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Introduction

Generally speaking, until really quite recently – well into the 20th century in fact – treatment by most available medicines was at best only marginally beneficial and at worst positively harmful.

(William C. Bowman, 1999)

This book deals with the concept of receptors – a fundamental idea in science and medicine. Receptors are defined as proteins at the cell surface and within cells that mediate the effect of chemical messengers and hormones and the actions of many drugs in the body.¹ Although this concept is approximately 100 years old, it was not until the 1960s that it became fully accepted and exploited in the scientific community.

The receptor concept is one of those ideas in biomedical sciences which has had a great impact. Humans have utilized plant and other natural extracts as medicines to alleviate pain and illness for millennia. Yet, Sir Henry Dale, as a young medical student at the turn of the twentieth century, could describe his great disappointment when he realized just how few (perhaps fewer than 20) useful drugs were available to him, and how little was known about how even the effective ones worked.² Many of these drugs, such as amyl nitrite, atropine, digitalis, ephedrine, cocaine, morphine, physostigmine, quinine and salicylates, were in fact of ancient origin.

Since its introduction, the concept of receptors has served as a scientific basis for understanding how such drugs act in the body and has provided a significant impetus to the development of new drugs to target these receptors. This fits the argument, as proposed by Drews, that drug research has contributed more to the progress of medicine during the past century than any other scientific factor.³ Now, at the beginning

2 A Short History of the Drug Receptor Concept

of the twenty-first century, the World Health Organization's fifteenth model list of essential medicines (2007) contains 325 individual drugs, including 12 antiretroviral medicines for the prevention and treatment of HIV/AIDS. The economic impact of drug research and prescription drugs is now overwhelming. According to an NCPA report in 2000, France spends 1.6 per cent of its gross domestic product (GDP) on drugs, Britain 1.1 per cent and Japan 1.5 per cent. In 2007 health-care in the USA was 6.6 per cent of GDP (which was \$2.2 trillion) and retail spending on prescription drugs reached a record \$227.5 billion.⁴

In academia, receptors are now the *raison d'être* for most research in pharmacology and pharmaceutical sciences, and understanding their role in signalling in the nervous system lies at the very heart of neuroscience. However, the receptor is also a keystone concept in other scientific and medical disciplines, including biochemistry, immunology, chemotherapy, molecular biology, physiology and toxicology. An indication of this significance can be seen in journal citations. From a simple search of the National Library of Medicine's Gateway database, for articles published between 1960 and 1969, there were 5107 journal citations with *receptor* or *receptors* in the keywords, title or abstract; between 1990 and 1999, there were more than 314,000 such journal citations. The distinctive position that the drug receptor concept holds in pharmacology leads medical historians as well as pharmacologists on a quest to learn more about the historical development of this core idea of modern medical science. This book deals with the history of the receptor concept and aims to present the development of this idea in its contemporary context.

Research methods and approaches

The receptor concept was born in the last decade of the nineteenth century. To write a history of scientific ideas from a cultural perspective was the inspiration behind this book, but it was also a problem. Venturing into the area of the 'history of ideas' seems to be a somewhat outdated approach. The 'history of great ideas' is one of the classic topics of the traditional 'Whiggish' history of science and medicine, and descriptions of revolutionary concepts and innovations fill the pages of many of the older monographs in the field. This old style of writing tends to portray the history of medical concepts as a progress-oriented success story ending in the era of modern scientific medicine. This style of writing on the history of ideas is still prevalent as representatives of various medical disciplines publish flattering accounts of their respective specialities.⁵

Practising physicians or medical researchers often link the rise and fall of ideas purely to the thoughts and concepts of the scientists concerned.

By contrast, the challenge we faced was that of describing and analysing the history of the drug receptor concept in its cultural context. This follows the more recent trend in studies of scientific and medical concepts where they are related to research institutes and hospitals, methods, experimental settings, epistemic objects, researchers, patients and the public in general – to mention only a few. Meanwhile, there are many publications that describe well-defined research cultures, each with a specific style of thought, experiment and research. Often, these publications focus on isolated aspects, for example, the involvement of politics in scientific decision-making, research and gender problems, research and therapeutic reasoning, or the relation between medical experimentation and social and medical institutions.⁶ For good reasons, most recent edited volumes on the history of medical innovations try to label their contributions according to the topics mentioned above. They aim to demonstrate different perspectives on the history of innovations and to describe and analyse specific factors which influence the research process.⁷ There remain two problems in relation to this procedure. First, there is the danger of losing sight of the fact that a multitude of quite different aspects may be involved in the development of a particular idea. Second, the history of concepts or ideas is not itself treated as a separate research topic – perhaps because of the fear of slipping back into the old Whiggish formula or because science studies venture into this area from other starting points.⁸

This book delivers a history of the receptor concept as an idea in its cultural contexts. Here we apply the word ‘culture’ in its broadest sense, as the actions and rituals of human beings in ordering their world.⁹ Our refusal to narrow the term ‘culture’ enabled us to identify many different factors and aspects which have moulded the story of the receptor concept. This way, our approach resembles that of the historian of chemistry, Jack B. Morrell, who ‘suggested a way in which social history of science could be written which did not downgrade science as cognition, which bypassed the sterile dichotomy between internal and external history of science, and which avoided any form of naïve reductionism’.¹⁰ Morrell’s work focuses on research schools and scientific networks, including factors such as recruitment, training, the careers of scientists, and the power of directors of scientific institutions. The cognitive side of science and its social and cultural practice are very much interrelated, and this is what we want to show in this book when writing about the history of the receptor concept.¹¹

As the historian Peter Moraw has pointed out, researchers do not leave their social connections in the cloakroom when entering the lab.¹² Indeed, the birth of the receptor concept was the outcome of circumstances in the lives of its two founding fathers, the physiologist John Newport Langley (1852–1925) and the immunologist and bacteriologist Paul Ehrlich (1854–1915). Scientific debates, career issues, religious faith and politics invaded the lab, or at least influenced the direction of research. Langley and Ehrlich independently invented the concept of receptors, but it was an idea not solely developed on the basis of scientific knowledge. Especially in the case of Ehrlich, it involved fantasies partly born from novels. The final concept was so flexible that it was resistant to falsification, and Ehrlich promoted ‘receptors’ like a new product. The concept was then discussed internationally, but within a context of competing theories and a scientific community of pharmacologists that adhered to rigid nineteenth-century traditions. The concept was also confronted with contemporary trends in medicine that favoured the improvement of therapy rather than lengthy programmes of basic research. Langley, Ehrlich and other protagonists of the idea died early or were relative outsiders in pharmacology. Receptor research was disrupted by the two world wars, the concept was hard to operationalize with current techniques and was challenged by competing research strands. But it finally made its breakthrough.

Although the receptor concept eventually proved to be an effective tool in pharmacology, ours is not a success story. It is a story of originality, but also one of chance, of lucky and unlucky coincidences, of ups and downs. Even today, the concept is debated. With hindsight it is less astonishing that it took 60 years for the concept to be accepted, than that it was finally accepted at all. The fate of the concept depended on social networks in pharmacology and medicine. It was developed and applied by single researchers and their collaborators (research groups) in Germany (Ehrlich), the UK (Langley, Clark, Black), and the USA (Ahlquist, Moran). But between around 1905 and 1950 it was also denied and rejected by networks of leading pharmacologists/physiologists in Germany, the UK and the USA.

The starting points for our analysis are the actors and their works. The papers of the various researchers, published in contemporary journals, enabled us to trace the development of individual theories. But the papers are complemented by the examination of textbooks that reflected the state of the art and the standing of the receptor concept in contemporary pharmacology. Moreover, archival materials as well as the oral history method have been used to complement the published sources

and to contextualize the receptor research. This helped us analyse the biographies of the main actors and the circumstances of their lives. Such material also helped us consider the contemporary fashions in medicine, the zeitgeist, together with the scientific networks that influenced the fate of the receptor concept. Archival sources were examined in Berlin, Freiburg, Graz, Cambridge, Edinburgh, London, New York and Augusta; they ranged from specific biographical material to material on institutions.¹³ Oral history was restricted to specific cases, where gaps in knowledge and explanation still existed and could not be closed with printed and unprinted materials. This is especially true for the research on Raymond P. Ahlquist (1914–83), who played an important role in promoting the receptor concept after 1945. Because of all the problems linked with this method,¹⁴ we see oral history only as an auxiliary tool, the results of which have to be cross-checked with textual material whenever possible.¹⁵

Using these sources as a base, it was possible to write the history of a scientific concept informed by approaches of social constructivism. We focused on pharmacology as a field that was predominantly inspired by the new idea of receptors, and the history of this special discipline of medicine formed the background of our work.

The background: theories of drug action before 1900

Theorizing about the ways in which drugs and poisons act on the human body is as old as our Western medical tradition. Such ideas have been closely linked with contemporary understandings of how the body functioned and of the nature of disease.

In Greek antiquity, Hippocrates (c. 460–c. 370 BC) and his followers defined physical health as the balance of four cardinal humours (fluids) of the body: ‘blood’, ‘phlegm’, ‘yellow bile’ and ‘black bile’. Each of these four humours was characterized by a pair of primary qualities. Blood was described as hot and wet, yellow bile as hot and dry, phlegm as cold and wet, and black bile as cold and dry. Disease was interpreted as an imbalance between the four humours. Treatment therefore aimed at restoring the equilibrium, usually by regulating the patients’ lifestyle, that is, exercise and rest, sexual activity, clothing, housing and, in particular, diet. If, for example, a patient suffering from a fever was considered to be overly ‘hot and dry’, the Hippocratic healer advised eating foods that were ‘cold and moist’, such as barley gruel or seafood. If an excess of a humour was diagnosed, the opening of a vein (phlebotomy) was thought to remove this excessive matter through bloodletting.

Drugs were often understood as a means to evacuate excessive or harmful humours and were thus classified according to the way they expelled matter: as emetics (vomiting), purgatives (laxatives), diaphoretics (sweating), diuretics (increasing the excretion of urine), expectorants (facilitating the coughing up of mucus), cholagogues (supporting the excretion of bile) and emmenagogues (bringing forth menstruation). Primary qualities were also ascribed to drugs, and treatment followed the principle of *contraria contrariis curantur* (opposites are cured by opposites). A phlegmatic patient, for example, who suffered from an abundance of cold and wet humours, required treatment with a heating and drying drug such as thyme.

The remedies of Hippocratic medicine were mostly made from plants, but some were also made from substances of animal origin, for example cuttlefish eggs, deer horn, blister beetle or castoreum (from the beaver). A number of mineral substances such as common salt, soda, alum, sandarach (disulfide of arsenic), antimony and some copper salts were also employed. The knowledge of a drug's effects appears to have been derived from therapeutic experience and (largely oral) tradition.¹⁶

In Roman times, the imperial physician Galen of Pergamon (AD 129–c. 200) developed a more elaborate pharmacological system on the basis of the Hippocratic principles. This attributed the four primary qualities to drugs and, in addition, stipulated certain degrees of efficacy, from zero up to four or five. Water, for example, was described as cooling at a degree of zero and rose-water as first-degree cooling.¹⁷ Opium, according to Galen, was cooling in the fourth degree and the flesh of a viper moderately heating and strongly drying.¹⁸ The rationale of Galenic drug treatment still followed the Hippocratic principle of *contraria contrariis* in applying remedies that produced effects opposite to those of the disease. For example, a 'hot' fever required 'cooling' drugs. Drugs with opposite qualities were also combined in the hope of producing compound remedies that had intermediate degrees of efficacy and that would be both safe for the patient and appropriate for many conditions. The most famous of these were universal remedies or panaceas, such as 'theriac', which included both viper flesh and opium, in addition to many other ingredients.¹⁹

Like the Hippocratic healers, Galen also advocated therapy through evacuating overabundant humours. He theorized that each drug attracted the humour that was proper to it, in the same way that the body attracted its appropriate nutrients or a lodestone attracted pieces of iron. The cholagogue drug scammony, for instance, was said to attract yellow bile from jaundiced patients, and safflower and *Cnidian* berry to draw

phlegm from the body. There was even some speculation in Epicurean thought (with which Galen did not agree) that substances that attracted each other became entangled or interlocked through minute hook-like extremities.²⁰

In ancient Greco-Roman culture, though not strictly in Hippocratic medicine, such 'rational' attempts at pharmacology and pharmacotherapy often went hand-in-hand with religious and magical forms of healing. As the cause of disease might lie in both environmental conditions and divine wrath, praying to the gods, sleeping in the temple of Asklepios (the God of Healing), wearing amulets and performing diverse magical practices were believed to complement physical forms of treatment.²¹

During the Middle Ages, the Hippocratic humoral theory and Galen's doctrine of drug effects were authoritative guides for treatment. Reflecting the Christian worldview, however, writers emphasized that the success of a therapy always lay ultimately in the hands of God. This combination of religious and naturalistic or rational approaches to healing continued into the Renaissance (and beyond), regardless of the wider revolutionary changes that were brought about by the Reformation, the Copernican system and the discovery of the New World. Paracelsus (1493/94–1541), the most outspoken medical revolutionary of the period, despised Galen's teachings, but advocated the doctrine of 'signatures', according to which God had given certain signs to plants to allow human beings to recognize their healing properties. Thus a yellow plant such as saffron indicated its healing power in cases of jaundice, or the leaves of *Pulmonaria*, which display lung-shaped markings, hinted at their usefulness in treating respiratory diseases. With Paracelsus, alchemy became a major influence on therapy. He characterized substances according to three chemical principles: the inflammable 'sulphur', the volatile 'mercury', and 'salt', that is, the residuum after an alchemical procedure. Under Paracelsus' influence, so-called 'chemical' medicines of mineral origin, containing iron, lead, copper, sulphur, antimony, arsenic or mercury, gained prominence in pharmacotherapy. They had, in part, been used already in Hippocratic medicine, but their use by Paracelsus and his followers corresponded to a new chemical interpretation of bodily processes.²²

In the seventeenth century, iatrochemistry (medical chemistry) developed from these Paracelsian ideas as a specific orientation of learned medicine. Diseases were understood as the product of inner 'fermentations' and as an imbalance between acidity and alkalinity in the body. Depending on the diagnosed acid or alkaline character of a condition, an

alkaline or acid medicine was prescribed in order to neutralize the excess. Other theories of drug action reflected a vitalistic conception of disease. According to the Flemish physician and philosopher Jean Baptiste van Helmont (1579–1644), disease was an expression of an organ's disturbed vital principle, the *archaeus*. Remedies had a specific 'taste', the *sapor specificus*, which enabled the *archaeus* to recognize them as beneficial.²³

Under the influence of René Descartes (1596–1650) and his followers, mechanistic interpretations of bodily functions as well as of the actions of drugs developed as an alternative to those vitalistic and chemical speculations. Iatromechanism, which flourished in the late seventeenth and eighteenth centuries, attempted to apply Robert Boyle's (1627–91) corpuscular understanding of chemical processes and Isaac Newton's (1642–1727) notion of gravity to physiological and pharmacological phenomena. Poisonous mercury sublimate, for example, was believed to cause inflammation and gangrene of the stomach and the guts through minuscule 'fiery spikes', and metallic mercury was thought to dissolve 'coagulations' and to act as a purgative through the weight and motion of its rotund particles.²⁴ During this period the concept of a 'specific' remedy, that is, of a drug that healed a specific disease through some hidden property or unexplainable power, was launched by those who were critical of chemical or mechanistic speculation. The English physician Thomas Sydenham (1624–89) famously praised the (quinine-containing) Peruvian bark, a drug first brought to Europe by Jesuit missionaries in the 1630s, as a true 'specific' against intermittent fever (that is, malaria). Diseases were supposed to be classifiable in the same way as plants in botany, and specific remedies against specific kinds of disease were supposed to be identified on an empirical basis.²⁵

Mechanistic, chemical, vitalistic and empiricist approaches to the understanding of drug effects continued to compete with each other throughout the eighteenth century and beyond. Distinctive systems of medicine that developed in this period had characteristic predilections in pharmacotherapy, for example, the rival systems of Friedrich Hoffmann (1660–1742) and Georg Ernst Stahl (1659–1734), who for a time both taught medicine at the University of Halle in Germany. Hoffmann and his students propagated mechanistic interpretations of drug action; they proposed that opium, as a hypnotic and analgesic drug, worked by thinning the blood, which distended the arteries of the brain or made blood serum seep out of the vessels, pressing on and obstructing the nervous fibres. For Stahl, by contrast, opium dazed and stupefied the soul, which not only guided physiological movements, but was also the force behind the body's salutary expulsion of harmful matter. Stahl's were therefore

very sceptical about the therapeutic value of opium, which (as they saw it) paralysed the 'healing force of nature', whereas Hoffmann's followers had no objections against using this powerful drug in treatment, if it was applied with due caution.²⁶

Alongside the various scientific interpretations, religious views continued to be relevant. Hoffmann, shortly before his death, wrote a work on natural theology or 'physicotheology', in which he praised God's providence in having put salutary mineral springs in the earth, and in letting certain plants grow specifically in those places and countries where they were most needed for the treatment of certain endemic diseases. Other writers used the example of useful medicinal plants to demonstrate, in the teleological fashion of natural theology, 'God's power, wisdom and benevolence' towards mankind.²⁷

From the late seventeenth century, chemical tests, *in vitro* experiments on blood, animal experimentation and human trials were employed to explore the mode of action of drugs and poisons. Often such experiments were used to support a particular point of pharmacological theory. Some trials, however, were performed to decide on the general question of whether poisons acted 'by sympathy', for example by stimulation of nerve endings in the stomach wall which propagated the effect through the body, or by way of absorption into the blood and distribution through the circulation. In the early nineteenth century the theory of drug effect via absorption became dominant, especially through the animal experiments of the Paris physiologist and physician François Magendie (1783–1855).²⁸

At this time new pharmacological theories and treatments had become fashionable. Brunonianism, named after the Scottish physician John Brown (1735–88), claimed that illness was characterized by either a lack of bodily excitement (asthenic diseases) or over-excitement (sthenic diseases). To restore a balance, a mixture of alcohol and opium (laudanum) was used as a stimulant for asthenic conditions, and a vegetable diet or bloodletting was recommended for sthenic diseases.²⁹ Towards the end of the eighteenth century, the German physician Samuel Hahnemann (1755–1843) introduced the system of homoeopathy. Breaking with the Galenic principle of treatment by *contraries*, Hahnemann taught that substances producing symptoms *similar* to those of the disease should be used in therapy. This principle of *similia similibus curentur* (treat like with like) together with the principle of 'potentiation' of a drug's effect by way of extreme dilution (to transfer the drug's power to the solvent) alienated homoeopathic physicians from their more conventional colleagues.³⁰ Despite this variety of new theories of drug action, medical

practice largely continued to follow Galenic principles until well into the nineteenth century.

As was the case in other areas of medicine, pharmacology was, for a period, influenced by Romanticism, especially in the German-speaking countries. Following Newton's work on attraction and repulsion around 1700, chemists throughout Europe had become interested in studying the chemical affinities between substances. By the beginning of the nineteenth century, this theme had become part of a wider culture. In 1809 Johann Wolfgang von Goethe (1749–1832) used the concept of '*Elective Affinities*' ('*Wahlverwandtschaften*') in his novel of the same name to describe and understand human relationships. Unsurprisingly, the concept of affinities also featured in Romantic pharmacological writings, especially as it had similarities with Galen's ideas about the selective attractive powers of drugs. Karl Friedrich Heinrich Burdach (1776–1847) used these terms to explain the difference in pharmacological efficacy between substances, and Friedrich Sobernheim (1803–46) postulated '*specific elective affinities*' ('*spezifische Wahlverwandtschaften*') between certain drugs and body parts. In Sobernheim's view, strychnine had a specific affinity to the spinal cord, digitalis and tobacco to the nerves of the heart, alcohol to the brain, mercury to the salivary glands, ergot to the nerves of the uterus, and sulphur to the skin.³¹

Yet in the same period pharmacology experienced a decisive empirical turn, first in France with the experimental work of Magendie, and then in German universities, where pharmacology was first institutionalized as a laboratory-based medical discipline. Magendie's programme for physiological research was simply to record the phenomena of life obtained through experiments and to distrust any higher, vitalistic 'principles'. It was hoped that the observed phenomena would be reducible, eventually, to physical and chemical laws. This experimentalism and reductionism applied also to Magendie's pharmacological work. Benefiting from the contemporary work of pharmacist-chemists, from 1813 onwards he examined, in animals and healthy and ill human beings, the effects of various alkaloids that had been isolated from plant sources, such as morphine (from opium), emetine (from ipecacuanha roots), quinine (from Peruvian bark), and strychnine (from *nux vomica*), as well as pure chemical substances such as prussic acid and iodine. This emphasis on studying the effects of 'pure' substances rather than the traditional compound remedies marked an important new departure in the history of pharmacology.³² Thus, depending on new developments in chemistry and particularly physiology, Magendie's experimental approach was adopted by others, especially his most famous student, the physiologist

Claude Bernard (1813–78), as a model to study the effect of drugs and poisons as well as physiological processes in general. Bernard, for example, showed in animal experiments that the point of attack for the paralysing arrow-poison curare was where the endings of the motor nerves met the muscle fibres.³³

This type of pharmacology was initially deeply embedded in physiological research as the subject became institutionalized as a laboratory discipline. At the University of Dorpat, Estonia, in 1847, the German professor Rudolf Buchheim (1820–79) created the first laboratory for experimental pharmacology. It was initially self-funded and used by his doctoral students, one of whom, Oswald Schmiedeberg (1838–1921), went on to become, in 1872, professor of pharmacology at the new German Reich University of Strasbourg, established after the Franco-Prussian war of 1870/71. Alsace had been annexed to Germany, and Strasbourg was generously funded by the state to make it the German ‘model university’. Schmiedeberg was thus able to found a large institute of pharmacology, which soon attracted postgraduates and visiting researchers from many countries and set an example for the establishment of similar institutes at other German universities.³⁴

Both the Buchheim-Schmiedeberg school of experimental pharmacology and the French line of drug research within experimental physiology avoided theorizing about the nature of drug action. While the modes and sites of action of many substances, as well as their metabolism in the animal body, were studied extensively, broader pharmacological theories were not formulated. As Schmiedeberg wrote in 1867 (when still an assistant to Buchheim in Dorpat) with regard to theories about the action of chloroform, there were too many premature theories. Better, then, ‘with all the means of physics and chemistry [and] on the basis of physiology [to] establish new, indubitable facts through experimentation and observation’.³⁵ This emphasis on observable ‘facts’ reflected the general positivism of the natural sciences of the nineteenth century, and the influence of the Buchheim-Schmiedeberg school on the study of drugs continued well into the twentieth century (see Chapter 3 below).

It was unclear, however, how certain drugs selectively affected particular tissues or organs. A strand of pharmacological theory developed from the notion that specific relations between the chemical structure of a substance and its effects in the body might be identifiable. Magendie himself had hinted at this and one of his former students, the English physician James Blake (1814–93), demonstrated in the 1840s that inorganic compounds with the same macroscopic crystalline structure produced

similar physiological effects when infused intravenously. By the 1860s chemistry had sufficiently developed to enable other researchers to show structure-activity relations for organic substances as well. In London, Benjamin Ward Richardson (1828–96), later known for his contributions to public health, studied the action of various amyl compounds in the frog and found that slight modifications in the chemical composition of a compound led to small variations in its effects on the animals. He thus suggested that the chemical law of substitution might have its counterpart in a ‘physiological law of substitution’. In Edinburgh, a similar line of investigation was followed by the pharmacologist Thomas Richard Fraser (1841–1920) and the chemist Alexander Crum Brown (1838–1922), who compared the physiological action of salts and substitution products of various alkaloids, including strychnine, morphine, codeine, nicotine and atropine. They showed, for example, that whatever the ‘normal’ effect of the alkaloid, a change in one of the nitrogen atoms (from tertiary to quaternary form), invariably produced a curare-like paralysing action.³⁶ However, this kind of detailed structural study was still rare; chemistry was not routinely used in medical drug research until the twentieth century.

By the early twentieth century, a scientific controversy had developed over whether pharmacological action depended directly on a substance’s chemical structure or rather upon its physical properties, and therefore only indirectly upon its chemical constitution. Advocates of a chemical theory of drug action faced opposition from adherents of the so-called ‘physical theory’,³⁷ a controversy which formed the backdrop to the development of the receptor theory of drug action. Another important general question was how substances acted upon animal and human cells. Rudolf Virchow’s (1821–1902) classic work on *Cellular Pathology*, published in 1858, established the view that disease could be understood as an expression of morphological changes and disturbed functioning in cells.³⁸ Microscopic investigations using dyes that selectively coloured certain types of cells and cellular structures became important. From the 1890s attempts were also made to study the selective action of poisons on cells, for example by the Leipzig pharmacologist Rudolf Boehm (1844–1926), and subsequently by one of his pupils, Walther Straub (1874–1944).³⁹ The old notion of ‘affinities’ between certain drugs and parts of the body gained new significance through this research. This was the immediate background of the development of the receptor concept, and it is therefore in this period, between the 1870s and 1890s, that the narrative of this book begins.

Outline of the book

Chapters 1 and 2 analyse the origins and early development of the receptor concept by the Berlin immunologist and Nobel laureate Paul Ehrlich and the Cambridge physiologist John Newport Langley. Between 1878 and 1905, these two scientists approached the idea from quite different fields of research outside of pharmacology. Ehrlich was chiefly interested in bacterial toxins and antitoxins; he came to the idea of cell receptors via the development of his immunological *side-chain theory*, which explained the mechanism by which toxins are bound by immune cells and by which antitoxins are produced in the body. Langley was mainly interested in the physiology of the autonomic nervous system, and he examined the effect of drugs and poisons on nerve endings and muscles. He postulated the '*receptive substance*' as the site of action for nicotine- and atropine-like drugs. Langley and Ehrlich constructed two different receptor theories which came together only after 1905. The first two chapters of this book show how the development of the receptor concept by Ehrlich and Langley was an outcome not only of their intellect and originality, but also of their personal decisions and career paths, and of several different issues then debated in medical research.

The receptor idea was not, however, immediately accepted in pharmacology. Chapters 3 and 4 examine the debate about the receptor idea and competing theories of drug binding and the transmitter concept. Chapter 3 argues that resistance to the idea of receptors arose after 1905 because there were several competing theories of drug action, and, with the technologies available, it was difficult to test these ideas. Furthermore, the main representatives of academic pharmacology, such as Walther Straub in Germany and Arthur Robertson Cushny (1866–1926) in England, were strong advocates of a theory of drug action centred on physical, rather than chemical, explanations. Chapter 4 is devoted to the history of the transmitter concept; it explains why influential representatives of physiological and pharmacological research, including Sir Henry Hallett Dale (1875–1968) and Otto Loewi (1873–1961), were less interested in receptors than in transmitter substances in the nervous system. Chapters 3 and 4 together show that the empiricist experimental style developed by Rudolf Buchheim and Oswald Schmiedeberg and their reluctance to build broad pharmacological theories continued to dominate the scientific community of pharmacologists.

Chapter 5 deals with the elaboration of the receptor concept in the late 1920s and early 1930s when it regained prominence through the work of the British pharmacologist Alfred Joseph Clark (1885–1941). He

was initially open-minded about the 'physical' and 'chemical' (receptor) theories of drug action and adopted a quantitative approach to better understand the effect of drugs on cells. He determined that certain *minute* quantities of drugs could influence cells only through specific areas of the cell, and concluded that receptors must be responsible for the transmission of drug effects (*receptor occupancy theory*). Clark's successor in the Edinburgh Chair of Materia Medica, John Henry Gaddum (1900–65), went on to develop the concept of competitive antagonism of drugs for receptors. Subsequently, Clark's receptor occupancy theory was further refined and modified in the 1950s by R.P. Stephenson (1925–2004) (also in Edinburgh) and by the Dutch pharmacologist E.J. Ariëns (1908–2002). But throughout this period, receptors remained hypothetical entities.

Chapters 6 and 7 cover the consolidation of the receptor concept in pharmacology. Although the receptor theory became quite widely accepted by the 1950s, it was not the central focus of pharmacological research. As Chapter 6 makes clear, even the important studies of the American pharmacologist Raymond P. Ahlquist (1914–83) did not immediately change this situation. In 1948, Ahlquist divided the receptor for the neurotransmitter adrenalin into alpha- and beta-receptors, a distinction that was crucial to the impact and later pharmacological exploitation of receptors. The evidence for the existence of different sub-types of receptors answered many questions that had arisen from the multiple and often opposing effects of a single drug in the body. Ahlquist, however, was a relative 'outsider', his personality and his cautious way of presenting his results, set against the dominant background of the neurotransmitter research, were not conducive to a wider dissemination and adoption of the receptor concept. After more research on chemical mediation of drug effects, and the modifications of Clark's theory by Ariëns and Stephenson, it became easier to apply Ahlquist's refinement in clinical pharmacology. A critical breakthrough for the receptor concept arrived with selective receptor-blocking drugs: in 1965, Sir James Black introduced the first therapeutically useful β -blocking agent, propranolol. For his work on receptor-subtype-selective drugs he received the Nobel Prize in Physiology or Medicine in 1988.

Chapter 7 describes how the consolidation of the concept was achieved with the isolation and purification of receptor proteins and their visualization in the late 1970s and 1980s. Since then a multitude of receptors and receptor families have been described and their mechanisms of signal transduction delineated. This last chapter has been written from the perspective of a neuropharmacologist (Robert Halliwell) who is active in this field of research. Given our historical closeness to this period, the

narrative provided here is somewhat more technical and involved than in the previous chapters. However, the non-specialist reader will take from it an appreciation of how important the receptor concept has become to biomedical research and how receptors were eventually transformed from more or less useful hypothetical constructs into material objects of scientific inquiry.

We want to show that the history of the development and impact of the receptor idea on pharmacological problems by no means represents a simple success story. On the contrary, we demonstrate that the receptor idea, although developed in the last years of the nineteenth century, went through periods of acceptance and rejection before critical pharmaco-therapeutic breakthroughs occurred in the 1960s. While certain episodes of the 'receptor story' have been told in articles and book chapters by other authors, most notably John Parascandola, Joseph Robinson and Arthur Silverstein,⁴⁰ our book is the first to give a comprehensive and detailed examination of the origins and development of the receptor concept and a historical explanation for its slow acceptance in pharmacology. The history of the idea of receptors serves as an example of how research programmes and medical disciplines are shaped by the combination of intellectual, biographical and social factors.

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