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"Receptive Substances": John Newport Langley (1852–1925) and his Path to a Receptor Theory of Drug Action

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Introduction

The concept of specific receptors that bind drugs or transmitter substances onto the cell, thereby either initiating biological effects or inhibiting cellular functions, is today a cornerstone of pharmacological research and pharmaceutical development. Yet, while the basic ideas of this concept were first explicitly formulated in 1905 by the Cambridge physiologist John Newport Langley (1852–1925), drug receptors remained hypothetical entities at least until the end of the 1960s. Without doubt, the development of receptor-subtype specific pharmaceuticals—especially the beta-adrenergic receptor antagonist propranolol (introduced in 1965)—promoted the acceptance of the receptor concept in pharmacology. It was only in the 1970s, however, that receptors began to be isolated as specific proteins of the cell membrane and that their composition and conformation began to be explored. During the last twenty years the modern techniques of molecular biology have helped to determine the genetic basis of receptor proteins, to identify their amino acid sequences, and to further elucidate their remarkable structural diversity as well as their similarities and evolutionary relationships. Numerous receptor types and subtypes have since been characterized.[1]

Unsurprisingly therefore, the origins of the receptor theory have attracted the interest of historians of medicine and science. In particular, John Parascandola has traced the beginnings of the receptor idea in the work of Paul Ehrlich (1854–1915) and J N Langley.[2] More recently, the roots of the receptor concept in Ehrlich's immunological research, i.e. his famous "side chain theory", have been examined in great detail by

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[1] R G Shanks, 'The discovery of beta adrenoceptor blocking drugs', in M J Parnham and J Bruinvels (eds), *Discoveries in pharmacology*, Amsterdam, Elsevier, 1983–86, vol. 2, pp. 37–72; P G Waser, 'The cholinergic receptor', ibid., vol. 3, pp. 157–202; S E Cozzens, *Social control and multiple discovery in science: the opiate receptor case*, Albany, State University of New York Press, 1989; J D Robinson, *Mechanisms of synaptic transmission: bridging the gaps (1890–1990)*, Oxford University Press, 2001, pp. 143–70, 199–218. On the history of research into neurotransmission, see also J-C Dupont, *Histoire de la neurotransmission*, Paris, Presses Universitaires de France, 1999.

[2] J Parascandola and R Jasensky, 'Origins of the receptor theory of drug action', *Bull. Hist. Med.*, 1974, **48**: 199–220; J Parascandola, 'The development of receptor theory', in Parnham and Bruinvels, op. cit., note 1 above, vol. 3, pp. 129–56. See also A-H Maehle, C-R Prüll and R F Halliwell, 'The emergence of the drug receptor theory', *Nature Reviews Drug Discovery*, 2002, **1**: 637–41.

Arthur M Silverstein.[3] Ehrlich's work on receptors has also been related to the complex circumstances of his academic career in a recent article by Cay-Rüdiger Prüll.[4] By contrast, we are only roughly oriented about Langley's path to the receptor concept.[5] In fact, besides Gerald Geison's discussion of Langley as a member of Michael Foster's Cambridge School of Physiology,[6] historians have generally neglected the extensive research of this, in his own day, eminent scientist.

This paper intends to redress that historiographical imbalance and thus to enhance our historical understanding of the origins of the drug receptor theory and of one of its founders. After a brief account of Langley's life, this paper gives a detailed analysis of how he developed, over a period of thirty years and in diverse research contexts, his ideas on the mode of action of drugs, culminating in 1905 with the first full formulation of his concept of "receptive substances". In particular, the influence of other British and of Continental scientists on Langley's thought and experimentation will be considered. This essay will illustrate how his ideas on drug receptors emerged from several different issues that were then debated in physiology, and how they depended on specific physiological research methods of the time. It will also show how Langley defended his concept against his scientific critics and how he refined and elaborated upon the receptor idea during this process. It will finally highlight how Langley used references to Ehrlich's earlier side chain theory to consolidate his own concept of receptive substances, but simultaneously asserted his intellectual independence from the German Nobel Prize winner. While Ehrlich was in fact the first who developed, in the context of immunology, a receptor concept as such, Langley first proposed a receptor theory of *drug action*. This drug receptor theory, in turn, was later utilized in Ehrlich's chemotherapy. Langley's path to the receptor idea, as this paper will make clear, was independent from that of Ehrlich and deeply embedded in the physiological research of his time.

J N Langley: A Cambridge Man from Start to Finish

Born at Newbury on 10 November 1852, the son of a private schoolmaster, Langley was first educated at home and then at Exeter Grammar School before he entered St John's College, Cambridge, in October 1871.[7] With the aim of qualifying for a career in the Civil Service, he initially studied mathematics, history and other literary subjects, but changed his

[3] A M Silverstein, *Paul Ehrlich's receptor immunology: the magnificent obsession*, San Diego, Academic Press, 2002.

[4] C-R Prüll, 'Part of a scientific master plan? Paul Ehrlich and the origins of his receptor concept', *Med. Hist*., 2003, **47**: 332–56.

[5] See Parascandola and Jasensky, op. cit., note 2 above, pp. 200–1, 211–6; M R Bennett, 'The concept of transmitter receptors: 100 years on', *Neuropharmacology*, 2000, **39**: 523–46.

[6] G L Geison, *Michael Foster and the Cambridge School of Physiology: the scientific enterprise in late Victorian society*, Princeton University Press, 1978, pp. 236–44, 313–27. Langley is mentioned in passing in M Weatherall, *Gentlemen, scientists and doctors: medicine at Cambridge, 1800–1940*, Woodbridge, Boydell Press, 2000.

[7] The biographical details of this section have been taken from: 'Langley, John Newport', entry no. 3949 in Register, St John's College, Cambridge; W M Fletcher, 'John Newport Langley: in memoriam', *J. Physiol*., 1926, **61**: 1–27; *idem*, 'John Newport Langley—1852–1925', *Proc. R. Soc. Lond*., series B, 1927, **101**: xxxiii–xli; R du Bois-Reymond, 'John Newport Langley zum Gedächtnis', *Ergebisse der Physiologie*, 1926, **25**: xv–xix; C S Sherrington, 'Langley, John Newport', in J R H Weaver (ed.), *Dictionary of National Biography 1922–1930*, Oxford University Press, 1937, pp. 478–81; G L Geison, 'Langley, John Newport', in C C Gillispie (ed.), *Dictionary of Scientific Biography*, New York, Charles Scribner's Sons, 1973, vol. 8, pp. 14–19.

plans in his second year and began to read natural sciences. Langley was especially attracted by the classes in elementary biology, embryology and physiology, which were held by (later Sir) Michael Foster (1836–1907), then a Fellow, and Praelector of Physiology, at Trinity College. Even before Langley graduated BA in 1875, Foster involved him in his research. Langley's first study was concerned with the physiological effects of the drug jaborandi (containing pilocarpine), which he examined in the frog, dog, rat and rabbit, noting in particular its decelerating effect on the heart rate and a similarity of its action with that of the alkaloid physostigmine.[8] In the same year, 1875, Foster made him his Demonstrator, in succession to Henry Newell Martin (1848–1896), who had left Cambridge for a professorship at Johns Hopkins University in Baltimore.

In 1877 Langley was elected to a Fellowship at Trinity College, and in the subsequent year he received his MA. By this time he had become interested in the effect of pilocarpine on salivary secretion, which he studied in the dog and cat.[9] Animal experimentation had been legally regulated for the first time in Britain in 1876. The Cruelty to Animals Act of this year required among other things that animals, especially dogs and cats, be anaesthetized during experiments (unless insensibility defeated the object of the investigation).[10] This legal requirement was also reflected in Langley's published descriptions of his animal experiments. While he had before mentioned his use of anaesthetics only in passing, he now stated this fact prominently and explicitly.[11]

Some of his research on salivary secretion was carried out in the laboratory of the Heidelberg physiologist Wilhelm Kühne (1837–1900), where Langley worked for several months during 1877. The physiology of glandular secretion developed into Langley's first major research field, in which he worked until about 1890, combining morphological, physiological, and chemical methods of investigation.[12] This area of interest was supplemented by anatomical and histological studies into the then debated problem of cerebral localization and into neurodegeneration.[13]

[8] J N Langley, 'Preliminary notice of experiments on the physiological action of jaborandi', *Br. med. J.*, 1875, **i**: 241–2; *idem*, 'On the physiological action of jaborandi', *Proc. Cambr. Phil. Soc.*, 1875, April, pp. 402–4; *idem*, 'The action of jaborandi on the heart', *J. Anat. Physiol.*, 1875, **10**: 187–201.

[9] *Idem*, 'The action of pilocarpin on the sub-maxillary gland of the dog', *J. Anat. Physiol.*, 1876, **11**: 173–80; *idem*, 'On the physiology of the salivary secretion. Part II. On the mutual antagonism of atropin and pilocarpin, having especial reference to their relations in the sub-maxillary gland of the cat', *J. Physiol.*, 1878, **1**: 339–69.

[10] The Cruelty to Animals Act, 1876, clauses 3 and 5. On the history and debate of this piece of legislation, see R French, *Antivivisection and medical science in Victorian society*, Princeton University Press, 1975; N A Rupke (ed.), *Vivisection in historical perspective*, London, Routledge, 1990.

[11] For example, Langley, 'The action of pilocarpin', note 9 above, p. 174 (with reference to experiments on dogs): "In every case the animal was placed under anaesthetics during the operation and killed at its close; the anaesthetics employed have been various, most frequently morphia or chloroform, occasionally chloral hydrate, or croton chloral hydrate."

[12] For a summary account, see *idem*, 'The salivary glands', in E A Schäfer (ed.), *Text-book of physiology*, Edinburgh, Pentland, 1898–1900, vol. 1, pp. 475–530.

[13] E Klein, J N Langley and E A Schäfer, 'On the cortical areas removed from the brain of a dog, and from the brain of a monkey', *J. Physiol.*, 1883, **4**: 231–47; J N Langley, 'The structure of the dog's brain', *J. Physiol.*, 1883, **4**: 248–85; *idem*, 'Report on the parts destroyed on the right side of the brain of the dog operated on by Prof. Goltz', *J. Physiol.*, 1883, **4**: 286–309; J N Langley and C S Sherrington, 'Secondary degeneration of nerve tracts following removal of the cortex of the cerebrum in the dog', *J. Physiol.*, 1884, **5**: 49–65; J N Langley and A S Grünbaum, 'On the degeneration resulting from removal of the cerebral cortex and corpora striata in the dog', *J. Physiol.*, 1890, **11**: 606–28. For the general context of this research, see E Clarke and L S Jacyna, *Nineteenth-century origins of neuroscientific concepts*, Berkeley, University of California Press, 1987.

In 1883 Langley was elected a Fellow of the Royal Society of London, and in 1884 he took up his new posts as Lecturer in Natural Science at Trinity College and as University Lecturer in Histology. Over the years Langley assumed the role of Foster's deputy in the Cambridge Physiological Laboratory. From the late 1880s Langley became interested in the structure and function of the vegetative or "involuntary" nervous system, which had been examined morphologically and physiologically by his senior colleague Walter Holbrook Gaskell (1847–1914). In the early 1880s Gaskell had demonstrated the existence of both inhibitory and accelerator fibres in the vagus nerve of cold-blooded animals, providing in this way a simple explanation for the wide range of cardiac effects of vagus stimulation that had puzzled earlier physiologists. Building on this finding, his subsequent research explored the hypothesis that not only the heart but all involuntary muscles were innervated by two different, antagonistic types of visceral nerve fibres. By 1886 he had distinguished morphologically the visceral (vegetative) fibres stemming from the thoracic part of the spinal cord (i.e. the sympathetic system) from the fibres that originated from its cervico-cranial and sacral regions (i.e. the parasympathetic system). Moreover, Gaskell had pointed out that the actions of the thoracic part of the vegetative nervous system were antagonistic to the actions of the other two parts.[14]

Against this background, a methodically important observation was made by Langley and a medical collaborator, William Lee Dickinson (1863–1904) of Caius College, Cambridge. They found that nicotine selectively blocked nervous conduction in sympathetic ganglia, i.e. that it interrupted the transmission of nerve impulses from the preganglionic to the post-ganglionic nerve fibre. By electrically stimulating the nerve fibres running to and from a ganglion, before and after local application of a nicotine solution to the ganglion, it could then be distinguished which fibres ended in the nerve cells of the ganglion and which simply passed through it.[15] In the following years Langley used nicotine and other drugs as tools for a detailed functional and structural analysis of the sympathetic and parasympathetic systems, to which he gave the now common collective name "autonomic nervous system".[16] In 1893 Langley became president of the Neurological Society of Great Britain and in 1899 president of the Physiological Section of the British Association for the Advancement of Science. As the new century started, he was an internationally recognized expert in the research field of the vegetative nervous system.[17]

[14] Cf. Geison, op. cit., note 6 above, pp. 313–19; J N Langley, 'Walter Holbrook Gaskell, 1847–1914', *Proc. R. Soc. Lond.*, series B, 1915, **88**: xxvii–xxxvi. On the history of research into the vegetative nervous system prior to Gaskell and Langley, see Clarke and Jacyna, op. cit., note 13 above, pp. 308–70; and for a brief summary account, E H Ackerknecht, 'The history of the discovery of the vegetative (autonomic) nervous system', *Med. Hist.*, 1974, **18**: 1–8.

[15] J N Langley and W L Dickinson, 'On the local paralysis of peripheral ganglia, and on the connexion of different classes of nerve fibres with them', *Proc. R. Soc. Lond.*, 1889, **46**: 423–31.

[16] For summary accounts, see J N Langley, 'Presidential address, Section I—Physiology', *Report of British Association for 1899*, pp. 881–92 (on the nomenclature, p. 883); *idem*, 'The sympathetic and other related systems of nerves', in Schäfer (ed.), op. cit., note 12 above, vol. 2, pp. 616–96; J N Langley, 'The autonomic nervous system. Presidential address', *Brain*, 1903, **26**: part I, 1–26; *idem*, 'The nomenclature of the sympathetic and of the related systems of nerves', *Zentralblatt für Physiologie*, 1913, **27**: 149–52; *idem*, *The autonomic nervous system*, part I, Cambridge, W Heffer & Sons, 1921 (no second part of this monograph appeared).

[17] *Idem*, 'Das sympathische und verwandte nervöse Systeme der Wirbeltiere (autonomes nervöses System)', *Ergebnisse der Physiologie*, 1903, **2**: part 2, 818–72; *idem*, 'The autonomic nerves', *Nederlandsch Tijdschrift voor Geneeskunde*, 1905, no. 16, pp. 1013–30.

In 1896 he had been awarded an Sc.D., and in 1903 he succeeded Foster to the Chair of Physiology, having been Deputy Professor of Physiology since 1900.

Back in 1894, he had already taken over the editorial responsibilities for Foster's *Journal of Physiology*, saving the periodical in a financial crisis. From then on Langley owned the *Journal*, and until the end of his life he edited it with great commitment, often virtually rewriting other authors' manuscripts. In particular, he insisted that papers were written in the most efficient format and were thus concise and short. In this way he forcefully promoted the modern style of scientific writing.[18] Langley soon made it to the top of the scientific establishment. In 1897/8 he served on the Council and in 1904/5 as Vice-President of the Royal Society.

In 1905 Langley first published, in the *Journal of Physiology*, his concept of "receptive substances".[19] His subsequent work in this area remained part of his research in neurophysiology, a field which he continued to cultivate until the end of his life. In the years leading up to the First World War, Langley oversaw, in addition to his research and teaching duties, the work on a new building for the School of Physiology, which opened in June 1914.[20] Even during the war he was able to keep his research going, studying, for example, together with Japanese co-workers the phenomena of nerve regeneration and of muscular atrophy after denervation—in search of better treatments for injuries.[21]

Langley was not only fully devoted to his research and his academic duties, but was also, for most of his life, a keen athlete. His greatest talent here was ice-skating, a sport in which he even devised official rules and was called upon as an appeal judge in international competitions.[22] Langley died on 5 November 1925, after very brief illness, at his house in Madingley Road, Cambridge, to which he had moved from Trinity College after he had married Vera Kathleen Forsythe-Grant in 1902. At the end of his life he held honorary degrees from the universities of Dublin, St Andrews, Groningen, and Strasbourg.

Mutual Antagonism of Poisons and its Implications for Drug Action Theory

In the mid-1870s, the young Langley undertook his first original physiological investigation in connection with Foster's research into the origin of the heartbeat.[23] Sydney Ringer (1835–1910) had given a sample of an alcoholic extract of jaborandi to Foster, who

[18] Cf. the obituary on Langley by W M Fletcher in the *Journal of Physiology*, note 7 above, pp. 12–13.

[19] J N Langley, 'On the reaction of cells and of nerve-endings to certain poisons, chiefly as regards the reaction of striated muscle to nicotine and to curari', *J. Physiol.*, 1905, **33**: 374–413. For a detailed discussion of this paper, see below.

[20] On Langley's engagement for the new building, which was funded by a donation from the Drapers' Company, see University of Cambridge, Department of Manuscripts and University Archives, 'The Professor of Physiology 1878 to 1925', UA CUR 39.37, pp. 17, 31, and Department of Physiology, 'History of Lab Building 1912–14 . . . Papers in connection with building of Physiol. Lab. Box II'.

[21] J N Langley and T Kato, 'The rate of loss of weight in skeletal muscle after nerve section with some observations on the effect of stimulation and other treatment', *J. Physiol.*, 1915, **49**: 432–40; J N Langley and M Hashimoto, 'On the suture of separate nerve bundles in a nerve trunk and on internal nerve plexuses', *J. Physiol.*, 1917, **51**: 318–45; J N Langley, 'On the separate suture of nerves in nerve trunks', *Br. med. J.*, 1918, **i**: 45–7; J N Langley and M Hashimoto, 'Observations on the atrophy of denervated muscle', *J. Physiol.*, 1918, **52**: 15–69.

[22] Fletcher, 'John Newport Langley: in memoriam', note 7 above, pp. 14–15.

[23] See Geison, op. cit., note 6 above, pp. 193–235, 242–4.

passed it on to Langley for physiological testing. Langley noted in his animal experiments (on the dog, rabbit, and frog) a significant slowing of the heartbeat after the drug extract had been injected. Such an effect could be interpreted as the consequence of a stimulating action of jaborandi on ''inhibitory fibres'' of the vagus nerve ending in the heart.[24] However, this slowing effect could still be produced after curare had been administered, which was then widely held to paralyse nerve endings.[25] Langley therefore concluded that jaborandi acted ''probably ... more peripherally than the endings of the vagus nerves''.[26]

This view conflicted, however, with that of the Paris physician and experimental pathologist Edmé Félix Alfred Vulpian (1826–1887), who had proposed that jaborandi stimulated the endings of inhibitory vagus fibres in the heart, based on experiments in which curare appeared to prevent jaborandi's slowing effect on the heartbeat.[27] Langley was in this way drawn into a more detailed examination of the drug's cardiac action. In one of his experiments, described by him as ''perhaps the most decisive'', he curarized an anaesthetized rabbit until respiration almost ceased. Through a tracheotomy, artificial respiration was maintained. Subsequent electrical stimulation of the peripheral end of the animal's left vagus nerve no longer had any effect on the heart. Nevertheless, when the rabbit was then subcutaneously injected with an aqueous extract of jaborandi, a marked decrease of the frequency of its heartbeats (from 250–270 per minute to 120 per minute) occurred within ten minutes. This finding confirmed Langley's initial hypothesis that jaborandi ''produces this slowing by acting on something else than on the inhibitory nerve-fibres going to the heart''.[28]

In an earlier series of experiments, on the frog, Langley had found that jaborandi increased the inhibitory (slowing) effect of vagus stimulation on the heart. However, by injection or local application of atropine, even hearts that had been stopped in this manner could be brought back to their rhythmic beat.[29] In further experiments on frogs, he investigated this antagonistic action of jaborandi and atropine on the heart. Applying solutions of the two substances directly to the heart of a frog whose brain and spinal cord had been destroyed, Langley showed ''that a definite quantity of atropia can only prevent a proportionate definite quantity of jaborandi from producing its effects on the heart'' and ''that the condition of the heart ... depends on the relative amounts of jaborandi and atropia present''.[30] Moreover, the antagonism between the two poisons could also be demonstrated locally, by way of direct application, in different parts of the heart, for example, only in the auricles, or the sinus venosus, or the ventricles. This observation suggested to Langley that the drugs acted directly on the whole neuromuscular tissue of the heart—not on some localized nervous mechanism that caused and controlled the heartbeat.[31]

[24] Langley, 'Preliminary notice', note 8 above, p. 242.

[25] This view on the mode of action of curare went back to experiments by Claude Bernard in the 1840s and 1850s. See J M D Olmsted, *Claude Bernard, physiologist*, London, Cassell, 1939, pp. 223–8.

[26] Langley, 'On the physiological action of jaborandi', note 8 above, p. 404.

[27] Cf. Geison, op. cit., note 6 above, p. 242; Langley, 'The action of jaborandi on the heart', note 8 above, p. 189.

[28] Ibid., p. 190.

[29] Langley, 'Preliminary notice', note 8 above, p. 242; *idem*, 'On the physiological action of jaborandi', note 8 above, pp. 403–4.

[30] *Idem*, 'The action of jaborandi on the heart', note 8 above, pp. 194–5.

[31] Cf. ibid., pp. 197–8.

In this way Langley's study supported Foster's view that the heartbeat had a muscular, not a nervous origin.[32] Yet, this was not its only significance. At the very start of his research career Langley had hit upon a problem that would recur time and time again in the course of his experimental work and that ultimately led him to his theory of receptive substances: do drugs act directly on the effector cells (in this case, the heart cells) or do they primarily affect the endings of nerves terminating in the organ tissues? Moreover, how do drugs combine with the tissues that they affect? And how do they cause changes in the cell's function? At the time, the young Langley believed that an action of jaborandi on the muscle tissue alone, and not at all on nerve cells, was "a supposition very difficult to accept".[33] But he did recognize that the problem required further investigation.

In his next series of experiments Langley was able to use the alkaloid pilocarpine, which had been isolated from jaborandi bark and leaves in 1875.[34] Jaborandi was known to produce salivation in human beings and higher animals.[35] In experiments on the sub-maxillary gland of the dog Langley showed that pilocarpine and atropine acted as mutual antagonists with regard to salivary secretion: the secretion caused by pilocarpine could be stopped through atropine, restarted by pilocarpine, stopped again by atropine, and so on. Comparing this with his earlier findings, he concluded that "the secretion or absence of secretion is dependent on the relative quantity of the two poisons present, just as is the stand-still or beat of the heart".[36]

In 1877, the Zurich physiologist Balthasar Luchsinger (1849–1886) published an experimental study on the antagonism between pilocarpine and atropine on the secretion of sweat glands in the cat. Luchsinger gave a very graphic description of the mutual antagonism between the two alkaloids by stating that their actions combined algebraically "like wave crests and hollows, like plus and minus".[37] Langley's interest was immediately aroused, as this appeared to be a parallel case to his own observations on the antagonistic effects of pilocarpine and atropine on the salivary secretion of the dog. In further experiments, on the sub-maxillary gland of the cat, Langley found that this antagonism was not quite as simple as Luchsinger had described it. The mutual antagonism was dose-dependent and thus incomplete. If large doses of atropine had been applied, pilocarpine could produce secretion less fully; and when very large doses of pilocarpine were administered, this did not produce secretion, and this condition could not be antagonized by atropine. Nevertheless, Langley followed Luchsinger in an essential point. The Swiss researcher had concluded that the effect of the antagonism between the two alkaloids depended "simply and solely upon the relative number of the poison molecules present" and that the antagonistic alkaloids bound chemically to the "living protein" (protoplasm) of the cell. In this way compounds between

[32] Geison, op. cit., note 6 above, p. 242.

[33] Langley, 'The action of jaborandi on the heart', note 8 above, p. 198.

[34] Pilocarpine was isolated by A W Gerrard of University College Hospital, London; see 'The alkaloid of jaborandi', *Chemist and Druggist*, 1875, June 15, p. 192.

[35] See, for example, experiments with jaborandi on the sub-maxillary gland of the dog described in 'Vulpian on the action of jaborandi and atropia on perspiration', *London Medical Record*, 1875, March 3, p. 132; and Langley, 'Preliminary notice', note 8 above, p. 242.

[36] Langley, 'The action of pilocarpin', note 9 above, p. 180.

[37] B Luchsinger, 'Die Wirkungen von Pilocarpin und Atropin auf die Schweissdrüsen der Katze. Ein Beitrag zur Lehre vom doppelseitigen Antagonismus zweier Gifte', *Pflüger's Archiv für Anatomie und Physiologie*, 1877, **15**: 482–92, on p. 488. Quotation in Langley's translation, cf. Langley, 'On the physiology of the salivary secretion', note 9 above, p. 339.

either the stimulating or the inhibiting poison and the cell's protein molecules were formed, depending on the mass of each poison present and their relative affinity to the protoplasm.[38] While Langley was still unsure about the question whether the poisons acted on the nerve endings in the salivary gland or on the gland cells themselves, he elaborated on Luchsinger's idea of a chemical union between drug molecules and cell components:

> . . . we may, I think, without much rashness, assume that there is some substance or substances in the nerve endings or gland cells with which atropin and pilocarpin are capable of forming compounds. On this assumption then the atropin or pilocarpin compounds are formed according to some law of which their relative mass and chemical affinity for the substances are factors. In the analogous case with inorganic substances, other things being equal, these are the sole factors. To take the simplest case, if *a* and *b* are both able to form, with *y*, the compounds *ay*, *by*, then *ay* and *by* are both formed, quantity of *ay* and *by* depending on the relative masses of *a* and *b* present and their relative chemical affinity to *y*.[39]

Langley realized that, in view of the incomplete antagonism between pilocarpine and atropine, the laws for the formation of inorganic compounds were only applicable to this case with ''some modification'', but he was convinced that ''the action of mass'' had been ''clearly shown'' in his study.[40] Without doubt, his later ideas on receptive substances and on chemical binding between drugs and cells were foreshadowed in these remarkable considerations of the late 1870s.

During the following ten years Langley was largely preoccupied with the physiology and histology of glands, working in this field with rigorous precision and sense for detail.[41] Yet he also kept an interest in the questions of drug antagonism. This interest was particularly fuelled by the work of the Würzburg pharmacologist Michael Joseph Rossbach (1842–1894), who attacked the theory of a mutual antagonism between certain poisons. According to Rossbach, a tissue once paralysed by an alkaloid could not be restored to its former condition by applying another alkaloid. In experiments likewise carried out on the sub-maxillary salivary gland (of the dog), the Würzburg scientist had found that the stoppage of secretion through atropine could be overcome by physostigmine only if the atropine dose had been small. He explained this with the hypothesis that the alkaloids had two points of attack on the gland: the nervous part and the glandular part. Small doses of atropine were thought to paralyse merely the nerve for secretion, i.e. the chorda tympani, leaving the gland cells unaffected. In this case, physostigmine could then still produce a flow of saliva by stimulating the gland cells. If however a large dose of atropine was given, nerve fibres as well as gland cells would be paralysed, so that physostigmine would then be unable to restore secretion.[42]

Langley, using pilocarpine instead of physostigmine as the stimulating agent, provided experimental evidence against Rossbach's view. Experimenting on the sub-maxillary gland

[38] Luchsinger, op. cit., note 37 above, pp. 488, 491–2.

[39] Langley, 'On the physiology of the salivary secretion', note 9 above, p. 367.

[40] Ibid.

[41] For a list of Langley's publications in this area, see Fletcher, 'John Newport Langley: in memoriam', note 7 above, pp. 16–18.

[42] M J Rossbach, 'Neue Studien über den physiologischen Antagonismus der Gifte', *Pflüger's Archiv für Anatomie und Physiologie*, 1879, **21**: 1–38, on pp. 33–8.

of the anaesthetized cat, he paralysed the chorda tympani by intravenous injection of atropine: electrical stimulation of the nerve no longer led to salivary secretion. He then restored the secretion by injection of pilocarpine into the duct of the gland, and stopped the salivary flow again by giving intravenously another dose of atropine. According to Rossbach's interpretation, this second dose of atropine would have paralysed the gland cells. Nevertheless, Langley could again produce secretion by injecting more pilocarpine, and even after this flow had been stopped again by atropine, yet more pilocarpine could still restore it—while the chorda tympani remained paralysed throughout.[43]

On the basis of these findings Langley held on to his view that there was a mutual antagonism (within a certain dose range) between the two poisons, pilocarpine and atropine. They acted on the same tissue, forming "chemical compounds" with it, and the result depended "on their relative chemical affinity to the tissue and the mass of each present".[44]

Experiments with Nicotine and Adrenalin

Those pharmacological issues, which Langley had addressed in his work on the heartbeat and on glandular secretion, emerged again in the 1890s, in the new context of his research on the autonomic nervous system. As mentioned above, Langley and Dickinson had recognized, in 1889, that nicotine poisoning could be used as an investigative tool in the analysis of the sympathetic system, because it selectively paralysed the nerve cells of sympathetic ganglia.[45] A question that was linked with this finding was whether other poisons likewise affected nerve *cells*, or rather the *endings* of nerve fibres. From experiments on frog hearts, Langley and Dickinson concluded that nicotine acted upon nerve cells in the heart, whereas muscarine and its antagonist atropine appeared to exert their effects on the peripheral endings of the vagus fibres leading to the heart.[46] In a further series of trials they tested several other alkaloids and poisons, including picrotoxin, apomorphine, codeine, cocaine, curarine, brucine, and strychnine, in view of their point of attack, i.e. nerve cell body or nerve ending, by examining their effect on the superior cervical ganglion and on the cervical sympathetic of the anaesthetized rabbit. More generally, Langley and Dickinson also hoped to uncover differences in the poisons' mode of action that might open up "a new line of physiological investigation". However, there were inconsistencies between the effects observed after local application and after intravenous injection. Nicotine remained the clearest example of a poison that seemed to affect nerve *cells* (i.e. the cell body) rather than the endings of nerve fibres.[47]

[43] J N Langley, 'On the antagonism of poisons', *J. Physiol.*, 1880, **3**: 11–21.

[44] Ibid., p. 19.

[45] Langley and Dickinson, op. cit., note 15 above. See also J N Langley and W L Dickinson, 'On the progressive paralysis of the different classes of nerve cells in the superior cervical ganglion', *Proc. R. Soc. Lond.*, 1890, **47**: 379–90; J N Langley and H K Anderson, 'The action of nicotine on the ciliary ganglion and on the endings of the third cranial nerve', *J. Physiol.*, 1892, **13**: 460–8.

[46] J N Langley and W L Dickinson, 'Pituri and nicotin', *J. Physiol.*, 1890, **11**: 265–306.

[47] J N Langley and W L Dickinson, 'Action of various poisons upon nerve-fibres and peripheral nerve-cells', *J. Physiol.*, 1890, **11**: 501–27. On the tradition of physiological experimentation with alkaloids, going back to the work of François Magendie, see J E Lesch, *Science and medicine in France: the emergence of experimental physiology, 1790–1855*, Cambridge, MA, Harvard University Press, 1984.

As the histological work of Santiago Ramón y Cajal (1852–1934), Rudolf von Koelliker (1817–1905) and others provided evidence for a discontinuity between nerve endings and nerve cells,[48] Langley began to doubt his former interpretation and tended to believe that nicotine did not actually affect the nerve cells in the ganglion but rather the endings of the pre-ganglionic fibres that terminated close to them.[49] However, after cutting the pre-ganglionic nerve fibres and allowing them to degenerate for up to twenty-six days, local application of nicotine to the superior cervical ganglion still caused its characteristic effects. This experimental result, reported by Langley in 1901, seemed to confirm the exceptional role of nicotine as a substance attacking nerve cells rather than the endings of nerve fibres.[50]

Though favouring the new neurone theory over the old concept of a continuous network of nerve fibres and nerve cells, Langley kept an open mind on this more general issue. He adopted the terminology of the new theory, ''because the facts cannot be expressed in terms of both theories without extraordinary verbiage''. Believing in independence of histological and of physiological evidence, Langley held that even in the event that the neurone theory would have to be abandoned, his physiological observations would still remain valid.[51]

Yet, the issue of the precise point of attack of a drug or poison was brought up again at this time through the new physiological research with extracts of the suprarenal gland (containing adrenaline), in the wake of the pioneer study in this field by the Harrogate physician George Oliver (1841–1915) and the Professor of Physiology at University College London, Edward Albert Schäfer (1850–1935). One observation made by Oliver and Schäfer, which became particularly important for Langley, was that suprarenal extract seemed to produce the typical rise in arterial blood pressure by directly acting on the smooth (unstriated) muscle tissue of the blood vessels. When Oliver and Schäfer added suprarenal extract to the perfused arterial system of frogs whose central nervous system had been destroyed, the arterioles contracted so much that the flow of the circulating perfusion fluid came almost to a standstill. Moreover, when the brachial nervous plexus of an anaesthetized dog was cut on one side, but left intact on the other side, intravenous injection of suprarenal extract caused equally on both forearms a prolonged diminution of size (measured with a plethysmograph). Also this spoke for a direct action of the extract on the muscle tissue of the arterioles, rather than for an effect on nerves.[52] German physiologists soon reported other experimental findings that likewise supported the view that suprarenal extract acted directly on muscle tissue, not on nerve endings. Max Lewandowsky (1876–1918) of the Physiological Institute in Berlin showed in an experiment on the cat that the extract continued to produce contraction of the smooth muscles of the eye and eye socket (innervated by sympathetic nerves) even after the sympathetic cervical ganglia had been excised and the post-ganglionic nerve fibres allowed to degenerate.[53] Moreover, by expanding upon

[48] For a recent summary of the origins of the discontinuity or neurone theory, see Robinson, op. cit., note 1 above, pp. 1–30.

[49] J N Langley, 'On the stimulation and paralysis of nerve-cells and of nerve-endings. Part I', *J. Physiol*., 1901, **27**: 224–36, on p. 224.

[50] Ibid., p. 229.

[51] Cf. ibid., pp. 224–5.

[52] G Oliver and E A Schäfer, 'The physiological effects of extracts of the suprarenal capsules', *J. Physiol*., 1895, **18**: 230–76, on pp. 239, 245–7.

[53] M Lewandowsky, 'Ueber die Wirkung des Nebennierenextractes auf die glatten Muskeln, im Besonderen des Auges', *Pflüger's Archiv für Anatomie und Physiologie*, 1899, pp. 360–6.

experiments made by Oliver and Schäfer, the Göttingen physiologist Heinrich Boruttau (1869–1923) demonstrated that suprarenal extract also acted directly on somatic striated muscle tissue—not on motor nerve fibres.[54]

For Langley, this all meant that there was apparently a second substance, besides nicotine, that directly affected cells rather than nerve endings. He repeated Lewandowsky's experiment on the cat's eye and was able to confirm his findings.[55] He also returned to his tried and tested experimental model, the sub-maxillary gland of the cat, and found that suprarenal extract caused secretion even after the superior cervical ganglion had been removed and ten days had been allowed for the post-ganglionic secretory nerve fibres to degenerate.[56] These results spoke for a direct action on the effector cells, i.e. the muscle cells and gland cells, respectively.

Langley was probably the first who pointed out the striking parallels between the effects of suprarenal extract and of electrical stimulation of sympathetic nerves.[57] There were, however, considerable differences in the effect of suprarenal extract on various tissues innervated by autonomic nerve fibres. Differences occurred also in the effect of nicotine on ganglia. It paralysed the upper cervical ganglia and the ganglia of the lateral chain more easily than those of the solar plexus. Moreover, there were differences in nicotine's efficacy between related species, such as dogs and cats, and even between individual animals of the same species. Langley speculated that the reaction to nicotine depended "upon the presence of a special chemical substance in the nerve-cells or on the nerve-endings", and that there had to be differences "in the chemical constitution of protoplasm" that were responsible for the alkaloid's varying efficacy in different animals. Without naming Paul Ehrlich, or any other researcher in the nascent field of immunology, Langley drew attention to "recent investigation[s] upon toxins and anti-toxins", which had shown "what enormous effects on the organism these differences in chemical constitution may bring about".[58]

In these speculative remarks, made in 1903, Langley had come very close to the idea of drug receptors in cells. In fact, two years later he was to formulate his concept of "receptive substances". In the meantime, however, a student of Langley, Thomas Renton Elliott (1877–1961), had taken up his professor's observation of the parallelism of effect between suprarenal extract and sympathetic nerve stimulation.

The Idea of Receptive Substances

Working with "adrenalin", which had been isolated from suprarenal glands by Jokichi Takamine (1854–1922) in 1901, Elliott provided further examples of "the broad rule that the action of the substance [i.e. suprarenal extract] upon plain muscle simulates that of electrical excitation of the sympathetic nerves supplying each particular

[54] H Boruttau, 'Erfahrungen über die Nebennieren', *Archiv für die gesamte Physiologie*, 1899, **78**: 97–128, on pp. 109–11.

[55] J N Langley, 'Observations on the physiological action of extracts of the supra-renal bodies', *J. Physiol.*, 1901, **27**: 237–56, on pp. 244–5.

[56] Ibid., pp. 241–2.

[57] Ibid., p. 256. This observation places Langley also in the history of the discovery of chemical neurotransmission. In 1946 Ulf Svante von Euler provided persuasive evidence that noradrenaline was the transmitter substance of sympathetic nerves. See Robinson, op. cit., note 1 above, pp. 56, 123–4; Dupont, op. cit., note 1 above, pp. 46, 173–4.

[58] J N Langley, 'The autonomic nervous system. Presidential address', note 16 above, pp. 6–7.

muscle''.[59] He also investigated some apparent exceptions to this rule. In May 1904, in a preliminary communication to the Physiological Society, the young researcher made his—today famous—suggestion, that adrenalin was ''secreted by the sympathetic paraganglia'' and might be ''the chemical stimulant liberated on each occasion when the [nervous] impulse arrives at the periphery''.[60] While this proposal has placed Elliott firmly in the history of the concept of chemical neurotransmission,[61] his thoughts on how the muscle cell received the stimulus of the ''chemical excitant'', and reacted with a change of tension of the muscle fibres, were important for the development of the receptor idea.

Langley and Lewandowsky had been criticized for their view that suprarenal extract acted directly on muscle cells by Thomas Gregor Brodie (1866–1916), Professor-Superintendent of the Brown Institution, and Walter Ernest Dixon (1871–1931), then Assistant to the Downing Professor of Medicine at Cambridge. Reporting their own experiments and experimental results obtained by other researchers, Brodie and Dixon argued that adrenalin affected the sympathetic nerve endings, not the peripheral tissues themselves. In particular, they suspected that Langley and Lewandowsky had not allowed enough time in their degeneration experiments for the sympathetic nerve endings completely to disappear before the suprarenal extract was tested.[62] Elliott addressed this criticism. In an experiment on a cat, he excised the ciliary and superior cervical ganglion of the left side. Nearly ten months later he tested the effect of intravenous injection of adrenalin on the animal's iris: the typical dilation of the pupil appeared even more quickly and was more extensive on the operated side than on the normal side. In Elliott's mind there was no doubt that the sympathetic nerve endings had entirely degenerated after such a long time and that the adrenalin therefore could not have acted on them.[63]

Another critical argument, brought forward by Brodie and Dixon, came from an experiment that the latter had made with apocodeine. Dixon had shown that the contraction of the muscle tissue of blood vessels that was typically produced by adrenalin could be almost completely prevented by previous injection of apocodeine. Yet, subsequent injection of barium chloride still led to vasoconstriction. This meant (for Brodie and Dixon) that the muscle tissue as such had not been injured by the apocodeine, and that therefore both apocodeine and adrenalin had acted on the nerve endings terminating in the blood vessels.[64]

Against this background of conflicting experimental evidence Elliott suggested that it was neither the nerve endings nor the contractile fibres of the muscle cell that were affected by adrenalin. He proposed instead that the ''substance'' that was excited by adrenalin was the ''myoneural junction'', i.e. the link between nerve ending and muscle cell, which he believed to originate from, and to be sustained by, the muscle cell. This hypothesis

[59] T R Elliott, 'The action of adrenalin', *J. Physiol*., 1905, **32**: 401–67, on p. 402. On the identification of the active principle of the suprarenal glands, see E M Tansey, 'What's in a name? Henry Dale and adrenaline, 1906', *Med. Hist*., 1995, **39**: 459–76, on pp. 465–6, 472–3.

[60] T R Elliott, 'On the action of adrenalin', *J. Physiol*., 1904, **31**: xx–xxi, on p. xxi.

[61] See Robinson, op. cit., note 1 above, pp. 56–9; Bennett, op. cit., note 5 above, pp. 530–1; Dupont, op. cit., note 1 above, p. 47.

[62] T G Brodie and W E Dixon, 'Contributions to the physiology of the lungs. Part II. On the innervation of the pulmonary blood vessels; and some observations on the action of suprarenal extract', *J. Physiol*., 1904, **30**: 476–502, on pp. 500–1.

[63] Elliott, op. cit., note 59 above, pp. 431–2.

[64] Brodie and Dixon, op. cit., note 62 above, pp. 497–8.

explained for him also why adrenalin affected only those tissues that had a sympathetic innervation. The union with sympathetic nerves during phylogenetic development, he believed, led in the muscle cells to the growth of a special "substance" which could be excited by adrenalin. The nature of this substance, i.e. of the myoneural junction, determined whether the impulse travelling down a sympathetic nerve led to contraction or inhibition (relaxation) of the muscle fibres. In this way the differences in adrenalin's action in different tissues could be explained.[65] Moreover, Elliott speculated that the other parts of the autonomic nervous system, i.e. the parasympathetic nerves and the autonomic ganglia, and also the skeletal nerves leading to striated muscle, had a different type of junction from that in the sympathetic nerves.[66] From these considerations, it was only a very small step for Elliott's teacher Langley, who probably guided his student's thoughts in this difficult and controversial matter,[67] to formulate the concept of "receptive substances".

In December 1905, in his classic paper on "receptive substances", Langley critically reviewed the evidence that had so far been provided on the direct action of certain drugs and poisons on cells. In particular the experiments involving degeneration of the nerve fibres before a drug's effects were tested, as carried out by Lewandowsky, Elliott, and himself, appeared crucial to him. In the light of Brodie's and Dixon's criticism, Langley gave details of another experiment of his own on a cat, in which he showed that an extract made from "Burroughs and Wellcome's supra-renal tabloids" produced the typical adrenalin effects on the head (eyes, sub-maxillary gland etc.) fourteen and a half months after the superior cervical ganglion had been excised. The point that certain poisons acted directly on cells, for example, nicotine on nerve cells, or adrenalin, pilocarpine and atropine on unstriated muscle cells and gland cells, seemed now to him quite well established.[68] There remained, however, two problems that required a more differentiated account of the drugs' mode of action.

The first problem was that the efficacy of adrenalin on unstriated muscle differed considerably between the various tissues in the body, even between tissues that were innervated by the sympathetic nervous system. The second problem was Dixon's finding that apocodeine prevented the vascular constricting action of adrenalin, but not that of barium chloride, which suggested that adrenalin acted on nerve fibres, not on muscle fibres. In response to these problems Langley proposed that adrenalin did not directly stimulate the muscle cell's "contractile substance *quâ* contractile substance", but that it acted on "accessory protoplasmic substances" of the cell. Intrinsic differences in these accessory substances could explain the differences in adrenalin's efficacy on various (unstriated) muscle tissues.[69]

Langley next turned to nicotine and its effect on striated, skeletal muscle to further support this hypothesis. In the anaesthetized fowl, intravenous injection of nicotine caused

[65] Elliott, op. cit., note 59 above, pp. 434–7.

[66] Ibid., p. 437–8. On the history of the identification of acetylcholine as the transmitter in these other synapses, see Robinson, op. cit., note 1 above, pp. 55–68, 70–6; Dupont, op. cit, note 1 above; E M Tansey, 'Sir Henry Dale and autopharmacology: the role of acetylcholine in neurotransmission', in C Debru (ed.), *Essays in the history of the physiological sciences*, Amsterdam, Rodopi, 1995, pp. 179–93.

[67] Elliott acknowledged his "indebtedness for advice" to Langley, but also to Gaskell and H K Anderson. Elliott, op. cit., note 59 above, p. 467.

[68] Langley, op. cit., note 19 above, pp. 374–80. On the preparation of the tabloid extract, *idem*, op. cit., note 55 above, p. 237.

[69] *Idem*, op. cit., note 19 above, pp. 375–6.

a characteristic prolonged, tonic contraction of the gastrocnemius muscle of the leg, even after the sciatic and internal peroneal nerve had been cut in order to exclude any central nervous influence. Also when the internal peroneal nerve had been "paralysed" through nicotine (i.e. when electric stimulation of the nerve no longer led to a muscular contraction), a larger dose of nicotine still caused the gastrocnemius to contract. This indicated that nicotine acted then directly on muscle cells. Intravenous injection of curare abolished the nicotine-induced tonic contraction, and further injection of nicotine brought it on again, i.e. the two poisons acted as mutual antagonists. As Langley pointed out, the relation between nicotine and curare was the same as the relation between pilocarpine and atropine, which he had described twenty-seven years earlier in his experiments on the sub-maxillary gland. Accordingly, he suggested that nicotine and curare acted upon the same "protoplasmic substance or substances" of the muscle cell. Whether these substances combined predominantly with nicotine (resulting in stimulation) or with curare (leading to relaxation) depended on "the relative amount of the two poisons" present.[70]

In the next series of experiments Langley cut the peroneal nerve, excised a piece of it, and allowed periods of between 6 and 40 days for the peripheral part of the nerve to degenerate. Functional regeneration was excluded in tests with electro-stimulation of the proximal part of the cut nerve, and the degeneration of the nerve endings was confirmed in histological examinations. Yet, injection of nicotine still produced the typical tonic contraction, the responsiveness of the muscle to the poison actually being increased; and curare still exerted its antagonistic effect on the nicotine contraction. Moreover, direct electrical stimulation of the muscle after injection of nicotine or after injection of curare could still produce some contraction.[71]

From these observations Langley drew the critical conclusion that "neither the poisons nor the nervous impulse act directly on the contractile substance of the muscle but on some accessory substance", and he continued: "Since this accessory substance is the recipient of stimuli which it transfers to the contractile material, we may speak of it as the *receptive substance* of the muscle."[72] Referring briefly to Ehrlich's side chain theory of immunity (see below), Langley speculated that a receptive substance might be "a side chain molecule of the molecule of contractile substance". He remained cautious though, adding that to him there seemed to be no advantage at present in "attempting to refer the phenomena to molecular arrangement".[73]

However, having produced evidence for the action of adrenalin as well as of nicotine and curare on "accessory" or "receptive" substances of the cell, Langley dared to generalize. He suggested that alkaloids such as pilocarpine, atropine, and strychnine, likewise acted in this manner, as might other internally secreted substances (i.e. hormones), such as secretin, thyroidin, and "the various stimulating chemical bodies formed by the generative organs".[74] More than this, Langley proposed a general rule:

So we may suppose that in all cells two constituents at least are to be distinguished, a chief substance, which is concerned with the chief function of the cell as contraction and secretion, and

[70] Ibid., pp. 380–93.
[71] Ibid., pp. 393–9.
[72] Ibid., p. 399.
[73] Ibid., pp. 399–400.
[74] Ibid., p. 400.

receptive substances which are acted upon by chemical bodies and in certain cases by nervous stimuli. The receptive substance affects or is capable of affecting the metabolism of the chief substance.[75]

With these conclusions Langley had laid the foundations of the theory of drug receptors in cells. He had also made a fundamental contribution to the further development of basic physiology, as the receptor idea became central to our modern understanding of endogenous neural, endocrine and immune regulation. Significantly though, Langley located his ''receptive substances'' *in* the cell rather than *on* the cell. In this respect his receptor concept was quite different from the modern one, which describes receptors within the cell as well as in the membrane.

Obviously, Langley's ''receptive substances'' had resemblances to Ehrlich's ''side chains'' that would bind bacterial toxins to the cell and which (when produced in excess) would be separated from the cell to act as anti-toxins or antibodies in the blood. But when Langley formulated his concept of receptive substances in 1905, Ehrlich still believed that the side chain theory was applicable only to toxins, not to drugs, chiefly because drugs did not seem to be firmly fixed in the tissues and could easily be washed out of them by solvents.[76] Langley, on the other hand, did think of a chemical union between the cell's receptive substances and the drug. Returning to the analogy with binding in inorganic chemistry that he had used in his discussion of pilocarpine and atropine, he spoke now of the formation of ''nicotine-muscle compounds'' and ''curare-muscle compounds''. Which of these two kinds of compounds prevailed depended ''upon the mass of each poison present and the relative chemical affinities for the muscle radicle [i.e. the receptive substance or side chain]''. Moreover, he speculated that the biological effect of either contraction (through binding of nicotine) or inhibition (through binding of curare) was caused by different ''chemical re-arrangements set up in the muscle molecule by the combination of one of its radicles''.[77] It was only in 1907, partly due to Langley's work on receptive substances and alkaloids, that Ehrlich changed his mind and proposed the existence of ''chemoreceptors'' for drugs.[78]

Langley's receptor concept also had obvious similarities with Elliott's concept of the ''myoneural junction'' that was thought to be acted upon by a nervous impulse or chemical stimulant. In fact, Langley acknowledged that Elliott's work on adrenalin especially had ''made the issues clearer'' for him.[79] He also agreed with Elliott's hypothesis that it was the nature of the myoneural junction that determined whether a nerve impulse resulted in contraction or inhibition. Langley suggested that a cell could make two kinds of receptive substances, ''motor'' and ''inhibitory'', and that the effect of a nervous impulse on the cell depended on the proportion of these two receptor types.[80]

However, he disagreed with his student about how the receptive substances may have been formed and how they had obtained their characteristics during phylogeny. According

[75] Ibid., p. 411.

[76] See Parascandola and Jasensky, op. cit., note 2 above, pp. 205–10. For a full discussion of Ehrlich's side chain theory of antibody formation, see Silverstein, op. cit., note 3 above, pp. 77–94.

[77] J N Langley, 'Croonian Lecture, 1906.—On nerve endings and on special excitable substances in cells', *Proc. R. Soc. Lond.*, series B, 1906, **78**: 170–94, on p. 181.

[78] Parascandola and Jasensky, op. cit., note 2 above, pp. 210–11.

[79] Langley, op. cit., note 19 above, p. 412.

[80] Ibid.

to Elliott, in developing a union with nerve endings, the cell grows a specific myoneural junction. On this supposition, Langley expected that in the nerve-degeneration experiments the myoneural junction, or the receptive substance, degenerated as well, leading to a diminished physiological response to the application of drugs. But as the experiments with adrenalin and nicotine had shown, cells were even more sensitive to the drugs after denervation. Langley had also performed some experiments with adrenalin, nicotine, and strychnine on chicken embryos, which showed in very early developmental stages quite marked effects and therefore did not support Elliott's suggestion. Finally, the variety of effects caused by sympathetic nerve stimulation and adrenalin in various tissues, and the incomplete parallelism between the two, spoke in Langley's view against Elliott's simple explanation. As Langley saw it, the various body cells had a constant tendency to vary in their chemical composition, which upon the formation of a functional connection with a nerve merely became ''fixed''. Different parts of the nervous system formed their connection with the peripheral tissues at different periods of phylogenetic development. In this way different types of receptive or ''synaptic'' substances were established.[81]

Yet Elliott did not agree with this interpretation. In a subsequent study on the innervation of the bladder in various animal species, he called his teacher's theory of receptive substances ''a doctrine of inflexibility''. In particular, he criticized Langley for attributing too little influence to the nature of the nerves that entered the tissues during phylogeny and had put too much emphasis on independent chemical changes of the peripheral (muscle) cells. As Elliott expressed it, Langley's view did ''not clearly ascribe a determinant value to the entering nerve, which must knock patiently unheard until the cell chances to develope [*sic*] the proper receptive substance''.[82] However, by the time this criticism was published, in 1907, Elliott had already left Cambridge for his clinical education at University College Hospital, London, and this specific debate between the two researchers seems to have been discontinued.[83]

Criticisms and Further Development of Langley's Receptor Concept

On 24 May 1906 Langley gave the Croonian Lecture to the Royal Society on the topic of his new concept of receptive substances, adding some more experiments with nicotine and curare, made on the frog and toad.[84] Immediately afterwards he visited the European continent further to disseminate his ideas. On 28 May he spoke to the Morphological-Physiological Society of Vienna about ''Nerve endings and special receptive substances in cells''.[85] In the following year, 1907, Langley presented his receptor concept at the Seventh International Congress of Physiologists in Heidelberg. Reporting experiments with local application of nicotine solutions to various muscles of the frog, he elaborated upon his evidence for different kinds of receptive substances. The results of these trials, which

[81] Ibid., pp. 405–10, 413. See also Langley, op. cit., note 77 above, p. 193.

[82] T R Elliott, 'The innervation of the bladder and urethra', *J. Physiol.*, 1907, **35**: 367–445, on p. 442.

[83] Cf. H H Dale, 'Thomas Renton Elliott 1877–1961', *Biographical Memoirs of Fellows of the Royal Society*, 1961, **7**: 53–74, on pp. 65–6.

[84] Langley, op. cit., note 77 above, pp. 185–8.

[85] *Idem*, 'Über Nervenendigungen und spezielle rezeptive Substanzen in Zellen', *Zentralblatt für Physiologie*, 1906, **20**: 290–1.

included also tests on denervated muscles and with the antagonist curare, indicated that the frog muscle had at least two types of receptive substances for nicotine: one leading to a slow and prolonged (''tonic'') contraction, and the other causing a rapid and brief contraction (''fibrillar twitching''). Both types could be located in the region of nerve endings as well as in other parts of the muscle fibre. Since local application of veratrine caused yet another pattern of contraction, Langley presumed that there had to be further types of receptive substances in the muscle. In general, he considered these substances to be radicles of the contractile molecule of the muscle cell, and he suggested that those near the nerve endings might have undergone a special development.[86]

However, Langley's arguments for the existence of receptive substances in cells encountered quickly the criticism of other researchers. At the same Congress of Physiologists he was confronted with a critical paper by one of his former collaborators, Rudolf Magnus (1873–1927), who was then a lecturer in the Pharmacological Institute of Heidelberg University.[87] Magnus focused on one of Langley's key arguments for receptive substances: the mutual antagonism of nicotine and curare on the denervated muscle. The Heidelberg pharmacologist acknowledged the general validity of the method of testing poisons after degeneration of nerves, in order to establish whether or not they acted on the peripheral tissues or on nerve endings. But he was not convinced that the mutual antagonism between two poisons actually said something about their specific point of attack. Langley had concluded that curare bound, like nicotine, to receptive substances of the muscle cells, because he had found that curare abolished the nicotine-induced contraction of the denervated muscle. Magnus reported against this his own experiments on the muscle of the rabbit, in which the relevant nerves had been cut and allowed to degenerate. In these trials he used physostigmine instead of nicotine as the stimulant agent and antagonist of curare. He found that physostigmine failed to produce a contraction in the denervated muscle from the twenty-seventh day after section of the nerves. This spoke for an action on nerve endings and, according to Langley's logic, the antagonist curare would therefore also act on nerve endings. This example showed, according to Magnus, that the conclusion about the point of attack on curare depended on which antagonist had been used. If one used nicotine, as Langley had done, the evidence suggested that curare acted on the muscle cell. If one used physostigmine, like Magnus, one was led to conclude that curare affected the nerve endings. In other words, ''nothing at all'' could be found out about a poison's point of attack from trials with its antagonists. Magnus politely emphasized that he did not wish to criticize Langley's doctrine of receptive substances as such, but he made it clear that one of the

[86] *Idem*, 'Nouvelles observations sur la nature non-spécifique des terminaisons nerveuses motrices et sur l'existence de radicules «réceptives» dans le muscle', *Archives Internationales de Physiologie*, 1907, **5** : 115–8. A full account of the experiments underlying Langley's theory of two kinds of nicotine receptors is given in *idem*, 'On the contraction of muscle, chiefly in relation to the presence of ''receptive'' substances', *J. Physiol*., 1907, **36**: 347–84; 1908, **37**: 165–212; 285–300; 1909, **39**: 235–95.

[87] In 1908 Magnus became professor in Utrecht, where he founded the first pharmacological institute of the Netherlands. See O Magnus, *Rudolf Magnus, physiologist and pharmacologist, 1873–1927*, ed. L M Schoonhoven, Amsterdam, Koninklijke Nederlandse Akademie van Wetenschappen, and Dordrecht, Kluwer Academic Publishers, 2002. Magnus' joint work with Langley in the Cambridge Physiological Laboratory was published as: J N Langley and R Magnus, 'Some observations of the movements of the intestine before and after degenerative section of the mesenteric nerves', *J. Physiol*., 1905, **33**: 34–51.

Cambridge professor's "proofs" for it, the mutual antagonism between nicotine and curare on the denervated muscle, had to be discounted.[88]

In the discussion following Langley's and Magnus' presentations, Langley suggested that the receptive substances of the denervated rabbit muscle had degenerated in addition to the nerve endings, which explained why Magnus had no longer obtained a contraction on injection of physostigmine. Yet this argument constituted a certain contradiction to Langley's earlier observation that denervated muscle cells actually showed an increased sensitivity for drugs such as nicotine and adrenalin. On the other hand, Magnus had to admit that curare might have two points of attack: the nerve ending and the muscle cell.[89] By the following year both researchers had collected more evidence to support their divergent points of view. Magnus argued from experiments conducted by himself, by Langley's Cambridge collaborator Hugh Kerr Anderson (1865–1928) and others that similar inconsistencies resulted about the point of attack of atropine if one drew conclusions from its antagonistic action to pilocarpine and physostigmine.[90] Langley demonstrated different kinds of contraction after nicotine and after physostigmine had been applied to muscle, and concluded from this that there had to be "different receptive radicles" for the two poisons.[91] In this way, Magnus' criticism led eventually to a greater complexity of Langley's receptor concept.

Langley also had to consider recent results of Hermann Fühner (1871–1944) of the Pharmacological Institute in Würzburg, who had studied the muscular effects of the curare-like substance guanidine for his Habilitation thesis.[92] Fühner had found that guanidine chloride failed to produce the usual contraction ("fibrillar twitching") of the frog's gastrocnemius when it was applied to the muscle eleven and thirteen days after its nerve had been cut. For the Würzburg researcher this suggested an action of guanidine (and, by extension, of curare) on nerve endings, which would have degenerated by that time. Yet, he obtained some guanidine contractions again from the sixteenth and eighteenth day onwards and explained this by proposing regeneration of the nerve endings.[93] In Langley's view, Fühner's hypotheses about degeneration and then regeneration in the absence of a connection to the central nervous system were untenable. Moreover, Langley referred to denervation experiments on another leg muscle, the sartorius, which showed with histological staining that the nerve endings needed about six weeks to degenerate and did not begin to regenerate until the sixty-ninth day. Accordingly he did not accept Fühner's evidence for guanidine's action on nerve endings rather than on muscle cells.[94] Still, the experiments of the Würzburg pharmacologist illustrated the uncertainties inherent in the nerve-degeneration method, and in this way cast doubt over another element in Langley's argument for the existence of receptive substances in cells.

Criticism came not only from German researchers but also from colleagues at home. Stimulated by Langley's ideas on receptive substances and Ehrlich's on chemoreceptors,

[88] R Magnus, 'Kann man den Angriffspunkt eines Giftes durch antagonistische Giftversuche bestimmen?', *Pflüger's Archiv für die gesamte Physiologie*, 1908, **123**: 99–112, on p. 106.

[89] Ibid., p.107.

[90] Ibid., pp. 108–12.

[91] Langley, 'On the contraction' (1908), note 86 above, p. 299.

[92] H Fühner, 'Curarestudien. I. Die periphere Wirkung des Guanidins', *Archiv für experimentelle Pathologie und Pharmakologie*, 1907, **58**: 1–49. Guanidine produces fibrillar twitching followed by curare-like paralysis of the muscle.

[93] Ibid., pp. 35–9, 44, 48.

[94] Langley, 'On the contraction' (1908), note 86 above, pp. 298–9.

Walter Dixon, who had become a lecturer in pharmacology at Cambridge, published in 1909 a study of the specific action of strychnine on the spinal cord. Working with emulsions of spinal cord, he and his collaborator in the Pharmacological Laboratory, Philip Hamill (1883–1959), did not find any evidence for a chemical combination of the alkaloid with the nervous tissue. They therefore questioned the existence of specific receptors for vegetable alkaloids. Yet, based on another series of experiments, in which they examined the effects of secretin on the pancreas, they proposed that there were receptor substances for the body's own internal secretions. Poisons, they hypothesized, might act by liberating specific hormones, which would then combine with hormone receptors.[95] Doubts about Langley's concept of receptive substances were also raised from a chemical point of view. George Barger (1878–1939) and Henry Hallett Dale (1875–1968), then working at the Wellcome Physiological Research Laboratories, showed that a wide range of structurally differing amines apparently mimicked the physiological effects of sympathetic nerve stimulation. However, they could not identify a common structural component that was specific for these "sympathomimetic" amines. On these grounds they were sceptical about Langley's suggestion that drugs entered into chemical combinations with specific receptive side chains of the cell.[96]

Perhaps the most lasting challenge to Langley's concept of receptive substances arose, however, from a new theory of the mode of action of drugs, which was then developed by the Freiburg pharmacologist Walther Straub (1874–1944). Inspired by studies of drug absorption, made by his academic mentor Rudolf Boehm (1844–1926) in Leipzig,[97] the young Straub extended this line of research during a stay at the Zoological Station in Naples in the spring of 1905. His experimental model was the isolated heart of the marine snail, *Aplysia*, on which he examined the effects of muscarine and its antagonist atropine. Muscarine caused typically a slowing of the heartbeat. Straub concluded from his experiments that this effect occurred only as long as the poison entered the heart cells. The effect did not depend, in his view, on an action of muscarine within the cell itself. What was important was rather the gradient in the poison's concentration between the outside and the inside of the cell membrane, or the "concentration potential" as he called it, which kept the process of absorption in motion. After the cells had become saturated with muscarine, a further increase of its concentration outside the cell had no further effect. On this basis Straub developed a "potential poison theory" (*Potentialgifttheorie*): while the poison was entering the cell, the membrane was unable to excrete the cell's waste products. These accumulated and damaged the cell, leading to cessation of its functions. In Straub's opinion, this theory was applicable not only to muscarine but to other alkaloids as well, such as pilocarpine, physostigmine and nicotine, and also to the hormone adrenalin. Moreover, the antagonism between muscarine and atropine could be explained with the hypothesis that atropine slowed the absorption of muscarine into the heart cells.[98]

[95] W E Dixon and P Hamill, 'The mode of action of specific substances with special reference to secretin', *J. Physiol*., 1909, **38**: 314–36. See also Langley, 'On the contraction' (1909), note 86 above, pp. 293–4.

[96] G Barger and H H Dale, 'Chemical structure and sympathomimetic action of amines', *J. Physiol*., 1910, **41**: 19–59, on p. 56.

[97] R Boehm, 'Einige Beobachtungen über die Nervenendwirkung des Curarin', *Archiv für experimentelle Pathologie und Pharmakologie*, 1895, **35**: 16–22.

[98] W Straub, 'Zur Kinetik der Muskarinwirkung und des Antagonismus Muskarin-Atropin', *Pflüger's Archiv für die gesamte Physiologie*, 1907, **119**: 127–51.

This essentially *physical* theory of drug action stood in marked contrast to the concept of specific chemical binding of drugs to receptive side chains as proposed by Langley and (subsequently) Ehrlich. As Straub put it rather bluntly in his Freiburg inaugural lecture in 1908, any remarks on a direct relationship between the chemical structure and physiological effect of a drug were mere speculation.[99] Langley took Straub's observations seriously, but provided an explanation for them that was in harmony with his chemical theory. As long as the poison combined chemically with the receptive substances they ''set up a stimulus'' to the cell. When they were saturated, there was no more stimulus and thus no further effect. Similarly, the antagonism between atropine and muscarine could be explained with the hypothesis that atropine combined with the receptive substances and in this way prevented the effect of muscarine.[100]

Langley also used the similarities with Ehrlich's side chain theory to support his own concept of receptive substances. He interpreted these as ''atom-groups of the protoplasm'' of the cell. Two such atom-groups had to be distinguished: the ''receptive'' and the ''fundamental''. When chemical substances bound to the receptive atom-groups, they would alter the protoplasmic molecule of the cell and in this way change the cell's function. In less differentiated cells these atom-groups could also split off from the cell and act as antibodies, as suggested in Ehrlich's theory of immunity. In more differentiated cells, such as those of the muscles and glands, the receptive atom-groups had undergone a ''special development'', which enabled them to combine with hormones or with alkaloids. Due to those cells' connection with nerve fibres these further developed atom-groups tended to concentrate in the region of the nerve endings. The ''fundamental'' atom-groups, by contrast, were essential for the cell's life. If a chemical substance bound to such a group, the cell would be damaged and die. Langley pointed out that this latter type of atom-groups had been demonstrated in Ehrlich's recent experiments with arsenic compounds on trypanosomes (i.e. the protozoa causing sleeping sickness). If arsenic bound to the chemoreceptors of the trypanosomes, these micro-organisms were destroyed.[101]

By making this distinction, Langley used, on the one hand, the side chain theory of Ehrlich to bolster his own concept of receptive substances. In 1908 Ehrlich had been awarded the Nobel Prize for his studies into immunity. As Langley put it, his hypothesis of receptive substances constituted ''an extension of Ehrlich's side chain hypothesis''.[102] On the other hand, Langley preserved the originality of his own research by making it clear that Ehrlich's studies into drug binding were concerned with a different type of receptor from the one that he had examined in his experiments with nicotine and curare.

[99] W Straub, *Gift und Organismus. Öffentliche Antrittsrede, gehalten am 26. Februar 1908 in der Universitäts-Aula*, Freiburg i. Br. and Leipzig, Speyer & Kaerner, 1908, pp. 11–13. On the early history of studies into the relationship between structure and effects of drugs, see W F Bynum, 'Chemical structure and pharmacological action: a chapter in the history of 19th century molecular pharmacology', *Bull. Hist. Med.*, 1970, **44**: 518–38.

[100] Langley, 'On the contraction' (1909), note 86 above, pp. 291–2.

[101] Ibid., pp. 294–5. On Ehrlich's chemotherapeutic experiments on trypanosomes, see Parascandola and Jasensky, op. cit., note 2 above, pp. 216–20; Silverstein, op. cit., note 3 above, pp. 130–1; M Weatherall, *In search of a cure: a history of pharmaceutical discovery*, Oxford University Press, 1990, pp. 58–60.

[102] Langley, 'On the contraction' (1909), note 86 above, p. 295.

Langley emphasized that he had arrived at his own receptor concept "by entirely different experiments and by a different line of argument" and that he had proposed the binding of drugs to side chains at a time (1905/6) when Ehrlich had not yet considered this possibility.[103] Significantly, Langley did not adopt the term "receptor", which Ehrlich had introduced in 1900 in the context of his immunological research,[104] nor Ehrlich's neologism "chemoreceptors" of 1907. He continued to employ his own term "receptive substances".

One of Langley's postgraduate students, the later Nobel Prize winner Archibald Vivian Hill (1886–1977), provided in 1909 further evidence for his professor's essentially chemical receptor theory and against the "physical view". Hill used a different approach to the problem by performing a quantitative and mathematical analysis of the contractions produced by nicotine, and the relaxation caused by its antagonist curare, in the frog's rectus abdominis muscle. He also examined these physiological effects at different temperatures. The formulas at which he arrived led him to the firm conclusion that nicotine as well as curare formed reversible, chemical combinations with a constituent of the muscle.[105] Langley's predominantly qualitative evidence for the existence of receptive substances in cells was thus endorsed by an analysis of quantitative data. Nevertheless, the physical theory of drug action as introduced by Straub became a strong competitor of the "chemical" drug receptor theory, and remained so during the 1910s and 1920s.[106] It was only after Langley's death that the quantitative arguments for drug receptors were further developed by the pharmacologist Alfred Joseph Clark (1885–1941).[107] Langley himself, while acknowledging further developments in a physical theory of the specific action of poisons (for example, theories about differences in the permeability and solvent power of the cell membrane), stayed committed to his concept of receptive substances and to a chemical theory of drug effects.[108] In his final synthesis of his research into the autonomic nervous system, published in 1921, he declared:

> The known physical characters of drugs are insufficient to account for the effects they produce, though they account for a difference in rate of action; in consequence I consider that there is a chemical combination between the drug and a constituent of the cell—the receptive substance. On the theory of chemical combination it seems necessarily to follow that there are two broad classes of receptive substances; those which give rise to contraction, and those which give rise to inhibition.[109]

[103] Ibid.

[104] See Prüll, op. cit., note 4 above.

[105] A V Hill, 'The mode of action of nicotine and curare, determined by the form of the contraction curve and the method of temperature coefficients', *J. Physiol*., 1909, **39**: 361–73.

[106] For the continuing debates over a chemical versus a physical interpretation of drug action, see J Parascandola, 'The controversy over structure-activity relationships in the early twentieth century', *Pharmacy in History*, 1974, **16**: no. 2, 54–63.

[107] See, in particular, A J Clark, *The mode of action of drugs on cells*, London, Edward Arnold, 1933. For accounts of Clark's contribution to the development of the receptor theory, see J Parascandola, 'A. J. Clark: quantitative pharmacology and the receptor theory', *Trends in Pharmacological Sciences*, 1982, **3**: 421–3; *idem*, op. cit., note 2 above, pp. 148–53; D H Clark, *Alfred Joseph Clark 1885–1941. A memoir*, Glastonbury, C & J Clark, 1985, pp. 13–22; Robinson, op. cit., note 1 above, pp. 144–6; Maehle, Prüll and Halliwell, op. cit, note 2 above, pp. 640–1.

[108] J N Langley, 'Note on the action of nicotine and curare on the receptive substance of the frog's rectus abdominis muscle', *J. Physiol*., 1910, **40**: lviii–lix; *idem*, 'The antagonism of curare and nicotine in skeletal muscle', *J. Physiol*., 1914, **48**: 73–108, on p. 106; *idem*, 'Persistence of the central somatic effect of strychnine after a large dose of nicotine', *J. Physiol*., 1918, **52**: xliv–xlv.

[109] *Idem*, *The autonomic nervous system*, note 16 above, p. 44.

Conclusions

This paper has illustrated the complexities that were involved in the conceptualization of the drug receptor, one of the major ideas in twentieth-century biomedical science. Langley's path to a receptor concept of pharmacological action was neither straightforward nor the result of a specific research plan. His ideas about the interaction of drugs and poisons with cells developed intermittently over a period of thirty years and in diverse research contexts. The main contexts were the physiology of glandular secretion and of the autonomic nervous system. In addition we can identify a number of subsidiary contexts, such as the emerging theory of mutual antagonism of drugs, Ehrlich's side chain theory of immunity, early hormone research, the beginnings of the neurone theory, and the first ideas about chemical neurotransmission.

While our historical reconstruction allows us to recognize and follow the inner logic of Langley's intellectual route to his concept of receptive substances, it also identifies the various influences from other British and from German medical scientists upon his thought and experimentation. In retrospect, Elliott's ideas about the action of adrenalin on the "myoneural junction" appear to have been especially relevant in Langley's final steps towards his receptor concept. Those influences were also relevant, as some of the key methods employed by Langley in proving the existence of receptive substances were contested at the time. As we have seen, fundamental questions were raised about the validity of antagonistic drug trials, and there were considerable uncertainties involved in the method of nerve degeneration. The question whether antagonistic drugs such as nicotine and curare, or pilocarpine and atropine, acted on nerve endings or directly on the effector cells (muscle cells, gland cells etc.), remained undecided for many researchers despite the experimental evidence provided by Langley.

These inherent methodological problems are an important clue for our understanding of the difficulties in the recognition of the receptor concept. Another reason for these difficulties was the direct competition between Langley's (and later Ehrlich's) *chemical* ideas about drug binding and *physical* theories of drug action in the wake of Straub's influential studies on the heart of *Aplysia*. Despite Hill's early quantitative evidence in favour of Langley's receptive substances, the controversy over a chemical versus a physical effect of drugs on cells remained unresolved beyond the time of Langley's death in 1925. Through Clark's further quantitative analysis of pharmacological effects, given in his book of 1933, *The mode of action of drugs on cells*, receptor theory was re-asserted and definitely put on the map of theoretical pharmacology. But even then, it remained just that, a theory, until receptor proteins began to be isolated from cell membranes in the 1970s. Langley's concept of receptive substances was vindicated in this way, and since then, receptors have become objects of extensive scientific exploration and manipulation.