PART I

Basic Neuropharmacology
SOUP OR SPARKS: THE HISTORY OF DRUGS AND SYNAPSES

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1.1 ACTION OF CURARE

Claude Bernard (1813–1878; Fig. 1.1a) recalled that, “in 1845, Monsieur Pelouze gave me a toxic substance, called curare, which had been brought to him from America” [1]. He injected some into a frog. The frog became paralyzed. A “physiological dissection” showed that the heart was beating, blood was flowing, and the intestines were motile. He stimulated motor nerves with a shock from an inductorium powered by a battery made of alternating zinc and copper plates charged with vinegar. In the curarized frog the muscles contracted when stimulated, but not when the motor nerve was shocked. Curare might be blocking nerve conduction. To check this, he prepared a pithed frog, ligaturing off the arterial circulation to the legs but leaving their nerves intact. When he stimulated the nerve running down the leg, the muscles contracted. Then he injected curare. The upper part of the frog’s body became flaccid and respiration stopped. When he pinched the skin on the frog’s back, the legs were pulled up, just as in a normal frog. In the curarized anterior part of the frog the sensory nerves and spinal cord obviously worked even though the motor nerves did not. Muscles throughout the preparation contracted when stimulated directly. The drug acted on motor nerves. In isolated nerve–muscle preparations the muscle contracted when it or the nerve was stimulated. When the nerve was soaked in curare solution, the muscle still responded to nerve stimulation. When the muscle was soaked in the drug, it no longer contracted when the nerve was stimulated but did contract when stimulated directly. The poison does not block most of the motor nerve; it acts somewhere after the nerve has entered the muscle.

To us Bernard’s work with curare is straightforward science. To his contemporaries it was a dazzling display of how experiments can reveal how the body works and vivid proof that a drug may target a specific site in the body [3]. According to Bernard’s student, Paul Bert, Bernard had a “love of certainty” [4]. “He discovered as others breathed.” He was aware not only of “the endless multiplicity of unknown data in physiology, but also their subordination to the general laws of matter and their obedience to experimental method.” The thesis of this chapter is that working out precisely how curare acts provided the conceptual framework for much of neuropharmacology.

Bernard found that low doses of curare paralyzed the limb muscles but did not block the contractions of the diaphragm. These animals lived and recovered when

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aTo keep the bibliography within bounds many references are to reviews rather than original papers. Information about the lives and works of Nobel Laureates come from nobelprize.org. Information about individual drugs is from [2], which has excellent historical sections.
they rid themselves of the drug. Curare introduced into the stomach did not poison the animal. When the gastric juice was removed and injected, it paralyzed the subject. Hence curare was not absorbed from or destroyed by the stomach. He considered curare to be “an instrument which dissociates and analyzes the most delicate phenomena of the living mechanism” [5].

His experiments were bedeviled by using different preparations of the drug; curare is a generic term for arrow poisons from the Amazon Basin [6]. After its discovery by Europeans it was years before Alexander von Humboldt (1769–1859) found an old native who had “the impassive air and pedantic tone formerly found in the European pharmacist” and who showed him how it was done. It was a water extract of the bark from a climbing vine of the genus *Strychnos*—which took a knowing eye to identify—with the water boiled off to leave a tar-like residue. By the 1880s chemists had found that there are different alkaloids in the curare from different regions which were categorized by their packaging: pot, calabash, and tube. The latter was the most potent and its active principle is ($\oplus$)-tubocurarine chloride hydrate ($\oplus$ TC). All but the finer points of its structure were worked out in the 1930s (Fig. 1.2).

### 1.2 BERNARD’S CAREER

Bernard presented his work on curare to the French Academy of Sciences, which met weekly. The academy was founded in 1666. In 1835 it began to issue the *Comptes Rendus*, where Bernard published [7]. He also wrote books describing his major discoveries, and his popular article on curare thrilled readers with his vivid description of the curarized animal: “All though the ages poetic fiction has sought to awaken our pity by representing living creatures locked in inanimate bodies” [8]. His early discoveries established his reputation and in 1854 he was appointed to a new chair in general physiology at the Sorbonne. It was a time when many universities were building up science. In 1858 he moved to the chair of medicine at the Collège de
France. The Emperor Napoleon III, after a lengthy talk at a social gathering, had a laboratory built for him in 1864. He joined the “40 immortals” in the Académie Française in 1868, and the next year was appointed to a seat in the Senat.

He was born in the village of St. Julian to a family of Burgundian vintners [9]. His father was a poor school master. As a lad he wanted to be a writer. At 19 he came to Paris “with almost no paraphernalia except a tragedy which had never been acted and a farce-comedy which had some success at a small theater in Lyons” [4]. He carried an introduction to a prominent critic, who read his work and advised him to take up a profession and write on the side. In medical school he was a mediocre student; in the final examination he placed 26 out of 29. He had a talent for doing beautiful dissections, which is why the physiologist François Magendie (1783–1855) asked him to assist in preparing facial nerves for experiments. Magendie had demonstrated the separation of motor and sensory nerves in the roots of the spinal cord and in 1821 had founded the first physiological journal: the Journal de Physiologie Expérimentale. The leading French pharmacists were isolating potential drugs from plants; Magendie often tested their products. Had he tested curare it would probably have satisfied him to observe the paralysis. Once in a laboratory all of Bernard’s hitherto hidden talents flashed into view. He influenced many by his teaching. The scientific content of Bernard’s lectures was high, but organization might collapse. If his line of thought “escaped him, he followed it without rebellion, leaving his speech drooping, his lecture in confusion, while he listened softly to what it said to him” [4].

His personal life was deeply troubled. He married for money. His wife wanted him to practice medicine—as Magendie always did—so they would have a splendid
income. Bernard had time only for science. Even more troubling she was an ardent opponent of vivisection, writing her husband long letters denouncing his practices and enlisting their two daughters in her cause. When he fell ill at the end of 1877, he diagnosed his own doom [10]. Experiments, including some with curare, were unfinished: “What a pity, it would have been good to finish it” [4]. He was the first scientist given a state funeral in France.

The story of the action of curare I have presented so far is, as any working scientist will appreciate, far too simplified. There was an appreciable literature before Bernard, primarily showing the deadly effects of the poison were due to suffocation; artificial respiration kept curarized animals alive [6]. After Bernard published his results, Alfred Vulpian (1826–1887) proposed that the target for curare is the motor end plate of the muscle fibers, which had just been discovered [11, 12]. One of Bernard’s students then described in detail the motor end plates in lizard muscles and thought that he could distinguish those that had been exposed to strong curare solutions from normal [13].

1.3 SCIENTISTS, PATRONS, AND MONEY

There is a fundamental difference between the histories of science and scientists and those of art and artists or politics and politicians. Without Michelangelo the painting on the ceiling of the Sistine Chapel would be completely different; without Claude Bernard we would still know where curare acts—and all of his other discoveries as well. Scientists are placing pieces in a jigsaw puzzle that is predetermined by the laws of nature and evolutionary history—physical and organic. But this does not mean that great scientists are less important than great artists, musicians, or politicians. Bernard and his contemporary Louis Pasteur (1822–1895) led by sweeping the cobwebs of vitalism out of French biology. Their fame stimulated public interest in and support for science. Thinking of public support reminds us of another aspect of history that is too often slighted. Michelangelo and his assistants painted the ceiling of the Sistine Chapel, but only because of Pope Julius II. He compelled Michelangelo to move to Rome to repaint the ceiling and financed the project from the vast resources of the Catholic Church. Paying for the salaries, supplies, laboratories, and the like is even more important in science. Hence, as we go along, I will call attention to some patrons of science and to some of the sources of funds for paying for research.

1.4 A CHANGING WORLD

In Bernard’s lifetime Europe changed almost beyond comprehension. He came to a Paris of medieval streets. When he died it was crisscrossed by wide boulevards lined with stone-faced apartments and shops with large glass windows under wrought-iron balconies and shining at night in the light of gas lamps. Over the nineteenth century the population of Europe increased almost fourfold, despite millions emigrating for opportunities elsewhere. The world population had started growing rapidly at the beginning of the eighteenth century (Fig. 1.3a) [14]. A major reason for such rapid growth was improvements in agricultural practice. With better nutrition people lived longer. With more people who took in more energy for work there was an explosive
expansion of industry. The energy of the workers was then supplemented by energy from fossil fuels trapped as steam. Over the nineteenth century the gross domestic product (GDP) per capita more than doubled (Fig. 1.3b). The increases in wealth and population led to the founding of universities and medical schools (Fig. 1.3c). The number of scientists was rapidly expanding. In France, the medieval universities had been torn asunder by the revolution. They were reformed and supplemented by the establishment of new schools specifically oriented to training in the professions. They were all supervised by the Université de France.

There was also an explosion in the availability of information. Steam presses slashed the cost of printing. There was an enormous increase in newspaper

Figure 1.3  Some of the changes in the modern era. (a) World population. Note the change in rate at about 1700. To my mind the growth of science follows a similar curve. The estimated population at year 0 is about 200 million. (Data from Robert W. Fogel, Nobel Laureate in Economics, 1993) [14]. (b) The rise in the GDP in the Netherlands and the increase in national wealth. The Netherlands was chosen for the example because of the reliability of the data from the Groningen Growth and Development Centre [www.ggdc.net]. (c) The numbers of still-existing medical schools in Germany and France as a function of time. (d) The number of newspapers printed on a weekday in London. The bar for 1821 is too small to be seen, so the figure is indicated above it [15].
circulation (Fig. 1.3d) [15]. Therefore many citizens knew of Bernard’s work on curare and of advances in medical care, like the development of anesthesia—positive reinforcements for supporting science.

1.5 GERMAN-SPEAKING UNIVERSITIES

A political map of the Germany of 1800 shows a hodgepodge of kingdoms, principalities, bishoprics, and free cities united only by language and culture. During the Reformation the medieval universities had been taken over by the “states” [16, 17]. As population and wealth increased, so did support for the universities, and new ones were founded. Professors were expected to enlarge knowledge as well as to teach, and they decided what would be taught and what would be investigated. The goals for the universities had been enunciated by the first dean of the faculty of philosophy in Berlin, Johann Gottlieb Fichte (1762–1814), in a series of “Addresses to the German Nation” delivered in 1808–1809. Universities were built on three maxims: the freedom of the individual, of research, and of the nation. University life then was much like today; Fichte was the first rector in Berlin but soon had a conflict with the faculty and resigned.

The universities were open to all who had graduated from a classical high school, or “Gymnasium”. They had been started in 1815 and spread rapidly, and the States paid for education. There was no tuition, but some of the university lecture courses charged fees. The top 10% or so of the students worked for a doctorate, which supposedly attested to competence to work as a scholar in the field, though it was recognized that in medicine this ideal was seldom achieved.

A professorial chair was worth fighting for; as Max Weber (1864–1920) famously wrote, “many are called but few chosen”. There was a well–recognized pecking order among the universities, and professors competed to move up the ladder. The first pharmacology department was founded at the German-speaking University of Dorpat in Estonia in 1847 [18]. The first pharmacology department in Germany opened in 1849, and they spread rapidly throughout the country, partly because they were so useful to the booming German Chemical Cartel.

In 1870 Napoleon III declared war on Prussia. He found himself fighting all of the German states. After their victory they formed the German empire, and many of the states allocated part of their share of the enormous reparations extracted from the French to strengthen their universities. A major beneficiary was Strasbourg, in Alsace, which was taken over by Prussia. Oswald Schmiedeberg (1838–1921), who had studied at Dorpat, was appointed professor of pharmacology. He discovered that vagal stimulation slows the heart and became known as the “father of pharmacology” because 40 of his students obtained chairs. The professor of pathology was Bernhard Naunyn (1839–1925). In 1873 the two founded the Archiv für Experimentelle Pathologie und Pharmakologie.

1.6 MICHAEL FOSTER

Synaptic neuropharmacology would flourish in Great Britain—astonishing to anyone who had surveyed the situation there in 1850. Oxford and Cambridge were
assemblies of private corporate colleges, with their medieval, ecclesiastical roots largely unpruned [19]. Only members of the Church of England could be awarded degrees. The fellows were forbidden to marry. Pushed by German competition, they were transformed into scientific powerhouses by the leadership of men like Michael Forster (1836–1907; later Sir Michael; Fig 1.1b) [20]. Bernard was his inspiration; Foster wrote: “he has been to me as a father in our common science” [9].

Foster studied medicine at University College London (UCL)—known to its detractors as “the godless institution on Gower Street”—because he was a non conformist. He spent a year in Paris but never “saw Bernard’s face.” After six years in medical practice he became an instructor at UCL and then Fullerian professor at the Royal Institution in London. He worked on the snail heart, trying unsuccessfully to determine whether beating is myogenic or neurogenic. The choice of preparation shows his affinity for Darwin’s ideas—evolution became bedrock in British physiology. He moved to Cambridge—without a university appointment—to a teaching position at Trinity College; this sidestepped the religious and marriage problems. Foster’s remit was to develop biological science. They gave him £400—roughly $80,000 in the year 2000—for equipment, a room loaned by the university, and an assistant, Henry Newell Martin (1848–1893). A year after Foster’s arrival the religious tests at Cambridge and Oxford were abolished when Parliament, after years of acrimonious debate and reports by royal commissions, amended the charters to remove the religious requirement and to permit fellows to marry.

Foster invited interested students to see the body at work: muscles contracted, nerves conducted, exocrine glands secreted. Many found this thrilling and yearned to work on living things with their own hands. He persuaded the best to become botanists, histologists, embryologists, or physiologists—wherever there was a need. “He was a discoverer of men rather than facts” [21]. He sold research, “in this way only lies salvation”. He also provided scientists for other institutions. In 1876 he arranged for Martin to move to Johns Hopkins, which was just opening the first German-style university in the United States.

In 1878 Cambridge constructed a Biological School building, even though legally Foster and many of his staff were not part of the university. Finally in 1883, following a report by another royal commission and an act of Parliament, Foster was appointed professor of physiology. His *Textbook of Physiology*, first published in 1877, went through many editions in many languages, almost surely becoming the most widely used physiology textbook of the time [22]. It is filled with detailed descriptions of experiments and illustrations of the raw data. The 1893 edition concludes that it is not known how the motor nerve excites the muscle. Curare is not mentioned. There is no overview of the autonomic nervous system. Atropine, a product of the deadly nightshade, *Atropa belladonna*, blocks the action of the vagus on the heart and is said to act either on the muscle itself or on the “ultimate nerve endings” (Fig. 1.2). Atropine also blocks salivary and sweat gland secretions in response to nerve impulses and dilates the pupil. Muscarine is an alkaloid from the poisonous mushroom *Amanita muscaria*. Schmiedeberg was the first to isolate it and then he showed that it mimics the action of the vagus (Fig. 1.2). Drugs were known that acted on transmission between nerve and effector, but there was no integrating overview whatsoever.

In England the physiologists also taught histology. This was one of their strengths, since they all could do their own microanatomy. As his group grew, Foster turned the
teaching over to his protégés, a step that was welcomed by the students. Charles Scott Sherrington (later Sir Charles, 1857–1952, Nobel Laureate 1932), a student in the 1880s, found Foster “an appalling lecturer” and “never saw him do any demonstration” [21]. Often the young are not kind to their elders. Pharmacology came to Cambridge in 1899 in the form of Walter Ernest Dixon (1871–1931), who was appointed as an assistant to the Downing professor of medicine [23]. He had trained at St. Thomas’s Hospital London, where he worked on the addictive properties of cannabis and mescaline. “Pharmacological teaching in England, before Dixon began, was an unappetizing mixture of half obsolete material medica and empirical therapeutics. In Dixon’s hands it became a lively adventure in experimental science” [24]. The first pharmacology department in Britain opened in 1905.

Foster persuaded a rich student, Albert George Dew-Smith (1848–1903), to set up a company to manufacture apparatus. After a few years the firm was reorganized with Horace Darwin (1851–1928), Charles’s fifth son, as a partner and designer; the joint enterprise became the Cambridge Instrument Company [25]. There was a strong antivivisection movement in Britain, and in 1876 a law was enacted regulating the use of experimental animals. Concerned about how the law would operate, Foster organized the Physiological Society. It met periodically to discuss the workings of the law, but some scientific talk slipped in. Soon there were formal scientific sessions, which included the demonstrations Foster loved. Dew-Smith provided the financial support for starting the Journal of Physiology, which from the beginning had some foreign editors. Then Foster initiated international physiological congresses. The first was held in Basel in 1889. He served as secretary of the Royal Society from 1881 to 1903. His major achievement there was to persuade the fellows that it was appropriate for the society to provide scientific advice to the government.

1.7 GASKELL AND LANGLEY

Walter Holbrook Gaskell (1847–1914) followed his teacher Foster by working on the heart beat [26]. After years of careful work he showed that there are no nerve cells in the base of the ventricle of the turtle heart but that it could beat for at least 30 h when isolated—the beat is myogenic. Gaskell then worked on the structure of the involuntary nervous system, which he summarized in a book [27]. From there he turned to work on the evolutionary origin of the vertebrates. He inspired physiology students; “he spoke on controversial points with a half-suppressed enthusiasm which was eminently infectious” [24].

John Newport Langley’s (1852–1925; Fig. 1.4a) first paper began “Dr. Foster, having received from Dr. Ringer…a small quantity of the alcoholic extract of jaborandi, placed the drug in my hands and requested me to observe its physiological action” [28]. It was an extract of Pilocarpus jaborandi, a medicinal plant from South America, which contained the alkaloid pilocarpine. Langley found that pilocarpine slowed the frog heart or the beating of its isolated parts. Atropine antagonized pilocarpine. The plant was chewed to induce salivation. This led Langley to a 15-year study of salivary glands [29].

In 1890 he started working with the alkaloid nicotine, from the tobacco plant, Nicotiana tabacum (Fig. 1.2) [30]. When injected it produced a bewildering variety of
effects. He pinpointed sites of action by exposing a tissue, blotting it with a paper, and then—using a fine brush of sable hair—placing a $0.05\,\mu\text{L}$ drop of nicotine solution on its surface. He found that nicotine acted on autonomic ganglia, first exciting and then blocking, but had no effect on the pre- or postganglionic axons. Curare antagonized the stimulation by nicotine; atropine did not.

Working on frog and chicken skeletal muscles, he found that the results depended on the muscle chosen for study [31]. With a muscle like the frog sartorius, where there are seldom more than two end plates on a fiber, low concentrations of nicotine placed near the nerve endings elicited a brief burst of twitches. These are called twitch fibers. Following the contractions there was a block in neuromuscular transmission. The excitatory effect was blocked by curare at lower doses than required at the ganglia. Elsewhere on the twitch fibers there was no response unless the nicotine concentration was increased by orders of magnitude. Other muscles, like the frog rectus abdominis, are made up of fibers that are sensitive to nicotine almost all along their lengths, which became known as tonic fibers. Langley did not know that tonic fibers have end plates all along their length. The tonic fibers give a sustained contraction when nicotine is applied. Other muscles contain a mixture of the two types of fibers, so their response to nicotine was bewildering indeed. It did not faze Langley, who preached “get facts, then theory will take care of itself” [20]. Muscle denervated 100 days earlier still responded to nicotine. His view on the mechanism was based on Paul Ehrlich’s (1854–1915; Nobel Laureate 1908) hypothesis that protoplasm is one giant molecule and that drugs act on its side chains. Hence Langley concluded that the drug acts “directly on the muscle. In the muscle there are two substances to take into account, the sarcoplasm and the differentiated contractile substance. ...I take it that the contractile molecule has a number of ‘receptive’ or side-chain radicals, and that nicotine, by combining with one of these causes tonic contraction, and by combining with another, causes twitching, and that the latter is a much less stable part of the molecule” [31].
He summarized the anatomy and physiology of the autonomic nervous system in a book in which he described the evidence for two components, which he named sympathetic and parasympathetic [32]. The effects of parasympathetic stimulation are mimicked by muscarine, pilocarpine, and choline and blocked by atropine. He called these cholinophil. Most effects of sympathetic stimulation are mimicked by adrenaline (see below) and were called adrenophil. Sympathetic stimulation causes sweat glands to secrete but adrenaline does not. Sweating is blocked by atropine and stimulated by choline and the rest. In his view, there were cholinophil and adrenophil receptors, but they could be either excitatory or inhibitory depending on the chemical changes in the tissue when the drug combined with the receptor.

Langley edited the *Journal of Physiology* for 30 years. Edit is too light a word. Almost invariably he would heavily correct papers and sometimes he would rewrite them completely. When Foster left, Langley became professor of physiology. He had much to do. The staff was excellent, the facilities deplorable. Three investigators shared a former coal cellar. Finally in 1914 a splendid new building was opened paid for by a London company, the Drapers’. Companies such as this are descendents of the medieval guilds which are now given over to good fellowship and good works. His research was supported by grants from the Royal Society and the British Medical Association. He inspired students by how relentlessly he worked at a problem and with his success in putting together the puzzle, not by warmth of personality. Langley was a brilliant figure-skater. One student thought this caught his essence: “brilliant technique on an icy background” [29].

1.8 **THE SYNAPSE**

Langley’s papers at the beginning of the twentieth century vividly show the uncertainties about the pathway from nerves to muscles or glands. Was there cytoplasmic continuity? Were cells surrounded by membranes, and if so was there a gap between the nerve and the structure it innervated? The best microscopes revealed no membrane and no gap. Most electrophysiologists were convinced that the unseen membranes existed and thought that nerve impulses were transmitted by momentary changes in their properties [33]. In 1897 Sherrington proposed that the attributes of reflexes are due to the properties of the junctions between individual nerve cells, at structures he called synapses [34]. He pictured the synapse as a gap between the neurons bounded by the apposing membranes of the two cells. Synapses accounted for one-way conduction in the reflex arc and for the delay added onto the passage of the nerve impulses traversing the arc. However, synaptic delay is extremely short and transmission can be repeated at short intervals. Too fast, they argued, for a chemical reaction between a hypothetical transmitter and receptor, let alone further chemical reactions to produce an effect. Transmission must be electrical, just as it is down the nerve axon.

Camillo Golgi (1843–1926) and Santiago Ramón y Cajal (1852–1934) shared the Nobel Prize for Physiology or Medicine in 1906 for their work on the structure of neurons. They developed treatments that stained randomly selected neurons in their entirety: cell bodies, axons, and dendrites. Cajal argued that therefore there is no continuity between the cytoplasm of the individual neurons. As he said in his lecture, “it must be admitted that the nerve currents are transmitted from one
element to another as a consequence of a sort of induction or influence from a
distance.” Golgi was more cautious, suggesting that at least some parts of the brain
were made of an extensive reticulum rather than individual cells.
The Nobel Prizes, first awarded in 1901, rewarded outstanding investigators and
publicized scientific progress. Citizens were elated when a fellow countryman won a
Nobel Prize and were willing to see more of their taxes go toward science so they
might do better in the international competition.
Ross Harrison (1870–1959) did not receive the Nobel Prize voted for him because
none were awarded in 1917 due to the “Great War” [35]. Harrison placed bits of frog
spinal cord in a drop of lymph on a sterile cover slip sealed over a hollow slide. For
weeks he watched axons grow out from a ganglion cell, sometimes at a rate of 50
µm/h. The axons grew out to muscle fibers in the culture, which then contracted
spontaneously [36]. There must be a synapse between the motor nerve and muscle.

1.9 DALE AND LOEWI

Among the Cambridge students inspired by Langley and Gaskell was Henry Hallett
Dale (1875–1968; later Sir Henry) [37]. He did well in physiology and was awarded a
research fellowship which enabled him to spend two years preparing a thesis as a
candidate for a fellowship at Trinity College. Under Langley’s direction Dale did a
morphological census of the various classes of fibers in a mixed nerve. It was dull
work and did not get him the fellowship. Disappointed, he moved to London for the
clinical part of the medical course. The clinicians “felt it obligatory to speak with a
kind of oracular authority” with little scientific basis [37]. He won a fellowship to
work in the Physiology Department at UCL. The fellowship was endowed by the
writer George Eliot (1819–1880) in memory of her long-time companion George
Henry Lewes (1817–1878). The professor was Ernst Henry Starling (1866–1927), who
was then collaborating with his brother-in-law William Maddock Bayliss (1860–
1924; later Sir William). They had just discovered the first hormone, secretin. Dale
was asked to study the effects of large doses of secretin on the histology of the
pancreas, work which he did not enjoy.

In 1902 Otto Loewi (1873–1961) came over from Germany for a few months to
meet British scientists and to improve his English [38]. Dale tried to help with words
and phrasing, but soon learned that his enthusiastic friend was not interested: “No. I
have no time to learn English correctly; I wish to speak it fast.” The British were
charmed with his fractured outpourings: “some of his achievements in that line have
had a legendary survival, still being known…60 years later.” Loewi also spent several
weeks with Langley in Cambridge. At that time Loewi was an assistant in the
Department of Pharmacology at Magdeburg, where the professor was Hans Horst
Meyer (1853–1939). Meyer had shown that the deadly tetanus toxin is taken up in
nerve endings and transported up the axons into the central nervous system (CNS),
where it acts. Then he turned to kidney pharmacology. Loewi liked working with
drugs, which he defined as “chemicals which when injected into an animal or applied
to a tissue result in the publication of a scientific paper.”

Loewi had attended the University of Strasbourg where, at the insistence of his
parents, he enrolled in medicine. Initially he “played hooky” from medicine, favoring
lectures on architecture and philosophy which he loved [39]. One day, to obtain a
required signature, he went to Naunyn’s class, hoping to get the signature before the lecture began. He was late, so he stood in the doorway waiting for it to be done. He was fascinated by the lecture, so he came again and became an enthusiastic student of medical science. Schmiedeberg directed his doctoral thesis. Loewi was surprised by the crowding and poor equipment in the British laboratories. In the German universities there was no fretting about funds or writing of grant proposals. The governments paid the bills but gave them “far-reaching autonomy,” accepting “the universities proposals and paying the endowments and debts of the departments. ...If the debts were excessive the department got a warning—and a little later the payment” [39].

After Loewi returned home, Dale visited Germany: first to Magdeburg and then to Frankfurt-am-Main, where he spent four months working in Ehrlich’s department. There “I had no results of my own worthy to record” [37]. Back in London, he had a job at UCL, at £150 per year, less than his fellowship had paid, so he was receptive when approached by Henry S. Wellcome (1853–1936; later Sir Henry; Fig. 1.4b), the proprietor of the huge pharmaceutical company Burroughs Wellcome.

1.10 HENRY WELLCOME

Wellcome had grown up in a farming community in Minnesota, where as a lad he worked in his uncle’s drug store [40]. The office above was occupied by William James Mayo (1861–1939), who with his brother later established the Mayo Clinic. He encouraged young Wellcome to attend the Philadelphia College of Pharmacy, considered the best in the country. There he met Silas Burroughs (1846–1895). After graduation Wellcome worked in Peru and Ecuador, obtaining specimens of plants the inhabitants used medicinally. Burroughs had moved to London. He invited Wellcome to join him there in a company which would manufacture the new compressed medicinal pills. The compression process had been developed by an English artist for making better lead pencils. In Britain most physicians were still rolling their own pills. The Burroughs Wellcome Company made the pills and advertised them vigorously in professional journals, and by the time Wellcome was 30 the company had facilities around the world and he was very rich. The partners fought bitterly and were dissolving their partnership when Burroughs died of pneumonia. Wellcome became sole proprietor.

Wellcome understood that only research could expand the pitifully short list of useful drugs, so he set up The Wellcome Research Laboratories in Physiology in a southern suburb of London. They started by producing diphtheria antitoxin in horses. The antitoxin had been developed at the Pasteur Institute, but Wellcome was the first quantity producer. For its first 10 years the laboratory did no research.

1.11 ERGOT AND ADRENALINE

Wellcome wanted some real research done at his laboratory so he offered Dale £400 per year (equivalent to about $60,000 in 2000). Dale’s advisers all warned him that “I would be selling my scientific birthright for a mess of commercial potage” [24]. Still he would have “a marrying income” and be free from teaching, so he accepted, with the
proviso that his salary would be raised to £600 in two annual increments. Wellcome suggested that “when convenient, he would be glad to have me make some investigations on the pharmacology of ergot” [37]. Parke Davis & Co advertised that its ergot preparation was biologically standardized and Wellcome was eager to compete. Ergotamine is produced by a fungus, *Claviceps purpurea*, which infests rye and other grains (Fig. 1.2). It causes gangrene of the extremities, along with agonizing burning pain. Its toxicity had been known to the Assyrians, and it had been used by midwives to bring on delivery when labor was delayed well before it was adopted by physicians.

Wellcome was also interested in marketing adrenaline, which had been discovered in 1895 when Oliver and Schäfer injected an adrenal extract and recorded an increase in blood pressure that almost shot the mercury out of their manometer. Dale knew a great deal about adrenaline, because a close friend from Cambridge, Thomas Renton Elliott (1877–1961), had worked on it [41]. Following earlier work by Langley and others, Elliott showed: “In all vertebrates the reaction of any plain [smooth] muscle to adrenalin is of a similar character to that following excitation of the sympathetic (thoracico-lumbar) visceral nerves supplying that muscle. The change may be either contraction or relaxation” [42]. Denervated smooth muscles that had been innervated by the sympathetic system still respond to adrenaline and their sensitivity is enhanced. The last sentence of Elliott’s abstract when he presented this work to the Physiological Society was: “Adrenaline might then be the chemical stimulant liberated on each occasion when the impulse arrives at the periphery” [43]. This audacious idea did not make it into his paper, probably because Langley did not like it. When Elliott finished his work with adrenaline, he did not receive a fellowship so he entered medical school in London.

The link between ergot and adrenaline was discovered by Dale. One day he was measuring the effects of graded doses of ergot extract on the blood pressure of a spinal cat. When the tests were almost finished a sample of dried adrenals from the Burroughs Wellcome factory was delivered. He was to determine its adrenaline content. No need to waste the cat. When Dale injected the adrenal extract, the blood pressure fell, “and with the confidence of inexperience I condemned the sample without hesitation.” The same result a week later made him realize that he had made a “really shocking howler.” Ergot blocked excitatory effects of adrenaline without touching its inhibitory actions. It also blocked excitatory effects of sympathetic nerve stimulation. It did not block inhibitory effects of adrenaline or of nerve stimulation. Shortly thereafter, Dale was named the director of the laboratory.

He and George Barger (1878–1939), a chemist at the Institute, then studied more than 50 amines for what they christened their “sympathomimetic” actions—another term that has become part of the language. The closer the resemblance to adrenaline, the more potent the amine. Noradrenaline is a stronger exciter and weaker inhibitor than adrenaline. At the time noradrenaline was not known to occur in the body, so they passed over the implications.

1.12 HISTAMINE

One of the amines they worked with was histamine, which they had found in their ergot extracts and later showed was produced by bacterial action on histidine. It stimulates many smooth muscles but when injected causes a dramatic fall in blood
pressure: Its effects are much like anaphylactic shock. A few years later colleagues at the Institute showed that histamine is in the body. Working on the isolated guinea pig uterus one day, comparing the stimulation of contraction caused by histamine and by horse serum, Dale was startled to find that the serum was working at unexpectedly low concentrations. He inquired about the previous use of the guinea pig and learned that it had been injected with small amounts of horse serum in an assay of antitoxins. He picked up the clue and showed that the previous exposure to the serum in vivo sensitized the smooth muscle to subsequent challenges with serum: the basis for anaphylactic shock.

1.13 ACETYLCHOLINE

Working one day with a crude extract made from ergot on the spinal cat, Dale was startled to see the blood pressure fall to zero. He thought he must have clumsily injected enough air to stop the heart pumping: “And then, as I was hanging up my blouse, assuming that my mornings work was done, I caught sight of the recording drum out of the corner of my eye, and saw that the manometer float was rapidly returning to the level of the blood pressure record before the injection” [43a]. A second injection also temporarily stopped the heart. He injected atropine. Now the extract had no effect. He told his chemistry colleague, Arthur James Ewins (1882–1957), that the extract contained a substance that acted like muscarine. Ewins promptly isolated the base as a platinum salt, but determining its structure with a tiny sample was a formidable task. “That evening, in fact as I was getting into bed,” Dale remembered a report he had read eight years before that low concentrations of acetylcholine (ACh) slowed the heart. The next morning he asked Ewins “to get to work and make me some acetylcholine as soon as possible… Before many hours had passed we knew beyond doubt that the active principle we had found in the ergot salt was, indeed, physiologically indistiguishable from acetylcholine” [43a]. With this hint, Ewins identified his platinum salt as that of ACh.

Soon they showed that ACh acted like muscarine on heart, smooth muscle, and glands. And both were antagonized by atropine. Like nicotine it stimulated secretion from the adrenal medulla, where the ACh action was blocked by paralyzing doses of nicotine. They coined the terms nicotinic and muscarinic to describe the two actions of ACh. They were tantalizingly close to the answer: the result “gives plenty of scope for speculation.” But they did not think of an experiment to make the leap.

1.14 NATIONAL INSTITUTE FOR MEDICAL RESEARCH

Meanwhile Dale had moved. In 1908 the Liberal government in Britain passed a budget in the Commons that initiated unprecedented social reforms, a vast program modeled on what the Germans had achieved in Bismarck’s time. They established old-age pensions, workman’s compensation, an 8-h workday for miners, medical inspection of children, and unemployment insurance. The budget was only implemented after a prolonged fight with the House of Lords and two general elections. In 1912 the emboldened liberals included national health insurance in the budget. A small fraction of the premiums— “one penny per head per annum per insured
person”—was set aside for medical research. The government established the Medical Research Council (MRC) to spend the funds.

Dale was appointed director of the Department of Biochemistry and Pharmacology at the National Institute for Medical Research (NIMR) in London, which was established by the MRC. Dale was delighted to leave Wellcome, who too often made promises that were not implemented because he headed off on an expedition—he was an ardent archeologist and collector—before leaving instructions. The development of the NIMR was sidelined by the outbreak of World War I. Dale worked on antiseptics, antiamoebic dysentery agents, and “wound shock,” concluding that treatment should be by “the addition by transfusion to the circulating blood of a fluid...—blood or plasma” [43a]. In 1920 the NIMR finally moved into quarters in Hampstead. Dale and his family were already living in a small manor house on the site rented from the MRC. Dale became its director in 1928.

1.15 LOEWI’S EXPERIMENT

The decisive experiments on synaptic transmitters were started on the Monday after Easter in 1920 at 3:30 in the Pharmacological Laboratory of the University of Graz Austria; Loewi had become professor there in 1909. Here is the experiment in his words [39]. (Note that a Straub canula is a glass tube that can be slipped though the stump of the aorta into the single ventricle of the frog’s heart.) “The hearts of two frogs were isolated, the first with its nerves, the second without. Both hearts were attached to a Straub canula filled with a little Ringer solution. The vagus nerve of the first heart was stimulated for a few minutes. Then the Ringer solution that had been in the first heart was transferred to the second heart [Fig. 1.5a]. It slowed and its beats diminished just as if the vagus had been stimulated. Similarly when the accelerator nerve was stimulated and the Ringer from this period transferred, the second heart speeded up and its beats increased.” How clever to use frog hearts both for releasing the chemicals and performing the bioassays.

He called the substance released by vagal stimulation vagusstoff. It disappears rapidly if left in the ventricle and its effect on the second heart is blocked by atropine. They tested pilocarpine, muscarine, choline, and ACh by placing solutions in a heart for a time and then seeing whether the solutions had lost their potency when transferred to a second heart. Only ACh did. They then showed that hearts contained an esterase that broke down ACh. The esterase was inhibited by low concentrations of physostigmine, an alkaloid from the seeds of Physostigma venenosum from West Africa. It had been isolated in 1864 and used in the treatment of glaucoma since 1877. Loewi and his group showed that physostigmine inhibits what became known as acetylcholinesterase (AChE). Hence, when the effects of nerve stimulation on an organ were enhanced by physostigmine, it was likely that ACh was being released.

Years passed before Loewi’s experiment was generally accepted as reproducible. It is not as easy as it sounds. Loewi was lucky because the winter frogs he started with had low levels of AChE; frogs are seasonal animals. All of the experiments he reported were done in February and March [44]. Usually AChE must be inhibited for the experiment to work, so there were many failures around the world. He submitted
his paper on 20 March, 1921, almost a year after the initial experiment, presenting results from 14 experiments on frogs and 4 on toads. There must have been many failures during the summer. Finally in 1926 he was invited to supervise a demonstration at the International Congress of Physiology in Stockholm. Happily— unlike so many demonstrations—it worked 16 times on the same hearts. He was required to stand away from the apparatus, because some claimed that he dispensed ACh from under his fingernails.

The experiment of stimulating the sympathetic supply to the heart and transferring the excitation in the Ringer solution was easier to reproduce, because the released transmitter is not dealt with rapidly. The effect of the excitatory chemical was blocked by ergotamine, which also antagonizes adrenaline. The potency of the transferred Ringer was increased by doses of cocaine that by themselves were ineffectual; cocaine was known to potentiate adrenaline. The material in the Ringer had the characteristics of adrenaline. Exceptionally frog sympathetic postganglionic nerve fibers release adrenaline rather than noradrenaline.

A question Loewi delighted in chewing over was how he had the idea for his experiment in the first place, as he described it: "The night before Easter Sunday… I awoke, turned on the light, and jotted down a few notes on a tiny slip of thin paper. I fell asleep again. It occurred to me at six o'clock in the morning that during the night I had written something most important, but I was unable to decipher the scrawl. The next night, at three o'clock, the idea returned. I got up and immediately went to the laboratory." [39]. It may have grated on his competitors that this was his first major venture into neuropharmacology. His previous work had been on nutrition, kidney pharmacology, and the effects of digitalis on the heart.

Figure 1.5 Great discoverers. (a) The first published record of the Loewi frog heart experiment. At the arrows the fluid in the heart was replaced with Ringer withdrawn from a heart whose vagus had been stimulated for 15 min. (b) Otto Loewi. (c) Henry Dale. ([b,c) copyright © The Nobel Foundation.] (d) Shosaku Numa.
Adolph Hitler (1889–1945) became the chancellor of Germany early in 1933. The Achilles’ heel in the German university system was that professors were civil servants. Every Jew or person of Jewish ancestry teaching in a German university was fired. Wilhelm Sigmund Feldberg (1900–1993) was told by the professor of pharmacology in Berlin to leave immediately and never to come back [45]. Hundreds of others had similar dismissals. A few weeks later Feldberg met with a representative of the Carnegie Foundation who had a list of opportunities abroad for displaced German scholars. Regretfully, none fit Feldberg. Feldberg mentioned that if an opening surfaced he felt sure Sir Henry Dale would recommend him. This jogged the representative’s memory. Searching his notes he saw that that Dale had told him that there was a place for Feldberg at the NIMR [46].

Feldberg had spent two years in England, first with Langley and then with Dale. Now he returned with a wonderful present: an ultra sensitive bioassay for ACh measuring the contractions of the physostigmine-treated dorsal body wall muscle of the leech. It is so sensitive that they could take the venous effluent from a mammalian tissue in a physostigmine-treated animal, cool it, and let it flow over the leech muscle, which contracted if ACh had been released. Feldberg and co-workers in Berlin had just shown that ACh is released in the adrenal medulla when the sympathetic preganglionic nerve is stimulated.

Dale had seldom come to the laboratory after he had become director—now he was there every free moment. He had assembled a formidable group of co-workers. John Henry Gaddum (1900–1965) had turned from medicine to pharmacology when a girl at a ball told him of an opening in Dale’s laboratory [46, 47]. George Lindor Brown (1903–1971) was an Oxford-trained electrophysiologist recruited to expand the available techniques [48]. He had finished constructing his electronics and was ready to go. Soon they were joined by Marthe Louise Vogt (1903–2002), a skilled microdissector who left Germany voluntarily because she so detested the Nazis.

There was a stream of discoveries. The cat superior cervical ganglion released ACh when the preganglionic nerve was stimulated. The amount that could be released was larger than the initial ACh content, so ACh is synthesized in the ganglion. So much ACh was released that the reinjection of outflow stimulated the postganglionic fibers—therefore the ACh released surely stimulated them also. Some postganglionic sympathetic fibers, like those innervating sweat glands, release ACh. Dale coined the terms adrenergic and cholinergic.

Stimulation of the motor axons liberated ACh at skeletal muscles. When the muscle was denervated, vigorous contraction elicited by direct stimulation did not release ACh. ACh was still released when contraction was blocked with + TC. Frustratingly they could not get a muscle to contract when ACh was injected into its arterial circulation. Reasoning that the ACh reaching the tiny end-plate region would be dilute: “We attempted a nearer approach to these supposed conditions of its natural release, by a method which enabled us, after a brief interruption of the arterial blood supply, to inject a small dose of acetylcholine, in a small volume of saline solution, directly and rapidly into the empty blood vessels of the muscle. The responses which we thus obtained were of an entirely different kind from any which had previously been recorded. A dose of about 2 gamma of acetylcholine, thus injected at close range into the vessels of a cat’s gastrocnemius, produced a
contraction with a maximal tension equal to that of the twitch produced by a
maximal motor nerve volley, and of a rapidity but little less than that of the motor
nerve twitch.” Vogt did the difficult dissections. Brown showed that the close
injection elicited a short burst of action potentials in the muscle fibers. ACh was
still released when contraction was blocked with + TC. Twenty-four papers and
abstracts on ACh from Dale’s laboratories were published from 1934 to 1936.
Feldberg was an author on all of them, because he did the assays.

Their results were presented at meetings of the Physiological Society. Not every-
body liked them. The criticism was led by John Carew Eccles (1903–1997; later Sir
John; Fig 1.6a), a dynamic Australian who was always primed for the attack [49]. After
graduating in Medicine from Melbourne, he had come to Oxford as a Rhodes Scholar
in 1925. His sport—one of the selection criteria for a Rhodes—was pole-vaulting.
He started graduate study in 1927 under Sherrington. Speed still made chemical
transmission at fast synapses seem impossible—it was “soup” versus “sparks.”

1.17 NOBEL PRIZE OF 1936

The Nobel Prize for Physiology or Medicine in 1936 went to Loewi (Fig. 1.5b) and
Dale (Fig. 1.5c) “for their discoveries relating to chemical transmission of nerve
impulses.” In his lecture in Stockholm Dale cited 11 papers from the group; he was
an author on 5. Naturally enough some searched the literature to cite those who had
scooped the Laureates. Chemical transmission had been suggested repeatedly,
starting with Emil Heinrich Du Bois-Reymond (1818–1896), who had been a
professor in Berlin. Such diggings are a diversion. It was not hard to think that
transmission might be chemical; it was hard to devise experiments to test the
hypothesis.

When the Germans entered Austria in 1938 Loewi and two of his sons were jailed
until he gave up his Nobel Prize money as ransom. After several years in temporary
positions he became a research professor at New York University (NYU). His
wife was kept in Austria until 1941, when she turned over her family property in

Figure 1.6  (a) Sir John Eccles. (b) Sir Bernard Katz (copyright © The Nobel Foundation.)
Italy to the Nazis. The Nazis devastated the German universities and enhanced those abroad. In Britain it seemed to one younger neuroscientist “that through most of my scientific lifetime the most distinguished of my seniors mostly spoke with guttural accents” [50].

1.18 ELECTRIC ORGAN

The electric organ of *Torpedo* is made up of a huge stack of motor nerve endings and end plates in series. Albert Fessard (1916–2003) worked with the preparation, so Feldberg traveled over to France to collaborate [51]. They set up the spinal preparation in a shielded cage. The amplifiers, recording apparatus, and engineer were outside. Only Feldberg was within, cautioned not to touch the animal—doing so would generate a nasty electrical artifact. He was to inject ACh in the artery and call out “now.” He called but the engineer hastily stopped the recording. A huge artifact. The engineer was worried about damaging his amplifier. Feldberg was put into rubber gloves and boots as insulation. “Now.” Another artifact. Feldberg asked for another try. “Now.” No response. “Fine,” said Feldberg, “I injected saline.” With the next “now” he injected ACh; there was the already familiar huge voltage spike, which they now knew was the discharge of the electric organ [46].

The biochemist David Nachmansohn (1899–1983) was in France working on the electric organ [52]. He had trained with Otto Meyerhoff (1889–1951; Nobel Prize 1922) in Berlin but had been driven out by the Nazis. The electric organ had been found to contain astonishing concentrations of AChE. Nachmansohn began to purify it.

1.19 ECCLES, KUFFLER, AND KATZ

In 1937 Eccles returned to Australia as director of the Kanematsu Institute at Sidney Hospital, a department of diagnostic pathology whose director is expected to do research and is given financial support. Soon he had a small group. Stephen Kuffler (1913–1980) came from a landowning family in Hungary; they were wealthy but lost all in the Great Depression [53–55]. After graduation from medical school he worked as a pathologist, before hurriedly leaving Vienna. He had had some dangerous involvement in politics, which he thereafter shied away from. Unlicensed to practice medicine in England he went to Australia and was employed as a pathologist in the Sidney Hospital. Kuffler was invited for tennis on the court behind the Eccles’ house; after all he was a former Austrian tennis champion. Eccles persuaded him to join the laboratory to learn electrophysiology.

In late 1939 they were joined by Bernard Katz (1911–2003; later Sir Bernard; Fig. 1.6b), who was a Carnegie fellow [50]. Born in Leipzig, his father, a fur merchant, had come from Russia. At age nine he was at the top in the entrance examination for a prestigious gymnasium but was rejected because he was a foreign Jew. He was admitted to another school and then to the medical course at the University of Leipzig. When he received the M.D. in 1933 he was awarded a prize, given to him in private as a “non-Aryan.” He wanted to work on muscle under the
director of the Biophysics Laboratory at UCL, Archibald Vivian Hill (1886–1977; Nobel Prize 1922). Katz arrived in London in 1935 with a letter of introduction and £4 (a bit over £100 today). Within a year he and Hill published together. He received a Ph.D. at UCL and then headed for Sidney.

Eccles was working on mammalian muscle. Katz thought this far too difficult—frogs would be better. He remembered: “Stephen roaring with laughter when I showed him how to ‘take the frog’s trousers off’ ” (i.e., slip the skin off the rear legs) [55]. They placed the sartorius muscle in a chamber that had a maneuverable electrode in its floor, and stimulated the sciatic nerve. Poisoning transmission with + TC, they found areas on the muscle where they could record a localized potential change, the end-plate potential (EPP). The EPP was lengthened when the bathing solution also contained physostigmine. However, the electrical signals were complex and not easily interpreted.

World War II broke up the collaboration. Katz served in the Australian armed forces. Eccles worked on military problems. Kuffler received a research fellowship and did some further experiments on frog muscle, and in 1944 he and his Australian wife moved to the University of Chicago to the laboratory of Ralph Gerard (1900–1974).

1.20 NACHMANSOHN

Nachmansohn left for the United States before the war and in 1942 took a position at Columbia University [56]. He was working on the purification and properties of AChE, but it was difficult to get Torpedo for starting material. The U.S. Army asked him to investigate the effects of organophosphates on the enzyme. Some were known as potent insecticides and there was intelligence that the Germans were investigating them as potential war gases. Nachmansohn told them he would need a steady supply of electric eels from the Amazon, which an Army procurement officer dubbed “the craziest request of the war.” Nonetheless the eels came. Nachmansohn’s group showed that diisopropyl phosphorofluoridate (DFP) phosphorylates the serine on the active site of AChE and by the 1950s developed agents capable of reactivating the poisoned enzyme, such as pyridine-2-aldoxime methyl chloride (pralidoxime). Their crystallization of AChE opened the way for others, years later, to determine its structure. The reversible AChE inhibitors, such as physostigmine, bind to the active site of AChE where they are hydrolyzed just as ACh is, but at such a slow rate that they tie up the enzyme. On the other hand, the turnover of ACh by AChE is one of the fastest enzymatic conversions known.

Nachmansohn and his colleagues also showed that ACh is formed by extracts of the electric organ provided with choline and adenosine triphosphate (ATP) provided that fluoride is added to inhibit ATPase. This was revolutionary. There was no previous evidence that ATP is involved in synthetic reactions. The paper was rejected by three eminent journals. The enzyme, now called choline acetyltransferase, requires a coenzyme, which was identified by Fritz Albert Lipmann (1899–1986; Nobel Laureate 1953) as coenzyme A. Nachmansohn convinced himself that ACh is involved in axonal transmission. He convinced few others, but his dogged adherence to this mistake tends to obscure his achievements.
1.21 POSTWAR SCIENCE

World War II destroyed so much and so many, but it did increase public awareness of what scientists could do, so it was relatively easy afterward to persuade governments to keep money going to science. After a pause for economic recovery, the money began to flow and science was transformed. Figure 1.7a shows a U.S. example: the growth of the budget of the National Institute of Neurological Diseases and Stroke (NINDS). The growth in dollars is almost exponential, but the picture is altered when corrected for the decline in the purchasing power of the currency (Fig. 1.7a). The money fueled an enormous growth in the number of scientists (Fig. 1.7b) and in the number of papers published on the actions of drugs on synapses (Fig. 1.7c). The American universities expanded to cope with the student veterans,

Figure 1.7 Some measures of research in neuropharmacology. (a) The budget of the NINDS filled circle (●); The budget corrected for the buying power of the dollar (○) open circle in 2000. (b) The membership of the British Pharmacological Society. (c) The number of papers cited in the Ovid database in the category of drugs acting on synaptic transmission.
whose tuition and living expenses were paid for by the G.I. Bill, which surely must rank among the wisest legislations ever enacted.

1.22 BOVET

During the war + TC came into use to relax patient’s muscles during surgery. Less anesthetic is needed for analgesia than for muscle relaxation so with + TC there is less toxicity. + TC has side effects, such as histamine release, so synthetic blocking agents were developed: some act like + TC and others act like nicotine, first stimulating and then blocking. A leader in the synthesis and testing of these compounds was Daniel Bovet (1907–1992; Nobel Laureate 1957). A native of Switzerland, he worked in France until 1947 when he and his wife, the pharmacologist F. Bovet-Nitti, moved to a new laboratory at the Instituto Superiore di Sanità in Rome. Bovet had a genius for thinking like a receptor, detecting the key operational parts of a complicated molecule such as + TC, and then synthesizing simpler compounds targeting the same receptor. One of his + TC substitutes is succinylcholine, which is hydrolyzed rapidly by ChE, so its blockade is readily reversible. He also pioneered in the development of histamine blockers and of antagonists for adrenergic receptors.

1.23 ION CHANNELS

Alan Lloyd Hodgkin (1914–1998; later Sir Alan) and Andrew Fielding Huxley (later Sir Andrew) showed how the squid giant axon generates action potentials by changes in Na⁺ and K⁺ permeabilities triggered by changes in membrane potential. The permeabilities are little changed by low temperature, which suggests that the ions flow through channels in the membrane. The Na⁺ channel is blocked reversibly by local anesthetics and irreversibly by toxins such as tetrodotoxin, from the Japanese puffer fish, Spheroides rubripes [57]. The toxins were used to label the protein of channels for isolation and eventual cloning. Toxins that target the K⁺ channel were discovered much later.

1.24 SOUP, NOT SPARKS

After the war Eccles wrote several influential reviews on the mechanism of synaptic transmission [58]. He conceded that neuromuscular transmission might have a chemical component but was adamant that the synapses in the CNS were electrical, both excitatory and inhibitory. As Kuffler said about him years later, “he has often been wrong, but only about important things” [54]. Chemical transmission at fast synapses would be on firm ground only when the electrophysiologists convinced themselves that it is so—until then the “soup” versus “sparks” argument would go on interminably.

The way was opened by Gerard and his colleague Gilbert Ling, a step that Gerard always downplayed because “techniques are not very important” [59]. They pulled glass microelectrodes by hand, filled them with half-strength Ringer, and manipu-
lated the tip toward a frog muscle fiber. Abruptly the pipette tip became negative to the external solution. They were measuring the resting potential of the cell. Glass fits comfortably with cell membranes, which reseal around the electrode after penetration. They could not measure action potentials, because their microelectrodes had such a high resistance that the time constant of the input stage of their electronics was too slow to follow a fast event. Hodgkin and William L. Nastuk (1917–1965) filled microelectrodes with 3 M KCl solution and used an amplifier input circuit able to cope with a high input resistance to record action potentials from skeletal muscle fibers [60]. Soon plans for making electromechanical micropipette pullers were published, then machines became commercially available, and the game was wide open.

Katz brought his Australian bride to London in 1946; he had been appointed Henry Head Fellow of the Royal Society. When the microelectrode flashed onto the scene, he returned to the neuromuscular junction, working with a graduate student, Paul Fatt. In + TC when the microelectrode was at the end plate and the nerve was stimulated, they recorded the EPP [61]. Raising the + TC concentration diminished the EPP; the drug was making less nicotinic acetylcholine receptor (nAChR) available. Anti-AChEs elongated the EPP. Using a second microelectrode to change the muscle membrane potential at the end-plate region, they showed that no EPP is seen at about 0 mV and that when the inside of the fiber was made positive the EPP was hyperpolarizing. This is because the ACh opens ion channels at the end plate that permit both Na\(^+\) and K\(^+\) to flow though, bringing the potential to about 0 mV, which is known as the reversal potential. The reversal was the conclusive evidence that at the neuromuscular junction (NMJ) transmission is chemical, not electrical. When ACh binds to the nAChR, it opens a chemically gated ion channel.

They then discovered small, randomly occurring depolarizations at the end plate. The depolarizations were eliminated by + TC and increased in amplitude and lengthened by anti-AChEs. They are miniature end-plate potentials (MEPPs). The ACh is released in packets or quanta of thousands of ACh molecules. Quanta may have been an unfortunate name, because it suggested to some that the packets contain a fixed number of transmitter molecules. In fact, the number can be varied over a wide range [61, 62]. The EPP is generated by the almost synchronous release of hundreds of quanta. The discovery of the MEPPs coincided with the development of tissue preparation techniques that permitted electron microscopists to see cell membranes as well as the vesicles in the motor nerve ending and in other chemical presynaptic endings.

Nastuk filled a microelectrode with ACh\(^+\) and ejected graded amounts by adjusting electric current flow—ionophoresis [63]. ACh applied to the end-plate region opens the ion channels, but much higher concentrations are required at other parts of the muscle membrane, so the nAChR is concentrated at the end plate. Two ACh molecules usually bind to the nAChR to open the ion channel. The channel opens for a mean duration of 1 ms, determined first by statistical analysis of ACh “noise.” Other agonists open channels for different durations, depending on how rapidly they come off the nAChR. Erwin Neher and Bert Sakmann developed the patch technique to see individual channels opening. They started by observing nAChR channels on frog muscle fibers away from the end plate, where far fewer are found per unit area. They shared the Nobel Prize in 1991. Katz and Steven Thesleff showed that steady application of ACh results in a diminishing end plate current [64].
The nAChR is becoming desensitized. Other workers showed that in the desensitized receptor the affinity for ACh is increased.

1.25 ACTIONS OF +TC

+TC blocks ACh binding to the nAChR. But this is not the end of the story. The extent of the block of the nAChR by +TC varies with the potential across the end-plate membrane [65]. Part of the blocking action occurs because the drug enters open nAChR channels and plugs them. The amount of the charged drug entering the channel depends on the potential across the membrane. +TC also increases quantal output from stimulated motor nerve endings [66]. There are nAChRs on the presynaptic terminal; ACh and other agonists decrease quantal output and reduce the amount of ACh loaded into recycling vesicles [62]. There are receptors for a number of other transmitters and hormones on the motor nerve terminals [67].

Katz’s papers are models to emulate: lucid, effective choice of short words and stripped of excess verbiage. His “perceptiveness in distinguishing the important from the unimportant was legendary” [50]. Such abilities were not always agreeable to his students; “there are many stories of experiences, sometimes quite traumatic, of presenting to him the first draft of a paper.” He was careful and critical and eminently fair minded.

1.26 SYNAPTIC VESICLES

Synaptic vesicles containing ACh were isolated from mammalian brain and from the electric organ [68]. Victor P. Whittaker and others showed that the electric organ is a rich source and the vesicles unusually large. They found that along with the ACh the vesicles contain one ATP per four AChs and both are released by exocytosis. ATP itself is a transmitter at other junctions [69]. Studies on the electric organ elucidated the mechanism for loading ACh into the vesicles and showed that there are distinct pools of vesicles in the nerve endings [62, 68].

The most potent toxins known are made by Clostridium botulinum. A mouse has a 50 : 50 chance of being killed by an injection of 18 million toxin molecules [67]. They kill by blocking neuromuscular transmission. The toxins bind specifically to motor nerve endings and inject an active fragment into the cytoplasm. Transmission at other synapses is blocked if the active fragment is injected presynaptically. The toxins are Zn$^{2+}$-containing enzymes that target proteins involved in quantal release. Different bacterial strains produce different toxins that target different proteins, which enabled some of the proteins essential for exocytosis to be identified. Who then would have thought that these toxins would be used in huge amounts in cosmetic pharmacology?

1.27 CLONING THE nAChR

Electric organs are a splendid source of nAChR. It is made up of four subunits, and the first 54 amino acids in each of the chains were determined, a painstaking job with
the techniques available at the time. Shosaku Numa (1929–1992; Fig. 1.5d) and his
group at Kyoto University prepared messenger ribonucleic acid (RNA) from electric
organ and from 2.4 μg produced a complementary deoxyribonucleic acid (cDNA)
library with about 200,000 clones [70]. They made small DNA probes for parts of the
α-chain and then used them to search the library. It was a race of the kind seen more
and more frequently since money expanded science: Laboratories in Britain, France,
and the United States were working on the same lines. Numa’s laboratory ran on
16-h days [71]. They first determined the composition of the α-unit; there are two of
these in each nAChR, and they have ACh binding sites. Then they addressed the
other three chains. The chains can reassemble spontaneously into functioning
receptors. Other nAChRs are made up of different combinations of subunits. This
was the first dazzling demonstration of the power of molecular neuropharmacology
that figures so prominently in the rest of this book.

1.28 HOW CAN CHEMICAL TRANSMISSION BE SO FAST?
The venom of the Formosan snake, *Bungarus multicinctus*, contains a polypeptide,
α-bungarotoxin, that binds irreversibly to the nAChR. The density of the nAChRs at
the NMJ was measured with the electron microscope by labeling them with radio-
active α-bungarotoxin. The density of the AChE was measured by reacting them with
radioactive DFP [72]. Much of the AChE is on a fibrous network in the synaptic cleft.
These densities, the rate constants for the reactions, an estimate of the number of
ACh molecules in a quantum, and the diffusion equations were the raw material for a
mathematical model of the generation of an MEPP [73]. When ACh is released from
the vesicle into the narrow synaptic cleft, the local concentration is high. It diffuses
across the gap saturating first the AChE in its path and then the nAChRs
immediately opposite the release point. The remaining ACh diffuses along the end
plate, combining with additional nAChRs to open more channels. The mean time for
ACh to come off of the nAChRs is 1 ms. The nAChR is a low-affinity receptor, but
because release is quantal, it is exposed to high concentrations of ACh, which it binds
and then releases rapidly. Almost all of the ACh released from the nAChR is
hydrolyzed by AChE before it can rebind.

1.29 ECCLES AND CENTRAL SYNAPSES
Eccles and his colleagues had been inserting fine metal electrodes into the cat spinal
cord to record extracellularly from the cell bodies of motoneurons, so his group was
ready to try glass microelectrodes. Astonishingly the submicroscopic tips survive
being pushed through centimeters of spinal cord. They recorded intracellularly from
their first motoneuron in June 1951 [34]. Activating a monosynaptic reflex by
stimulating sensory axons from muscle stretch receptors, they recorded transitory
depolarizations in the motoneurons. The depolarizations were named excitatory
postsynaptic potentials (EPSPs). The more intensely the sensory nerve was stimu-
lated, the larger the EPSP. When the EPSP reached a threshold level, the motoneur-
ons fired an action potential. Next Eccles and his group inserted double-barrelled
microelectrodes: one barrel to record potential changes and the second to pass a
current to set the potential of the motoneuron’s membrane. Just as at the end plate, the EPSPs became hyperpolarizing when the inside of the cell was electrically positive. The reversal potential is about $+3 \text{ mV}$. From the moment he first saw reversal the most ardent “spark” became an enthusiastic salesman for “soup.”

Stimulation of an inhibitory pathway produced a slight hyperpolarization with a reversal potential of about $-80 \text{ mV}$, an inhibitory postsynaptic potential (IPSP). By using a double-barreled microelectrode to ionophoresce ions into the motoneuron cell body, they showed that the reversal potential shifted to a more depolarized level after the $\text{Cl}^-$ concentration was elevated, so the ion channel opened during inhibition is permeable to $\text{Cl}^-$. Hitherto they had thought that this inhibitory pathway was monosynaptic, but now they found an inhibitory interneuron, so the same cell was not both excitatory and inhibitory. They also discovered a presynaptic inhibitory mechanism which decreases the amount of transmitter released by an excitatory nerve ending.

Eccles shared the 1963 Nobel Prize with Hodgkin and Huxley. After 26 years of intense, driving, single-minded intracellular work on neurons he finally enjoyed 22 years of retirement in the Swiss mountains, working at a somewhat less intense pace on theory.

### 1.30 ADRENERGIC TRANSMITTERS IN CNS

Clearly there must be additional synaptic transmitters in the mammalian CNS. Obvious possibilities were adrenaline and noradrenaline. In 1954 Vogt demonstrated that noradrenaline is also found in the brain. The Nobel Prize in 1970 was shared by Ulf von Euler (1905–1983) and Julius Axelrod (1912–2004) for work on adrenergic systems. What a study in contrasts. Von Euler’s father and godfather were Nobel Laureates in Chemistry and his mother was a noted botanist. He studied medicine at the Karolinska Institute; four years after matriculation he was an assistant professor of pharmacology. He worked in England with both Dale and A. V. Hill and also in Belgium and Germany. He became a professor at the Karolinska in 1939. Axelrod was born to poor parents in New York City [74]. He obtained a bachelor’s degree in chemistry at the City College of New York, which at that time had no tuition charges. Graduating in 1933, at the nadir of the depression, he was rejected by medical schools so he worked as a lab assistant, a chemist in industrial hygiene where he lost an eye in a lab accident, and then in a research division of NYU. Along the way he earned an M.A. at night. At NYU his boss was Bernard B. Brodie (1907–1989): “generally called Steve Brodie. This referred to a saloon keeper named Steve Brodie, who at the beginning of the previous century had jumped off the Brooklyn Bridge to win a bet” [74a]. Brodie turned Axelrod onto the joys of research. In 1949 they moved to the newly established National Heart Institute in Bethesda. Axelrod was appointed head of pharmacology there in 1955, the same year he received a Ph.D. degree from the George Washington University.

Both von Euler and Axelrod measured amines by their fluorescence and put radioactive labels on compounds to follow their movements and metabolic transformations. Von Euler found that noradrenaline is packaged in large granules in adrenergic nerve endings, analogous to the smaller ACh-containing vesicles.
at cholinergic endings. Axelrod showed that noradrenaline is broken down by monoamine oxidase but that most of the noradrenaline released from adrenergic neurons is transported intact back into cells—a new and unexpected mechanism for terminating transmitter action. The transmitter taken back into the nerve terminal is repackaged and released again. The uptake is blocked by cocaine, which accounts for its ability to potentiate sympathetic stimulation.

In the late 1940s numbers of derivatives of iminodibenzyl were synthesized and tested for their effects. A few with sedative properties were used in clinical trials. One of these, imipramine, had no quieting effect on agitated patients but by lucky chance was found to benefit depressed patients. It became the model compound for the tricyclic antidepressants. Axelrod showed that they block the reuptake of noradrenaline.

1.31 CARLSSON

Arvid Carlsson (Nobel Laureate 2000) was working on Ca\(^{2+}\) metabolism. At age 32 he applied for an associate professorship but was rejected on the ground that his subject was at a dead end. Stimulated so forcefully to shift fields, he went to work with Brodie for five months in 1955. When Carlsson arrived in the laboratory they were investigating 5-hydroxytryptamine (5-HT). It had been discovered in serum and in the gut; now they found it in the brain. They measured it with the spectrophotofluorimeter, which they had devised for detecting amines in biological samples.

They were also studying reserpine, an alkaloid from *Rauwolfia serpentina*, a shrub found in the Indian subcontinent. It had been used for centuries in Indian medicine but had just been introduced in the west for the treatment of hypertension. Its adverse reactions were sedation and, less commonly, psychotic depression. Brodie and his collaborators found that reserpine depleted the brain of 5-HT. Back in Sweden Carlsson and his collaborators showed that reserpine depleted brains of noradrenaline and that after treatment stimulated sympathetic postganglionic axons released less transmitter.

They wanted to see whether the reserpine effect could be reversed by restoring catecholamines to normal levels. Catecholamines do not penetrate the blood–brain barrier, so they decided to give a precursor that can penetrate, DOPA (3,4-dihydroxyphenylalanine). DOPA put reserpine-treated rabbits back on their feet in no time. When they measured the noradrenaline in these brains they were astonished to find it still was low. Reserpine is antagonized by monoamine oxidase inhibitors, so they reasoned that DOPA must be converted to an amine. The first step in the pathway between DOPA and noradrenaline is dopamine. Dopamine had never seemed of interest because it has little effect on tissues innervated by the autonomic nervous system. They developed a method to measure dopamine. In the brain there is more dopamine than noradrenaline, and dopamine disappears with reserpine treatment and is restored by DOPA. The effects of reserpine treatment resemble those of the Parkinson syndrome, and they found that normally dopamine is in high concentration in the basal ganglia, so they suggested that DOPA might be useful in treating the disease.

Flushed with success, Carlsson went to London in 1960 to present at a symposium. “The central figure was Sir Henry Dale, a Nobel Laureate aged 85
but still remarkably vital. He dominated the scene, and the participants, many of whom were his former students, treated him with enormous respect, like school children their headmaster, although many of them had indeed reached a mature age.” Carlsson’s conclusions were summarily dismissed. “Dale expressed the view that L-DOPA is a poison, which he found remarkable for an amino acid” [74a]. Dale’s group pitched in to dismiss his work with equal certainty. How Carlsson must have enjoyed recounting this in his own Nobel lecture.

Carlsson and his co-workers devised histochemical methods to see precisely where catecholamines are in the brain. Within a few years they localized dopamine, noradrenaline, and 5-HT. At the next major meeting, in 1965, there was no argument whether or not these amines were important in the brain. Other investigators then carried into the clinic the role of the loss of dopamine in Parkinson’s and its restoration by L-DOPA.

As we have seen, the tricyclic antidepressants, such as imipramine, were discovered in the 1950s and in the early 1960s were found to block noradrenaline uptake into nerve terminals. In the late 1960s Carlsson and collaborators found that they also blocked 5-HT uptake and developed selective inhibitors for this transporter. The best known is fluoxetine (Prozac).

1.32 SECOND MESSENGERS

Although many transmitters open ion channels, there must be other ways for them to act on target cells. Adrenergic transmitters or hormones alter cell metabolism, for instance, stimulating the liver to break glycogen down to glucose. Carl Ferdinand Cori (1896–1984) and Gerty Theresa Cori (1896–1957; Nobel Laureates 1947) elucidated the pathway by which glycogen is broken down to glucose. The enzyme phosphorylase is the rate-limiting step in glycogen breakdown. Earl W. Sutherland (1915–1974; Nobel Prize 1971) found that adrenaline increased the activity of phosphorylase in homogenates of liver cells. These homogenates also contained an enzyme that brought phosphorylase activity back to baseline without significantly altering its molecular weight. This enzyme inactivated phosphorylase by removing phosphate. In liver slices exposed to adrenaline phosphorylase becomes labeled with radioactive phosphate. The enzyme is turned on by being phosphorylated and turned off when the phosphate is removed.

Phosphorylase was not activated by adding adrenaline to homogenates. But when they also provided ATP and Mg\(^{2+}\) to the homogenates, adrenaline activated phosphorylase. They centrifuged the homogenate and worked with the soluble fraction, which contains the phosphorylase. Adrenaline did nothing. The crucial experiment was to resuspend the particulate fraction in ATP and Mg\(^{2+}\) and then expose it to adrenaline. This suspension contained a heat-stable substance that activated phosphorylase when added to the soluble fraction. The activating factor was precipitated by Ba\(^{2+}\), so it was probably a phosphate compound. With the available techniques, it promised to be a long job characterizing the activator from the trace amounts formed by the particulate fraction. They showed that it was an adenine ribonucleotide. Sutherland wrote to a friend telling him what he knew of the properties of his activator. The friend recalled a description he had received from another investigator of a derivative produced when ATP is digested in barium.
hydroxide. The properties seemed identical. This made it much easier to characterize the activator as adenosine 3',5'-monophosphate (cAMP).

Hence, adrenaline acts on a receptor on the cell membrane. This activates the enzyme adenylyl cyclase, so cAMP is formed. It acts as a second messenger that activates the kinase that activates phosphorylase. The cAMP is destroyed by phosphodiesterase, which is inhibited by alkaloids such as caffeine and theophylline. Sutherland’s discoveries flung open the door for the enormous quantity of work that still continues on cellular signaling systems. An offshoot was the characterization of muscarinic ACh receptors, the identification of their second messengers, and establishing that these messengers could open some ion channels and close others.

Trying not to move too far from the past, I shall merely note that the Nobel Prizes to Edmond H. Fisher and Edwin G. Krebs in 1992, Alfred G. Gilman and Martin Rodbell in 1994, and Arvid Carlsson, Paul, Greengard, and Eric R. Kandel in 2000 were all for work building brilliantly on Sutherland’s.

1.33 AMINO ACID TRANSMITTERS

Some Crustacean muscles have a dual innervation: excitatory and inhibitory. Neither excitation nor inhibition is affected by adrenergic or cholinergic drugs. Picrotoxin, a convulsing drug isolated from the seed of Anamirta coecilus, a climbing shrub from southeast Asia, blocks the effects of stimulating the inhibitory axon [75]. By the late 1950s such preparations could be ordered from the catalog, because enough money was going into biomedical research to support chemical companies specializing in the research market. The active part of this preparation, which has a difficult chemistry, is picrotoxinin (Fig. 1.2). Other workers had been looking in brain homogenates for small molecules that might be transmitters. One possibility was the unusual amino acid γ-aminobutyric acid (GABA). It inhibited excitation and its action was blocked by picrotoxin.

What about the excitatory transmitter for crustacean muscle? A Columbia medical student spent a summer seeing which amino acids caused the muscles to contract, finding that glutamate was the by far the most effective [76]. This was one of the first steps in proving that glutamate is the excitatory transmitter. Synapses in the mammalian CNS were investigated by ejecting test chemicals by ionophoresis [34]. Glutamate depolarized motoneurons. At first it was thought that this action might be nonspecific, but its identification as a transmitter was supported by the crustacean results. Aspartate is also an excitatory transmitter in the CNS. Both GABA and glycine are inhibitory transmitters in the vertebrate CNS.

1.34 KUFFLER

One of the laboratories working to expand the list of transmitters was Kuffler’s [53–55]. He liked to shift preparations every few years, picking a new one that seemed promising and that tested his dissecting skills — an approach that would not survive today’s grant evaluation system. They studied Crustacean stretch receptors and showed that they receive an inhibitory innervation from the CNS. The inhibition was blocked by picrotoxin and mimicked by GABA. They fractionated CNSs from 550
lobsters and tested the fractions for inhibitory molecules [77]. By far the most potent was GABA, which they then showed was much more concentrated in inhibitory than in excitatory axons. They worked on the snake neuromuscular junction, treating the preparation with collagenase and then pulling the nerve terminals away. The muscle fiber was covered with oil and droplets of solution slid onto the naked end plate. They determined that somewhat fewer than 10,000 ACh molecules were needed to generate a MEPP [78]. Kuffler’s last contribution was the discovery of a “late slow” EPSP in postganglionic cells in frog autonomic ganglia produced by the release from the presynaptic neurons of a peptide resembling luteinizing hormone releasing hormone. This was one of the first demonstrations that more than one transmitter can be released at synapses. Further work revealed how complicated transmission is in the autonomic ganglia, with a series of EPSPs with different time scales and an IPSP as well and, of the importance of peptides released at synapses.

Kuffler had learned the lesson of Dale’s group at the NIMR: how effectively work on the nervous system could be done by a closely interacting combination of specialists—physiologists, pharmacologists, anatomists, and biochemists—all backed by a first-rate technical staff. In 1959 Kuffler and nine colleagues established a section in the Department of Pharmacology at the Harvard Medical School. The chair was Otto Krayer (1899–1982). Krayer was not Jewish but left Germany when he rejected a chair from which a Jew had been ejected. After Krayer died Kuffler’s section became the Department of Neurobiology at Harvard. His admiring colleagues regarded the establishment of the new department as a miraculous navigation of the shoals of academic politics. It became a model for many others around the world. Kuffler was skilled at keeping a group of highly distinguished and hard-driving researchers at peace with one another. Humor was his main weapon. His colleagues restricted him to “two puns a day,” but this rule was frequently violated.

1.35 END OF THE ERA

Dale left the laboratory after receiving the Nobel Prize. When Wellcome died, Dale was named in his will as one of the five trustees for the Wellcome Trust [37]. The other scientific trustee was Elliott, who had become professor of medicine at UCL. Two years later Dale became the chairman of the Trust. It was a difficult and challenging job. Wellcome left everything to the Trust, which was charged with running the company, dealing with his vast collections, and supporting research. The will was lengthy and detailed but was vague on crucial points and even self-contradictory. Moreover, the business was not what it had been; Wellcome had paid it too little attention in his last years. The death duties were enormous. The trustees took the hard decision that they had no money for science—first they must pay off the duties and invest to restore the company’s health. In the foundation’s first 20 years only £1 million was disbursed for research. The company was saved by its U.S. branch, which had strong research—Gertrude B. Elion (1905–1998) and George H. Hitchings (1918—1999) were Nobel Laureates in 1988— and excellent management. After Dale retired as a trustee on his 85th birthday, the Trust was directed by a series of able men, who continued to plow profits back into research. It worked. By 1991 the Wellcome Trust was disbursing over £100 million a year to support scientific research. Dale died eight years after his retirement, at age 93.
Feldberg, like Kuffler, was known for his sense of humor. His after-dinner speeches to the Physiological Society were classics. In his nineties he was still experimenting. He permitted a group to film his work, purportedly for educational use. In truth they were antivivisection activists who reported him to the British Home Office. His license to use animals was revoked. He died soon after, having endured the very problem that had so plagued Claude Bernard a century and a half before.

1.36 CONCLUSIONS

In a little more than a century enough of the mechanism for chemical synaptic transmission was worked out to make much of neuropharmacology coherent. Most of the crucial observations came from experiments with poisons from nature. We have progressed from the observation that curare blocks transmission from motor nerve to muscle to the precise identification of the +TC binding sites on the nAChR.

My view is that the advance of science has been like the flow of water down a channel. Starting as a trickle for several centuries, swelling to a ripple in the seventeenth century, and now surging forward as a towering wave. The energy for building up this surge has come from the growth of human population and productivity, starting at about 1700 and continuing unabated to the present. I have written about the part of the scientific surge that is my subject by assigning progress to a few leaders riding on the crest of the wave, ignoring thousands of others. This is manifestly unfair, especially because many of the archetypes I have chosen were friends or acquaintances. Otto Loewi was an especially dear friend and thanks to his vivid descriptions I feel as though I have rubbed shoulders with Starling, Langley, Schmiedeberg, and others of that generation. My defense is that without archetypes you cannot convey any idea of what people actually did, what they were like, and the conditions in which they worked. I can only apologize to the multitude whose contributions have been ignored. When I studied the lives of my archetypes, the importance of things I had taken for granted became unmistakable: laboratories, money, fellowships, scientific meetings and societies, friends, students, collaborators, journals, and, at the top of the list, teachers. Which is why—again picking arbitrary examples—I have given each of these at least a nod.

The astonishing success and growth of neuropharmacology have been underwritten by enlightened governments. There is also a bleak reverse side in the story. Progress is not inevitable. German science was fostered by thoughtful and supportive governments. The Nazis distorted scientific policy for their abhorrent political aims. They discarded admirable people, crippling German science while unwittingly benefitting their foes. Some argue that scientists should stick to theirs laboratories and let others tend to the bigger picture. History does not agree.

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REFERENCES


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