey West of Los Alamos. West, born in Taunton, Somerset, in 1940, had read physics at Cambridge, taken a doctorate at Stanford in 1966 and in the 1970s founded the particle theory group at Los Alamos, which he led for many years. Scaling laws were familiar to him from the physics of quarks and gluons. Brown telephoned him. West met Brown and his doctoral student Brian

Enquist, a plant ecologist, and the three began a collaboration that linked the University of New Mexico, Los Alamos and the Santa Fe Institute. West has said that he first treated it almost as a hobby, and that it took about a year of intense work before they had a theory.

The theory, published in *Science* in April 1997, proposed that quarter-power scaling arises from the networks that distribute resources inside organisms: blood vessels in animals, vascular plumbing in plants. It rested on three assumptions. The network is *space-filling*, branching until it reaches every part of the body. Its terminal units (capillaries, in mammals) are the same size in a mouse and a whale. And natural selection has shaped it to minimise the energy needed to pump fluid through it.

The argument can be sketched without the full mathematics. Picture the circulation as a tree that branches again and again, each vessel dividing into n smaller ones, from the aorta down to the capillaries. To fill space, each generation of vessels must be shorter than the last by a factor of $n^{-1/3}$: the cube root appears because the region of the body each vessel serves shrinks in volume by a factor of n at each branching. In the large arteries, where the heart's pulse travels as a wave along elastic walls, minimising energy loss requires the total cross-sectional area to stay the same at each branching, so that the wave is not reflected; each vessel's radius then shrinks by $n^{-1/2}$. Put together, the volume of a single vessel (length times cross-section) shrinks by $n^{-1/3} \times n^{-1} = n^{-4/3}$ per generation, while the number of vessels grows only by n. The great vessels near the heart therefore hold most of the blood, and their volume, measured in units of a capillary, grows as the number of capillaries to the power four-thirds. Blood volume in mammals is a roughly fixed fraction of body mass. If blood volume is proportional to M and also grows as the number of capillaries to the power $4/3$, then the number of capillaries grows as $M^{3/4}$. Each capillary supplies about the same amount of oxygen whatever the size of the animal, so metabolic rate grows as $M^{3/4}$ too.

In the smallest vessels, where flow is slow and viscosity dominates, the energy-minimising rule is different: a branching law found by the physiologist Cecil Murray in 1926, in which the cube of the parent vessel's radius equals the sum of the cubes of its daughters'. The model includes both regimes, and the clean exponent of $3/4$ emerges only in the limit of very large animals.[16]

In 1999 West, Brown and Enquist gave the argument a more general form in a paper titled "The Fourth Dimension of Life." Natural selection, they argued, has maximised the effective surface through which organisms exchange energy and materials (the total surface of the capillaries, say, or of the leaves) while keeping internal transport distances short. A fractal-like branching network lets an exchange surface scale as though it were a volume, and the quarter-powers follow as if organisms lived in four dimensions rather than three. The title should not be taken literally: nothing in an organism is four-dimensional. The point is that the exchange surface grows with size the way a volume would, which is what pushes the exponent from $2/3$ up to $3/4$.

The work was widely celebrated. It combined fluid mechanics, geometry and natural selection to derive a biological law that had been an empirical curiosity for sixty years. It also launched a larger programme. In 2004 Brown, with James Gillooly, Andrew Allen, Van Savage

and West, proposed a *metabolic theory of ecology*, combining the three-quarter law with the effect of temperature on biochemical reaction rates to predict rates of growth, reproduction and mortality, and the flow of energy and materials through ecosystems.[17] Not everyone was persuaded.

Cities

In the early 2000s West and his colleagues turned the same questions on human societies. Cities, too, are sustained by branching networks: water mains, electrical cables, roads. And if larger animals live more slowly, do larger cities?

The key paper was published in 2007 by Luís Bettencourt, a Portuguese theoretical physicist then at Los Alamos, with the economist José Lobo, Dirk Helbing, Christian Kühnert and West. They gathered statistics for cities in the United States, Germany, China and the European Union, defining cities as unified labour markets (in the United States, metropolitan statistical areas), and fitted each quantity Y to a power of population N:

$$Y \propto N^{\beta}.$$

The exponents β fell into three groups. Quantities tied to individual needs, such as jobs, houses and household water and electricity use, grew in proportion to population ($\beta \approx 1$). Quantities of infrastructure, such as petrol stations, electrical cables and road surface, grew more slowly ($\beta < 1$): bigger cities needed less of them per head, an economy of scale like that of a large animal. And quantities tied to social interaction, such as wages, patents, research employment and GDP, but also serious crime and new cases of AIDS, grew faster than population ($\beta > 1$).

Table 10.1: Selected urban scaling exponents β, where $Y \propto N^{\beta}$ and N is city population (from Bettencourt et al., 2007, Table 1)

Quantity	**Data**	β
New patents	US, 2001	1.27
Private R&D employment	US, 2002	1.34
Total wages	US, 2002	1.12
GDP	China, 2002	1.15
Serious crimes	US, 2003	1.16
Total employment	US, 2001	1.01
Total housing	US, 1990	1.00
Length of electrical cables	Germany, 2002	0.87
Road surface	Germany, 2002	0.83
Petrol stations	US, 2001	0.77

The popular summary, which West made famous in lectures and in *Scale*, is that the exponents sit about 15 per cent above or below one: roughly 1.15 for the good and the bad (wages, patents, crime) and 0.85 for infrastructure. In practice that means each doubling of a city's population brings about 11 per cent more of the former per head, since $2^{0.15} \approx 1.11$, and needs about 10 per cent less infrastructure per head. The round exponents are fair summaries, but the table

shows how much the individual values vary, from 0.77 for petrol stations to 1.34 for private research employment. In 2013 Bettencourt proposed a theory for these numbers, in which a city is a network of social interactions that its infrastructure exists to make possible; for an idealised city it predicts exponents of $5/6$ and $7/6$.[18]

The analogy with organisms runs in both directions. In biology the exponents are below one, and larger animals live more slowly. In cities the socioeconomic exponents are above one, and larger cities live faster: the 2007 paper cited earlier studies showing that people walk faster in bigger cities. The authors drew a disturbing inference. Growth driven by superlinear scaling accelerates rather than levelling off, and can be sustained only if major innovations arrive at ever shorter intervals. It is a speculation, and they presented it as one.

Outcomes and Legacy

The Santa Fe Institute did not create complexity science alone. Chaos theory grew up in the 1970s in Santa Cruz, Paris, Los Alamos and elsewhere; self-organisation was studied in Brussels and Stuttgart; network science grew up largely outside Santa Fe. But the institute gave the field a name, a meeting place, a book series and a model of how to organise it.

Institutions. Centres for the study of complex systems multiplied in the decades that followed, among them the New England Complex Systems Institute and the Complexity Science Hub in Vienna, founded in 2015, as well as many university centres. The Santa Fe Institute outlived its founders. Its presidents after Cowan included the physicist Edward Knapp, the biologist Ellen Goldberg, Geoffrey West (2005–09), the archaeologist Jeremy Sabloff and, from 2015, the evolutionary theorist David Krakauer. In 2024 it published a four-volume collection of *Foundational Papers in Complexity Science*, with new commentaries.

Agent-based modelling. The approach of the El Farol bar and the artificial stock market, building a population of heterogeneous, adaptive agents in a computer and watching what they collectively do, has spread far beyond Santa Fe. Its most consequential use has been in epidemiology. On 16 March 2020 Neil Ferguson's group at Imperial College London published Report 9 on the coronavirus pandemic, which modified an individual-based simulation model originally built for pandemic influenza planning and projected about 510,000 deaths in Great Britain and 2.2 million in the United States if nothing were done. It was a major influence on the British government's decision to impose a national lockdown a week later, and its assumptions were argued over for years. Individual-based epidemic models have their own lineage in epidemiology, and the Imperial model was not a Santa Fe product, but the general idea that a population can be simulated person by person, with the macroscopic outcome left to emerge, is one the institute did much to promote. In economics, agent-based models remain outside the mainstream but have found a place in some central banks: in 2016 the Bank of England published an agent-based model of the British housing market, built with Doyne Farmer's group at Oxford, to explore limits on mortgage lending.[19]

Network science. In 1998 Duncan Watts and Steven Strogatz, then at Cornell, showed that

adding a few random long-range links to an orderly network produces a "small world" in which any two nodes are separated by only a few steps. In 1999 Albert-László Barabási and Réka Albert at Notre Dame showed that networks that grow by preferential attachment, in which new nodes prefer to link to nodes that already have many links, develop a few highly connected hubs and a power-law distribution of connections.[20] Neither paper was a Santa Fe product, though Watts later joined the institute's external faculty and network science soon became central to its work. Preferential attachment is, in effect, an increasing-returns process of the kind Arthur studied: the rich get richer, as in a Pólya urn.

Econophysics. The term was coined by the physicist H. Eugene Stanley at a conference in Kolkata in 1995, for the application of statistical physics to financial and economic data. Its early work on fat-tailed price distributions came largely from physicists in Boston, Paris and elsewhere, and its relation to the Santa Fe economics programme is one of shared ancestry rather than descent.

Metabolic ecology. The metabolic theory of ecology became one of the most cited and most argued-over frameworks in ecology in the 2000s. Whatever the fate of the precise exponent, it encouraged ecologists to treat energy flow, temperature and body size as threads connecting levels of biology from cells to ecosystems.

Disorder in physics. In October 2021 the Nobel Prize in Physics was awarded for contributions to the understanding of complex physical systems. Half went to Syukuro Manabe and Klaus Hasselmann for climate modelling; the other half went to Giorgio Parisi, for discovering how disorder and fluctuations interact in physical systems, work that began with his solution, around 1980, of the mean-field theory of spin glasses. It was not a prize for the Santa Fe Institute, and Parisi worked in Rome. But it recognised the body of physics, from Anderson and Edwards's spin glasses onwards, on which the founders drew when they argued that statistical physics could be carried into biology, computation and economics. Parisi himself, with Ugo Bastolla, published an important analysis of Kauffman networks in 1998.

The Costs of Crossing

The Santa Fe Institute was built to do what this book celebrates: to make a lasting trading zone in which specialists from incompatible fields had to find common ground. Its record also shows four ways in which border-crossing goes wrong, and it is to the institute's credit that several of the corrections came from its own circle.

Beautiful numbers that turned out to be wrong. Kauffman's square-root law for the number of attractors rested on simulations of networks small enough for the computers of the 1960s. With larger networks, the growth turned out to be faster. In 2003 Björn Samuelsson and Carl Troein at Lund proved that the average number of attractors in critical Kauffman networks grows faster than any power of N, which disposed of the square root altogether.[21] The biological side fared no better. Kauffman's comparison relied on gene counts estimated from the amount of DNA in a cell; genome sequencing showed that gene number is not proportional to

DNA content, and that humans have about 20,000 protein-coding genes, not 100,000. Barbara Drossel's standard review concluded that both the biological data and the simulation data behind the original correspondence were wrong. Bornholdt and Kauffman have since argued that when noise is added to the networks, as in real cells, square-root scaling returns for the biologically relevant attractors, and that the central idea, cell types as attractors of a gene-regulatory network, has held up. It has: it is now a common framework in systems biology. But the number that made the theory famous was an artefact.

A slogan outran its evidence. The edge of chaos is the clearest case at Santa Fe of an idea that spread faster than it could be tested. Mitchell, Hraber and Crutchfield removed its main experimental support, and the general claim that evolution drives adaptive systems to the boundary of chaos has never been established. Some real systems, among them certain neural circuits, do seem to operate near critical points, and the question remains open. But by the time the correction appeared, the phrase was in the subtitles of books. In June 1995 the journalist John Horgan asked in *Scientific American*, in an article titled "From Complexity to Perplexity," whether complexity science was a science at all. He reported that some Santa Fe researchers doubted that a unified theory of complex adaptive systems was possible, and argued that computer models of complex systems could never be verified as physical theories could, only made more or less persuasive. In 1997 the institute's president, Ellen Goldberg, told *Nature* that it had a reputation for being "flaky," and a resident researcher worried that good scientists had been deterred by the impression that it was seeking a theory of everything.[22] The founders' grand ambition, a general theory that would do for complex adaptive systems what thermodynamics had done for heat, has not been realised. What the institute produced instead was a set of models, methods and analogies that proved useful in particular fields. That is a great deal. It is not what was promised.

Universal laws met messier data. The quarter-power laws were questioned almost at once. In 2001 Peter Dodds, Daniel Rothman and Joshua Weitz at MIT re-examined the classic data and found that for mammals under about ten kilograms, and for birds over much of their size range, the old two-thirds exponent could not be rejected; they also argued that the derivations of three-quarters, the West–Brown–Enquist model included, did not justify rejecting it. In 2008 Savage, Deeds and Fontana, one of them a co-author of the metabolic theory, worked through the model's own mathematics and found that for animals of realistic size it predicted an exponent nearer 0.81 than 0.75, outside the range the data supported. In 2010 Tom Kolokotrones and colleagues showed that on logarithmic axes metabolic rate against body mass is not a straight line but slightly curved, so that data dominated by small animals give exponents near two-thirds and data dominated by large ones near three-quarters. Measurements of real vascular networks have since found branching patterns that the model's symmetrical tree does not capture. None of this shows that networks are irrelevant to metabolism; it shows that the "universal" three-quarter law is an approximation over part of the range, and that a theory which seemed to derive it exactly derived something more complicated. Urban scaling met a similar problem. In 2015 a team led from University College London by Elsa Arcaute and Michael Batty redrew the boundaries of the cities of England and Wales thousands of times, using different thresholds of population density and commuting, and found that most indicators scaled linearly and that,

where they did not, the exponent varied considerably with how the city was defined.[23] A scaling law is only as universal as the definition of the thing being scaled. Organisms have skins. Cities do not.

The outsider story and the insiders' reasons. The legend of Brian Arthur, as told in Waldrop's book and later journalism, is of a lone thinker rejected by a closed-minded profession until the physicists of Santa Fe recognised his worth. In 1998 Paul Krugman, himself a pioneer of increasing returns in trade theory, replied in an essay titled "The Legend of Arthur" that the story was largely false. Increasing returns had a long history in economics; trade theory had been rebuilt around them by Krugman, Elhanan Helpman and others from the late 1970s; by the economists' own bibliographic database some 140 papers on the subject had appeared in mainstream journals by 1987; and in Krugman's view Arthur's models resembled earlier work by Thomas Schelling and left aside conceptual problems that economists had already addressed. Krugman's verdict is itself partisan, and Arthur's lock-in model and its probability theory were genuinely new. But the episode shows how easily the history of an interdisciplinary institute becomes a story of enlightened outsiders and benighted insiders. The economists who resisted had reasons. Models with many equilibria and no way to choose among them, or simulations with dozens of adjustable parameters, are hard to test against data, and economics had learned to distrust models that could explain anything. The artificial stock market illustrates the risk. In 2002 Norman Ehrentreich found that the mutation step in its genetic algorithm was biased in a way that tended to create the appearance of technical trading, and that in a corrected version the artificial investors moved closer to the rational-expectations outcome, with much weaker complex behaviour.[24] The physicists' freedom from the economists' assumptions was sometimes also a freedom from the economists' hard-won caution. Complexity economics has not displaced the mainstream. Its methods are increasingly used; its claim to be a new foundation for the discipline remains a claim.

Coda

The convent on Canyon Road is no longer the institute's home, and most of its founders and early figures are dead: Cowan in 2012, Holland in 2015, Pines in 2018, Gell-Mann in 2019, Philip Anderson in 2020. What they built has outlasted most of the specific claims made there. Kauffman's attractors survive as a way of thinking about cell types; his square root does not. The edge of chaos survives as a question; as an answer it was withdrawn by the institute's own circle. Kleiber's law survives as a good approximation over much of the range of mammals, while the derivation that seemed to explain it exactly is still argued over. Arthur's urns survive wherever economists discuss path dependence.

Perhaps the most durable thing the founders made was the place itself: a small institute with no departments, where an ecologist from Albuquerque and a particle theorist from Los Alamos could work on the same problem, and where researchers could test one of its most famous ideas and publish the negative result in its own series. The monastery image is only half right. Monasteries keep their doctrines. The institute's better moments came when it did not.

Notes

[1]The dates of the two founding workshops (5–6 October and 10–11 November 1984) and their funding by the Carnegie Corporation and the MacArthur Foundation are given in David Pines, "Foreword" to the 1988 edition of Pines, ed., *Emerging Syntheses in Science: Proceedings of the Founding Workshops of the Santa Fe Institute* (Redwood City, CA: Addison-Wesley, 1988). The new preface to the SFI Press edition dates the discussion transcript to 6–7 October 1984. The room, the ages of those present and the exchange with Cowan are from Stephen Wolfram, "My Part in an Origin Story: The Launching of the Santa Fe Institute," *Stephen Wolfram Writings*, 2019, https://writings.stephenwolfram.com/2019/06/my-part-in-an-origin-story-the-launching-of-the-santa-fe-institute/. Gell-Mann recalled that Schwartz lent the boardroom of the School of American Research, though in the same interview he placed the workshops in November and December: Murray Gell-Mann, interview, Web of Stories, https://www.webofstories.com/play/52270. Philip Anderson also placed both 1984 workshops at the School of American Research: P. W. Anderson, "Complexity II: The Santa Fe Institute," *Physics Today* 45, no. 6 (June 1992).

[2]P. W. Anderson, "More Is Different: Broken Symmetry and the Nature of the Hierarchical Structure of Science," *Science* 177, no. 4047 (4 August 1972): 393–96, which describes itself as an expanded version of a Regents' Lecture given at the University of California, La Jolla, in 1967; Warren Weaver, "Science and Complexity," *American Scientist* 36, no. 4 (1948): 536–44.

[3]George A. Cowan, *Manhattan Project to the Santa Fe Institute: The Memoirs of George A. Cowan* (Albuquerque: University of New Mexico Press, 2010), which includes chapters on the White House Science Council and the institute's early years. Cowan died on 20 April 2012. On Metropolis's and Gell-Mann's positions, see GoodWork Project, *Review of the Santa Fe Institute*, GoodWork Project Report Series 22, https://www.thegoodproject.org/s/Santa-Fe.pdf; on the location, Klaus Taschwer, "Vom Mekka zur Denkfabrik: Das Institut für Komplexitätsforschung," *Gegenworte* 13 (2004): 44–48. Philip Anderson, often named as a founder in popular accounts, took part in the founding workshops and became central to the economics programme, but is not usually counted among the founding group.

[4]On the name, Christophe Schinckus, "The Santa Fe Institute and Econophysics: A Possible Genealogy?," *Foundations of Science* 26, no. 4 (2021): 925–45; on the March 1984 registration and the move into the convent, Taschwer, "Vom Mekka zur Denkfabrik." On the premises, Gell-Mann, interview, Web of Stories, https://www.webofstories.com/play/52272 and https://www.webofstories.com/play/52273; Michael Haederle, "George Cowan, Founding President of Santa Fe Institute: 1920–2012," *Pacific Standard*, 20 April 2012, which gives 1987 for the convent and 1994 for the move; and David C. Krakauer, "The Cormac McCarthy I Know," *Nautilus*, 2 November 2022, on the Hurley house. Some accounts associate the convent with the church of Cristo Rey on Canyon Road; I have not found a source that confirms this. On staffing, C. Macilwain, "Santa Fe Centre Seeks Second Wind," *Nature* 389 (1997): 106–7.

[5]Anderson, "Complexity II." Arthur later put Citicorp's initial support at roughly a couple of million dollars: W. Brian Arthur, talk on complexity economics at the Santa Fe Institute (2019), transcript at https://sites.santafe.edu/~wbarthur/Papers/SFI%202019%20CE%20talk.pdf.

[6]Philip W. Anderson, Kenneth J. Arrow and David Pines, eds., *The Economy as an Evolving Complex System*, Santa Fe Institute Studies in the Sciences of Complexity, vol. 5 (Redwood City, CA: Addison-Wesley, 1988), the proceedings of the Evolutionary Paths of the Global Economy Workshop, Santa Fe, September 1987. The count of contributors by department is from Schinckus, "The Santa Fe Institute and Econophysics." Participants, the length of the meeting, Kauffman's question and Arrow's message are from Arthur's 2019 talk and from W. Brian Arthur, "Economic Complexity: A Different Way to Look at the Economy," *SFI 30: Foundations and Frontiers*, 2014, https://medium.com/sfi-30-foundations-fro

ntiers/economic-complexity-a-different-way-to-look-at-the-economy-eae5fa2341cd.

[7]Biographical details from Arthur's curriculum vitae at the Santa Fe Institute; on IIASA, "How to Achieve Scientific Excellence," IIASA blog, 2 May 2018, https://blog.iiasa.ac.at/2018/05/02/how-to-achieve-scientific-excellence/. Arthur describes the origins of his interest in the introduction to W. Brian Arthur, *Increasing Returns and Path Dependence in the Economy*, foreword by Kenneth J. Arrow (Ann Arbor: University of Michigan Press, 1994). Some popular accounts single out Ilya Prigogine's theory of dissipative structures as his inspiration; Prigogine's work belonged to the same intellectual climate, but I have not found Arthur himself naming it as the decisive influence.

[8]W. B. Arthur, Yu. M. Ermoliev and Yu. M. Kaniovski, "A Generalized Urn Problem and Its Applications," *Kibernetika*, no. 1 (1983), translated in *Cybernetics*, and reprinted in Arthur, *Increasing Returns and Path Dependence*; W. Brian Arthur, "Competing Technologies, Increasing Returns, and Lock-In by Historical Events," *Economic Journal* 99, no. 394 (1989): 116–31. The six years of rejections are reported in "How to Achieve Scientific Excellence."

[9]W. Brian Arthur, "Inductive Reasoning and Bounded Rationality," *American Economic Review* 84, no. 2 (1994): 406–11; W. Brian Arthur, John H. Holland, Blake LeBaron, Richard Palmer and Paul Tayler, "Asset Pricing under Endogenous Expectations in an Artificial Stock Market," in W. Brian Arthur, Steven N. Durlauf and David A. Lane, eds., *The Economy as an Evolving Complex System II* (Reading, MA: Addison-Wesley, 1997), 15–44.

[10]S. A. Kauffman, "Metabolic Stability and Epigenesis in Randomly Constructed Genetic Nets," *Journal of Theoretical Biology* 22, no. 3 (1969): 437–67; Kauffman's work at MIT appears in W. S. McCulloch, J. Y. Lettvin, R. Moreno-Diaz and S. A. Kauffman, "Neurophysiology," MIT Research Laboratory of Electronics, *Quarterly Progress Report* 88 (15 January 1968). B. Derrida and Y. Pomeau, "Random Networks of Automata: A Simple Annealed Approximation," *Europhysics Letters* 1, no. 2 (1986): 45–49. For a clear modern account, see Barbara Drossel, "Random Boolean Networks," arXiv:0706.3351 (2007; revised 2008).

[11]The comparison and figures are set out in Stefan Bornholdt and Stuart Kauffman, "Ensembles, Dynamics, and Cell Types: Revisiting the Statistical Mechanics Perspective on Cellular Regulation," *Journal of Theoretical Biology* 467 (2019), which revisits the 1969 argument fifty years on.

[12]Kevin Kelly, *Out of Control: The New Biology of Machines, Social Systems, and the Economic World* (Reading, MA: Addison-Wesley, 1994), chapter 17, based on interviews with Langton; Kevin Kelly, "Entries in the First Artificial Life 4-H Show," *Whole Earth Review*, Spring 1988. The proceedings are Christopher G. Langton, ed., *Artificial Life*, Santa Fe Institute Studies in the Sciences of Complexity, vol. 6 (Redwood City, CA: Addison-Wesley, 1989).

[13]N. H. Packard, "Adaptation toward the Edge of Chaos," in J. A. S. Kelso, A. J. Mandell and M. F. Shlesinger, eds., *Dynamic Patterns in Complex Systems* (Singapore: World Scientific, 1988), 293–301; Christopher G. Langton, "Computation at the Edge of Chaos: Phase Transitions and Emergent Computation," *Physica D* 42 (1990): 12–37; Melanie Mitchell, Peter T. Hraber and James P. Crutchfield, "Revisiting the Edge of Chaos: Evolving Cellular Automata to Perform Computations," *Complex Systems* 7 (1993): 89–130.

[14]Max Kleiber, "Body Size and Metabolism," *Hilgardia* 6, no. 11 (1932): 315–53; Max Kleiber, "Body Size and Metabolic Rate," *Physiological Reviews* 27, no. 4 (1947): 511–41, which gives the fitted exponent of 0.756, the average of about 70 kilocalories per kilogram$^{3/4}$ per day, and the reasons for preferring 3/4 to Samuel Brody's 0.73.

[15]Herbert J. Levine, "Rest Heart Rate and Life Expectancy," *Journal of the American College of Cardiology*

30 (1997): 1104–6, which gives an average of about 7.3×10^8 heartbeats per lifetime, with a standard deviation of 5.6×10^8, across the mammals in its sample. The calculations in the primer are mine.

[16]West's account of the collaboration is in Edwin Cartlidge, "Yeah, but What about the Crayfish?," *Physics World*, https://physicsworld.com/a/yeah-but-what-about-the-crayfish/, and in Geoffrey West, *Scale: The Universal Laws of Growth, Innovation, Sustainability, and the Pace of Life in Organisms, Cities, Economies, and Companies* (New York: Penguin Press, 2017). The model is Geoffrey B. West, James H. Brown and Brian J. Enquist, "A General Model for the Origin of Allometric Scaling Laws in Biology," *Science* 276, no. 5309 (1997): 122–26. The sketch here follows the explicit reconstruction in Van M. Savage, Eric J. Deeds and Walter Fontana, "Sizing Up Allometric Scaling Theory," *PLoS Computational Biology* 4, no. 9 (2008): e1000171.

[17]Geoffrey B. West, James H. Brown and Brian J. Enquist, "The Fourth Dimension of Life: Fractal Geometry and Allometric Scaling of Organisms," *Science* 284, no. 5420 (1999): 1677–79; James H. Brown, James F. Gillooly, Andrew P. Allen, Van M. Savage and Geoffrey B. West, "Toward a Metabolic Theory of Ecology," *Ecology* 85, no. 7 (2004): 1771–89.

[18]Luís M. A. Bettencourt, José Lobo, Dirk Helbing, Christian Kühnert and Geoffrey B. West, "Growth, Innovation, Scaling, and the Pace of Life in Cities," *Proceedings of the National Academy of Sciences* 104, no. 17 (2007): 7301–6, from whose Table 1 the figures in Table 10.1 are taken; Luís M. A. Bettencourt, "The Origins of Scaling in Cities," *Science* 340, no. 6139 (2013): 1438–41.

[19]Neil M. Ferguson et al., "Report 9: Impact of Non-Pharmaceutical Interventions (NPIs) to Reduce COVID-19 Mortality and Healthcare Demand," Imperial College COVID-19 Response Team, 16 March 2020, https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-9-impact-of-npis-on-covid-19/; Rafa Baptista, J. Doyne Farmer, Marc Hinterschweiger, Katie Low, Daniel Tang and Arzu Uluc, "Macroprudential Policy in an Agent-Based Model of the UK Housing Market," Bank of England Staff Working Paper no. 619 (October 2016). The general case is argued in J. Doyne Farmer and Duncan Foley, "The Economy Needs Agent-Based Modelling," *Nature* 460 (2009): 685–86.

[20]Duncan J. Watts and Steven H. Strogatz, "Collective Dynamics of 'Small-World' Networks," *Nature* 393 (1998): 440–42; Albert-László Barabási and Réka Albert, "Emergence of Scaling in Random Networks," *Science* 286 (1999): 509–12.

[21]Björn Samuelsson and Carl Troein, "Superpolynomial Growth in the Number of Attractors in Kauffman Networks," *Physical Review Letters* 90, no. 9 (2003): 098701; Drossel, "Random Boolean Networks"; Bornholdt and Kauffman, "Ensembles, Dynamics, and Cell Types."

[22]John Horgan, "From Complexity to Perplexity," *Scientific American* 272, no. 6 (June 1995); Macilwain, "Santa Fe Centre Seeks Second Wind."

[23]Peter Sheridan Dodds, Daniel H. Rothman and Joshua S. Weitz, "Re-examination of the '3/4-Law' of Metabolism," *Journal of Theoretical Biology* 209, no. 1 (2001): 9–27; Savage, Deeds and Fontana, "Sizing Up Allometric Scaling Theory"; Tom Kolokotrones, Van Savage, Eric J. Deeds and Walter Fontana, "Curvature in Metabolic Scaling," *Nature* 464 (2010): 753–56; Mitchell G. Newberry, Daniel B. Ennis and Van M. Savage, "Testing Foundations of Biological Scaling Theory Using Automated Measurements of Vascular Networks," *PLoS Computational Biology* 11, no. 8 (2015): e1004455; Elsa Arcaute, Erez Hatna, Peter Ferguson, Hyejin Youn, Anders Johansson and Michael Batty, "Constructing Cities, Deconstructing Scaling Laws," *Journal of the Royal Society Interface* 12, no. 102 (2015): 20140745.

[24]Paul Krugman, "The Legend of Arthur," *Slate*, 14 January 1998, archived at https://web.mit.edu/krugman/www/legend.html, responding to John Cassidy, "The Force of an Idea," *New Yorker*, 12 January

1998, and to M. Mitchell Waldrop, *Complexity: The Emerging Science at the Edge of Order and Chaos* (New York: Simon & Schuster, 1992); Norman Ehrentreich, "The Santa Fe Artificial Stock Market Re-Examined: Suggested Corrections," Betriebswirtschaftliche Diskussionsbeiträge 45/02, Martin-Luther-Universität Halle-Wittenberg, 2002.

Further Reading

M. Mitchell Waldrop, *Complexity: The Emerging Science at the Edge of Order and Chaos* (Simon & Schuster, 1992). The classic narrative of the institute's early years, built around Arthur, Kauffman, Holland and Langton and based on extensive interviews. Vivid and readable, but it is the main source of the Arthur legend and should be read alongside Krugman's response.

Melanie Mitchell, *Complexity: A Guided Tour* (Oxford University Press, 2009). The best general introduction to the science, by one of the authors of the edge-of-chaos critique. Clear on cellular automata, genetic algorithms, networks and scaling, and candid about what complexity science has and has not achieved.

P. W. Anderson, "More Is Different," *Science* 177 (1972): 393–96. Four pages that remain the best short statement of why emergence is a scientific problem rather than a mystical one.

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Part IV

The Age of Big Data and Convergence (1990–Present)

Chapter 11

The Industrialisation of the Code: The Human Genome Project (1990–2003)

A Garage in Seabright

On 22 May 2000 a graduate student at the University of California, Santa Cruz, sent an email to one of his professors. The student was Jim Kent, and he was forty years old. He had spent most of his working life not in biology but writing graphics and animation software for early personal computers, and had run his own small animation-software business for more than a decade before going back to university to study the molecular biology of a nematode worm. The professor was David Haussler, a computer scientist whose group had been applying machine-learning methods to biological sequences. Haussler had a problem, and in the previous few weeks it had begun to look insoluble.

In December 1999 Eric Lander of the Whitehead Institute in Cambridge, Massachusetts, had asked Haussler's group for help in finding the genes in the raw output of the publicly funded Human Genome Project. Haussler saw that the genes could not be found until the output had been assembled into something that could be called a human genome, and that nobody yet had a program to do it. Twenty laboratories in six countries had by then read the sequence of tens of thousands of large pieces of human DNA, each cloned in bacteria. But most of those pieces had been read only roughly. Each was represented by a handful of unordered, unoriented fragments, and nobody had yet laid the pieces end to end. Across the whole collection there were some four hundred thousand fragments inside about thirty thousand clones. Meanwhile a private company in Maryland, Celera Genomics, was assembling its own version of the genome on one of the largest computer installations in civilian hands, and its president, Craig Venter, had told Congress in April that the public project's data were an unordered collection of more than half a million fragments. Haussler had started writing the assembler himself. By May it was not working, and he wrote to Kent that things looked grim.

Kent's email proposed a simpler approach, one that would merge the overlapping fragments greedily, clone by clone, and use every other scrap of evidence available (the sequences of mes-

senger RNAs, short tags from expressed genes, the paired ends of cloned fragments whose distance apart was roughly known) to put the merged pieces in order. Haussler replied with one word: "Godspeed."

Kent worked in the garage of his house in the Seabright neighbourhood of Santa Cruz, by one account spending a fortnight on the idea in secret before telling anyone. Over the four weeks from 22 May he wrote about ten thousand lines of code, and he typed so hard and for so long that, as Haussler later told the *New York Times*, he had to ice his wrists at night to keep going. Haussler, for his part, assembled around a hundred desktop computers with Pentium III processors, some bought for the purpose and others diverted from student use, and linked them into a makeshift parallel machine. On 22 June 2000, Kent ran his program, which he called GigAssembler, across the whole data set and produced the first assembly of the public human genome sequence. Celera finished its own assembly three days later, on the night of 25 June. On 26 June, in the East Room of the White House, the President of the United States announced that a first survey of the human genome was complete.[1]

The story of a lone programmer racing a corporation is the version that newspapers liked, and it is true as far as it goes. But by June 2000 the human genome had been fifteen years in the planning and ten in the making. It had required the chemistry of fluorescent dyes, the physics of lasers, the statistics of random sampling, the engineering of robotic factories, the politics of two governments and a British charity, and a much-argued experiment in paying philosophers and lawyers to think about the consequences before they arrived. Biology had never before depended so thoroughly on people who were not biologists.

The Science: A Book Without Spaces

As we saw in Chapter 7, DNA is a double helix: two long chains wound round each other, each a string of four chemical units, or bases, called adenine, cytosine, guanine and thymine (A, C, G and T). The bases on one chain pair with those on the other by a strict rule, A with T and G with C, so that the sequence of one chain fixes the sequence of its partner. A *base pair* is one rung of the ladder, and it is the natural unit for measuring length. The order of the bases along a chain is the information. Reading a genome means writing down that order, letter by letter, from one end of each chromosome to the other.

A human cell keeps its DNA in forty-six chromosomes: twenty-three pairs, one of each pair inherited from each parent. One copy of the full set (a *haploid* genome) runs to about three billion base pairs; a person, carrying two copies, has about six billion. Any two people's genomes are about 99.9 per cent identical, which is why a single sequence could serve as a reference for everyone, and also why the remaining 0.1 per cent, some three million differences, matters so much.

The textbook picture of a genome is a string of genes, each specifying a protein. The real picture is stranger. A gene that codes for a protein is broken into pieces, called *exons*, separated by stretches of non-coding DNA called *introns* that are cut out of the RNA copy before it is

translated. The exons of all the genes together, which geneticists call the *exome*, make up only about 1.5 per cent of the human genome, and the parts of them that actually code for protein a little less. Some of the rest controls when and where genes are used, some codes for RNA molecules with jobs of their own, and a very large fraction consists of copies of things that have copied themselves.

These are the *repeats*, and they are the central technical fact of this chapter. About half of the human genome derives from *transposable elements*, stretches of DNA that, over hundreds of millions of years, have made copies of themselves and inserted the copies elsewhere. The most numerous is the *Alu* element, about three hundred base pairs long, which is present in more than a million copies and makes up about a tenth of the genome. Longer elements called LINEs (long interspersed nuclear elements), of which the most important family is LINE-1, account for about a fifth; a complete LINE-1 runs to some six thousand base pairs, though most copies are truncated. Copies of the same element are not identical, because each has accumulated its own mutations since it was inserted, but many are similar enough to be confused. Add to these the *segmental duplications*, large blocks of chromosome that have been copied wholesale, and the satellite DNA that fills the centromeres with the same short motif repeated thousands of times over, and the result is a text in which many paragraphs appear, with small variations, in many places.[2]

This matters because no machine has ever read a whole human chromosome in one pass. Every method used in this period read short stretches, a few hundred letters at a time. Reading a genome meant breaking it into fragments, reading the fragments, and then putting them back together by finding where they overlapped. If the text were random, overlaps would be unambiguous. Because it is full of repeats, a fragment that falls entirely inside an Alu element could belong in any of a million places. The Human Genome Project was, in the end, two problems: a problem of reading, which was solved by chemistry, optics and engineering, and a problem of reassembly, which was solved by mathematics and computing.

The Science: Reading and Reassembling

In 1977 two methods for reading DNA were published within months of each other. The first, by Allan Maxam and Walter Gilbert at Harvard, was chemical. A DNA molecule was labelled with radioactive phosphorus at one end, and four samples of it were treated with reagents that broke the chain at particular bases: at guanines; at adenines; at cytosines and thymines alike; and at cytosines alone. Each reaction was tuned to break each molecule, on average, only once, so that it produced a collection of labelled fragments whose lengths marked the positions of that base. Run side by side through a gel, the four collections could be read to give the sequence of at least a hundred bases from the labelled end.

The second method, from Frederick Sanger's laboratory at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, was enzymatic, and it became the method on which the human genome was built. It exploited the way a cell copies DNA. An enzyme called DNA polymerase builds a new strand along a single-stranded template, adding one nucleotide

at a time to the growing end, always choosing the base that pairs with the next base on the template. Each new nucleotide is attached through a chemical group (a hydroxyl group on the sugar's 3′ carbon) that the next nucleotide will need in its turn. Sanger's trick was to add, alongside the normal building blocks, a small proportion of a modified nucleotide that lacked this group: a *dideoxynucleotide*. The polymerase accepts the modified nucleotide without complaint, but once it is in place nothing more can be attached. The chain stops.

Suppose the reaction contains plenty of all four normal nucleotides and a little dideoxy-A. Each time the polymerase reaches a T on the template it must insert an A, and it occasionally picks the dideoxy version and stops. Across billions of copies, the result is a collection of new strands that end at every position where an A belongs. Do the same in three other tubes with dideoxy-C, -G and -T, label the products, and separate each collection by size in a thin slab of polyacrylamide gel under an electric field, which pulls the negatively charged DNA through a tangle of polymer so that short strands travel faster than long ones and strands differing by a single base end up in different places. The four lanes, side by side, form a ladder, and the sequence can be read straight off it from bottom to top. In the 1970s and early 1980s the labels were radioactive, the gels were poured by hand between glass plates, the ladders were recorded on X-ray film, and the reading was done by a person with a ruler and a lightbox. A good read gave a few hundred bases.

The first step towards industrialisation came from the California Institute of Technology, in the laboratory of the biologist and inventor Leroy Hood. Hood had already led the development of automated machines for sequencing proteins and synthesising DNA, and a company, Applied Biosystems, had been formed in 1981 to sell them. Lloyd Smith, a young chemist with a doctorate in biophysics who joined Hood's laboratory in 1982, found manual sequencing laborious and repetitive, and set out to automate it. The key was colour. Instead of a radioactive label that looked the same in all four reactions, Smith attached a different fluorescent dye to the starting piece of DNA (the *primer*) used in each of the four reactions: derivatives of fluorescein, NBD, tetramethylrhodamine and Texas Red, which glow at different wavelengths from green through to red. The chemistry for attaching dyes to primers was published in 1985 by Smith with Sam Fung, the brothers Michael and Tim Hunkapiller and Hood. Because each reaction now had its own colour, all four could be run down a single lane, where a laser near the bottom of the gel excited the dyes as the bands passed and a detector fed the colours directly into a computer. The description appeared in *Nature* on 12 June 1986, and Applied Biosystems, where Michael Hunkapiller had been in charge of research and development since 1983, began selling a commercial version, the 370A, the same year. The company's patent for the detector describes an argon-ion laser operated at two wavelengths, 488 and 514.5 nanometres, and a spinning wheel of colour filters in front of a photomultiplier.

Two further changes turned this instrument into a factory machine. First, the dyes were moved from the primers to the dideoxynucleotides themselves, so that every chain carried a colour that announced how it ended and a single reaction tube did the work of four. Second, the slab gel was replaced by capillaries: hair-thin tubes of fused silica, filled with a polymer solution, through which DNA could be driven by much higher voltages because the narrow tubes shed heat quickly. Run ninety-six capillaries in parallel and refill them automatically between

runs, and a human is needed only to load plates of samples. The machine that did this for the Human Genome Project was the ABI Prism 3700, announced in 1998 by PE Biosystems, as Perkin-Elmer's Applied Biosystems business was then known. It analysed ninety-six samples at a time and, according to its makers, could complete up to sixteen runs a day. Its detector used a "sheath-flow" design, in which the DNA leaves the ends of the capillaries into a stream of fluid and is read there, away from the glass walls that would scatter the laser light; capillary-array instruments built on this principle had been developed independently by Norman Dovichi's group at the University of Alberta and by a group at Hitachi, and both designs were licensed to Applied Biosystems for the 3700.[3]

Reading was only half the problem. For putting the pieces back there were two broad strategies, and the argument between them shaped the project.

The first, *hierarchical* or *clone-by-clone* sequencing, broke the problem into manageable parts. The genome was first cut into large pieces, each a hundred thousand bases or more, which were inserted into *bacterial artificial chromosomes* (BACs) and grown in bacteria. The clones were then mapped: each was cut with enzymes to give a characteristic pattern of fragment sizes, a fingerprint, and clones with similar fingerprints were inferred to overlap. From the map, a set of clones that covered the genome with minimal overlap was chosen, and each clone was then broken into small fragments, sequenced at random and reassembled on its own. Because each clone came from one known place, a repeat inside it could only be confused with other repeats in the same hundred-odd thousand bases. The public project's 2001 paper drew on nearly thirty thousand such clones, which together contained 4.26 billion bases, an average of about 145,000 each.

The second strategy, *whole-genome shotgun* sequencing, skipped the map. The entire genome was broken at random into fragments of a few known sizes, both ends of each fragment were read, and the whole lot was assembled at once by computer. The paired reads from the two ends of a fragment, whose distance apart was approximately known, could tie together pieces separated by a repeat too long for a single read to cross. The method was cheaper and faster, because it dispensed with years of mapping. Whether it would work on a genome as large and repetitive as the human one was the question.

Science Primer: Coverage and gaps

Imagine scattering short reads at random along a genome. How many must you read before the whole thing is covered? In 1988 the mathematicians Eric Lander and Michael Waterman worked out the answer, originally for the problem of building maps from randomly chosen clones, and it applies equally to reads.

Let G be the length of the genome, L the length of each read, and N the number of reads. The *coverage* (or redundancy) is

$$c = \frac{LN}{G},$$

the average number of reads that cover any given base. If reads land independently at random, the number covering a particular base follows a Poisson distribution with mean

c, and the probability that a base is covered by no read at all is

$$P(\text{uncovered}) = e^{-c}.$$

At 1-fold coverage, $e^{-1} \approx 0.37$: more than a third of the genome is still unread, even though you have read as many letters as the genome contains. At 5-fold coverage, $e^{-5} \approx 0.0067$, so about 0.7 per cent is missing. For a human genome of 3×10^9 bases, that is still some twenty million unread bases.

The same reasoning predicts the number of gaps. With 500-base reads, 5-fold coverage needs $N = cG/L = 3 \times 10^7$ reads. A read ends a contiguous block (a *contig*) if no other read starts within its length, which happens with probability about e^{-c}, so the expected number of gaps is about $Ne^{-c} \approx 3 \times 10^7 \times 0.0067 \approx 200{,}000$, with an average length of $L/c = 100$ bases. At 8-fold coverage the uncovered fraction falls to about 0.03 per cent and the gaps to about sixteen thousand; at 10-fold, to under three thousand.

These figures are ideals. They assume reads fall uniformly at random and that every overlap, however short, can be detected; in practice some DNA does not clone or sequence well, overlaps must be tens of bases long to be trusted, and repeats create false joins. Real projects needed more coverage than the formula suggests, and directed "finishing" work to close the last gaps. But the arithmetic explains two numbers in this chapter: why the public consortium's first draft had more than 150,000 gaps, and why Celera, with about 5-fold coverage of its own, chose to combine its reads with the public data.[4]

Santa Cruz, Santa Fe and the Salk

The idea of reading the whole human genome occurred to several people at almost the same time, for quite different reasons.

The first to act on it was Robert Sinsheimer, a biophysicist who had spent twenty years at Caltech working on the small bacteriophage ϕX174 (in 1959 he had shown that its DNA was single-stranded, an exception to the rule that Chapter 7 describes) and who had become chancellor of the University of California, Santa Cruz, in 1977. Sinsheimer had watched physicists and astronomers ask for, and get, very large sums of money, and he wondered whether biology was missing opportunities simply because biologists did not think on that scale. He also had a practical reason. The University of California had received a gift of $36 million towards a ten-metre telescope which it was now obliged to return, and in November 1984 he wrote to the university's president suggesting that the money be used instead to found an institute at Santa Cruz to sequence the human genome. To test the idea he invited a dozen scientists from other institutions to a workshop on his campus, from the evening of Friday 24 May to the morning of Sunday 26 May 1985, under the title "Can We Sequence the Human Genome?" Among them were Walter Gilbert, Leroy Hood, David Botstein, George Church, John Sulston, Bart Barrell of Sanger's laboratory, Hans Lehrach and the mathematician Michael Waterman. By Sinsheimer's account they arrived extremely sceptical and left confident that the job could be done, though

not all of them were sure that it should be. The plan came to nothing: the money did not come to Santa Cruz, and Sinsheimer's institute was never built.

The idea surfaced next in print. On 7 March 1986, Renato Dulbecco of the Salk Institute, a Nobel laureate for his work on tumour viruses, published a short essay in *Science* arguing that cancer research had reached a turning point. Viruses had revealed the existence of cancer genes, he wrote, but could not explain how a normal cell progresses step by step to malignancy; for that, researchers needed to know all the cell's genes. He proposed sequencing the human genome as a national effort, one whose significance he compared to that of "the conquest of space," and suggested it would be better still as an international one.

The decisive push came from an unexpected direction. The United States Department of Energy was the descendant of the Atomic Energy Commission, and through its national laboratories it had funded research on the biological effects of radiation since the Manhattan Project. In December 1984 it had co-sponsored a meeting at Alta, in Utah, to ask whether the new techniques of DNA analysis could detect an increased rate of inherited mutation among the children of the survivors of Hiroshima and Nagasaki. The answer was no, not without an enormous programme. Charles DeLisi, a physicist by training who had joined the department in 1985 as director of its Office of Health and Environmental Research, read a draft report on the problem that autumn and concluded that the enormous programme was worth doing. If one human genome were sequenced as a reference, he reasoned, variation could be measured against it. In March 1986 his office held a workshop at Santa Fe, organised by Mark Bitensky of the Los Alamos National Laboratory, to assess the costs and feasibility. The delegates agreed on the scientific and medical value, argued about the cost (then put at $3 billion), the error rate and the large amount of non-coding DNA, and recommended setting up a steering committee to plan the work. DeLisi moved money within his budget and secured a dedicated line of $13 million in the federal budget submitted in January 1987.

To many biologists, the involvement of the weapons laboratories was not reassuring. The department's culture was that of physics: large machines, large budgets, managed teams, engineering milestones. Biology was funded mostly through the National Institutes of Health in small grants to individual investigators who chose their own problems. For a physicist, three billion base pairs was an instrumentation problem. For many biologists, it was an expensive way to collect data that nobody had asked a question about, most of it from DNA that was widely called "junk". The fear was that money for the project would come out of the grants that kept their laboratories alive, and that a generation of young scientists would be turned into technicians.

The argument was settled, as these things often are, by a committee. The National Research Council of the National Academy of Sciences convened one in 1986 under the biochemist Bruce Alberts, and its report, published in 1988, recommended that the project go ahead, but on biologists' terms. It called for new money, not money diverted from existing research, rising to $200 million a year, which over fifteen years it judged "would not be excessive". Mapping should come first, together with technology development and pilot projects; large-scale sequencing should wait until it became cheaper. Model organisms, such as yeast, worms, flies and mice,

should be studied in parallel, because the human genome would be uninterpretable without them. In effect, the report wrapped the physicists' vision in a biologists' programme.[5]

An Ethics Budget

The National Institutes of Health, more cautious than the Department of Energy at first, moved quickly once the report appeared. In 1988 it created an Office for Human Genome Research and appointed as its head one of the most famous biologists in the world. James Watson was sixty, director of Cold Spring Harbor Laboratory, and thirty-five years past the double helix. The Department of Energy and the NIH signed an agreement to cooperate in October 1988; the office became the National Center for Human Genome Research, with Watson as director, in October 1989; and the project officially began on 1 October 1990, with a target date for completion in 2005.

At a press conference on 1 October 1988, Watson was asked about the social implications of the project. According to the philosopher Eric Juengst, who later ran the programme that resulted, Watson answered by announcing on the spot that a share of the budget, somewhere between three and five per cent, would be set aside to study them. By most accounts it had no precedent in American science. The money would go not to laboratories but to philosophers, lawyers, historians, social scientists and clinicians, to examine what the knowledge would do to privacy, insurance, employment, medicine and the idea of human difference. The programme became known by its acronym, ELSI (Ethical, Legal and Social Implications). It was funded initially at three per cent of the NIH genome budget, a figure later raised to four and then five per cent.[6]

Watson knew the history of eugenics, which had flourished at Cold Spring Harbor itself in the early twentieth century, and the decision can be read both as conscience and as a shield against critics. Either way, it bought something new: social scientists embedded in a scientific project while the technology was still being built, rather than invited in afterwards to explain what had gone wrong.

The working group that planned the programme was chaired by Nancy Wexler, a clinical psychologist whose mother had developed Huntington's disease in 1968. Wexler had spent years among the families around Lake Maracaibo in Venezuela, where the disease was unusually common, collecting blood samples and building pedigrees. Samples from the Venezuelan families helped James Gusella's laboratory to find a genetic marker for the disease in 1983, and she helped to organise and lead the international collaboration, assembled by her father's Hereditary Disease Foundation, that found the gene itself in 1993. She knew from her own family what it meant to be able to test for a disease that could not be treated, and she brought that knowledge to the questions the programme asked: who should be told, who should be able to find out, and who should be prevented from using the answer.

Fragments and Patents

Watson's tenure ended against the background of a row about who owned the genome.

Craig Venter had come to science late. Born in 1946, he had served as a navy hospital corpsman at Danang during the Vietnam War, and went to university on his return. By the late 1980s he was running a laboratory at the National Institute of Neurological Disorders and Stroke, and was an early and enthusiastic user of Applied Biosystems' fluorescent sequencers. Rather than read genes slowly and completely, Venter read them quickly and partially. Genes that are active in a tissue are copied into messenger RNA; the RNA can be copied back into DNA, called cDNA; and reading a few hundred bases from one end of each cDNA gives a short, unique tag for an expressed gene. In June 1991 Venter and his colleagues reported tags from more than six hundred cDNA clones from the human brain, 337 of them from genes not previously known. They called them *expressed sequence tags*, or ESTs.

The NIH, with the support of its director, Bernadine Healy, filed patent applications on the tagged sequences: 337 of them in June 1991, followed by thousands more. The idea of patenting fragments of genes whose function was unknown outraged many genome scientists, Watson among them; he was reported to have called the decision "sheer lunacy". He argued that genes were products of nature, that a patent race would wreck international collaboration, and that the applications should never have been filed. The public quarrel soured his relations with Healy, but the immediate trigger for his departure was different: an NIH review, pressed by Healy, of his holdings in biotechnology companies, which raised questions of conflict of interest. On 10 April 1992 he resigned. The Patent and Trademark Office rejected the applications, in part because the function of the genes was unknown, issuing its final rejection in August 1993; in February 1994 Healy's successor, Harold Varmus, decided not to appeal and withdrew the rest.[7]

Venter left the NIH in 1992 to run a new non-profit institute, The Institute for Genomic Research (TIGR), in Gaithersburg, Maryland (it moved to nearby Rockville in 1995), funded with $70 million from the venture capital firm HealthCare Ventures in return for commercial rights to its discoveries, which went to a sister company, Human Genome Sciences.

Watson's successor arrived in April 1993. Francis Collins was a physician who had first trained as a physical chemist, taking a doctorate at Yale in 1974 before turning to medicine; at the University of Michigan he had helped to find the genes for cystic fibrosis in 1989 and, as part of the Huntington's collaboration, for Huntington's disease. He was a committed Christian who would later write a book about his faith, and a careful manager, and he would run the American side of the project for the next decade.

By then the project was becoming international in fact as well as in name. In Britain, the Wellcome Trust, a medical research charity, funded a new sequencing centre that opened in 1993 at Hinxton, south of Cambridge. It was named after Fred Sanger, and its director was John Sulston, a worm biologist who had traced the lineage of every cell in the nematode *Caenorhabditis elegans* and, with Robert Waterston of Washington University in St Louis, had spent a decade mapping and then sequencing its genome. The worm was the pilot for the human, and it brought the human project something besides technique: a culture. The worm community had long shared

its unpublished results through a newsletter, the *Worm Breeder's Gazette*, and Sulston and Waterston had grown used to releasing their data as soon as it was produced.

In February 1996, at the first International Strategy Meeting on Human Genome Sequencing, held at the Princess Hotel in Southampton, Bermuda, the leaders of the sequencing centres turned that habit into a rule. The *Bermuda Principles*, introduced and defended by Sulston and Waterston, required every centre funded for human sequencing to release its assembled sequence of more than a thousand bases into a public database automatically, preferably within twenty-four hours, and to make the finished, annotated sequence public at once. The rule helped centres coordinate and check each other's work, and it had a political purpose too. Sequence placed in the public domain the day it was produced could not be patented by anyone else on the strength of having read it. By early 1998 the principles had become formal funding policy.[8]

A Bacterium Read Whole

Meanwhile, at TIGR, Venter was doing something the public project had decided not to do. In collaboration with Hamilton Smith of Johns Hopkins, who had shared a Nobel Prize for the discovery of the restriction enzymes that cut DNA at specific sequences and had spent decades working on the bacterium *Haemophilus influenzae*, TIGR broke the bacterium's entire genome into random fragments, read about 24,000 of them, and assembled them by computer with no prior map. The assembly took thirty hours of computer time. The 140 gaps that remained were closed by directed work. On 28 July 1995 the team published the complete sequence of 1,830,137 base pairs, the first genome of a free-living organism ever read, with 1,743 predicted genes.

The demonstration was decisive for bacteria, which have small genomes and few repeats. Whether it would scale to the human genome was a different matter, and in May 1997 the journal *Genome Research* printed the two sides of the argument back to back. James Weber, a geneticist, and Gene Myers, a computer scientist at the University of Arizona, proposed a whole-genome shotgun for the human genome: read both ends of tens of millions of random fragments of several different lengths to about ten-fold coverage and let the paired ends resolve the repeats. Phil Green of the University of Washington replied that a whole-genome shotgun was less likely to succeed than the clone-by-clone approach and offered no compensating advantage, such as lower cost; the clone-based method, he pointed out, also let different centres try different strategies on their own clones without duplicating each other's work. Behind the argument lay the repeats. A misassembly in a clone could be found and fixed within that clone; in a genome assembled all at once, a false join could link pieces from different chromosomes.[9]

Green's authority on the point was considerable, because he had written much of the software that the public project used to turn raw traces into reliable sequence. His program *phred*, developed with Brent Ewing and colleagues, read the signal from a fluorescent sequencer and called the bases, and his program *phrap* assembled the reads. Phred's most influential feature was not its accuracy but its honesty: for every base it called, it estimated the probability that the call was wrong.

Science Primer: What a quality score means

A sequencing machine does not see letters. It sees four overlapping traces of fluorescent intensity, one for each dye, rising and falling as bands pass the detector. Usually one peak clearly dominates and the call is easy. Sometimes peaks are small, crowded, or of two colours at once, and the call is a guess. Phred measured features of the trace around each peak (how evenly spaced the peaks were, how much the competing colours intruded) and, by calibrating against reads of known sequence, converted them into an estimated error probability p for each base. It reported this as a *quality score*:

$$Q = -10 \log_{10} p.$$

The logarithm turns a probability spanning many orders of magnitude into a convenient number. A base with a one-in-ten chance of being wrong has $Q = 10$; one in a hundred, $Q = 20$; one in a thousand, $Q = 30$; one in ten thousand, $Q = 40$. Each additional ten points means ten times fewer errors.

Quality scores made sequence data accountable. They allow simple arithmetic: the expected number of errors in a read is the sum of its error probabilities, so a 500-base read in which 400 bases have $Q = 30$ and 100 have $Q = 15$ (where $p \approx 0.03$) should contain about $400 \times 0.001 + 100 \times 0.0316 \approx 3.6$ errors, almost all of them in the poorer stretch. They allowed an assembler such as phrap to prefer the high-quality read where two reads disagreed. And they let the project set standards that could be checked. The public consortium aimed for a finished sequence with fewer than one error in ten thousand bases, the equivalent of $Q40$ across the whole genome; the finished sequence of 2004 achieved about one error in a hundred thousand. The "phred score" outlived the machines it was designed for: every modern sequencing instrument reports its output on the same scale, and NHGRI's cost figures count capillary-sequencer bases only at $Q20$ or better.[10]

The Factory in Rockville

By 1998 the public project was on schedule for its maps and behind on its sequence. Only a small fraction of the human genome had been sequenced, and the planned completion date of 2005 looked hard to meet. In May 1998 the ground moved.

The instrument company Perkin-Elmer, which had absorbed Applied Biosystems in 1993, was about to launch the ABI 3700. Michael Hunkapiller, now head of its Applied Biosystems division, and the company's chief executive, Tony White, approached Venter with a proposal: a new company, eighty per cent owned by Perkin-Elmer, that would buy its new machines in bulk and use them to sequence the human genome by whole-genome shotgun in three years. Perkin-Elmer, Venter and TIGR announced letters of intent on Saturday 9 May 1998, and explained the plan at a press conference on Monday 11 May. It would be based in Rockville; it would install between two hundred and 230 of the new sequencers, at $300,000 each; it would sequence for about a fifth of the public project's cost per base; and it would make its data available, though

on its own terms, and seek patents on a few hundred genes. The company was soon named Celera Genomics.

Venter recruited Gene Myers from Arizona to build the assembler. Myers was one of the authors of the 1990 paper describing BLAST, which became one of the most widely used programs in biology for searching sequence databases, and he had argued for the human shotgun in print a year earlier. Now he would have to make it work, on a computer installation that Venter later described as some eight hundred Compaq Alpha processors with more than eighty terabytes of storage. Venter's argument was blunt: the public project's careful method was too slow, and a company with enough machines and enough computing could beat it.

The public response came within days. On 13 May 1998 the Wellcome Trust announced an extra £110 million for the Sanger Centre, bringing its total commitment to £205 million and doubling the share of the genome the centre would sequence, from a sixth to a third. The NIH accelerated its own programme, and in the spring of 1999 three American centres, the Whitehead Institute, Washington University and Baylor College of Medicine, ordered 162 of the same ABI 3700 machines that Celera was using. In March 1999, with its pilot phase over, the consortium launched full-scale production, aiming first at a "working draft": each clone read only roughly, enough to place most of its sequence, with finishing to come later. The production effort was concentrated in five large centres, known as the G5: the Sanger Centre, the Whitehead Institute (where Eric Lander, a mathematician who had taught managerial economics at Harvard Business School before turning to genetics, ran the genome centre), Washington University, Baylor College of Medicine in Houston, and the Department of Energy's Joint Genome Institute in Walnut Creek, California. Fifteen other centres in the United States, Japan, France, Germany and China made up the rest. China's share, about one per cent of the genome near the tip of the short arm of chromosome 3, was agreed in the late summer of 1999 at a strategy meeting near Cambridge, and the newly founded Beijing Genomics Institute began sequencing that autumn.

The two efforts were not entirely separate. Because of the Bermuda Principles, every base the public centres read appeared in GenBank within a day, where Celera could download it, and did. Celera's data, by contrast, stayed in Rockville. The asymmetry was a lasting source of bitterness.

The first test of Celera's method was the fruit fly. Gerald Rubin, who led the Berkeley Drosophila Genome Project, agreed to collaborate with Celera on the fly genome, whose euchromatic portion of about 120 million base pairs was some twenty-five times smaller than the human genome. Celera generated more than three million reads, finishing the sequencing in September 1999, and in November that year it held an "annotation jamboree", at which fly biologists and Celera's computational staff worked side by side to identify the genes. The genome was published in *Science* on 24 March 2000, with about 13,600 genes. Myers's assembler had worked. The assembly also drew on the Berkeley group's clone-based sequence and map, and critics noted that the fly was much simpler than the human. But it was no longer possible to say that a whole-genome shotgun of an animal could not be done.[11]

A Truce Over Pizza

By the spring of 2000 the race had become a matter of politics. On 14 March, Bill Clinton and Tony Blair issued a joint statement calling for the raw data of the human genome to be made freely available to scientists everywhere. Markets read the statement as a threat to companies whose value lay in owning genetic information. Celera's shares fell by a quarter that day, and the Nasdaq index of biotechnology stocks lost more than twelve per cent.

The White House wanted a joint announcement rather than a public brawl. The broker was Aristides Patrinos, who ran the Department of Energy's genome programme. Beginning on 7 May 2000 he arranged a series of secret meetings between Collins and Venter at his home, where, as Collins recalled at the White House press briefing in June, he served beer and pizza. The two men agreed to announce their drafts together and to publish their analyses at about the same time.

The announcement was made on 26 June 2000 in the East Room of the White House, with Collins and Venter both present and speaking, while Tony Blair joined by satellite from Downing Street, where he was accompanied by Fred Sanger. Clinton called the genome the most important and most wondrous map ever produced by humankind, and said that scientists were "learning the language in which God created life." He predicted that doctors would increasingly cure diseases such as Alzheimer's, Parkinson's, diabetes and cancer by attacking their genetic roots, and joked that the life expectancy of Blair's newborn son had just risen by twenty-five years. He also observed that all human beings, regardless of race, are more than 99.9 per cent the same.[12]

What had actually been achieved was less than the ceremony suggested, and the scientists said so. The public working draft covered about ninety per cent of the genome, with more than 150,000 gaps; Celera's assembly was a day old; and neither had been published or checked by outsiders. On 7 July, Haussler and Kent posted the public assembly on the internet from Santa Cruz; on the first day, about half a trillion bytes of data flowed out of the university's servers to laboratories around the world.

Two Papers, Two Journals

The papers appeared in February 2001, in different journals and on different terms. The International Human Genome Sequencing Consortium published its draft and analysis in *Nature* on 15 February, in a sixty-two-page paper with Eric Lander as first author and a byline running to hundreds of names. It described a collaboration of twenty groups in six countries, a draft covering about 94 per cent of the genome, and an estimate of 30,000 to 40,000 protein-coding genes; it also credited GigAssembler, by name, for merging the clones into a draft sequence. Celera's paper, with Venter as first author, appeared in *Science* the next day. It reported 27 million reads from the DNA of five individuals, giving about 5.1-fold coverage, and a consensus of 2.91 billion base pairs of euchromatin. About 26,600 genes had strong supporting evidence and some 12,000 more were predicted with weaker support.

The papers settled less than they appeared to. Celera's assemblies had not been made from its own reads alone: it had downloaded the public data, broken the public assembled sequence into artificial 550-base fragments, and combined them with its own reads to give an effective coverage of about eight-fold. In 2002 Robert Waterston, Eric Lander and John Sulston argued in the *Proceedings of the National Academy of Sciences* that this meant Celera's paper was not a test of the whole-genome shotgun at all, because the public data had supplied the long-range order and much of the sequence. Myers, Venter and their colleagues replied in the same journal that the public sequence had been delivered as hundreds of thousands of unordered fragments, and that Celera's paired reads had put them in order. Both sides had a point. The arithmetic of the Lander–Waterman formula shows why Celera's own five-fold coverage, with reads of about 550 bases, would have left well over a hundred thousand gaps between contigs, and why each side needed something the other had.

The terms of publication were another battle. *Science* agreed to publish Celera's paper without requiring its sequence to be deposited in GenBank, the condition normally imposed. Publicly funded scientists could instead download up to a million bases at a time from Celera's website without signing an agreement; commercial users had to sign an agreement barring them from commercialising results or redistributing the data. Harold Varmus, the former NIH director, questioned whether a journal should publish a paper without full access to its data, and Bruce Alberts, by then president of the National Academy of Sciences, called the terms for private users unworkable.[13] In January 2002 Venter left Celera, reportedly forced out by the parent company as it turned from selling data to developing drugs. In April he revealed that the DNA Celera had sequenced was largely his own, though it had been described as coming from anonymous donors. He later founded the J. Craig Venter Institute, and died in San Diego on 29 April 2026, aged seventy-nine.[14]

The public project carried on to finish its sequence. On 14 April 2003, in the month of the fiftieth anniversary of Watson and Crick's paper, the consortium declared the Human Genome Project complete, two years ahead of its original schedule. The "essentially complete" sequence covered about 92 per cent of the genome, with fewer than four hundred gaps. The total American funding for the project, including mapping, technology development and the ELSI programme, was about $2.7 billion. The consortium's paper describing the finished sequence, published in October 2004, reported 2.85 billion bases of euchromatin in 341 gaps, with about one error per hundred thousand bases, and lowered the estimate of protein-coding genes to between 20,000 and 25,000.

"Complete" was a term of art. The finished sequence omitted the heterochromatin, the densely packed, highly repetitive regions around centromeres and at the ends of some chromosomes, and most of the hardest duplicated regions. These were not filled until 2022, when an international Telomere-to-Telomere (T2T) Consortium, using new instruments that read single DNA molecules tens of thousands of bases long, published a gapless sequence of every chromosome except Y. It added nearly two hundred million base pairs, including all the centromeric satellite arrays and the short arms of five chromosomes, and found 1,956 gene predictions in the new sequence, 99 of them for proteins. The DNA came from a cell line derived from a hydatidiform mole, an abnormal growth in which both copies of each chromosome come from the

same father and are therefore identical, so that there was only one version of each to assemble. The Y chromosome followed in 2023.[15]

Outcomes and Legacy

The gene count. When the project was planned, the number of human genes was commonly put at around 100,000, with estimates ranging from about 80,000 to 140,000. The public draft of 2001 suggested 30,000 to 40,000; the finished sequence of 2004 suggested 20,000 to 25,000; and analyses since have settled at about 20,000 protein-coding genes, perhaps fewer, similar to the number in a mouse or a nematode worm. At the Cold Spring Harbor genome meeting in May 2000, the bioinformaticians Ewan Birney and David Stewart had opened a betting pool, GeneSweep, on the final count. In 2003, against an official count of 24,847, the prize went to Lee Rowen of the Institute for Systems Biology, whose guess was 25,947; she shared it with two others who had bet below 30,000. Complexity, it seemed, lay less in the number of parts than in how they are controlled and combined.

The collapse in cost. The most consequential legacy of the project was not its sequence but its effect on the price of sequencing. In 2005 the company 454 Life Sciences described a machine that read hundreds of thousands of DNA fragments in parallel in tiny wells on a plate, and in 2008 a team using its machines sequenced James Watson's genome for less than $1 million in about two months. In Cambridge, the chemists Shankar Balasubramanian and David Klenerman had founded Solexa to develop a method in which millions of DNA fragments, anchored to a glass surface, are copied one base at a time with fluorescent reversible terminators, a chemical descendant of Sanger's chain-stoppers that is unblocked after each base is imaged. Illumina bought Solexa in 2007, and in 2008 its machine sequenced the genome of a Yoruba man from Ibadan, Nigeria, to more than 30-fold coverage using reads of just thirty-five bases.[16] The reads were short and individually unreliable, but they were so numerous and so cheap that a genome could be read many times over and aligned against the reference that the Human Genome Project had produced. The reference was what made short reads useful. In January 2014 Illumina announced a system that it said could produce a 30-fold human genome for less than $1,000, including instrument depreciation, sample preparation and labour; on 29 September 2022 it claimed $200 for its newest machines running at full capacity.

Science Primer: Reading the cost curve

Figure 11.1 uses a logarithmic vertical axis, on which each gridline is ten times the one below. On such a scale a quantity that falls by a constant fraction each year traces a straight line, and a steeper line means a faster fall.

The dashed line shows what would have happened if sequencing had become cheaper at the pace of the computer industry. *Moore's law* is the observation, first made by Gordon Moore of Intel, that the number of transistors on a chip doubled at a regular interval, usually quoted as two years, so that the cost of computing halved on roughly the same

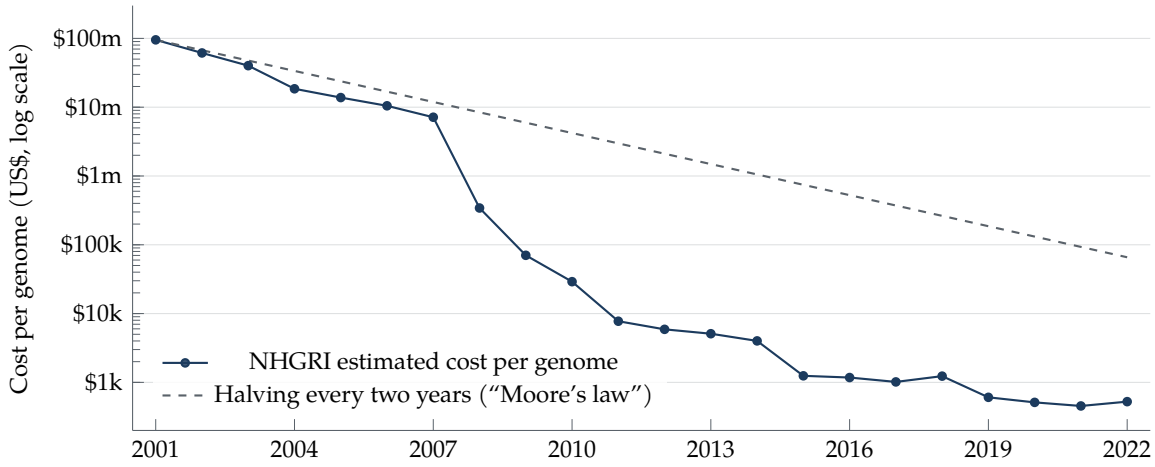


Figure 11.1: The estimated production cost of sequencing a human genome at NHGRI-funded centres, 2001–2022, against a hypothetical cost that halves every two years from the 2001 value. The steep fall after 2007 marks the change from capillary instruments to second-generation machines. Values are in current dollars, not adjusted for inflation, as compiled annually by Our World in Data (`https://ourworldindata.org/grapher/cost-of-sequencing-a-full-human-genome`) from K. A. Wetterstrand, “DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program,” `https://www.genome.gov/sequencingcostsdata`. The dashed line is my calculation.

schedule. Starting from NHGRI’s 2001 estimate of about $95 million, halving every two years for twenty-one years gives

$$\$95{,}000{,}000 \times 2^{-21/2} \approx \frac{\$95{,}000{,}000}{1{,}450} \approx \$66{,}000.$$

The actual estimate for 2022 was about $525, more than a hundred times lower. From 2001 to 2007, while sequencing still used capillary machines, the cost fell from $95 million to about $7 million, halving roughly every nineteen months, close to Moore’s pace. Between 2007 and 2011 it fell by a factor of nearly a thousand.

Two cautions apply. The figures are NHGRI’s estimates of production costs at the centres it funds (reagents, labour, instruments written off over three years, data submission) and exclude much else, including analysis. And they are not like-for-like. Until 2007 they assume a fresh genome read to six-fold coverage with Sanger’s method; from 2008 they assume a genome read to ten- to thirty-fold coverage on the new machines and aligned to the existing reference, a much easier task than assembling one from scratch. The 2001 figure is the estimated cost of a genome at that moment’s prices, not the cost of the Human Genome Project, whose sequencing NHGRI puts at somewhere between $500 million and $1 billion.[17]

Variation and disease. The reference genome was a starting point for measuring difference. The International HapMap Project, launched in October 2002 with partners in six countries, catalogued common variants and the blocks in which they are inherited together, beginning with 269 people from four populations. The 1000 Genomes Project, which ran from 2008 to

2015, sequenced 2,504 people from twenty-six populations. These catalogues made possible the *genome-wide association study*, in which hundreds of thousands of variants are tested at once for association with a disease. Thousands of associations have been found, but most have small effects, and together they explained less of the heritability of common diseases than was hoped.

The function of the rest. In September 2012 the ENCODE consortium, a large NHGRI-funded effort to map the functional elements of the genome, reported that 80.4 per cent of the genome participated in at least one biochemical event, such as being transcribed or bound by a protein, in at least one type of cell. The press widely reported this as the death of junk DNA. Evolutionary biologists objected that biochemical activity is not the same as function: a stretch of DNA can be copied into RNA by accident, and only a small fraction of the genome, under ten per cent by many estimates, shows the signs of having been conserved by natural selection. It was a collision between two disciplines' definitions of the same word.[18]

Personal genomics. The falling cost of reading DNA created a consumer industry. The best known of its companies, 23andMe, founded in 2006, sold saliva kits that genotyped hundreds of thousands of variants, and by 2024 it had tested more than fourteen million people. Its history traced the field's difficulties: an order from the US Food and Drug Administration in 2013 to stop marketing health reports until they had been reviewed, and a data breach, disclosed in 2023, that exposed information on about 6.9 million customers. On 23 March 2025 the company filed for Chapter 11 bankruptcy protection, and its co-founder Anne Wojcicki resigned as chief executive. The drug company Regeneron won an initial auction with a bid of $256 million, but after the auction was reopened, a non-profit organisation led by Wojcicki, the TTAM Research Institute, won with $305 million; a bankruptcy judge approved the sale in late June despite objections from several states, and it closed in July 2025. State attorneys general had urged customers to delete their data, and some did. The episode made concrete an old ELSI question: what happens to genetic data, which cannot be changed and is shared with relatives, when the company holding it fails.[19]

The clinic and the newborn. The genome's slower but more lasting effects have been in medicine. Sequencing the genome or exome of a child with an undiagnosed condition has become a standard test for rare diseases in many health systems, and tumour sequencing guides the treatment of many cancers. In October 2024 Genomics England, with NHS England, began the Generation Study, which aims to sequence the genomes of up to 100,000 newborn babies and screen them for more than two hundred rare conditions that can be treated in early childhood. It raises exactly the questions about consent and the right not to know that Nancy Wexler's working group set out to study in 1989.

From reference to pangenome. The reference genome was a mosaic: about seventy per cent of it came from a single anonymous donor from Buffalo, New York, and the rest from about nineteen others, most of European ancestry. In May 2023 the Human Pangenome Reference Consortium published a first draft of a *pangenome*, built from complete assemblies of both chromosome sets of forty-seven genetically diverse people, which represents the genome as a graph of alternative paths rather than a single line. It added about 119 million base pairs of sequence absent from the standard reference.[20]

A new discipline. Finally, the project turned a small specialty into a discipline. Bioinformatics existed before 1990, but within a decade it had its own departments and degree programmes; Charles DeLisi, by then at Boston University, started one of the first American doctoral programmes in the subject in 1999. The Genome Browser that Kent wrote in the months after GigAssembler, a web page on which any stretch of the genome can be viewed with genes, variants and repeats stacked beneath it, was serving some 150,000 users by 2015; with Ensembl, built at the European Bioinformatics Institute and the Sanger Institute, it became permanent infrastructure for biology. The protein structures that Chapter 12 describes could not have been predicted without the sequence databases that this industry filled.

Table 11.1: Some of the disciplines that met in the Human Genome Project

Discipline	Representative people	Contribution
Biochemistry and molecular genetics	Frederick Sanger, John Sulston, Robert Waterston, Francis Collins	Chain-termination sequencing; clone maps; the worm as pilot; disease-gene hunting.
Chemistry, optics and instrument engineering	Leroy Hood, Lloyd Smith, Michael Hunkapiller, Norman Dovichi	Fluorescent dye labels; laser detection; capillary arrays; the ABI 3700.
Mathematics, statistics and computer science	Eric Lander, Michael Waterman, Phil Green, Gene Myers, David Haussler, Jim Kent	Coverage statistics; phred quality scores and phrap; shotgun assembly; GigAssembler; the genome browser.
Ethics programme: founders and practitioners	James Watson, Nancy Wexler, Eric Juengst	The ELSI programme; research on genetic testing, privacy and insurance.
Science policy and administration	Charles DeLisi, Bruce Alberts, Aristides Patrinos	The Department of Energy's initiative; the 1988 report; brokering the 2000 truce.

The Costs of Crossing

The Human Genome Project is the largest example in this book of what we have called a trading zone: a place where biologists, chemists, engineers, mathematicians, programmers and ethicists exchanged what each had for what each needed, without fully sharing each other's assumptions. It worked. But it also shows what such exchanges cost, and four costs stand out.

Promises made in another discipline's currency. The project was sold to legislators in the language of medicine: cures for cancer, Alzheimer's and diabetes, the "book of life" read at last. That language was useful, because medicine was what Congress would pay for, but it was a promise made by geneticists on behalf of clinicians, and it was not theirs to keep. A decade after the White House ceremony, Collins himself wrote in *Nature* that the consequences for clinical medicine had "thus far been modest," and that the genome had not yet directly affected the health care of most people. Most common diseases turned out to depend on many variants of small effect, and knowing a gene's sequence does not tell you how to fix it. Real benefits came

later and more narrowly, in rare-disease diagnosis, cancer and pharmacology. A project that crosses borders to get funded may have to borrow another field's promises, and the debt falls due.[21]

Who owns what was read. The project's openness was won, not given. The NIH's own attempt to patent gene fragments set it publicly against the project's first director in the months before his resignation. Celera's restricted data led to a feud that consumed years of effort: two assemblies built in parallel, a publication deal that bent a journal's rules, and accusations in print that still colour the history. Whether the competition shortened the project, as Celera's defenders say, or the public plan of 1998 would have finished early anyway, is still argued. The larger question of ownership was settled not by scientists but by courts. On 13 June 2013, in *Association for Molecular Pathology v. Myriad Genetics*, the US Supreme Court ruled unanimously, in an opinion by Justice Clarence Thomas, that a naturally occurring DNA sequence is not patentable merely because it has been isolated, though synthetic complementary DNA can be. The ruling ended Myriad's exclusive control over testing for the breast-cancer genes *BRCA1* and *BRCA2*, more than two decades after Watson had denounced the NIH's own gene-fragment patents.[22]

An ethics experiment with mixed results. ELSI was a genuine innovation, and it produced a body of research on genetic testing, counselling, privacy and discrimination that shaped policy. Its most concrete legislative descendant, the Genetic Information Nondiscrimination Act, was introduced in Congress in 1995 and signed into law only on 21 May 2008. It forbids the use of genetic information by health insurers and by employers, but it does not cover life insurance, disability insurance or long-term-care insurance, it does not apply to employers with fewer than fifteen staff, and it does not bind the military. The project's own practices were not always exemplary either. The volunteers who gave blood in Buffalo in 1997 signed consent forms saying that no more than ten per cent of the final sequence was expected to come from any one donor; partly for technical reasons and partly under the time pressure of Celera's challenge, the consortium drew most of its sequence from a single library, and that one person's DNA makes up more than seventy per cent of the reference. In October 1998 the Roswell Park Cancer Institute's review board, which oversaw the donations, voted not to try to recontact the donors. The best-known consent failure of the period lay outside the project but inside its field. Between 1990 and 1992, researchers at Arizona State University collected blood from more than two hundred members of the Havasupai Tribe, who live in the Grand Canyon, for a study of diabetes. The samples were later used, without further consent, for studies of schizophrenia, inbreeding and the population's ancient migration from Asia, which contradicted the tribe's own account of its origins. Members of the tribe sued in 2004, and in April 2010 the Arizona Board of Regents settled, paying $700,000 to forty-one members and returning the samples. The ethicists had seen such problems coming; that did not prevent them.[23]

Whose genome, and whose science? Two fears accompanied the project from its start, and they were borne out to different degrees. The first was that genomics would be built on a narrow slice of humanity. It was. A 2016 analysis found that 81 per cent of participants in genome-wide association studies were of European ancestry, against 96 per cent in 2009; much of the remainder was of Asian ancestry, and only about 3 per cent were of African ancestry, which means that genetic risk predictions work best for the people who were already best served by

medicine. The pangenome and newer programmes are attempts to repair this, but the imbalance was built into the databases for two decades. The second fear was that big science would starve small laboratories. In 1990 the Utah biochemist Martin Rechsteiner mailed hundreds of letters to colleagues under the heading "Mediocre Science, Terrible Science Policy," and Harvard's department of microbiology asked one of its members, Bernard Davis, to call publicly for the project to be re-evaluated.[24] In money, the fear was largely unfounded: NHGRI's budget request for 2003 was about $467 million, under two per cent of an NIH budget that had doubled between 1998 and 2003 to some $27 billion. In culture it was partly realised. The project concentrated sequencing in a handful of very large centres, run like factories by managers, and that model has persisted in the institutes that succeeded them. Small laboratories now depend on the data such centres produce.

Coda

Jim Kent's assembler did the job it was written for. What lasted was the browser he wrote next, and the habit it embodied: put everything on the web, at once, for anyone. The Bermuda Principles had come from worm biologists swapping notes in a newsletter; the browser came from an animation programmer who had learned biology in middle age; the quality scores came from Phil Green's group in Seattle; the machines came from a chemist who found manual sequencing tedious and an industrial company that saw a market. None of them could have read the genome alone, and the project's most consequential decisions, about openness, patents and consent, were taken by people who were not sequencing anything at all. When the T2T consortium filled the last gaps in 2022, it did so with machines that read single molecules tens of thousands of bases long, reads that cross most repeats whole. With such reads, much of this chapter's argument over assembly would never have arisen; the arguments over ownership and consent would have arisen anyway.

Notes

[1]On Kent's work, see Nicholas Wade, "Grad Student Becomes Gene Effort's Unlikely Hero," *New York Times*, 13 February 2001; and Peggy Townsend, "A Visionary, a Genius, and the Human Genome," UC Santa Cruz News, 22 June 2015, https://news.ucsc.edu/2015/06/genome-anniversary/. Accounts of the computer cluster differ: Wade reports 100 Pentium III machines bought for about $250,000; the UCSC account says 100 Dell workstations were assembled for the project, about 30 of them bought at first and the rest diverted from student use; and an article in *Dr. Dobb's Journal*, "Some Assembly Required," June 2001, gives a cost of about $500,000. Venter's description of the public data is from his prepared testimony to Congress of 6 April 2000, https://clintonwhitehouse4.archives.gov/WH/EOP/OSTP/html/00626_4.html. The program itself is described in W. James Kent and David Haussler, "Assembly of the Working Draft of the Human Genome with GigAssembler," *Genome Research* 11, no. 9 (2001): 1541–48. Popular retellings sometimes add frozen peas and a diagnosis of carpal tunnel syndrome; the contemporary sources say only that he iced his wrists.

[2]International Human Genome Sequencing Consortium, "Initial Sequencing and Analysis of the Hu-

man Genome," *Nature* 409 (2001): 860–921, which estimated that about half the genome derives from transposable elements. The figures for Alu and LINE elements are from the same paper and later summaries of it; the size of the exome is from the National Human Genome Research Institute's fact sheet "The Cost of Sequencing a Human Genome," https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost.

[3]Allan M. Maxam and Walter Gilbert, "A New Method for Sequencing DNA," *Proceedings of the National Academy of Sciences* 74, no. 2 (1977): 560–64; F. Sanger, S. Nicklen, and A. R. Coulson, "DNA Sequencing with Chain-Terminating Inhibitors," *Proceedings of the National Academy of Sciences* 74, no. 12 (1977): 5463–67. Gilbert and Sanger shared half of the 1980 Nobel Prize in Chemistry for this work; Sanger had already won the 1958 prize, unshared, for the structure of insulin. Lloyd M. Smith et al., "Fluorescence Detection in Automated DNA Sequence Analysis," *Nature* 321 (1986): 674–79; Lloyd M. Smith, Sam Fung, Michael W. Hunkapiller, Timothy J. Hunkapiller, and Leroy E. Hood, "The Synthesis of Oligonucleotides Containing an Aliphatic Amino Group at the 5′ Terminus: Synthesis of Fluorescent DNA Primers for Use in DNA Sequence Analysis," *Nucleic Acids Research* 13, no. 7 (1985): 2399–2412. The laser and filter-wheel detector are described in Applied Biosystems' US Patent 4,811,218 (filed 1986). On Smith's motives, see Brendan Maher, "The First Automated DNA Sequencer," *The Scientist*, February 2006. The 3700 is described in a PE Biosystems product announcement in *Journal of the Association for Laboratory Automation* 3, no. 5 (1998); its throughput figures are the manufacturer's. On the sheath-flow detector, see Hitachi's research history, https://www.hitachi.com/rd/research/healthcare/genome/index.html; and "Norman Dovichi: Singing the Praises of the Unsung Hero," *Chemistry World*, https://www.chemistryworld.com/news/norman-dovichi-singing-the-praises-of-the-unsung-hero/6001.article.

[4]Eric S. Lander and Michael S. Waterman, "Genomic Mapping by Fingerprinting Random Clones: A Mathematical Analysis," *Genomics* 2 (1988): 231–39. The uncovered fraction e^{-c} follows from the same Poisson model; the worked numbers are my calculations, taking every overlap as detectable.

[5]Robert L. Sinsheimer, "To Reveal the Genomes," *American Journal of Human Genetics* 79, no. 2 (2006): 194–96; Robert L. Sinsheimer, "Historical Sketch: The Santa Cruz Workshop—May 1985," *Genomics* 5, no. 4 (1989): 954–56, reproduced with the list of the eighteen participants at https://genomics.ucsc.edu/?p=211118. Renato Dulbecco, "A Turning Point in Cancer Research: Sequencing the Human Genome," *Science* 231 (1986): 1055–56. Charles DeLisi, "Santa Fe 1986: Human Genome Baby-Steps," *Nature* 455 (2008): 876–77; on the Alta meeting, see the Department of Energy's Human Genome Project archive, https://doe-humangenomeproject.ornl.gov. National Research Council, Committee on Mapping and Sequencing the Human Genome, *Mapping and Sequencing the Human Genome* (Washington, DC: National Academy Press, 1988).

[6]On the announcement, see Eric T. Juengst, "Self-Critical Federal Science? The Ethics Experiment within the U.S. Human Genome Project," *Social Philosophy and Policy* 13, no. 2 (1996): 63–95; Juengst was chief of the ELSI branch at the National Center for Human Genome Research from 1990 to 1994. On the later increases, see Lisa Gannett, "The Human Genome Project," *Stanford Encyclopedia of Philosophy*, https://plato.stanford.edu/entries/human-genome/.

[7]Mark D. Adams et al., "Complementary DNA Sequencing: Expressed Sequence Tags and Human Genome Project," *Science* 252 (1991): 1651–56. David C. Holzman, report in *BioWorld Today*, 14 February 1994, https://www.bioworld.com/articles/490330; on Watson's criticism of the patent filings and the review of his shareholdings, see the same journal's report of 9 April 1992, https://www.bioworld.com/articles/494026; Watson's letter of resignation to Healy, dated 10 April 1992, is in the NHGRI archive, https://www.genome.gov. The fullest account of these years is Robert Cook-Deegan, *The Gene Wars: Science, Politics, and the Human Genome* (New York: W. W. Norton, 1994).

[8]Kathryn Maxson Jones, Rachel A. Ankeny, and Robert Cook-Deegan, "The Bermuda Triangle: The Pragmatics, Policies, and Principles for Data Sharing in the History of the Human Genome Project," *Journal of the History of Biology* 51, no. 4 (2018): 693–805.

[9]Robert D. Fleischmann et al., "Whole-Genome Random Sequencing and Assembly of *Haemophilus influenzae* Rd," *Science* 269 (1995): 496–512. James L. Weber and Eugene W. Myers, "Human Whole-Genome Shotgun Sequencing," *Genome Research* 7, no. 5 (1997): 401–9; Philip Green, "Against a Whole-Genome Shotgun," *Genome Research* 7, no. 5 (1997): 410–17.

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Further Reading

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John Sulston and Georgina Ferry, *The Common Thread: A Story of Science, Politics, Ethics and the Human Genome* (Joseph Henry Press, 2002). Sulston's account of the worm, the Sanger Centre, Bermuda and the race, written from the public side and unapologetic about it.

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J. Craig Venter, *A Life Decoded: My Genome, My Life* (Viking, 2007). Venter's autobiography. Partisan, as one would expect, but informative on ESTs, TIGR and *Haemophilus*.

Kevin Davies, *Cracking the Genome: Inside the Race to Unlock Human DNA* (Free Press, 2001). A contemporary narrative of the race by the founding editor of *Nature Genetics*, written while the dust was still settling.

Stephen Hilgartner, *Reordering Life: Knowledge and Control in the Genomics Revolution* (MIT Press, 2017). A sociologist's analysis of how the project redistributed control over data, credit and ownership. Demanding but rewarding.

Kathryn Maxson Jones, Rachel A. Ankeny, and Robert Cook-Deegan, "The Bermuda Triangle: The Pragmatics, Policies, and Principles for Data Sharing in the History of the Human Genome Project," *Journal of the History of Biology* 51, no. 4 (2018): 693–805. The definitive study of the Bermuda Principles, drawing on archives and interviews.

Online: NHGRI's history pages and oral histories, `https://www.genome.gov/human-genome-project`, which include a detailed timeline and digitised archival documents; and the UCSC Genome Browser itself, `https://genome.ucsc.edu`, still the easiest way to see what the sequence looks like.

Chapter 12

Folding the Unfoldable: From Rosetta to AlphaFold (1961–2024)

Group 427

In August 2020, in the middle of a pandemic, the people who judge the world's protein-structure predictions met online to look at the season's early results. The competition they ran, the Critical Assessment of protein Structure Prediction, or CASP, had been held every two years since 1994, and it worked on a simple principle: the assessors judged the predictions without knowing who had made them. Each entrant was a number. That summer one number, group 427, was producing models of proteins whose structures had not yet been published that matched the experimental answers more closely than anything the assessors had seen. One of them, Nick Grishin, remarked to his colleagues that the group had either come close to solving the folding problem or found some way to cheat.

Another assessor, Andrei Lupas of the Max Planck Institute for Developmental Biology in Tübingen, had a way to find out which. His laboratory had spent close to ten years trying to determine the structure of Af1503, a receptor that sits in the membrane of an archaeon, *Archaeoglobus fulgidus*, a heat-loving microbe. They had good X-ray diffraction data, but they could not turn the data into a structure. The protein had been entered in CASP as target T1100. Lupas's group took group 427's predictions and tried them as starting points for the calculation that had defeated them. The structure came out. "The model from group 427 gave us our structure in half an hour," Lupas later told *Nature*.

The organisers kept the secret until the conference itself, which opened on Monday 30 November 2020 on Zoom, Discord and AirMeet rather than in a hotel ballroom, with nearly a hundred research groups who between them had submitted more than 67,000 models of 90 targets.[1] That day the London company DeepMind announced that group 427 was its program, AlphaFold. Across all targets AlphaFold's median score on the competition's main accuracy measure was 92.4 out of 100. On the hardest category, proteins with no similar known structure to copy from, it was 87.0. The next morning, Eastern time, John Jumper, the physicist who led

the project, gave a talk describing in outline how it worked. John Moult, the computational biologist who had founded CASP, told *Nature* on the day the results were announced that in some sense the problem was solved, and in his concluding remarks at the end of the week, according to Lupas and his colleagues, he said that the prediction of single protein chains had been solved.

The problem he meant had been set out nearly sixty years earlier, by a biochemist at the National Institutes of Health with a test tube of enzyme. The people who answered it came from computer science, game design, theoretical physics, statistics and neuroscience as well as from biochemistry, and the answer itself raised the question of what it means to solve a scientific problem.

The Science: Strings That Fold Themselves

Proteins do most of the work in a living cell. Enzymes are proteins; so are the antibodies that recognise a virus, the haemoglobin that carries oxygen in the blood, the channels that let ions across a nerve-cell membrane, and the motors that make muscle contract. A protein is a chain built from twenty kinds of building block, the *amino acids*. All twenty share a common backbone section, which links to its neighbours through a *peptide bond*, and each carries a distinctive side chain: some small, some bulky, some electrically charged, some oily and averse to water. A gene specifies the order of the amino acids, as Chapter 7 described, and the cell's ribosomes join them in that order into a chain that may be a few dozen or several thousand units long.

Biochemists describe the result at four levels. The *primary structure* is the sequence itself, written as a string of letters, one per amino acid. The *secondary structure* is the local shape of short stretches: the alpha helix, a spiral held together by hydrogen bonds between each backbone unit and the fourth one along, which Linus Pauling published in 1951 (Chapter 7), and the beta sheet, in which extended stretches of chain lie side by side and bond to each other. The *tertiary structure* is the way those helices and sheets pack together into a compact three-dimensional object. The *quaternary structure* is the arrangement of several chains into a working assembly; haemoglobin, for instance, is four chains. Shape is what matters. An enzyme works because a handful of side chains from distant parts of the sequence come together in a precisely shaped pocket; a receptor works because its surface fits a particular hormone.

The main force that folds a chain is a negative one. Water molecules form a network of hydrogen bonds with each other, and oily side chains disrupt it, so the overall free energy is lower when the oily side chains are tucked away together in the interior of the protein, out of contact with water, and the charged and polar ones face outwards. On top of this *hydrophobic effect* come hydrogen bonds, attractions between opposite charges, the close packing of atoms against each other, and, in some proteins, covalent cross-links called disulphide bonds between the sulphur atoms of cysteine side chains. Each of these interactions is weak. A folded protein is typically only marginally more stable than its unfolded chain, by an amount comparable to a few hydrogen bonds.

Christian Anfinsen did the experiment that defined the problem. He had moved from Harvard in 1950 to head the Laboratory of Cellular Physiology and Metabolism at the National Heart Institute, part of the National Institutes of Health in Bethesda, Maryland, and he chose as his subject bovine ribonuclease, an enzyme that breaks down RNA, partly because a meat-packing company, Armour, could supply it in quantity. Ribonuclease is a single chain of 124 amino acids, held in shape by four disulphide bonds. In 8 molar urea, which disrupts the weak interactions, and with the chemical mercaptoethanol, which breaks the disulphide bonds, the enzyme unfolds into a floppy chain with no activity. When Anfinsen and his colleagues removed the urea and the mercaptoethanol and let the chain stand in air, it slowly regained almost all of its activity. The eight cysteines had to pair up into four bonds, and they could in principle do so in 105 different ways; they found the one correct pairing on their own. If instead the chain was allowed to form its disulphide bonds while still in urea, the result was a "scrambled" mixture with about one per cent of the normal activity, and adding a trace of mercaptoethanol, which lets the bonds break and re-form, converted the scramble back into native enzyme.[2]

The conclusion, which Anfinsen called the *thermodynamic hypothesis*, was that the native shape of a protein is the one with the lowest free energy in its normal surroundings, and that the information needed to reach it lies entirely in the amino-acid sequence. The 1961 paper, written with Edgar Haber, Michael Sela and Fred White, is the date usually given, though the first refolding observations went back to 1956 and 1957, and the hypothesis was formulated over several years of experiments. In 1972 Anfinsen received half the Nobel Prize in Chemistry for the work. The test tube also contained a hint that the cell does things differently: refolding took hours in the laboratory but happens in minutes in the body, a discrepancy that led to the discovery of an enzyme that speeds up the shuffling of disulphide bonds. Cells also have *chaperones*, proteins that stop newly made chains from clumping together before they fold. But the chaperones mostly prevent mistakes; they do not, as a rule, dictate the final shape. The shape is written in the sequence.

If the shape is written in the sequence, it ought to be possible to read it, and that is the protein-folding problem in its practical form: given a sequence, predict the structure. Almost at once a physicist pointed out why this might be hard.

Cyrus Levinthal had trained in physics, with a Berkeley doctorate in 1950 on nuclear reactions, before moving into molecular biology at MIT in 1957; in 1968 he went to Columbia to chair its biological sciences department, and he was one of the pioneers of displaying protein structures on computers. In a short paper of 1968 and a talk at a meeting at Allerton House, Illinois, in 1969, he pointed out that a protein chain has so many ways to arrange itself that it could not possibly find its native shape by trying them one at a time.[3] His numbers were rough and his example was a chain of 150 amino acids; he estimated 450 degrees of freedom and, even with the angles known only to a tenth of a radian, about 10^{300} possible configurations. Proteins, he noted, fold in a few seconds. His conclusion was not that folding was mysterious but that it must follow *pathways*: local interactions would form quickly and act as nuclei that guided the rest. He also suggested, against Anfinsen's view, that the native state need not be the lowest-energy state at all, only the first deep, stable trough that the chain reaches.

Levinthal did not present his argument as a paradox. Others did, and the version that most textbooks give, with its three states per amino acid and its age of the universe, is a later restatement.

Science Primer: Levinthal's arithmetic, done honestly

The version usually quoted matches the one set out in a 1992 paper by the physical chemists Robert Zwanzig, Attila Szabo and Biman Bagchi. Take a chain of about 100 amino acids, and suppose that the link between each pair of neighbours can be in one of three states. The number of possible shapes is

$$3^{100} \approx 5.2 \times 10^{47}.$$

Suppose the chain can try a new shape every 10^{-13} seconds, roughly the period of a molecular vibration, so 10^{13} shapes a second. Trying them all would take

$$\frac{5.2 \times 10^{47}}{10^{13} \text{ per second}} \approx 5.2 \times 10^{34} \text{ s} \approx 1.6 \times 10^{27} \text{ years},$$

using about 3.16×10^7 seconds in a year. The universe is about 1.4×10^{10} years old. Small proteins fold in thousandths of a second or less.

Every number here is a convenience. Real backbones have two main rotatable angles per amino acid, not one, which would make the count larger; but most combinations are impossible because atoms would collide, which makes it smaller. None of that matters, because the conclusion survives any plausible change of inputs: an unbiased random search is hopeless.

The useful lesson is about the word "unbiased". Imagine a combination lock with 100 dials of three positions each. Guessing the whole combination at random means trying up to 3^{100} settings. If instead each dial clicks when it reaches the right position, so that you can keep a correct dial and move on, the job takes at most $3 \times 100 = 300$ tries. Zwanzig, Szabo and Bagchi showed that a small bias of this kind is enough. In their model, if each locally incorrect state costs an energy penalty of only a few times the typical thermal energy (a few kT, where k is Boltzmann's constant and T the temperature), the time to fold falls from 10^{27} years to seconds or less. The paradox does not show that proteins are miraculous. It shows that the search must be biased, and asks what the bias is.

The Science: Landscapes and Funnels

The answer that emerged in the late 1980s and 1990s came from physicists, and it borrowed a language from the study of disordered magnets.

Peter Wolynes had trained as a chemical physicist at Harvard and was at the University of Illinois when, in 1987, he and Joseph Bryngelson published "Spin Glasses and the Statistical Mechanics of Protein Folding." Chapter 10 described spin glasses: magnetic alloys in which the

atomic magnets interact in conflicting ways, so that no arrangement can satisfy all of them at once, and the material freezes into one of an enormous number of disordered, nearly equivalent states. Physicists call this conflict *frustration*. Bryngelson and Wolynes saw that a random chain of amino acids would behave like a spin glass. Its many weak interactions would pull in different directions; there would be countless compact shapes with similar energies, separated by barriers; and the chain would get stuck in whichever one it happened to fall into. Real proteins do not behave like that, and the reason, they argued, is evolution. Natural selection has favoured sequences in which the interactions that stabilise the native shape are also mutually consistent, so that the native state is much lower in energy than the misfolded alternatives. They called this the *principle of minimal frustration*. It is an example of what this book calls structural isomorphism: the mathematics devised for a disordered alloy turned out to describe the problem a protein faces, and to say exactly what evolution had to do to solve it.

The image that made the idea widely understood is the *energy landscape*. Imagine every possible shape of the chain laid out as a position on a surface, and the free energy of each shape as its height. Levinthal's search corresponds to a flat golf course with a single hole: the ball can roll anywhere and finds the hole only by luck. The landscape of a real protein is shaped like a funnel. Its rim is wide, because an unfolded chain has an enormous number of shapes; its floor is narrow, because the folded protein has essentially one. Because the walls slope inwards, almost any move that makes more native-like contacts lowers the energy, and the chain drifts downhill along many different routes at once rather than following a single pathway. The walls are rough, with small pits in which the chain can be held up for a while, but in a minimally frustrated protein the slope wins.

The word *funnel* was used by the physical chemist Ken Dill in 1987. Its kinetic form was developed by Philip Leopold, Mauricio Montal and José Onuchic in 1992. Onuchic, a Brazilian physicist who had taken his doctorate at Caltech under John Hopfield (who shared the 2024 physics prize mentioned in Chapter 6) before moving to the University of California, San Diego, became one of Wolynes's longest-standing collaborators. In 1995 Wolynes, Onuchic and Devarajan Thirumalai published a short manifesto for what was soon called the "new view" of folding, and in 1997 Dill and Hue Sun Chan set out the contrast between Levinthal's golf course, the old pathway models and the funnel in a review whose title summarised the story.

The landscape theory explained why folding is possible and fast. It did not, by itself, tell anyone what shape a given sequence would take. To do that you would need to know the energy of every shape accurately enough to find the bottom of the funnel, and the energies involved, a small difference between large competing terms, were exactly the ones that physical models calculated worst. The most direct approach, simulating every atom of the protein and the surrounding water as they jostle under Newton's laws, was so expensive that a celebrated simulation published in 1998 followed a fragment of 36 amino acids for a single microsecond. In 2010 the computer scientist David Shaw's company, D. E. Shaw Research, used a special-purpose machine called Anton to follow small proteins folding and moving for up to a millisecond, a remarkable feat that still did not scale to the general problem.[4] For prediction, the field needed something cheaper than physics, and it found it in the record of shapes that experimenters had already measured.

An Archive of Shapes

The first protein structures were determined by X-ray crystallography: John Kendrew's myoglobin in 1958 and Max Perutz's haemoglobin in 1960, which shared the Nobel Prize in Chemistry in 1962 (Chapter 7). The principle is the one Bragg worked out for simple crystals. A protein crystal, a regular lattice of millions of identical molecules, scatters an X-ray beam into a pattern of thousands of spots. But the detector records only the brightness of each spot, not the *phase*, the relative timing of the waves, and both are needed to calculate an image of the molecule. Crystallographers recover phases in several ways. One, *molecular replacement*, borrows them from a model: if you already have a structure that resembles the unknown one closely enough, you can place it in the crystal, compute the phases it would give, and refine from there. If no good model exists, molecular replacement fails. That is what had happened to Andrei Lupas's receptor.

Two other methods joined crystallography. Nuclear magnetic resonance spectroscopy measures the magnetic interactions between atomic nuclei in a protein dissolved in water, which yield a set of distance constraints from which a structure can be built; Kurt Wüthrich received half the 2002 Nobel Prize in Chemistry for developing it. Cryo-electron microscopy freezes molecules in a thin film of glass-like ice and images them directly with an electron beam, averaging tens of thousands of noisy pictures. For decades it gave blurry results, but improvements in detectors and software in the 2010s brought it close to atomic resolution, and in 2017 Jacques Dubochet, Joachim Frank and Richard Henderson shared the Nobel Prize in Chemistry for it. Each method had its demands. A crystal structure needed crystals, which some proteins refuse to form; NMR worked best for small proteins; cryo-EM for large ones. A single structure could take a doctoral student years.

What made those years collectively useful was an archive. The Protein Data Bank was established in 1971 at Brookhaven National Laboratory on Long Island, under the chemist Walter Hamilton, after a symposium at Cold Spring Harbor that June; it started with seven structures.[5] Over the next decades structural biologists built a culture, eventually backed by the policies of journals and funders, in which publishing a structure meant depositing its coordinates where anyone could download them. The archive grew slowly for twenty years and then very fast (Figure 12.1). In 2020, the year of CASP14, it held about 173,000 entries; by the end of 2025, more than 247,000. Many entries are the same protein solved repeatedly, bound to different partners or drugs, and the number of distinct proteins is much smaller. Meanwhile, the sequencing industry described in Chapter 11 was filling databases with protein sequences read from genomes, and by the 2020s these held more than two hundred million. For almost every known protein, there was a sequence and no structure.

Fragments

David Baker came to proteins by a roundabout route. He was born in Seattle in 1962 to two scientists, the physicist Marshall Baker and the geophysicist Marcia Baker. At Harvard he began in

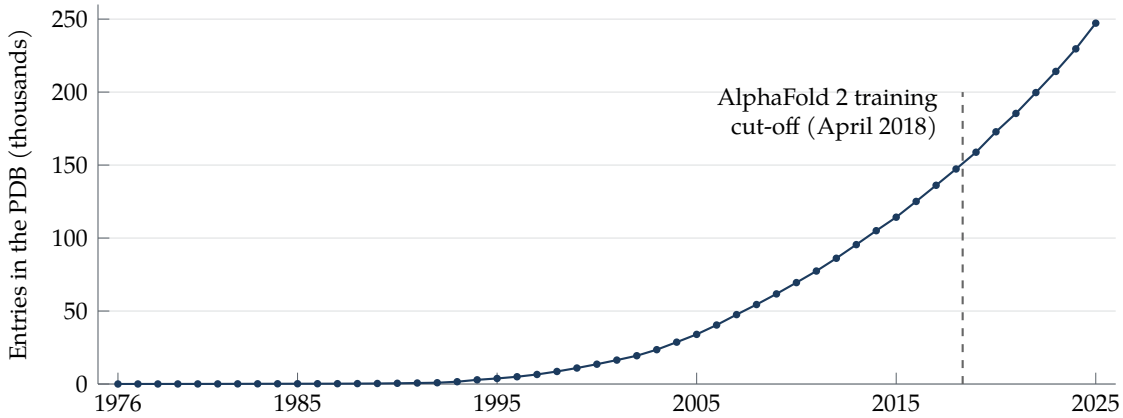


Figure 12.1: Total number of entries in the Protein Data Bank at the end of each year, 1976–2025. Data from the RCSB PDB's statistics page, "PDB Statistics: Overall Growth of Released Structures Per Year," https://www.rcsb.org/stats/growth/growth-released-structures, as retrieved in October 2026 (RCSB revises its yearly totals slightly as entries are updated). AlphaFold 2 was trained on structures released up to 30 April 2018 (Jumper et al., 2021). The numbers count entries, not distinct proteins.

social studies and turned to philosophy; a biology course in his final year, he has said, excited him enough to try research, and he graduated in biology in 1984. His doctorate at Berkeley, under Randy Schekman, was on how proteins are transported inside yeast cells. Only in a postdoctoral position in biophysics with David Agard at the University of California, San Francisco, did he begin working on folding, and when he joined the faculty of the University of Washington in Seattle in 1993, his laboratory did experiments on how small proteins fold.

The computational work began as a way to understand those experiments. The program that came out of it, Rosetta, rested on an observation about the archive. Short stretches of protein chain, a few amino acids long, tend to adopt a limited number of local shapes, and which shapes they adopt depends on the local sequence, though not decisively: the same short sequence may be a piece of helix in one protein and an extended strand in another. In 1997 Kim Simons, the statistician Charles Kooperberg, Enoch Huang and Baker described a method that exploited this. For each nine-amino-acid window of the target sequence, the program collected fragments of known structures in the PDB whose local sequences were similar. It then built a model by starting with an extended chain and repeatedly replacing the backbone angles of one window with those of one of its candidate fragments, keeping or rejecting each change by a Monte Carlo rule. Moves that improved a score were kept; moves that worsened it were kept only occasionally, with a probability that fell as the run went on, a procedure called simulated annealing that lets a search climb out of shallow traps early on and settle later. The score itself was statistical rather than physical, derived with Bayes's theorem from how often amino acids of each kind are found buried, exposed or touching each other in known structures.[6]

The fragments did the work that Levinthal's argument said was impossible to do by blind search. Instead of exploring every backbone angle, Rosetta explored only combinations of local shapes that real proteins had already used, and the archive supplied the bias. Later versions used fragments of three and nine amino acids, added a refinement stage with a physically based

energy that included the packing of atoms, hydrogen bonds and the cost of exposing side chains to water, and were extended from prediction to design, docking and much else. Baker's group entered Rosetta in CASP in 1998 and remained among the strongest groups for the next twenty years. From the start it was a shared project; former students and collaborators formed a consortium, the Rosetta Commons, so that laboratories in many countries could go on developing the same code.

Rosetta's searches were hungry for computing time, and in October 2005 Baker's group launched Rosetta@home, which used a platform developed at Berkeley for volunteer computing to run the program on home computers while their owners were not using them. By 2008, according to the university, some 200,000 volunteers were taking part. Some of them, watching the program's graphics as it searched, suggested an interactive version, in which they could steer the search themselves.

Players

The suggestion reached people who knew what to do with it. Zoran Popović, an associate professor of computer science at the University of Washington, was a specialist in computer animation; his colleague David Salesin was a leading researcher in computer graphics. With Baker they took on a doctoral student in computer science, Seth Cooper, who became the lead designer, and a postdoctoral researcher, Adrien Treuille. In May 2008 the university launched Foldit, a free online game built on Rosetta's energy function.

A Foldit player sees a protein as a coloured chain and can pull it, twist it, freeze parts of it, rebuild loops, shake side chains into better positions and launch short automatic optimisations. The game's score is Rosetta's energy, inverted so that lower energies give higher scores, and the screen flags problems: clashes between atoms, oily side chains left exposed to water, cavities in the core. The game begins with tutorial puzzles, because the players it was meant for, people with no training in biochemistry, had to learn the rules of protein structure by playing.

The first test was published in *Nature* in August 2010. Its authors were Cooper, Firas Khatib, Treuille, Janos Barbero, Jeehyung Lee, Michael Beenen, Andrew Leaver-Fay, Baker, Popović, and "Foldit players", a collective credit for the more than 57,000 people who had contributed through play and feedback. On ten puzzles whose answers were unknown at the time, the players matched Rosetta's automatic protocol on three and did better on five. They were especially good at things the algorithm handled badly: recognising when a whole sheet of strands needed rearranging, or when the backbone had to move to bury an exposed oily side chain. Teams divided labour, with some players specialising in opening up new arrangements and others in polishing them, and players began writing their own automated "recipes" and sharing them, so that the game came to explore search strategies as well as shapes.[7]

The result that made headlines came the following year. The Mason-Pfizer monkey virus was isolated in 1970 from a tumour in a rhesus monkey; it is a retrovirus that can cause an immune deficiency in macaques, though it belongs to a different group of retroviruses from

HIV and is unrelated to the simian immunodeficiency virus. Like HIV, it makes a protease, an enzyme that cuts the virus's proteins into working pieces, and such proteases are drug targets. HIV's protease works as a pair of identical chains, but the Mason-Pfizer protease had been crystallised as a single chain of 114 amino acids. Crystallographers in Poland and the Czech Republic, led by Mariusz Jaskolski in Poznań and Iva Píchová of the Czech Academy of Sciences, had good crystals and data, and for more than a decade they had been unable to solve the structure by molecular replacement: none of the available models was close enough. In 2011 the Foldit team posted the protein as a puzzle, starting from a set of poor models obtained by NMR. Within the three weeks the puzzle ran, one player, spvincent, improved the starting model substantially; a second, grabhorn, improved the core and the side chains; and a third, mimi, tucked in a loop. Their final model, from a team called the Foldit Contenders Group, was good enough for molecular replacement, and the refined crystal structure was completed a few days later. It showed a surface that could be targeted by drugs.[8] The players' teams were listed among the authors.

The story was widely retold as gamers solving in ten days what scientists had failed to solve in fifteen years. Both numbers are firmer in the retellings than in the paper, which says "for over a decade" and describes a three-week competition. More importantly, the players did not solve the structure on their own. They improved a model inside an energy function written by biochemists, on a platform designed by computer scientists, and the result was useful only because crystallographers had collected data that could test it. What the players contributed, and what Rosetta's automatic search had not, was the judgement to try large, awkward rearrangements that the algorithm would have rejected.

Popović described the lesson as a matter of turning novices into experts; the more lasting lesson may be the one Baker's group drew about algorithms. Strategies discovered by players were studied and built into Rosetta. In 2019 a paper in *Nature*, with "Foldit Players" again among the authors, reported that players had designed 146 entirely new proteins, 56 of which folded stably when made in bacteria; four had their structures determined, and they matched the players' designs closely. By then the players were designing proteins, not just predicting them, because Baker's laboratory had long since turned the problem around.

Building What Evolution Never Tried

If a program can find the sequence's lowest-energy shape, it can in principle do the reverse: start with a shape and search for a sequence whose lowest-energy shape it is. The first fully computational design of a protein sequence, a redesign of a small natural zinc-finger domain, was published by Bassil Dahiyat and Stephen Mayo at Caltech in 1997. Baker's group set out to make something nature had not.

In 2003 Brian Kuhlman and colleagues in Baker's laboratory described Top7, a protein of 93 amino acids with two helices packed against a five-stranded sheet in an arrangement not found in any known natural protein. The design alternated between choosing a sequence for a fixed backbone and adjusting the backbone for the sequence. When the protein was made, it

was extremely stable, and its crystal structure matched the design within 1.2 Å (an ångström is a ten-millionth of a millimetre, about the width of a hydrogen atom). It was the strongest evidence yet that the physical and statistical rules encoded in Rosetta were not merely good at recognising natural proteins but captured something real about what makes a chain fold.

Design became the larger part of Baker's work. The University of Washington established an Institute for Protein Design under him in 2012. His group and its collaborators designed enzymes for reactions no natural enzyme catalyses, proteins that assemble into cages, switches and sensors, and small binding proteins that block their targets. In 2020 they reported miniproteins designed to bind the spike protein of SARS-CoV-2 extremely tightly and block the virus from infecting cells in the laboratory.[9] In June 2022 South Korea's Ministry of Food and Drug Safety approved SKYCovione, a COVID-19 vaccine developed by SK bioscience in which pieces of the spike protein identified in David Veesler's laboratory are displayed on a self-assembling nanoparticle designed in Neil King's laboratory at the Institute for Protein Design, with an adjuvant supplied by GSK. The institute called it the world's first computationally designed protein medicine.

Evolution's Notebook

While Rosetta drew on the shapes in the archive, another approach drew on the far larger store of sequences. The idea is that evolution has already run the experiment of mutating every protein many times and keeping only the variants that still fold.

Suppose two amino acids lie far apart in a protein's sequence but touch in the folded structure: say, purely as an illustration, positions 30 and 85, one carrying a positive charge and the other a negative one, so that they attract each other. A mutation that reverses the charge at position 30 would leave two positive charges facing each other and would weaken or destroy the protein. It is likely to be eliminated by selection, unless position 85 changes in a compensating way. Across many species, then, the two positions should tend to change together. If you line up the sequences of the same protein family from thousands of organisms, an arrangement called a *multiple sequence alignment*, and look for pairs of columns that vary in concert, those pairs should tend to be in contact.

The idea is old. In 1994 Ulrike Göbel, Chris Sander, Reinhard Schneider and Alfonso Valencia showed that correlated mutations in alignments were indeed enriched among residues in contact, and Sander's group had already used alignments to improve the prediction of secondary structure with neural networks. But the predictions were too noisy to build structures from, for two reasons. There were not yet enough sequences. And correlation is transitive: if position A touches B, and B touches C, then A and C will also appear to vary together, even though they never meet. A simple count of co-variation mixes direct contacts with chains of indirect ones.

The fix came from statistical physics. In 2009 the statistical physicist Martin Weigt, working with Terence Hwa's group at the University of California, San Diego, and James Hoch's at

the Scripps Research Institute, analysed more than 2,500 bacterial signalling proteins and separated direct from indirect correlations by fitting a global statistical model to the whole alignment, a method they called *direct coupling analysis*. In 2011 two groups showed that the method was good enough to fold proteins. Debora Marks, a mathematical biologist at Harvard Medical School, Lucy Colwell, a mathematician at Cambridge, and Sander, by then at Memorial Sloan-Kettering Cancer Center in New York, working with the physicists Andrea Pagnani and Riccardo Zecchina in Turin, predicted contacts from alignments and used them to compute the three-dimensional structures of fifteen proteins, getting within 2.7 to 4.8 Å of the experimental structures over most of each chain. Faruck Morcos, Weigt, Onuchic, Hwa and others published a faster version of direct coupling analysis and applied it to 131 protein families.[10]

Science Primer: Reading contacts from an alignment

Here is a toy alignment of one protein from eight species, showing only three columns, labelled i, j and k. Each letter is an amino acid: K (lysine) is positively charged, E (glutamate) negatively charged, and A (alanine) and G (glycine) are small and neutral.

Species	1	2	3	4	5	6	7	8
Column i	K	K	K	K	E	E	E	E
Column j	E	E	E	E	K	K	K	K
Column k	A	G	A	G	A	G	A	G

Whenever column i is positive, column j is negative, and vice versa: the pattern of a salt bridge whose two charges have swapped places in some lineages. Column k varies too, but without regard to the others.

A standard way to measure how much knowing one column tells you about another is the *mutual information*,

$$I(i,j) = \sum_{a,b} p_{ij}(a,b)\, \log_2 \frac{p_{ij}(a,b)}{p_i(a)\, p_j(b)},$$

where $p_i(a)$ is the fraction of sequences with amino acid a in column i, and $p_{ij}(a,b)$ is the fraction with a in column i and b in column j. The logarithm compares how often a pair occurs with how often it would occur if the columns were independent. For columns i and j, only two pairs occur, (K,E) and (E,K), each in half the sequences, while each single letter has frequency one half. So

$$I(i,j) = 2 \times \tfrac{1}{2} \log_2 \frac{1/2}{(1/2)(1/2)} = \log_2 2 = 1 \text{ bit}.$$

For columns i and k, every pair occurs in a quarter of the sequences, exactly as independence predicts, so each logarithm is $\log_2 1 = 0$ and $I(i,k) = 0$.

Real data are noisier. If species 8 had E in column j instead of K, the calculation gives about 0.55 bits: still a signal, but weaker. Real alignments have hundreds of columns and need thousands of sequences, weighted so that many near-identical sequences from

closely related species do not count many times over.

Mutual information also has the transitivity problem described in the text. Direct coupling analysis avoids it by fitting a model of the whole alignment at once. It supposes that the probability of a sequence $a_1 a_2 \ldots a_L$ is

$$P(a_1, \ldots, a_L) \propto \exp\Big(\sum_i h_i(a_i) + \sum_{i<j} J_{ij}(a_i, a_j)\Big),$$

where h_i describes how much column i prefers each amino acid on its own and J_{ij} is a *coupling* between columns i and j. This is the form of the *Potts model* of statistical physics, a generalisation of the simplest model of a magnet in which each site can be in one of q states rather than pointing up or down; here $q = 21$, the twenty amino acids plus a gap. The model is chosen to reproduce the observed frequencies of single letters and pairs while assuming nothing else. If A and C are correlated only because both touch B, the model can explain their correlation through J_{AB} and J_{BC}, and J_{AC} stays small. The largest couplings are the best guesses for contacts. Physicists usually start from the couplings and ask what states a magnet will adopt; here the problem is run backwards, from the states to the couplings.

The method needed many sequences, and the genome projects described in Chapter 11, followed by the sequencing of DNA extracted directly from soil, seawater and the human gut, supplied them. In 2017 Sergey Ovchinnikov, Baker and colleagues combined co-evolutionary contacts from such metagenomic sequences with Rosetta to build models for 614 protein families of previously unknown structure. The same mathematics that had described the frustration of disordered magnets, and then the minimal frustration of proteins, now read contact maps out of evolution's record. But a contact map is not a structure, and the step from one to the other still relied on Rosetta-style search. The next advance came from treating the whole alignment not as a set of pairwise statistics but as an input to a learning machine.

The Blind Olympics

Every method in this chapter was tested in the same place. In the early 1990s, protein-structure prediction had a credibility problem. Methods were often tested on proteins whose structures their developers already knew, and it was all too easy, without any dishonesty, to tune a method until it gave the right answer. John Moult, at the University of Maryland Biotechnology Institute, proposed a remedy: a blind test. With Jan Pedersen, Richard Judson and Krzysztof Fidelis, he asked experimentalists who were about to solve structures to release the sequences in advance and withhold the answers until predictions had been submitted. The first round, CASP1, had 33 targets and 35 prediction groups, and its results were discussed at the Asilomar conference centre in California in December 1994.

CASP became a trading zone in the sense this book uses the term: a place where crystallo-

graphers, physicists, statisticians and computer scientists agreed on what counted as success without agreeing on how to get there. Independent assessors, different each round, judged the predictions. Every two years the field could see which ideas worked, and the results were brutal. For two decades, predictions for proteins with a close relative of known structure improved steadily, because they could copy it; predictions for genuinely new folds improved slowly. Through CASP12 in 2016, the best scores for the hardest targets stayed below 40 on the competition's main measure. Co-evolutionary methods began to change that: at CASP12, the best contact predictions were correct about 45 per cent of the time, and at CASP13 in 2018, about 70 per cent.[11]

Science Primer: How close is close? RMSD and GDT

To score a prediction, one superimposes the model on the experimental structure and measures how far each amino acid's central carbon atom (the alpha carbon) lies from its true position. Two summaries of those distances are common.

The *root-mean-square deviation* squares each distance d_n, averages over the N residues, and takes the square root:

$$\mathrm{RMSD} = \sqrt{\frac{1}{N}\sum_{n=1}^{N} d_n^2}.$$

The *global distance test*, introduced by Adam Zemla at Lawrence Livermore National Laboratory and used in CASP since 1998, asks instead what percentage of residues lie within a cutoff, for cutoffs of 1, 2, 4 and 8 Å, and averages the four percentages to give GDT_TS, a score from 0 to 100. (Strictly, each cutoff gets its own best superposition; the toy example ignores this.)

Take a small protein of ten residues and two models. In model A, eight residues are 0.8 Å from their true positions, excellent agreement, but a floppy loop of two residues is 10 Å off. In model B, every residue is 3 Å off: the overall shape is right, but no detail is.

$$\mathrm{RMSD}_A = \sqrt{\frac{8(0.8)^2 + 2(10)^2}{10}} = \sqrt{20.5} \approx 4.5 \text{ Å}, \qquad \mathrm{RMSD}_B = \sqrt{\frac{10(3)^2}{10}} = 3.0 \text{ Å}.$$

By RMSD, B looks better. By GDT, A has 80 per cent of residues within each of the four cutoffs, so GDT_TS $= 80$; B has none within 1 or 2 Å and all within 4 and 8 Å, so GDT_TS $= (0 + 0 + 100 + 100)/4 = 50$. GDT rewards getting most of the protein exactly right and forgives a few wild residues; RMSD is dominated by the worst ones. For predictions, where a single misplaced loop can ruin an RMSD, GDT is usually the fairer judge.

There is no exact threshold at which a prediction becomes as good as an experiment, because experimental structures have errors too. Moult's rule of thumb was that a GDT_TS of around 90 is competitive with experiment. In CASP14 AlphaFold's median across all targets was 92.4. Measured more strictly, by a version of RMSD that ignores the worst 5 per cent of residues, its median backbone error was 0.96 Å, against 2.8 Å for the next best method.

From Go to Proteins

Demis Hassabis was born in London on 27 July 1976. He learned chess at four and reached master standard at thirteen, with a rating of 2300 in 1990. At seventeen he co-designed and was lead programmer of *Theme Park*, a simulation game, at the British studio Bullfrog. He took a double first in computer science at Queens' College, Cambridge, in 1997, founded a games company, Elixir Studios, in 1998, and, after it closed in 2005, took a doctorate in cognitive neuroscience at University College London under Eleanor Maguire. His best-known paper from that period showed that patients with damage to the hippocampus, a brain structure needed for forming memories, also had difficulty imagining new experiences. In 2010 he founded DeepMind in London with Shane Legg and Mustafa Suleyman, with the aim of building general-purpose learning systems; Google bought it in 2014.

He had heard about protein folding much earlier. By his own account, a friend at Cambridge in the 1990s, Tim Stevens, who went on to work on protein structure, kept bringing the problem up. Later, as a postdoctoral researcher, he played Foldit, and he has said that he wondered then whether the intuition that its players brought to the game could be captured by a machine. In March 2016 DeepMind's program AlphaGo defeated the Go champion Lee Sedol by four games to one in Seoul, using deep neural networks trained partly on human games and partly by playing against itself. Go had been considered a game in which human pattern recognition would keep machines at bay for years. According to Hassabis, he told David Silver, who led the AlphaGo work, that it was time to try proteins. DeepMind assembled a small team that year, recruiting a handful of biologists to work with its machine-learning researchers.[12]

Their first system, entered in CASP13 in 2018 and later described in a paper led by Andrew Senior, did not rely on a new principle so much as on doing one step much better. Earlier methods predicted whether pairs of residues were in contact. AlphaFold trained a deep convolutional network, of the kind used to recognise images, to look at features of the multiple sequence alignment and predict a probability distribution over the *distance* between every pair of residues. These distributions were turned into a smooth energy-like function of the structure, which was minimised by gradient descent, the basic optimisation method of machine learning. On the 43 domains in the hardest CASP13 category, AlphaFold produced a model of high accuracy for 24, against 14 for the next best group; its best models had GDT scores around 60. It won clearly. It did not come close to experimental accuracy.

John Jumper had joined the team by then. He was born in 1985 in Little Rock, Arkansas, studied physics and mathematics at Vanderbilt University, graduating in 2007, and took an MPhil in theoretical condensed matter physics at Cambridge as a Marshall Scholar in 2008. He then spent about three years at D. E. Shaw Research in New York, working on computer simulations of proteins. He began doctoral work at the University of Chicago in 2011, under Tobin Sosnick and Karl Freed, and his thesis in theoretical chemistry, completed in 2017, developed machine-learning methods for simplified simulations of protein folding. In 2017, shortly after finishing it, he applied to DeepMind.[13] He brought a physicist's sense of what a protein structure must obey and a practitioner's knowledge of how simulations fail.

After CASP13 the team replaced its two-stage system, which predicted distances and then folded a structure to fit them. In the new design, developed under Jumper's leadership, the network would take the sequence and alignment and produce atomic coordinates directly, learning every stage at once.

Attention to Pairs

The new system, AlphaFold 2, borrowed its central mechanism from the study of language. In a sentence, the meaning of a word depends on other words that may be far away, and in 2014 researchers working on machine translation gave their networks a way to decide, for each word, which other words to consult. The mechanism is called *attention*. In 2017 a team at Google built a whole architecture, the Transformer, out of it, and it became the basis of the large language models that followed. A protein has the same property: the right shape for a residue depends on residues that are far away in the sequence but near it in space.

Attention works like this. Each element (a word, or a residue) carries a list of numbers that represents what the network currently believes about it. From this list the network computes three others: a *query* (what this element is looking for), a *key* (what it offers to others) and a *value* (what it will pass on). To update element i, the network compares i's query with every element's key, giving a score for each; converts the scores into weights that are positive and add up to one, using the *softmax* function (exponentiate each score and divide by the total); and adds up the values weighted accordingly. If three elements score 2, 1 and 0, the weights are e^2, e^1 and e^0, that is 7.39, 2.72 and 1, divided by their total of 11.11, giving 0.67, 0.24 and 0.09. Element i mostly listens to the first. Everything that decides the queries and keys is learned from data.

AlphaFold 2 kept two representations and refined them together through a stack of 48 blocks it called the *Evoformer*.[14] One is the alignment itself, a grid with a row for each related sequence and a column for each position, in which attention runs along rows and down columns, so that the network can learn which sequences and which positions to compare. The other is a grid with a row and a column for every residue, the *pair representation*, holding the network's current belief about the relationship between each pair of residues, including their distance. Information flows from the alignment into the pairs at every block, which is how co-evolutionary signals enter.

The new idea was in how the pairs were updated. Distances in three-dimensional space are not independent: if residue i is close to k, and k is close to j, then i cannot be far from j, the triangle inequality of geometry. AlphaFold 2's "triangle" operations update the entry for each pair (i, j) using, for every third residue k, the entries for (i, k) and (k, j): once through a multiplicative update and once through a form of attention in which the third side of each triangle biases the weights. The network is not forced to obey the triangle inequality, as a rigid rule would force it; it is given an architecture in which geometrical consistency is easy to learn, and it learned it.

A second module turned the pairs into coordinates. It treated each residue's backbone as a rigid object, a little triangle of three atoms with its own position and orientation, and began with all of them piled at the origin, a starting state the paper called a "residue gas". Over eight further blocks it moved and rotated each object. Its attention, which DeepMind called *invariant point attention*, worked with points defined in each residue's own frame of reference, so that its judgements did not change if the whole protein were rotated or moved in space; because its updates were also expressed in each residue's local frame, they rotated with the protein. A structure should not depend on which way up it is drawn, and building that in, rather than making the network learn it from examples, saved data and improved accuracy. Commentators often describe AlphaFold 2 loosely as "SE(3)-equivariant", after the mathematical group of rotations and translations in three dimensions; the paper's own, more careful wording is that the attention is invariant and the update equivariant. The output was then fed back through the whole network three more times, each pass taking the previous pass's output as extra input, a procedure the team called *recycling*.

The system was trained on structures in the PDB released up to 30 April 2018, about 170,000 of them, together with large sequence databases. It was then used to predict structures for some 350,000 sequences without known structures, and the confident predictions were added to the training set for a final model, a technique called self-distillation. It also learned to estimate its own reliability. For each residue it produced a confidence score from 0 to 100, the *pLDDT*, a prediction of how well the residue's local surroundings would match an experimental structure. Above 90 the prediction was usually excellent; below 50 it often meant a region with no fixed shape at all.

Nature published the paper online on 15 July 2021, with the source code and trained parameters released under an open licence. On the same day *Science* published RoseTTAFold, a network built in Baker's laboratory after CASP14, while the details of AlphaFold 2 were still unpublished, by a team led by Minkyung Baek. It used three tracks of information, for sequence, for pairwise distances and for coordinates, and exchanged information among them; it was somewhat less accurate than AlphaFold 2 but could predict a structure in as little as ten minutes on a single gaming computer, and it could model complexes of proteins. A week later DeepMind published predictions for almost every protein in the human body, and found confident predictions for 58 per cent of all residues, very confident ones for 36 per cent.

With the European Bioinformatics Institute, DeepMind opened the AlphaFold Protein Structure Database the same month, with more than 350,000 predicted structures covering the human proteome and those of twenty other organisms. On 28 July 2022 it was expanded to 214 million predictions, covering nearly every protein sequence in the main public catalogue, UniProt.[15] Twenty months after group 427 was unmasked, there was a predicted structure for almost every known protein.

Outcomes and Legacy

The prize. On 9 October 2024 the Royal Swedish Academy of Sciences awarded the Nobel Prize in Chemistry in two halves. One half went to David Baker "for computational protein design"; the other was shared by Demis Hassabis and John Jumper "for protein structure prediction". News reports often described it as shared jointly by all three, but the division mattered: the committee recognised two achievements, design and prediction, not one. The day before, the Physics prize had gone to John Hopfield and Geoffrey Hinton for the foundations of machine learning with artificial neural networks (Chapter 6). Hopfield had supervised Onuchic's doctorate; the borders of this chapter run through both prizes. Hassabis had been knighted earlier in 2024.

AlphaFold 3 and the question of code. On 8 May 2024 DeepMind and its sister company Isomorphic Labs published AlphaFold 3, which predicted the joint structures of complexes containing proteins, DNA and RNA, small molecules such as drugs, ions and chemically modified residues. Its structure module was replaced by a *diffusion* model, the family of generative methods used in image generators, which learns to turn random noise step by step into a plausible arrangement of atoms. Unlike AlphaFold 2, it was published without its code. Scientists could use it only through a web server, initially limited to ten jobs a day, and they could not use it to predict how proteins bind potential drugs. More than a thousand researchers signed a letter to *Nature* objecting that the paper did not meet the journal's own standards of reproducibility, and *Nature* published an editorial explaining its decision.[16] DeepMind released the code on 11 November 2024, with the trained parameters available to academic researchers on request and only for non-commercial use. Fully open alternatives followed, among them Boltz-1 from MIT at the end of 2024 and a preview of OpenFold3 from a consortium led by Mohammed AlQuraishi's laboratory at Columbia in October 2025.

Design by generation. In 2023 Baker's laboratory retrained RoseTTAFold as a diffusion model, RFdiffusion, that generates new protein backbones to order: a binder for a given target, a symmetrical cage, a scaffold that holds an enzyme's active site in place. In January 2025 the laboratory and colleagues at the Technical University of Denmark reported designed proteins that bound the three-finger toxins of cobras and mambas and protected between 80 and 100 per cent of mice from otherwise lethal doses. In November 2025 it reported antibodies designed from scratch that bound their targets as the models predicted. Design methods have moved faster than prediction did, because a designer can discard the many failures and keep the few successes; but each design still has to be made and tested in a laboratory.[17]

Integrative structures. AlphaFold's predictions became raw material for experimentalists. The nuclear pore complex, a gate in the membrane around the nucleus built from some thirty kinds of protein and about a thousand protein chains in all, had resisted complete description for decades. In June 2022 a team led by Martin Beck at the Max Planck Institute of Biophysics combined AlphaFold models of its parts with cryo-electron tomography to build a model covering more than 90 per cent of the human pore's scaffold, about 70 million daltons of protein, roughly twice what had been available before; other groups published similar work at the same time.

What changed for experimentalists. Experimental structural biology did not end. The PDB released more new entries in 2025, about 17,600, than in any previous year. What changed was the order of work. A predicted model became the first thing a crystallographer tried for molecular replacement, as Lupas had done, and cryo-EM maps were interpreted by fitting predictions into them. In 2023 a group led by Thomas Terwilliger compared 102 AlphaFold predictions with experimental electron-density maps that had not been used to make them. Even among residues predicted with very high confidence, about one in ten lay more than 2 Å from its experimental position, and many side chains were wrong. Their title gave the conclusion: predictions are valuable hypotheses that accelerate experiments but do not replace them. By DeepMind's count in November 2025, more than three million researchers in more than 190 countries had used AlphaFold.[18]

Drugs. In 2021 DeepMind spun off Isomorphic Labs, with Hassabis as chief executive, to apply AlphaFold-style methods to drug discovery. It raised $600 million in its first external funding round in March 2025 and $2.1 billion in May 2026. In 2025 Hassabis had said that the company's first AI-designed drugs would be in clinical trials by the end of that year; in January 2026 he said the company expected to begin trials by the end of 2026. As of October 2026, no Isomorphic-designed molecule had been publicly reported as given to a human.

CASP itself. The experiment that made the breakthrough visible nearly closed. Its grant from the US National Institutes of Health, about $639,000 a year, ran out in August 2025, and the University of California, Davis, which runs the Prediction Center, issued layoff notices. Google DeepMind provided a one-off gift expected to keep it going for about a year. CASP17 ran its prediction season in 2026, continuing categories, introduced at CASP15, for complexes with drug-like molecules and nucleic acids and for proteins that adopt several shapes, and adding one for immune complexes such as antibodies bound to their targets; its conference was scheduled for December 2026.

People. Baker has co-founded more than a dozen companies, and his institute continues to spin off more. Hassabis leads Google DeepMind. In June 2026 Jumper announced that, after nearly nine years, he was leaving DeepMind to join the AI company Anthropic.[19]

The Costs of Crossing

The protein-folding story is often told as the purest case for this book's argument: a problem that defeated one discipline for half a century fell to an alliance of several. That is broadly true. It is also incomplete in four ways.

Solved, in a sense. What AlphaFold 2 solved was the prediction of the static shape of single protein chains that resemble, at least distantly, proteins in the training data, and for which enough related sequences exist to build an alignment. Proteins move: many work by switching between shapes, and AlphaFold 2 usually gives one. Large parts of many proteins have no fixed shape at all, and AlphaFold could signal this with low confidence but not describe what such regions do. It was not designed to predict how a single mutation changes a protein's stability,

Table 12.1: Some of the disciplines that met in the protein-folding problem

Discipline	Representative people	Contribution
Biochemistry	Christian Anfinsen, David Baker	The thermodynamic hypothesis; folding experiments; Rosetta and protein design.
Physics and physical chemistry	Cyrus Levinthal, Peter Wolynes, José Onuchic, Ken Dill	The search problem; energy landscapes, funnels and minimal frustration.
Crystallography and structural biology	Walter Hamilton, Andrei Lupas, thousands of depositors	The PDB; the experimental structures used for training and testing.
Statistics and statistical physics	Charles Kooperberg, Martin Weigt, Riccardo Zecchina, Debora Marks	Bayesian scoring; direct coupling analysis; contacts from co-evolution.
Computer science and game design	Zoran Popović, David Salesin, Seth Cooper	Foldit and the use of players' judgement.
Machine learning and neuroscience	Demis Hassabis, John Jumper, Minkyung Baek	AlphaFold and RoseTTAFold.
Science organisation	John Moult, Krzysztof Fidelis	CASP and the blind test.

which is what a clinician with a patient's variant most wants to know, and before AlphaFold 3 it ignored the drugs, metals and partners that proteins bind. The organisers' introductory presentation at CASP14 ended with a slide listing several of these as the next problems, under the heading "Not an end, but a Beginning". Confidence scores help, but Terwilliger's comparison showed that even the most confident predictions contain errors that matter at the level of chemistry. A predicted structure in a database looks exactly like an experimental one, and the risk that it will be treated as one is real.

The archive behind the algorithm. AlphaFold learned from about 170,000 structures, each the product of months or years of experimental work, deposited over half a century by crystallographers, NMR spectroscopists and electron microscopists who were not on the paper and were not in Stockholm. It also depended on sequence databases built by the genome projects, on the co-evolutionary statistics developed by Sander, Weigt, Marks and their colleagues, and on the benchmark that Moult and Fidelis kept running for a quarter of a century, largely on government grants. The Nobel Committee's own background document cites much of this work, and the rules of the prize allow at most three laureates. But the popular story, in which a technology company solved biology's grand challenge, makes the archive invisible. The habit of open deposition that made the PDB possible was a choice made by a community in the 1970s, and its value was realised fifty years later by people outside it. The same is true of Foldit in a smaller way: the players who solved the monkey-virus protease are credited as "Foldit Contenders Group", which is more credit than most volunteers receive and less than an author's.

Open and closed. AlphaFold 2 was released with its code, and the AlphaFold database is free to all; these decisions spread the method faster than any paper could have done. Al-

phaFold 3 was not, at first: *Nature* published a paper whose central method readers could not run, and DeepMind defended a server-only release as a balance between access for researchers and the commercial interests of Isomorphic Labs, a company now raising billions for drug discovery. The code came six months later with restrictions. Meanwhile CASP, the neutral referee, survived its funding crisis in 2025 on a gift from the most successful competitor it had ever judged. None of this was improper, but it shows how much the field's openness depended on the choices of a single company. The commercial story has also run ahead of the evidence. Knowing a protein's structure is one step in drug discovery, and rarely the slowest; molecules still have to be made, tested in animals and run through clinical trials that take years and mostly fail. Hassabis's own timetable for Isomorphic's first trials slipped by a year. Experimental structures have guided drug design for decades, and the honest claim for AlphaFold is that it has made that step much cheaper, not that it has abolished the others.

Prediction without understanding. The energy-landscape theorists explained why proteins can fold; Rosetta combined a physical model with statistics drawn from known structures; AlphaFold learned a mapping from sequence and alignment to structure from data, and the reasons for any particular prediction lie in millions of learned parameters. It predicts what shape a protein adopts without saying how the chain gets there, and it relies on evolutionary information, so it does far better on natural proteins with many relatives than on a single sequence alone. Ken Dill and Justin MacCallum had distinguished three protein-folding problems in 2012: the code that links sequence to structure, the mechanism by which folding happens, and the practical task of prediction. AlphaFold transformed the third. Whether it has solved or sidestepped the first two is still argued. Some researchers, among them AlQuraishi, have described structure prediction as only one part of a much larger problem; Nazim Bouatta, a theoretical physicist at Harvard Medical School, put it more briefly: "Structure is not the final story."[20] It is possible that the networks have learned something close to the physics; some analyses suggest that they encode an approximation of the energy landscape. It is also possible that a field which once wanted to understand folding has accepted, because the results are so useful, a tool that predicts it instead. The borders this chapter celebrates were crossed by people looking for answers, and they found them. Not every answer was an explanation.

Coda

Lupas's receptor, Af1503, is a modest protein from a heat-loving microbe. His group had good data for almost a decade and could not use them; a model from a stranger's computer made them usable in half an hour. The data came first. The model was right because tens of thousands of earlier structures had been deposited, and was known to be right because the diffraction pattern said so. In Anfinsen's test tube, sixty years before, the chain had found its shape in a few hours with no help from anyone. Predicting where it would end up took most of the intervening time, a dozen disciplines and a great many people. How it gets there is still an open question.

Notes

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Further Reading

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Ken A. Dill and Justin L. MacCallum, "The Protein-Folding Problem, 50 Years On," *Science* 338 (2012): 1042–46. The state of the field just before deep learning, and the clearest statement of the three distinct folding problems.

Ken A. Dill and Hue Sun Chan, "From Levinthal to Pathways to Funnels," *Nature Structural Biology* 4 (1997): 10–19. The best introduction to energy landscapes, with the golf-course and funnel pictures.

Martin Karplus, "The Levinthal Paradox: Yesterday and Today," *Folding & Design* 2 (1997): S69–S75. A short, wry account of what Levinthal said and what was later made of it.

Seth Cooper et al., "Predicting Protein Structures with a Multiplayer Online Game," *Nature* 466 (2010): 756–60. The founding Foldit paper, readable by non-specialists, with a good account of what players did better than the algorithm.

Faruck Morcos et al., "Direct-Coupling Analysis of Residue Coevolution Captures Native Contacts across Many Protein Families," *Proceedings of the National Academy of Sciences* 108 (2011): E1293–1301. For readers who want the statistical physics of co-evolution in full.

John Jumper et al., "Highly Accurate Protein Structure Prediction with AlphaFold," *Nature* 596 (2021): 583–89. The paper itself; the main text is accessible, and the long supplementary information describes every component.

Andrei N. Lupas et al., "The Breakthrough in Protein Structure Prediction," *Biochemical Journal* 478 (2021): 1885–90. A short first-hand account of CASP14 by one of its assessors, including the Af1503 test.

Thomas C. Terwilliger et al., "AlphaFold Predictions Are Valuable Hypotheses and Accelerate but Do Not Replace Experimental Structure Determination," *Nature Methods* 21 (2024): 110–16. The most careful independent check of how good the predictions are, and the best antidote to hype.

Will Douglas Heaven, "This Is the Reason Demis Hassabis Started DeepMind," *MIT Technology Review*, 23 February 2022. A readable account of DeepMind's route to protein folding, based on interviews with Hassabis.

Epilogue: The Post-Disciplinary Future

Returning to Cambridge

Nearly two centuries have passed since the British Association met in Cambridge in 1833 and, by William Whewell's anonymous account, someone proposed a word for the people in the room. He wanted it because their sciences were drifting apart, and he hoped that a common name might help to hold them together. Within a few years he was naming the fragments as well. The tension between those two impulses runs through every chapter of this book.

The twelve stories did not resolve it, and they were not meant to. What they offer is evidence: about what crossed between disciplines, how it crossed, what it cost, and under what conditions it went well or badly. This Epilogue sets out what that evidence seems to show, and what it might mean for the problems now in front of science and for the people who will work on them.

What Crossed, and How

Methodological smuggling was the most reliable of the three mechanisms. When a tool moved into a field that already had a sharp question, the field could judge the result by its own standards, and the answer usually held. Snow's comparison of death rates by water company (Chapter 1), Luria and Delbrück's fluctuation test (Chapter 3), Gray and Hancock's resistive force theory (Chapter 8) and the iridium measurements at Gubbio and Stevns Klint (Chapter 9) are still taught, in recognisable form, in the fields that received them. The smuggled tool did not need its new users to share the world-view of the field it came from. It needed only to give a number they could check.

Smuggling did not, however, guarantee that the answer would be accepted quickly. Snow's analysis was right in 1855 and accepted only after his death. The iridium anomaly was measured in 1978, and the crater that confirmed its meaning was not published until 1991. A smuggled method can produce a result faster than the receiving field can build the community able to evaluate it, and the delay is part of the cost.

Structural isomorphism produced the deepest insights and the worst errors, and the line between them was usually the line between equations and resemblances. Where the shared structure could be written down and tested, it carried real knowledge across the border. The feedback equations that described an overcorrecting gun also described intention tremor (Chap-

ter 6). The equations of viscous flow that govern a sinking corkscrew also govern a swimming bacterium (Chapter 8). The statistical mechanics of spin glasses explained why evolved proteins fold and random chains do not (Chapter 12). Where the shared structure was only a likeness, as with Thompson's jellyfish and falling drops (Chapter 2), the cyberneticians' feedback loops in societies (Chapter 6), or the claim that adaptive systems evolve to the edge of chaos (Chapter 10), it inspired more than it explained, and sometimes it misled. The test that separated the two cases was usually simple: did the isomorphism make a prediction that someone could check, and did anyone check it?

The trading zone turned out to depend less on buildings than on objects. The pidgins that worked in these chapters formed around something concrete that both sides could handle: the equivalent circuit at the Radiation Laboratory (Chapter 5), seven agreed phages and a single strain of bacterium (Chapter 3), the reference genome and its browser (Chapter 11), and the blind targets of CASP (Chapter 12). Trading zones built under compulsion, with a single goal and a clear test, were very productive, but their working arrangements rarely outlasted the emergency, even where their people and institutions did (Chapters 4 and 5). The Macy conferences, which had neither compulsion nor a shared object, produced a vocabulary that spread widely and a common theory that never arrived (Chapter 6). The Santa Fe Institute showed that a trading zone can be made permanent, and that permanence does not guarantee that its grandest claims will hold; its most useful product may have been the habit of letting its own members test and publish against its ideas (Chapter 10).

What the Costs Showed

The Introduction promised that the costs of crossing would be part of the argument. Taken together, the twelve "Costs of Crossing" sections say three things that the successes alone would not.

First, the costs are not exceptions. Every chapter has them. In almost every story the crossing took longer than the popular version allows, credit went to fewer people than did the work, and the field being entered had reasons for its resistance that later accounts dismissed. The stories of lone outsiders defeating closed establishments were, almost without exception, wrong in their details and misleading in their lesson.

Second, the hardest step was often taken by insiders. The physicists who came to biology in the 1930s were looking for a paradox that was not there; the double helix was solved at the level of chemistry, and the pairing of the bases came from a chemist's correction of a textbook and from Watson's attention to replication (Chapters 3 and 7). Physics told Berg and Purcell how well a bacterium could sense its environment; genetics and biochemistry found how it actually did so (Chapter 8). Palaeontologists supplied the method for reading a sudden extinction in a patchy fossil record (Chapter 9). A border crossing frequently reframed a problem that the home discipline then solved.

Third, the costs fell unevenly. They fell on people whose work was hidden by secrecy, on

people whose contributions did not fit the story that was later told, and on people for whom the borders of their time meant more than an academic boundary: refugees from fascist Europe, prisoners of the Soviet state, a codebreaker prosecuted for his sexuality, a woman kept out of the room where her male colleagues took coffee after lunch. The history of interdisciplinary science is not only intellectual history, and it should not be told as if it were.

Recent studies of how research is funded and rewarded suggest that some of these costs are structural and continuing. An analysis of almost nineteen thousand proposals to the Australian Research Council over five years found that the more interdisciplinary a proposal was, the less likely it was to be funded. A study of some nine hundred scientists found that those whose work was more interdisciplinary were more widely cited but published less, which the authors put down to the extra difficulty of planning and carrying out research that spans fields; the penalty was smaller for people who kept working with the same collaborators.[1] Snow's problem, that no single reviewer is competent to judge every part of a cross-disciplinary argument, has not gone away.

Conditions That Help, Conditions That Hurt

No set of twelve histories can provide a formula. But some conditions recur often enough in these chapters to be worth naming.

A shared problem with a clear test. Crossings went fastest when everyone could see whether they had worked. At Bletchley the test was whether the decrypt read as German (Chapter 4). At CASP it was the distance between a prediction and an unpublished experimental structure (Chapter 12). Snow's natural experiment turned an argument about theories into a comparison of rates (Chapter 1). Where no such test existed, as in much of cybernetics and complexity science, enthusiasm filled the gap.

A pidgin built around shared objects. The successful trading zones did not ask their members to agree about everything. They agreed about a few things that could be passed back and forth: a circuit diagram, a strain of bacteria, a set of coordinates, a file format.

People who speak two languages. Almost every successful crossing had at its centre someone fluent in two fields. Luria was a physician with radiological training who had learned enough physics to talk to physicists (Chapter 3). Franklin brought a physical chemist's command of disordered materials to biological fibres (Chapter 7). Jim Kent had spent most of his working life writing graphics and animation software before he went back to university to study molecular biology (Chapter 11). John Jumper combined theoretical physics with years of protein simulation, and was already applying machine learning to folding in his doctoral work (Chapter 12). These people did not replace the specialists around them. They made it possible for the specialists to work together.

Protected time and space. The phage course at Cold Spring Harbor gave physicists and chemists a few intensive weeks in which to learn the methods of a new field, and it ran for twenty-six years (Chapter 3). The Research Laboratory of Electronics gave linguists, acousti-

cians and engineers room in a temporary wartime building that MIT kept for half a century (Chapter 5). Santa Fe gave its visitors freedom from departments and teaching (Chapter 10). Chapter 5 warns against crediting the buildings themselves; what mattered was time, money and the licence to work on a problem that belonged to no one.

Open data and common benchmarks. The Bermuda Principles, which put the human sequence into public databases within a day of its being read (Chapter 11), and the Protein Data Bank, filled over half a century by crystallographers who released their structures for others to use (Chapter 12), allowed people from other fields to enter without asking permission. A benchmark such as CASP allowed them to show that they had something to offer.

Against these stand four conditions that recur on the other side.

Secrecy, which erased the Polish codebreakers and the builders of Colossus from the record for a generation (Chapter 4), and, through commercial confidentiality, helped to keep a crater out of academic view for more than a decade (Chapter 9).

Hype, which sold the genome to legislators as a cure for common disease (Chapter 11), turned information theory into what Shannon called a bandwagon (Chapter 6), and put slogans in the titles of books before the evidence was in (Chapter 10).

Status hierarchies, which let a physicist dismiss palaeontologists as stamp collectors (Chapter 9), let senior men pass a junior colleague's data to her competitors (Chapter 7), and made it easy, in story after story, to credit the visitor from the higher-status field with the discovery.

Analogy without mechanism, the characteristic failure of the most exciting of the three mechanisms, which runs from Thompson's grids (Chapter 2) to the companion star that was supposed to send comets towards the Earth every twenty-six million years (Chapter 9).

The Problems in Front of Us

It is sometimes said that all the most urgent questions now facing science are post-disciplinary. That is too strong. Most good science is still done within disciplines, and much of it needs to be. But several of the largest problems of the present cannot be stated, let alone solved, within any one field, and each of them shows the patterns of the earlier chapters.

Climate. The World Meteorological Organization reported that 2024 was probably the first calendar year in which the global average temperature was more than 1.5 °C above the pre-industrial level, at about 1.55 °C, with an uncertainty of about 0.13 °C. A single year above that threshold is not the same as the long-term warming to which the Paris Agreement refers, but the direction is not in doubt.[2] Understanding and responding to it requires atmospheric physics, oceanography, chemistry, ecology, economics and politics, and the joins between them are where the difficulties lie. Integrated assessment models, which couple climate projections to economic models in order to estimate the cost of carbon emissions, are a trading zone of exactly the kind this book describes. The economist Robert Pindyck has argued that their damage functions and discount rates are so weakly grounded that the precision of their outputs is largely

illusory.[3] The Intergovernmental Panel on Climate Change, which turns the literature of many disciplines into assessments that governments approve line by line, is a trading zone between science and politics, and it shows how much depends on who sets the terms. In October 2026, at a session in Addis Ababa, governments suspended their meeting without agreeing when the working-group reports of the panel's seventh assessment should appear, and in particular whether they should be ready for the global stocktake under the Paris Agreement that concludes in 2028.[4]

Machine learning has entered the physical side of the problem too. Since February 2025 the European Centre for Medium-Range Weather Forecasts has run an operational forecasting model that learned the behaviour of the atmosphere from data rather than computing it from the equations of fluid dynamics. Like AlphaFold, it rests on an archive built by other methods: it was trained mainly on a reconstruction of past weather produced by the centre's physics-based system, and it starts each forecast from that system's analysis of current observations.[5] The new method does not replace the old one; it depends on it.

The brain. In October 2024 a consortium of more than a hundred laboratories published a complete wiring diagram of the brain of an adult fruit fly: some 139,000 neurons and about fifty million synaptic connections, traced first by artificial intelligence and then checked and corrected by scientists and volunteers. In April 2025 another consortium described a cubic millimetre of mouse visual cortex, with about 200,000 cells and more than five hundred million synapses, in which the activity of many of the neurons had been recorded while the animal watched films before the tissue was sliced and imaged.[6] These projects joined neurobiology, electron microscopy, machine learning and large-scale data management, and they are among the clearest current examples of crossing organised around shared objects and open data. They also raise the question with which Chapter 12 ended. A wiring diagram is not an explanation, any more than a predicted structure is an account of folding.

The brain also offers a cautionary case. The Human Brain Project, funded by the European Union from 2013 to 2023 at a cost of more than six hundred million euros, was criticised early by hundreds of neuroscientists in an open letter that objected to its governance and to the dominance of computer simulation over experimental and cognitive neuroscience; an independent review in 2015 called for corrective action and for the project to describe its goals realistically. It left behind a shared digital infrastructure that is still in use.[7] It is the kind of story this book has told several times: a trading zone whose terms were set by one of the parties, and a promise larger than the evidence.

Artificial intelligence and science. Chapter 12 described the most dramatic case so far of a method from computer science transforming a problem in another field, and the Nobel Prizes of 2024 recognised both that case and the neural networks on which it rests. The pattern of the earlier chapters suggests what to watch for. A study of research that used machine learning in seventeen fields found errors of a single kind, *leakage*, in which information from the test data finds its way into training and makes a method look better than it is, in 294 published papers.[8] That is Farr's problem in a new form: an imported method carrying blind spots that its new users did not know to look for. The anthropologist Lisa Messeri and the cognitive scientist

Molly Crockett have argued that AI tools can give researchers the impression that they understand more than they do, and can narrow the range of questions and methods a field pursues.[9] The opposite risk is also real: that the people who know a field best will dismiss a new tool because it comes from outside, as Snow's critics dismissed him. The histories in this book suggest that the useful response is neither. It is to treat the new method as Terwilliger's group treated AlphaFold's predictions: as valuable hypotheses, to be tested against the data by people who know what the data mean (Chapter 12).

Bilingual Scientists

If these histories have a lesson for education, it is not that every scientist should become a generalist. The border-crossers in this book were nearly all deep specialists first. The lesson is closer to bilingualism: depth in one field, and enough fluency in a second to work with the people who practise it.

Fluency here means more than vocabulary. The sociologists Harry Collins and Robert Evans have described what they call *interactional expertise*: the ability to talk the language of a specialist field well enough to understand its arguments and ask good questions, without being able to contribute to it directly.[10] The most important part of that language is a field's standard of evidence: what its members accept as a result, what they regard as an explanation, and what mistakes they have learned, often painfully, to avoid. Most of the failures in this book came from crossers who learned another field's vocabulary but not its standards. Luis Alvarez's mistake was not to bring physics into palaeontology; it was to treat palaeontologists' caution as ignorance (Chapter 9). The economists who resisted the Santa Fe models had reasons, rooted in hard experience with models that could explain anything, that the story of the enlightened outsider left out (Chapter 10).

Several practical consequences follow, none of them new. Students can be taught, early, to work on problems that belong to more than one field, alongside people trained differently from themselves. Short, intensive courses that teach the methods of one field to people from another have a long record, from the phage course onwards. Funders have created schemes for people who cross: the Burroughs Wellcome Fund's Career Awards at the Scientific Interface, for example, have since 2002 supported physical and computational scientists moving into biology.[11] And universities and funders can change the way they judge such work. A report from the American national academies observed in 2005 that hiring, promotion, tenure and grant review tend to favour work within established disciplines, and recommended ways to correct that.[12] The funding study described above suggests that, two decades on, the correction is incomplete.

The histories also suggest something less often said. Training for border-crossing should include the history of border-crossing, and in particular its costs. A student who knows how Farr's statistics misled him, why Thompson's analogies failed, and what secrecy did to the people of Bletchley is better prepared to cross than one who has heard only the triumphs. The question a bilingual scientist asks of a colleague from another field is not only "How does your discipline see this problem?" It is also "How would your discipline know if I were wrong?"

Chalk Lines

It may be better to think of the boundaries drawn in the nineteenth century not as fences but as chalk lines on the grass. That is a truer image than the silo with which this book began. A silo is solid and keeps things apart. A chalk line marks out a pitch on which a particular game can be played well. It tells the players where the boundaries are, so that they can agree on the rules. It wears away with use and has to be redrawn, and the lines are drawn differently from one season to the next. The grass runs on underneath.

The twelve chapters suggest that the lines were not drawn by nature, but that they were not drawn for nothing either. The best work in this book was done by people who knew exactly where the lines were, because they had played inside them, and who were free, when a problem required it, to step across. Whewell's word has outlasted his worries. *Scientist* names what people in different fields still have in common, and the fields themselves have multiplied far beyond anything he imagined. Both of his coinages turned out to be needed.

Notes

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[2]World Meteorological Organization, *State of the Global Climate 2024* (Geneva: WMO, 2025), released 19 March 2025, https://wmo.int/media/33461.

[3]Robert S. Pindyck, "Climate Change Policy: What Do the Models Tell Us?," *Journal of Economic Literature* 51, no. 3 (2013): 860–72.

[4]Climate Action Network, "IPCC AR7 Session Suspended, Deeply Disappointing Says CAN," 16 October 2026, https://climatenetwork.org/2026/10/16/ipcc-ar7-session-suspended-deeply-disappointing-says-can/. On the dispute over the timeline, see "IPCC: 'Frustrating and Disappointing' Meeting Leaves AR7 Timeline in Deadlock," *Carbon Brief*, 1 April 2026.

[5]European Centre for Medium-Range Weather Forecasts, "ECMWF's AI Forecasts Become Operational," 25 February 2025, https://www.ecmwf.int/node/29308; Simon Lang et al., "AIFS: ECMWF's Data-Driven Forecasting System," arXiv:2406.01465 (2024).

[6]FlyWire Consortium, Sven Dorkenwald et al., "Neuronal Wiring Diagram of an Adult Brain," *Nature* 634 (2024): 124–38; MICrONS Consortium, "Functional Connectomics Spanning Multiple Areas of Mouse Visual Cortex," *Nature* 640 (2025): 435–47. Figures are from the papers and from the institutions' announcements.

[7]"Brainstorm: Neuroscientists Protest against Europe's Human Brain Project," *Science|Business*, 10 July 2014; "Europe's €1B Human Brain Project Needs Urgent Reform, Report Says," *Science|Business*, 11 March 2015; "Neuroscience Project Completes 10-Year Runtime," *Healthcare in Europe*, 2023, https://healthcare-in-europe.com/en/news/human-brain-project-end-decade-insights.html.

[8]Sayash Kapoor and Arvind Narayanan, "Leakage and the Reproducibility Crisis in Machine-Learning-Based Science," *Patterns* 4, no. 9 (2023): 100804.

[9]Lisa Messeri and M. J. Crockett, "Artificial Intelligence and Illusions of Understanding in Scientific Research," *Nature* 627 (2024): 49–58.

[10]Harry Collins and Robert Evans, *Rethinking Expertise* (Chicago: University of Chicago Press, 2007).

[11]Burroughs Wellcome Fund, "Career Awards at the Scientific Interface," https://www.bwfund.org.

[12]National Academy of Sciences, National Academy of Engineering, and Institute of Medicine, *Facilitating Interdisciplinary Research* (Washington, DC: National Academies Press, 2005).

Further Reading

Harry Collins and Robert Evans, *Rethinking Expertise* (University of Chicago Press, 2007). A short, argumentative book that distinguishes kinds of expertise, including the "interactional" kind that border-crossers most need.

National Academy of Sciences, National Academy of Engineering, and Institute of Medicine, *Facilitating Interdisciplinary Research* (National Academies Press, 2005). The standard policy report, with surveys of researchers and university leaders; dated in places, but still the clearest statement of the institutional obstacles.

Lisa Messeri and M. J. Crockett, "Artificial Intelligence and Illusions of Understanding in Scientific Research," *Nature* 627 (2024). A careful account of what researchers hope for from AI and of the ways it might narrow science.

Robert Frodeman, ed., *The Oxford Handbook of Interdisciplinarity*, 2nd ed. (Oxford University Press, 2017). A wide-ranging collection on the theory and practice of interdisciplinary work, for readers who want the scholarly literature.