Otto Loewi, 1873-1961

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Otto Loewi, born on 3 June 1873, in Frankfurt am Main, was the son of Jakob Loewi, a wine-merchant of that city, by his wife, Anna Willstaedter. Throughout his life Otto retained very happy memories of his childhood and schooldays. For the nine years from 1881 to 1890 he attended in Frankfurt a Gymnasium of the old style, in which the studies were centred on the classical languages—Latin being studied for the whole nine and Greek for the six later years. He accepted for himself the not unfamiliar view that such an emphasis in education, during the formative years of boyhood, would have had a specially favourable influence on his personality, and on his general attitude to life and learning. In an ‘autobiographic sketch’, published in the year before he died, he recorded that, during these nine years at the Gymnasium, he obtained ‘fairly good marks’ in these literary subjects, but ‘poor marks’ in physics and mathematics. Without attempting to assess the respective shares in the result, of inborn aptitudes and of a particular educational routine, it may at least be accepted as a fact, that Loewi exhibited in later life an unusually wide range of knowledge and interests, for one whose main career and activities were concerned with one faculty of the natural sciences. There were, in any case, cultural influences at work on him during these years of his boyhood, other than those attributable to any part of his formal schooling. In addition to his residence in Frankfurt, his father had a small country estate in the Palatinate, on a slope of the Haardt Mountains, with an old manor house, a large garden and some vineyards; and Loewi retained enthusiastic memories of the holidays spent annually, during his schooldays, in surroundings which were so attractive and stimulating to a young imagination. And he recalled other visits during the same period to Belgium, and a life-long enthusiasm which he therewith acquired for the achievements of the early Flemish Masters of painting.

It is perhaps, not surprising then to learn from his recollections that, when the time came for matriculation at a University, and for choosing the course to be followed there, his own preference would have been for the history of art. His parents, on the other hand, presumably with a view to a safer prospect of income, urged him to qualify for a career in medicine; and he eventually accepted their advice.

On his own confession, however, though he duly matriculated at Strassburg as a student of medicine, he found little to attract him in the formal lectures

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dealing with its preclinical subjects. Schwalbe’s teaching of anatomy was exceptional in holding his interest, and otherwise he seems to have spent a good part of his first year in attending lectures on the history of architecture and on general philosophy; with the result that he narrowly escaped failure in his first medical examination (‘Physikum’), at the end of his fourth term. And then he spent a year at the University of Munich, where his medical studies appear again to have encountered a serious rivalry from the opportunities which that city offered for new artistic experiences—dramas from Scandinavia, Wagner’s operas, and the treasures of its museums and galleries.

It is, of course, not improbable that Loewi’s memory—like that of many of us—would have been apt to give an undue prominence to these distractions from the prior demands of his chosen course of study, when he recalled the happy freedom of his student years. He had certainly acquired a wide and vigorous interest in all aspects of the culture and the artistic heritage of Europe. On the other hand, he responded readily to personal and scientific distinction in his teachers; and, on his return to Strassburg in 1894, for his fourth academic year, a new enthusiasm for his medical studies was awakened by contacts with such eminent leaders as Nannyn in clinical medicine, Schmiedeberg in pharmacology, and Hofmeister in biochemistry. The strongest impression appears to have been made on him by Nannyn’s lectures and clinics; on the other hand, it was from Schmiedeberg that he sought a subject for the thesis which he had to present before graduation, and with it the opportunity for a first experience of practical research in the laboratory. Loewi could not recall any special reason for this choice, and, rather characteristically, explained it by a quotation from Goethe’s Faust—‘Du glaubst zu schieben und wirst geschoben.’ The subject which Schmiedeberg suggested—a quantitative measurement of the activities of hydrocyanic acid, arsenic and phosphorus on the isolated heart of the frog—hardly seems likely, in retrospect, to have excited a lively interest in pharmacology; but it was presumably intended to introduce the student to the methods then in current use. On the other hand, Loewi gained much from his contacts with other men then working in the department—Oscar Minkowski, Arthur Cushny, Karl Spiro and Walter Straub—with all of whom he was able to share new interests and to make more lasting friendships. It was through Spiro that he came to know, and to acquire a life-long enthusiasm for Friedrich Miescher’s comprehensive studies of the changes in the metabolism of the salmon in the Rhine, during the fresh-water phase of its life. A glance at the bibliography, at the end of this Memoir, will make clear, indeed, the frequency with which Loewi’s investigations, during a large part of his career, were to deal, often recurrently, with one or another of certain essentially metabolic problems, which had attracted and retained his interest. From a study of his publications, indeed, one might get the idea that a stronger educational background in chemical theory and practice might well have led him to seek his main scientific opportunity in biochemistry, rather than in pharmacology. He was aware, indeed, of the gap in his equipment; and after he had graduated at Strassburg,
and had enjoyed a long holiday in Italy which his parents then kindly arranged for him, he took a course of chemistry in Frankfurt and returned to Strassburg to work for some months under Hofmeister’s biochemical stimulus.

1897-1902

The time had come, however, in 1897, for Loewi at least to make trial of some more definite line of activity in medicine; and it seems that the interest which had been awakened by Nannyn’s clinical teaching was still strong enough to lead him first to accept an assistantship in the medical department of the City Hospital in Frankfurt, which had been offered to him by Professor von Noorden, who had specialized in his practice on nutritional disorders and dietetics. Loewi soon found the experience discouraging, however, and decided to seek an opening to a career offering opportunity for experimental researches, in more fundamental aspects of medical science. It seemed that he might find this in pharmacology, which had so far been largely concerned with drugs as agents for the experimental analysis of physiological functions, rather than with the discovery of a scientific basis for their rational uses as remedies. The modern closer association of pharmacology with practical therapeutics, and with the experimental discovery of new and more specifically effective remedies for the causes or the symptoms of different diseases, was then still many decades ahead; and Loewi, in any case, was to find his main pharmacological interest in the use of drugs to explore the nature of physiological activities, by studying the ways in which they specifically strengthened, reproduced, or interfered with these. It was, indeed, the study, on such lines, of the actions of certain alkaloids and natural bases, which was eventually to provide the clue to the best known and the most widely influential of all Loewi’s scientific enterprises and discoveries.

Having decided, then, to try his hand further in pharmacology, Loewi, on Professor Hofmeister’s advice, enquired in 1898 whether Dr Hans Horst Meyer, then the Professor of Pharmacology at Marburg a.d. Lahn, could offer him an opportunity; and he was fortunate in finding that Meyer had a vacancy for him. In the event he was to remain with Meyer’s department, as Assistant, Privat-Dozent and Associate Professor, for twelve years in all—seven at Marburg and then five more at Vienna, when Meyer was called to the Chair of Pharmacology there. Loewi soon acquired, and always kept, a deep respect for and devotion to Meyer, as a distinguished scientist, a fine personality and a trusted counsellor.

As will be seen again from the bibliography. Loewi’s researches during his earlier years at Marburg, until 1902, were chiefly concerned with biochemical problems of metabolism, though a pharmacological interest was given to some of them, by the use of phloridzin to produce an artificial diabetes, and by a study of the effect of camphor on the condition thus produced. Already in 1898 he had described a urea-forming enzyme in the liver; and in 1900 came several publications on the metabolism of nuclein. In 1901 he was tackling the question whether the animal body could form sugar from fat,
and reaching the conclusion that it could not; and then, in 1902, came what will surely be regarded as the most important discovery which he made, at that early stage of his independent activity in research. Nobody had so far succeeded in maintaining a nitrogenous equilibrium in the nutrition of an animal, when the amino-acid products of a complete hydrolysis were substituted for natural, unbroken proteins in the food; and the conclusion had till then been generally accepted, that an animal’s diet must contain proteins which had been, at most, only partially hydrolyzed by digestion, if it was to be able to build from them those which it required for the maintenance of its own tissues. Kutscher, however, had then recently shown that it was possible to disintegrate the proteins of an organ completely, into a mixture of their constituent amino-acids in their natural proportions, by a sufficiently prolonged trypic digestion. Loewi followed this clue; and, training his experimental dogs to accept such a mixture as the sole nitrogenous component of their diet, he had succeeded in maintaining them in nitrogenous equilibrium. I remember the late Sir Frederick Gowland Hopkins speaking to me with some enthusiasm of the importance of this discovery. It seems obvious, indeed, that it may have contributed to the background of his own decision, to test the effect on maintenance and growth of feeding rats on all the then known constituents of a normal diet, each in a state of chemical purification—a decision which, again, was to furnish the basis for his own leading part in the discovery of the ‘accessory food factors’, later to be known as ‘vitamins’.

**Visit to England**

The occasion for Loewi’s first meeting with Hopkins was provided by a few months’ visit which he made to England, in 1902. He wished to widen his experience of physiological technique, and had decided that England could at that time offer him better facilities for such a study of methods than were to be found in Germany, since the death of Carl Ludwig. He applied to the late Ernest Starling, the Professor of Physiology at University College, London, for the opportunity which he had in view; and this was readily offered. Loewi was naturally attracted by the dynamic quality of Starling’s character, his buoyant leadership and his contagious enthusiasm for his own subject of physiology; also by the gentler personality, the natural modesty and the wide scientific erudition and insight of Starling’s brother-in-law and frequent collaborator, the later William M. Bayliss. Loewi arrived at a time of vivid interest and exciting progress in the work of the laboratory at University College; for it was earlier in the same year, 1902, that Bayliss and Starling had discovered the hormone mechanism—by the liberation of ‘secretin’ and its carriage in the circulation—by which the presence of acid in the duodenum excited the secretory activity of the pancreas. The actions and properties of secretin, and of the ‘depressor substance’ which accompanied it in artificial extracts from the duodenal mucosa, were also providing various opportunities for experimental enquiries by others working in the laboratory—myself among them, holding then a George Henry Lewes Studentship.
Otto Loewi

Loewi was immediately and easily on terms of good fellowship with all of us there; and my own brief encounter with him was to develop later into a close friendship and a sharing of interests, for nearly 60 years. Others whom I remember as enjoying there the contacts with him, were W. A. Osborne, who was soon to depart for a Chair of Physiology in Australia, and F. S. Locke—a gifted amateur of physiology, who, in one of his active periods, had enriched its technique by his method of maintaining the activity of the isolated mammalian heart, perfused with his appropriate modification of Ringer's saline solution. Loewi's visit was to be a short one, and he had no plan to begin any research of his own during his stay. He sought the opportunity for acquiring experience by watching English physiologists at work, and discussing with them their methods, plans and ideas. He was then, indeed, as always, a voluble but interesting talker. One of the objects of his visit, we understood, was to acquire some conversational facility in English; but we soon learned that he was impatient of correction in his use of it. 'No', he would say, 'I have not time to learn English correctly; I wish to speak it fast.' And I find that some of his achievements in that line have had a legendary survival, being still known even to some English physiologists of the present generation, 60 years later. I remember meeting him on his return from a short visit to Oxford, where he had been welcomed by the physiological circle; and he had naturally felt greatly honoured when he was told that the veteran physiologist, who had then become the Regius Professor of Medicine, Sir John Burdon Sanderson, had expressed a special wish to meet him. It was characteristic of Loewi's buoyant reaction to a new view of a situation, that he seemed to find a further cause for pleasure, though hardly of the same kind, in discovering that Sir John's desire to meet him had been mainly due to a wish to hear Loewi's improvised English, the rumour of which had already reached Oxford. Loewi, indeed, had easily found himself at home in the friendly informality of the English physiological circle, which extended to the community, then a comparatively small one, of the Physiological Society; and he was ready then, and later in life, to speak with enthusiasm of the pleasure and profit which he enjoyed from the uninhibited character of that Society's meetings, in comparison with the more formal atmosphere of such meetings in his own country.

Loewi also paid a longer visit to Cambridge. According to my memory he stayed there for a week or two; and, as I have suggested in another connexion, I think that the contacts which he made there and the ideas which he then encountered, probably had a greater influence than he consciously recognized, in prompting his own best-known experimental achievement, nearly two decades later. Apart from the meeting with Hopkins, which I have mentioned already, Loewi had the opportunity, which he would certainly have used to the full, of learning about the several productive lines of research which were then in progress at Cambridge, in the narrow compass of its old Physiological Laboratory. And, of these, the one which he specially remembered was his first acquaintance, at close quarters, with Langley and
Anderson’s classical investigation of the detailed structure, relations and contrasted functions of the two divisions—sympathetic and parasympathetic in Langley’s nomenclature—of the involuntary, or autonomic, nervous system. It had long been known that the actions of certain vegetable alkaloids showed a curiously limited relation to functions of certain of the autonomic nerves, which had now been clearly assigned to the parasympathetic division; the effects of impulses in these being specifically paralyzed by atropine and, on the other hand, reproduced with a mimetic accuracy by muscarine. And in years then still recent, a comparably close, mimetic relationship had been observed by Lewandowsky, and a little later confirmed and extended by Langley himself, between the effects produced by extracts from the medulla of the suprarenal gland, and those of impulses in nerves of the thoracolumbar, sympathetic division of the autonomic system. T. R. Elliott also, then a young graduate working at Cambridge with the Coutts-Trotter Research Studentship, had already, at the time of Loewi’s visit, begun the series of brilliant studies of the actions of autonomic nerves, and especially of the then still puzzling fidelity with which those of the sympathetic division were reproduced by adrenaline—studies which were to lead him, only two years later, to make the first published suggestion, brief but quite definite, of a chemical transmission of the effects of sympathetic nerve-impulses, by the release of adrenaline at the nerve-fibre terminals. I do not suppose that Loewi, at the time of this first visit to Cambridge in 1902, would yet have heard any explicit suggestion of such a possibility; though he certainly met Elliott, and spoke to me especially, on his return to London, of the impression of brilliant promise which he had received from him. As I have already suggested elsewhere*, however, speculations about the meaning of these specifically neuromimetic effects were beginning to be current about that period, and especially in Cambridge circles. The late W. E. Dixon had then recently arrived there, to start an experimental course in pharmacology; and, soon after Elliott’s publication, in 1904, of his suggestion of a sympathetic-transmitter action for adrenaline, Dixon was to suggest a comparable function for muscarine in relation to parasympathetic effects, and even to put on record an attempt—thought not a seriously successful, or a well conceived one—to find experimental evidence for it. It seems reasonable, in any case, to suppose that ideas of the kind were waiting, as it were, to emerge in the Cambridge community, during Loewi’s visit there in 1902; and when he himself in the following year, after he had returned to Marburg, made an early and independent mention of the idea that muscarine might be released, to transmit the effect of vagus nerve impulses to the heart. But although Loewi, in much later years, was not unnaturally disposed to attribute some retrospective importance to this incident, it seems clear to me that it amounted to nothing more than a casual suggestion, which he made to the late Walter Fletcher whom he had also met in Cambridge, and who, in 1903, was making a short visit to Meyer’s Department in Marburg. Loewi, in any case, had

entirely forgotten the occurrence; it was Fletcher who reminded him of it, after 1921, in speaking of the important discovery which Loewi had then recently published. And, in any case, a potent and stable poison such as muscarine was a very unlikely candidate for the suggested transmitter function.

1902-1921

This middle period of Loewi’s career in research and teaching included the later years at Marburg, till 1904, when he moved with Hans Meyer to Vienna, remaining there till 1909, when he moved again to Graz, on being himself appointed Professor and Head of the Department of Pharmacology in its University. In spite of these two removals, involving changes in personal associations and academic responsibilities, the record of Loewi’s research activities shows no conspicuous breach of continuity, or any alteration in the range and variety of his scientific interests. In a brief review of all his experimental undertakings from 1902 till 1921, as shown in his publications over that period, we may take note of the emergence, from time to time, of items of discovery which were eventually to find their places in the chemical transmission scheme; though he and his collaborators do not appear to have had any direct awareness of this significance at the time when the observations were made.

On his return to Marburg, later in 1902, Loewi had resumed an important series of studies on the physiology and pharmacology of the function of the kidneys, which he had apparently begun already before his visit to England. The results of these were to form the subjects of a series of five communications, published from 1902 to 1905, by Loewi alone for the first two, and in joint authorship with visiting collaborators for the other three—Walter Fletcher, whose visit has already been mentioned, N. H. Alcock, who was later to go to Toronto as Professor of Physiology, and V. E. Henderson, who was already Professor of Pharmacology there, and who was to make more than one such co-operative visit to Marburg. There were, indeed, two further papers published by Loewi and Henderson, after the series on renal function, and making, perhaps, a nearer approach in their interest to the chemical-transmission theme, though with no conscious reference to it. These dealt respectively with the effect of stimulating vasodilator nerves, and with the influences of pilocarpine and atropine on the rate of circulation through a salivary gland. Also in 1905 came a publication, jointly with Hans Meyer, on a comparative investigation of the activities of synthetic amines related to adrenaline, and especially of ‘arterrenol’ (nor-adrenaline). These had been offered for investigation by the research staff of the Hoechst Farben-Fabrik. Loewi and Meyer compared adrenaline and its primary homologue for their pressor activities, and observed no important difference. H. D. Dakin, working in England, had independently been making a similar series; and he also had observed a similar approximate equivalence, in pressor action, between adrenaline and nor-adrenaline. It was some years later, in 1910, that I myself...
examined a wider series of amines, for the inhibitor as well as the augmentor components of their 'sympathomimetic' actions, and then observed that nor-adrenaline had, in its action as seen in the cat, a smaller ratio of inhibitor to augmentor effects than adrenaline had; and that, in this respect, it reproduced the total effects of sympathetic nerve stimulation in that species, with a more complete accuracy than did adrenaline itself. My own shortsighted reaction to this discovery, however, had been to regard it merely as creating a difficulty of detail for Elliott's suggestion of adrenaline as the sympathetic transmitter. And it was not till many years later, that Bacq, von Euler and others recognized, and eventually proved, that nor-adrenaline, which I had known in 1910 only as a synthetic artifact, was indeed the principal component, in mammals, of the peripheral sympathetic transmitter.

Loewi seems to have been engaged largely with other calls on his time for a few years after 1905; so it was not till 1908 that his name appeared again on publications recording the results of researches, mostly in collaboration with others, and on several widely different subjects. There were publications in that year with Hans Meyer on varying degrees of sensitiveness to tetanus; with Neubaur on phloridzin diabetes again, and the effect of diuretics on it; with Jonescu on a specific action of digitalis on renal function; and by Loewi alone on a new function of the pancreas. In addition to these, there were two with Fröhlich, one of a more general character, on functions of the autonomic nerves and the effects of drugs upon them, and the other on the occurrence of vaso-constrictor fibres in the chorda tympani. Neither of these, however, had more than a distant relation to the chemical-transmission story. Of much greater significance for its eventual development, though this was still unrecognized at the time of their publication, were two communications which followed, in 1909. One of these was by Loewi with Fröhlich, on the increased sensitiveness to adrenaline produced by cocaine, and the other with Mansfeld, on the action of physostigmine, in increasing responses to the stimulation of parasympathetic nerves.

Thenceforward, however, Loewi appears to have distributed most of his research energies and his attention, for some 12 further years, among the problems which have already been mentioned as recurrently attracting his interest. Treatment with digitalis, and the relation between the action of that drug and that of calcium ions, provide the subject of several of his publications in this period. Carbohydrate metabolism and experimental diabetes figure again as the subjects of several papers, and again in relation to the composition in kations of the nutrient medium for the heart, or other tissue, on which the observations are made. There is another series dealing with the action of the vagus on the heart, which again includes the effects, upon this action, of varying the calcium-content of the saline fluid, as well as the effect of other drugs upon the efficiency of the vagus stimulation. And at the very end of this period, in 1921, came three more publications, the fourth, fifth and sixth of the series, on the relation between the actions of the 'heart-drugs'—digitalis, etc.—and those of the physiological kations, especially of the calcium ion.
Otto Loewi
1921-1938

Early in this major and final period of Loewi's tenure of the Chair at Graz, he achieved and published his first demonstration of the chemical transmission of effects from the nerve-endings of the autonomic system; and during the remainder of it, he and his co-workers published the series of further papers, which reported their developments in detail of this very important discovery. Very naturally it soon won for Loewi a high reputation among medical research workers, widely beyond the circle of those with specially pharmacological interests. For that reason, it seems more suitable to devote a separate section to its closer consideration, and here to make briefer mention of other lines of research which Loewi also followed actively, with different collaborators, during this same final period, until he was compelled to leave Austria.

A glance at the bibliography, prepared from a manuscript left by Loewi himself and reproduced at the end of this Memoir, will be enough to show that some of these other groups of researches, published during this same period, represented renewals of his attack on pharmacological problems into which he, with a varied succession of colleagues and visiting investigators, had already begun his experimental enquiries, during earlier periods of his research activities. Such were, for example, his further renewed studies of the part played by the inorganic ions, and especially by the calcium content, of the blood or of an artificial nutrient fluid, in the effects of the glucosides of the digitalis series on the activities of the heart muscle, as well as in other drug actions. Another of his interests had been in the nature of diabetes, and its modification by drug actions; quite early in his research career, as we have seen, he was using the diabetic condition, as artificially produced by the administration of phloridzin, for such investigations. It is, accordingly, not surprising to find that the first publication of the discovery of insulin by Banting and Best, in 1921, and the immediate and world-wide interest which it excited, should have made Loewi, with many other investigators in many countries, eager to take part in the more fundamental exploration of the nature of the action of a hormone of such importance for normal physiology, as well as for special therapeutics. Accordingly, in spite of the primary claim upon his own research interest by his own demonstration of chemical transmission, published also in 1921, we find him producing, mainly from 1925 to 1928, with his colleague H. Häusler, another series of papers on the results of their experiments concerning the mode of the action of insulin. Other examples could be given; but a mere inspection of the list of his publications, over the forty years or so of his full and unhindered activity, should suffice to make clear the unusual width and variety of Loewi's general enterprise in research. There can be no doubt, indeed, that his experimental work with his own hands, and the inspiration and guidance which he gave to the many distinguished investigators who had been his assistants and students, would have entitled Loewi to high rank among contributors to the progress of scientific knowledge in many departments of pharmacology and biochemistry,
even if he had never been prompted to step suddenly beyond the normal limits of the research programme which he seemed thus to have been planning for himself, in order to carry out the simple but convincing experimental test, which immediately gave a new reality and impetus to the then rather widely discredited theory of the chemical transmission of nervous effects. There can, I think, be no doubt that this new adventure by Loewi, into a field of experiment and ideas in which he had till then shown no direct or conscious interest, was responsible for raising his status in the world of scientific opinion, from that of one of a number of distinguished contemporary pharmacologists, to that of a memorable pioneer, whose work opened a new vista of advance, in the special area of physiological and medical knowledge with which it was concerned.

**Loewi’s chemical transmission discovery**

In the ‘autobiographic sketch’ already mentioned, which Loewi contributed in 1960 to *Perspectives in biology and medicine*, he makes a kind of precautionary disclaimer, about the accuracy to be expected of such personal records. ‘... Yet fiction may come into play,’ he writes, ‘because a retrospective report may not always truly reflect the past as it happened.’ Anybody, I suppose, who has found himself called upon, over the years, to repeat his account of a personal experience on numerous occasions, must have been conscious of a temptation, at least, to make it more acceptable, by such trimming of details, or shifts of emphasis, as could be effected without weakening its essential veracity. We are entirely dependent, of course, on Loewi’s memory, for detailed knowledge of the extraordinary circumstances in which he was led to perform his rightly famous experiment; but, though he certainly had no lack of sprightly imagination, or of gift for picturesque description, I can testify that his own account of this incident has been free from such changes during the four decades since he first described it, except in a minor detail of timing. I suppose that I must have been one of the earliest to hear from him the remarkable story of the dream, from which he woke on two successive nights, with a strong conviction that the experiment which it had suggested was one of great importance. On the first occasion he had seized a scrap of paper, made on it what he thought to be a sufficient record, and fallen asleep again; only to find, next morning, that the scrawl on the paper was illegible, and that he had completely forgotten what it was about. According to my own memory of what he then told me, on waking again from the same dream on the following night, and feeling naturally determined not to lose the clue again, he made a careful record of what it had suggested; so that, on the following morning, he was able to take the chit with him to the laboratory, carry out the proposed experiment and obtain the predicted result. Loewi’s own final version of the affair, as given in the ‘autobiographic sketch’, differs from that which I had thus remembered, only in a detail which, perhaps, gives it an even stronger dramatic appeal. It describes how, on his second waking from the insistent dream, he was so anxious not to lose its message...
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again, that he rose from bed immediately, at 3 a.m., and hurried straight to the laboratory, to perform the successful experiment then and there, in the small hours. Obviously this, his own direct memory of how it happened, has a prior claim to acceptance, over one in which my own fallible memory was also involved.

In any case, however, the difference would have no kind of significance for the cardinal importance of the result of the actual experiment, which demonstrated for the first time the reality of the intervention of a chemical agent, in the transmission of the excitatory effect of a nervous impulse, across the small breach of continuity at neuro-effector or inter-neuronal junctions. So far, a process of this kind had been no more than a speculative suggestion. If its truth could have been experimentally established, it could have been accepted with confidence, to account for certain special features of the transmission at such junctions—the time-delay which it involved and its unidirectional character, for which there had been otherwise no satisfactory explanation; and, more particularly, the suggestively localized and closely neuro-mimetic actions of certain natural bases, especially of adrenaline and some of its homologues and, more recently, of acetylcholine. Hitherto, however, none among those of us who had been taking a particular interest in such speculations, had been able to think of a method by which they could be put to the practical test of experiment. And now Otto Loewi, who, by his own confession, had not paid any conscious attention to such ideas, at least for many years, had found himself mysteriously subjected to the repeated pressure of a suggestion, welling up as it were from some deeper sub-conscious level, and urging him to perform an experiment so simple in its design and its technique, that any reasonably dexterous student could easily have carried it out. And this experiment was actually to give him a simple and unambiguous answer, establishing the chemical transmission of nervous effects, at least at peripheral, autonomic, neuro-effector junctions, as an experimental fact.

The position appears to offer ample scope for psychological speculation. Loewi has himself recorded his own conviction, that, if he had considered the matter carefully in the daytime, he would undoubtedly have rejected the kind of experiment suggested by his dream, on the ground that, if a chemical agent were actually concerned in the transmission, it could not be expected to appear in more than the minute quantities required to act upon the immediately contiguous, effector cells. It may be, indeed, that similar considerations would have deterred even some of those who had retained a more conscious interest in the theory than Loewi had, from using so simple a means of putting it to the test. I do not believe, in fact, that any of them had thought of it. If I had done so myself, I do not think that I should have brushed it aside, as too simple to be worth trying. I find myself more in sympathy with an unidentified German colleague, who happened to be standing behind me when Loewi gave a demonstration of his experiment, at an International Physiological Congress in 1926. Seeing the ease with which the vagus inhibition of one isolated frog’s heart could be conveyed to another, by a mere
transfer of the saline contents with a pipette, he exclaimed, 'Ach! Warum habe ich nicht daran gedacht?' Why, indeed, should not anybody interested in such matters have thought of it, and tried it, at any time during the previous twenty years? The fact is that nobody did; and the admiration which I felt for Loewi's achievement was only enhanced, by the thought that his relative aloofness from this problem might well have made it easier for him to follow the mysterious prompting of his dream, and thus to adopt so elegantly simple a plan of experiment, to make with it, at one single step, so revolutionary an advance in the position of the chemical transmission theory, and thus to open the way widely to so much that has followed.

There was one feature, however, of Loewi's first published account of this crucial experiment, which I found more difficult to understand. In referring to the two different transmitters which he found to appear in the saline contents of the heart, in response to the stimulation of its inhibitor vagus nerve and of its augmentor-accelerator sympathetic nerve-supply, he referred to them merely in terms of their respective origins, as 'Vagus-stoff' and 'Accelerans-stoff'. He had thus appeared to ignore, or to be unaware of, the fact that there were two good chemical candidates, the respective sympathomimetic and parasympathomimetic activities of which had long entitled them, in theory, to be considered for the transmitter roles, if once the real existence of such a chemical transmitter function could be demonstrated. At our next encounter I ventured to rally him on this reticence. 'Why', I asked him, 'did you not say frankly that your vagus-substance might well prove to be something like acetylcholine?' He had replied that, of course, he believed it to be acetylcholine; but that, having recently, in an entirely different connexion, committed himself too rashly to a conclusion which he had subsequently had to withdraw, he was abnormally sensitive to the danger of publishing another speculative suggestion, lest it might prove also to be premature. Most fortunately, however, this attitude, which seemed to me to be one of excessive caution, did not prevent him, in the years that followed, even almost to the time when his research activities were rudely interrupted in 1938, from pursuing the comparison between the properties and behaviour of acetylcholine and those of his 'vagus-substance', by such methods as were applicable to the chemical and pharmacological comparison of extremely minute quantities. Many of these experiments were carried out in association with a succession of collaborators—Navratil, Engelhart, Hellauer. And their results, as a whole, not only succeeded in establishing the identity of the parasympathetic transmitter with acetylcholine, in all the properties and activities for which it proved practicable to compare them, but threw much additional light on the occurrence in nervous tissues of a substance with these characteristics. It was especially significant for further developments, that Loewi and his co-workers found that the vagus-transmitter, when liberated, was extremely susceptible to destruction by an enzyme, which was not merely, as I indeed had much earlier suggested, an esterase, but a specific cholinesterase, and that the action of this was readily inhibited by the
alkaloid eserine (physostigmine), the specific pupilloconstrictor action of which had been shown as long ago as 1905, by H. K. Anderson at Cambridge, to be due to its intensification and prolongation of the effects of impulses in the (parasympathetic) oculi-motor nerve-supply to the pupil. This rationalization of the effects of eserine, as essentially due to its prevention or delay of the destruction of acetylcholine, by its antagonism to the action of a cholinesterase, was to be of outstanding importance for the further study of cholinergic, chemical-transmitter mechanisms, and especially so for the extension of such experiments to the organs of warm-blooded vertebrates, and to those activities of acetylcholine which I had described as its ‘nicotine’ actions; the studies of Loewi and his colleagues having been limited, at least in intention, to its peripheral, ‘muscarine’ actions. Loewi, indeed, seems to have adopted, for a time, an attitude of almost obstinate scepticism, to what others of us had regarded as a possibility at least to be tested; namely, that these ‘nicotine’ actions of acetylcholine, on ganglion cells and on the motor end-plates of voluntary muscle fibres, raised the question whether even the transmission of the rapid effects of nerve impulses across such synaptic junctions, might not also be effected by the liberation there of acetylcholine. In the first Harvey Lecture which Loewi gave by invitation in New York, in 1933, he even, as it seemed to me, went out of his way to give public expression to his disbelief in such a chemical transmission of the effects of voluntary nerve impulses to voluntary muscle fibres. He was unaware, of course, that, at the time when he was thus disclaiming belief in such a possibility, some of my own colleagues were busy already with plans for putting it to the test of direct experiment, an essential condition of which would be the use of the protective action of eserine, which Loewi and his colleagues had discovered. By the time that he gave the Ferri Lecture to the Royal Society, in 1935, on what he still preferred to call the ‘humoral’ transmission of nervous impulses, the experimental evidence for such a process in the excitation of voluntary muscle fibres from motor nerve endings, and for acetylcholine as again the agent of the chemical transmission, had already been published in sufficient detail to carry conviction, and with Otto Loewi as with other experts in such matters. He was now able, accordingly, to give public acceptance to the identification of the transmitter from peripheral parasympathetic nerve-endings, at ganglionic synapses and from voluntary motor nerve endings, as acetylcholine itself; though he still preferred—rather surprisingly, I thought—to reserve judgement, with regard to the presumptive identification of the peripheral sympathetic transmitter, his own ‘Accelerans-stoff’, as adrenaline (or its primary homologue), although the first published proposal of the transmitter conception had been made by Elliott, more than thirty years earlier, to explain the closely sympathomimetic action of adrenaline, on effector cells which were, or had been, sympathetically innervated.

During the passage of more than a quarter of a century, the development of knowledge concerning these transmitter mechanisms has, of course, proceeded very far beyond the point which it had reached in 1935, when
Loewi gave his Ferrier Lecture. The chemical identification of the agents of cholinergic and adrenergic transmission has long since passed beyond the stage of doubt, or controversy; while, through the brilliant experimental achievements of Sir John Eccles and many others, the occurrence of a chemical transmission process at most of the synaptic junctions in the vast neuronal complexities of the mammalian central nervous system, seems already to have been firmly established in principle; although it seems further clear that other chemical transmitters, than those now accepted as functional in the peripheral system, have yet to be recognized and identified as responsible for the transmitter functions at central synapses. Such developments, and others, perhaps, not yet foreseen, are leading far from any which could have been contemplated when Loewi, in 1921, performed his simple but convincing demonstration with the isolated hearts of frogs; but it was this which first brought the chemical transmitter conception within the range of directly experimental proof and investigation, and opened the way to all that has followed, in that still expanding field of enquiry.

The award of a Nobel Prize to Otto Loewi for his part in these researches, in 1936, was greeted with general acclaim; and to me it was a matter for special pride and satisfaction to be joined with him in that award. By both of us it was greeted as a welcome new link in a scientific and personal friendship, already of long standing.

Personal and family life. Exile and re-settlement

Mention has been made already of the unusual width and variety of Loewi's cultural interests, even while he was still at the student stage of his university career. Throughout his life he seems to have retained this eagerness for new artistic and cultural experiences and contacts. He himself records that, having been naturally endowed with no special aptitude for making or listening to music, he set himself deliberately, and successfully, to acquire an appreciation of its intellectual and emotional appeal, with a resulting enthusiasm which came to take high rank in the scale of his pleasures. His enthusiasms and his dislikes were easily aroused, and given prompt and effective expression. He had an unabashed enjoyment of good food, good wine and good conversation, being himself a ready and uninhibited talker, but always worth hearing and never in danger of being a bore. He had a genuine enthusiasm for scientific ideas and achievement in general, as well as for those in his chosen lines of research activity. But, in addition, he had, in an eminent degree, the characteristics best summarized in his native language; he was a genuine 'Lebenskünstler'. With it all, he was capable of giving, and attracting, consistent and loyal friendship.

Loewi had found Marburg, where he held his first academic appointment with Hans Meyer, relatively poor in its social and cultural opportunities; but these could nowhere have been more lavishly at his disposal than in Vienna, whither he moved with Meyer in 1904. During his stay there he formed the habit of spending his annual holiday in Switzerland, and acquired a lasting
affection for the Engadine in particular. It was in Pontresina, in 1907, that he first met Professor Guido Goldschmidt, then Professor of Chemistry in Prague and Vienna, with his wife and their daughter Guida, who became Loewi's wife in 1908, and shared with him all the details of the removal to Graz in 1909, and of the establishment there of the attractive new home, where they were to spend the next twenty-nine happy years. Guida Loewi was to become the able mistress of their charming household, mother of their family of three sons and one daughter, perfect hostess to their many friends, constant and devoted companion to her husband and sharer in all his interests and experiences, happy, tragic and adventurous, until she died with a tragic suddenness in 1958, fifty years after their marriage. They had by then been living for some nineteen years in New York, where friendly invitation had enabled them to become peacefully re-settled with their family, after their expulsion from Austria twenty years earlier.

Till the final blow came, Graz, the second city of Austria, with its second Austrian university and medical school, had offered Loewi what seemed to be ideal conditions for his academic activities of teaching and research in his own chosen subject, together with the social and cultural privileges which meant so much to him and his wife and their growing family—drama, opera, concerts of music, museums of art and antiquity; not, of course, on the scale of the historic and world-famous institutions of Vienna, but excellent in their own setting, which, on the other hand, was even desirably free from the political and other distractions of what was still the Imperial Capital of a large part of Eastern Europe, when Loewi left it for the relative seclusion of Graz, with its attractive landscape setting. Even the First World War, beginning five years later, seemed to leave him, in his Graz Professorship, enviably free, by comparison with his colleagues in the other belligerent countries, to pursue the even tenor of his academic researches, little hampered by the demands of war-time emergencies.

After all these happy and fruitful years, amounting to about three-quarters of the whole period of Loewi's full scientific activity, and when the time for his normal retirement must already have been coming into view, the blow fell suddenly, in March 1938. With the Nazi occupation of Austria, German troops marched into Graz. The eldest son of the Loewis, and their daughter, both had the good fortune to be outside Austria at the time; but Loewi himself and the two younger sons were arrested and thrown into prison, together with a large number of other Jewish residents in Graz. He was liberated after two months of this brutal deprivation, and his sons a month later; but it was September of that year before he obtained permission to leave Austria, and then only at the cost of signing an instruction to a Swedish bank, to transfer securities, which were being held there for him, to a German bank under Nazi control. His cable, informing me that he was flying to London, found me urgently engaged with measures for safeguarding the valuable items of equipment and library in the National Institute for Medical Research, against risk of damage in the war, which all England was
even then expecting to begin. That immediate danger, however, was deferred for a year, and Loewi arrived safely and in remarkably good form. I have never ceased to admire the dauntless courage and enterprise with which he, with many others in comparable predicaments at that time, refused to waste time and energy in merely futile resentment, but devoted their abilities promptly to the quest for new careers, to the scientific advantages of the countries which offered them refuge and new opportunities. Loewi stayed with us then for a few weeks, during which he took me to call on Sigmund Freud, whom he had known in Vienna, and who was then resident in Hampstead, but already sadly afflicted by the jaw cancer, from which he was to die. Loewi then accepted a temporary appointment under the Belgian Foundation Franqui, and left for Brussels. Returning to friends in England for a holiday in the next year, 1939, he was caught by the outbreak of the Second World War, and found harbourage and opportunity in the Pharmacology Department under the late Professor J. A. Gunn at Oxford, until the middle of 1940. Then he was able finally to accept an invitation from the Medical School of the New York University, to join their faculty as a Research Professor of Pharmacology, with accommodation in the Department of Professor George B. Wallace, whose initiative was doubtless concerned in the proposal. Loewi arrived in New York on 1 June 1940, to take up this appointment, and thus to settle himself into a further and final stage of his career, at the age of 67. His wife and the other members of his family were able to join him in New York during the following year. Their financial means, in relation to the costs of living, were not, of course, to have the comfortable amplitude which they had enjoyed in Graz; but they readily and gratefully adapted themselves to more frugal standards. He became an American citizen in 1946.

Of the many honorary Degrees which Loewi received in these later years from universities in different countries, including those of Graz and Frankfurt, and of the honorary memberships to which he was elected, none gave him greater pleasure than his election to the Foreign Membership of The Royal Society in 1954.

This happy evening to Otto Loewi’s scientific career, which American generosity and respect for his achievement had provided, was to last for rather more than another twenty-one years. It was not to be expected that his work in the laboratory would produce further outstanding discoveries at that stage, and under these new conditions. He was able to tidy a few ‘loose ends’ of the work which had been so brutally interrupted, to regain his poise, and, as the years passed, to spend more of his time in writing articles and giving lectures, for which American centres of medical research were characteristically and increasingly generous with requests and invitations, as the rumour of what he had to offer grew and spread more widely. He and his wife were able, quite early, to form the habit of going annually, when the summer heat of New York became oppressive, to Woods Hole on the Massachusetts coast, with its world-famous centre for researches in marine
biology. There, for the rest of his life, he was able each summer to acquire new scientific interests, to make new friendships, and to renew others which had already been formed. As already mentioned, the long life-partnership was sadly terminated by Mrs Loewi's sudden death in 1958; and, not long afterwards, Loewi himself was the victim of a serious accident, when about to leave hospital. He had a fall, which broke his pelvis and seriously disabled him, and from the physical effects of which he never fully recovered. When I last saw him in New York, in October 1959, he could just push himself about in his apartment, with the support of a strong metal frame; but his brain was as alert as ever, as eager for reminiscences and discussion, and for new mental enterprise. Nor was he to be deprived of his annual enjoyment of months at Woods Hole; for American friends rallied round him in each of the remaining summers, and transported him thither by car. In the last letter which I received from him, dated from Woods Hole on 2 July 1961, he wrote: 'I love this place more than any other in the world known to me, except the Engadine in Switzerland.' It was good to think that he had thus been able, at last, to enjoy the two places which, in his affectionate judgement, were the best of both worlds.

And when Otto Loewi's life reached its natural ending on Christmas Day 1961, in his 89th year, its circumstances were such as he himself, with a connoisseur's instinct, might well have approved, or even desired, if he could have foreseen them. He received, on Christmas Eve, from a friend—maybe from Woods Hole—the present of a fine lobster. This being much to his liking, he ate the whole of it for his dinner, with a bottle of wine, which he shared with his nurse-housekeeper. And then, on the following morning, when he was speaking to a friend with his usual eager impetus, he stopped in the middle of a sentence; and they found that his life had flickered out.

The Director of the Woods Hole Laboratory, and his associates, with others who had there learned to know and to admire Otto Loewi, arranged for the reinterment of his ashes in the Churchyard there, on 17 August 1962, and for a commemorative lecture and meeting, at which his friends could recall his personality and the sparkle of his mind, and all that had so greatly endeared him to their community. I myself was unfortunately prevented, by a minor accident, from accepting a generous invitation to be present on this occasion, and to take part in the proceedings. Fortunately my friend and former colleague, Sir Lindor Brown, Sec. R.S., was able to be present, and to represent many British friends and admirers of Otto Loewi.

I have been greatly indebted to Otto Loewi's youngest son (now domiciled in England as Geoffrey Low) for information about his last hours, and for access to the documents which he left, including the MS. Bibliography, in the reading and verification of which I have been greatly assisted by Miss M. A. B. Venables, of the Library Staff of the Royal Society of Medicine. In the same connexion I have received greatly valued assistance from Professor Otto Krayer of the Harvard Medical School, and from the Springer-Verlag of Heidelberg. For the portrait here published I have been greatly indebted to Lady Simon, who kindly lent me
a print from a photograph taken by her husband, the late Sir Francis Simon, F.R.S., when Otto Loewi was in Oxford in 1940. It seems to me the most characteristic portrait of him which I have seen, and shows him at the age of 67, between his leaving Austria and his migration to America. For the preparation, from the original small print, of an enlargement more suitable for reproduction, I am indebted to Mr C. E. Fryer of the Art Department of the Wellcome Foundation Ltd.

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