# ERGEBNISSE DER PHYSIOLOGIE
## BIOLOGISCHEN CHEMIE UND EXPERIMENTELLEN PHARMAKOLOGIE

BAND 52

SPRINGER-VERLAG
BERLIN · GÖTTINGEN · HEIDELBERG

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## BIOLOGISCHEN CHEMIE UND EXPERIMENTELLEN PHARMAKOLOGIE

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# Otto Loewi †

By

H. H. Dale

Otto Loewi, born on June 3rd, 1873 in Frankfurt a. M., was the son of Jakob Loewi, a wine merchant in that city, by his wife, born Anna Willstaedter. Otto had many happy memories of his childhood, at home and at school. His schooling was of the conventional, humanistic type of the old-fashioned Gymnasium, centred on the Latin and Greek classics. He had vivid memories also of annual summer holidays, spent at his father's small country estate in the Palatinate, on a slope of the Haardt Mountains, with a pleasant house, a large garden and vineyards. There were holiday visits also to Belgium, from which he dated a lasting enthusiasm for early Flemish painting.

So far, there had been nothing to indicate the choice, for Otto Loewi's further educational course, or for his eventual career, of any of the natural scientific disciplines. He has himself recorded[1] that his own most natural choice would have been for the History of Art; but his parents, doubtless for good reason, wished that he should study to qualify in medicine. He accepted their decision, and duly matriculated at Strassburg, with a medical course in view. He apparently found little to attract him in the formal studies of the preclinical course, with the exception, perhaps a rather surprising one, of those in Anatomy. He was evidently much influenced by the personal characteristics of his teachers. In any case, he seems to have spent much of his time, and nearly all his enthusiasm, during his first University year, in hearing lectures on the history of architecture and on philosophical theory; with the result that he only passed his "Physikum" at the end of his fourth term. Then he spent a year at Munich, where his medical studies were inevitably in competition with further and abundant opportunities for deepening and widening his knowledge and enjoyment of a range of the arts drama, music, and the treasures of museums and galleries. Loewi retained, indeed, throughout his long life, and amid all the changes in his circumstances, the desire to use every opportunity for enlarging his artistic and cultural experiences in general, as well as for making contact with new developments in a range of the natural sciences. He has himself recorded that, having by nature no special aptitude

[1] Perspectives in Biology and Medicine — Autumn, 1960.

for making music, or even for an understanding enjoyment of it, he deliberately acquired an appreciation of its appeal, so that it came to take a high rank in the scale of his artistic pleasures.

On the other hand, he was evidently ready, as a student, to respond to evidence of personal or scientific distinction in his teachers. On his return in 1894 to Strassburg, a new enthusiasm for his medical studies was thus aroused in him by NAUNYN's lectures and clinics; so that, for the time, be began to think of a career in clinical medicine. He had first to find a subject, however, for a graduation thesis; and, for no special reason which he could recall, he went for this to SCHMIEDEBERG, who was then gaining a wide influence as one of the early Professors of Pharmacology. The subject which SCHMIEDEBERG gave him was not likely to afford him much more than a first experience of the relatively simple techniques, employed in the pharmacological researches of those days. The opportunity, however, brought him contacts, and more lasting friendships, with men of the calibre of OSCAR MINKOWSKI, ARTHUR CUSHNY, KARL SPIRO and WALTHER STRAUB; and it seems, indeed, to have been eventually effective in determining the main course of LOEWI's career. It was SPIRO, as LOEWI recalled, who first brought to his attention FRIEDRICH MIESCHER's classical studies of the changes in the metabolism of the salmon, during its fresh-water progress up the RHINE, and thus to the possibilities of chemical methods applied to biological problems.

When he had graduated at Strassburg, LOEWI's parents arranged for him first to enjoy a holiday in Italy, with free scope for the indulgence of his artistic interests. He had evidently retained, however, the sense of a deficiency on the chemical side of his training, for the future needs of a scientific career in Medicine; so that, on returning from the Italian holiday, he took a course of chemistry in Frankfurt before returning to Strassburg, to spend a few more months there under the stimulating influence of FRANZ HOFMEISTER, whose Department was already one of the centres of the effective emergence of the then new discipline of biochemistry. And if one looks at the list of all the scientific papers which LOEWI was to publish, during the four decades of his full activity in pharmacological teaching and research, and notes how often, and how recurrently, they were concerned with problems of nutrition and metabolism, it is easy to form the impression that he might well have chosen biochemistry as the subject of his life's work, if he had earlier had the opportunity, and the impulse, to obtain a stronger educational background in chemistry, and in organic chemistry especially.

The strong influence, however, which LOEWI had experienced from NAUNYN's clinical teaching had apparently not yet lost its effect. Before he finally decided to seek his major opportunity in pharmacology, he accordingly accepted a clinical assistantship under Professor VON NOORDEN, at the City Hospital in Frankfurt. He found the experience discouraging, however, and returned

after a year of it to Strassburg, where he sought the advice of Professor HOFMEISTER, on whose recommendation he enquired whether HANS HORST MEYER, then Professor of Pharmacology at Marburg a. d. Lahn, had a suitable vacancy in his Department. Thus he was to become, in 1898, Assistant in MEYER's department, and was to remain with him as Privat-Dozent and Associate Professor, for eleven years in all — seven years in Marburg, and four in Vienna, when MEYER was called to the Chair of Pharmacology there. During these years he acquired a deepening personal devotion to MEYER and a high regard for his scientific distinction and his wisdom; and their friendship continued after LOEWI himself, in 1909, became Professor of Pharmacology in Graz, where he was to remain in full activity until he was imprisoned and exiled by the Nazi invaders, in 1938.

Mention has been made of the biochemical and metabolic interest shown by a number of LOEWI's researches; and this was already obvious in his earlier publications from the Marburg laboratory. Already in 1898 he was describing a urea-forming enzyme in the liver, and in 1900 came several publications on the metabolism of nuclein. Even those which might be classified as pharmacological had apparently a biochemical aspect, as when phloridzin was given to excite a diabetes, and the effect of camphor on the condition so produced was studied. In 1901 he was publishing experiments giving a negative answer, to the question whether the body could form sugar from fat; and then, in 1902, came the publication of experimental results, for which a claim might well be made, as the most important of any which LOEWI achieved, until his famous demonstration, in 1921, of chemical neuro-effector transmission. In the 1902 publication LOEWI described nutritional experiments in which he had succeeded, where all others had failed till then, in maintaining dogs in nitrogenous equilibrium, on a diet in which the sole source of the nitrogen was a mixture of amino-acids, obtained by the complete tryptic digestion of the proteins of natural organs. LOEWI was in England for some months in that year, and was able to discuss these findings with the late Dr. (later Sir) FREDERICK GOWLAND HOPKINS. And I well remember a conversation in which HOPKINS spoke to me with enthusiasm, of the importance to nutritional science of this discovery; and it might, indeed, be regarded as an important step towards the experiments with a diet of chemically purified nutrients, which were later to lead HOPKINS himself to his own historic contribution to the discovery of the "vitamins".

It was in 1902 that LOEWI paid this, his first visit to England. He was anxious to improve his knowledge of the techniques of mammalian physiology, and judged that, at that time, he could learn more to his purpose in England than in Germany. With the ready agreement of the Professor of Physiology in University College, London, ERNEST H. STARLING, he made that Department the chief centre of his visit, during a stay of some months. STARLING's laboratory

was full of interest at the time, on account of his then recent discovery of secretin with his equally famous brother-in-law and frequent collaborator, WILLIAM M. BAYLISS. Others were there, exploring the possibilities of different developments from this discovery — myself among them, working with the support of one of the very few post-graduate research studentships which were then available. I thus met LOEWI for the first time, and we laid the foundations of a personal friendship, and a sharing of research interests, which was to last for nearly 60 years. He had not planned to do any research of his own on this short visit. He wished to learn the methods then in use in British laboratories, to make personal contacts with British physiologists, and to learn something of the problems on which they were engaged. Also he wished to learn enough English for ordinary scientific and social purposes — not, as he said, to speak it accurately, but to speak it fast. The legend of some of the impromptu translations, which he thus achieved, had a long survival in British physiological circles, at Oxford and Cambridge also, to which he made shorter visits from his London base, and in the Physiological Society. The latter was then a relatively small and intimate community, and LOEWI found the friendly informality of its meetings and discussions much to his liking.

A special mention should be made of the short stay which he made in Cambridge, where again he found a Physiological Department full of research and ideas. Mention has already been made of his meeting with HOPKINS; and he would have met WALTER FLETCHER also, who was then working with Hopkins. He would also have met JOSEPH BARCROFT, who was later to succeed LANGLEY as Professor of Physiology. Of more eventual significance, however, was his meeting at that time with Cambridge workers on the functions of the involuntary or autonomic nervous system, on the separate and contrasted functions of its sympathetic and parasympathetic divisions, and on the closely mimetic reproduction of their respective effects by adrenaline and by muscarine. In this connexion he would have met the veteran W. H. GASKELL, no longer active in this field, J. N. LANGLEY and H. K. ANDERSON, and, more especially, T. R. ELLIOTT, who was then still a post-graduation research student, but was already engaged on his remarkably brilliant and inclusive survey of the closely sympathomimetic actions of adrenaline. There was certainly a good deal of speculation among the Cambridge group then, with regard to the meaning of this correspondence, which survived the degeneration of the nerves. I do not think that ELLIOTT would then have mentioned the conception of adrenaline as the chemical transmitter of sympathetic effects; he put this forward two years later, and thus made the first published suggestion of such a specific, chemical transmission. LOEWI, on his return to London from Cambridge, made a special mention to me of the impression which he had formed of ELLIOTT, as a research worker of brilliant potentialities. And it would appear that, when he returned to Marburg, LOEWI's mind was still

busy, perhaps subconsciously, with the meaning of these neuromimetic actions, which had been so much "in the air" at Cambridge during his visit. For it is on record that, in the following year, 1903, when walking with WALTER M. FLETCHER, whom he had also met at Cambridge, and who was then on a visit to HANS MEYER's Department in Marburg, LOEWI suddenly exclaimed: "FLETCHER! Perhaps the vagus impulses inhibit the heart's action by liberating muscarine at the nerve endings!" The suggestion was evidently made quite casually. LOEWI himself promptly forgot it, and retained no conscious memory of it. It was FLETCHER who recalled it, after LOEWI's publication of his famous demonstration, in 1921. And, by that time, it was no longer necessary to think of a substance so improbable as the stable, poisonous alkaloid, muscarine, to act as the vagus-transmitter, the real existence of which had been so clearly established by LOEWI's practical demonstration.

There can be no doubt that LOEWI's high reputation as a discoverer, among scientists in general, has been mainly due to a recognition of the far-reaching importance of these experiments on chemical, neuro-effector transmission; and I must reserve a separate section of this Memoir for further details of this crowning experimental success of LOEWI's career. In the smaller circle, however, of those who are interested in the general development of the medical sciences, and of pharmacology in particular, during the first half, and especially during the first four decades, of the present century, it will certainly be felt that the fame of his greatest single achievement should not be allowed to overshadow unduly the importance of LOEWI's solid and widely ranging contributions to the advancement of knowledge, in several different sections of this pharmacological field — some of them bordering on, or even overlapping with, those of biochemistry. The mere list of his published researches during the period of his full activity from 1898 to 1938 — many of them carried out in co-operation with a succession of his departmental colleagues, or with visiting physiologists or pharmacologists from other centres and other countries — provides abundant evidence of the high rank as an investigator, and as a promoter of researches by others, to which LOEWI would in any case have been entitled, even if he had never received the mysterious impulse, to undertake the experiments which were to make his name most widely famous. A glance at the record will show that there were several subjects which, at intervals of some years, seemed to acquire a renewed interest for him, with the resulting appearance of successive groups of communications, in association with different collaborators. Such were the physiology and pharmacology of renal function, including the effects upon it of digitalis; carbohydrate metabolism, including the diabetes produced by phloridzin and the effects of other drugs upon it, and, later, after the discovery of insulin, the mode of the action of that hormone; and, again, the part played by inorganic ions, and especially by calcium ions, in the actions of drugs of the digitalis series on the functions of the heart,

and in other drug actions. I have already mentioned his early and very important demonstration of the body's ability to build its proteins from their constituent amino-acids. And there were several other investigations, pharmacological in aim and method, which might have served to quicken LOEWI's interest, during the period before 1921, to the possibility of a chemical, or, as he preferred to call it, a neurohumoral transmission of nervous effects. Such were the opportunity which he had, with HANS MEYER, to test some of the substances obtained in industrial research on the way to the synthesis of adrenaline, and including "arterenol" (i.e. *nor*-adrenaline); his discovery, with FRÖHLICH, of the increased sensitiveness to the specific effects of adrenaline produced by cocaine; and, with MANSFELD, of the action of physostigmine, in specifically increasing the responses of effector organs to the stimulation of parasympathetic nerves. From LOEWI's own reminiscences, however, it seems clear that, at the time when these observations were made, he had retained none of the interest, of which he had given momentary evidence some years earlier, in the chemical transmission possibility.

Concerning the range of LOEWI's other researches, it would, perhaps, be proper to regard them as having made their most important contribution to the classical period of pharmacology, when it still had relatively small and intermittent contacts with the traditional empiricism of therapeutics. LOEWI's full activities in research, cut short by some years of their normal term, would not, I think, in any case, have extended far into the modern period, with its revolutionary transformation of medicinal therapeutics itself into an experimental science, progressively employing the resources made available by advances in endocrinology, in immunology, in the chemotherapy of infections, in the synthesis of specifically active remedies for symptoms, and, indeed, in widening ranges of physiology, biochemistry, biophysics, and even of more fundamental disciplines. By the time that this great change was gathering speed, LOEWI was resettled, under the conditions of a new and hospitable country, offering opportunity, in the happy evening of his life, to gather memories from the years of his more active interests and achievements in research, and to expound the philosophy which these had taught him.

### Loewi's proof of neurohumoral (chemical) transmission

It is beyond doubt that the publications by LOEWI, beginning in 1921, of the direct evidence for neuro-effector transmission by chemical agents, which he alone and, later, with his colleagues, was able to obtain and to extend by experiments on the isolated hearts of frogs, changed the whole status and prospect of that conception. Till then, since ELLIOTT first put it forward tentatively, in 1904, to explain the closely sympathomimetic actions of adrenaline, it had remained, at best, an ingenious and, for a few physiologists, an attractive hypothesis. I had myself retained some special interest in it

from my own early association with ELLIOTT in experiments bearing on his idea; and this interest had been revived for me some ten years later, by experiments which I published in 1914, showing that acetylcholine had a potent and rapidly evanescent action, reproducing the peripheral effects of parasympathetic nerve impulses, at least as closely as adrenaline reproduced those of sympathetic nerves. For me, however, as for everybody else who had thought about it, the suggestion had seemed still to be experimentally intangible; and, so long as it could not be verified by direct experiment, it must remain only a speculative, and, to that extent, a practically unfruitful hypothesis. OTTO LOEWI himself seems, until 1920, to have regarded it as even more negligible; having apparently just glanced at it in 1903, he had forgotten all about it, and, with the majority of physiologists and pharmacologists, had taken no further conscious interest in it. It is, of course, only the more remarkable that, on the eve of Easter Sunday in 1920, the suggestion of an experimentally simple and straightforward method, for putting it to a practical test, should have come to him in a dream; and it was still more remarkable that, when the note which he made on waking had proved illegible on the following morning, and his memory blank even with regard to its purport, he should have found himself waking again, on the following night, from the same insistent dream, so as to be given another chance to follow its suggestion. According to his own latest account of what followed, which we must accept as authoritative, he rose immediately from his bed at 3 a.m., and hurried to his laboratory to carry out the experiment which his dream had again suggested, avoiding thus any risk that the memory of it might fade again, before he had been able to give it a trial. In his description of the whole incident[1], LOEWI records his own belief that, if such an experiment had been suggested to him when he was fully awake, he would have rejected the idea as absurd; on the ground that, even if a chemical transmission really existed, it would be impossible to suppose that the transmitting agents would be liberated in sufficient excess, to be found, in the fluid filling the frog's heart, in concentrations sufficient to transfer the effects to another heart. Whatever might have happened under different circumstances, the fact of importance is that LOEWI was not thus inhibited from trying the experiment, and that it was immediately and completely successful. Stimulation of the vagus and sympathetic nerves caused the liberation of an inhibitory and an accelerator substance, by which the respective nervous effects could be reproduced in another heart. Atropine and ergotoxine prevented the respective effects of the transmitters thus liberated, but did not interfere with their liberation.

I was inclined to rally LOEWI on what seemed to me his excessive caution, at that early stage, in referring to the transmitters, which he had demonstrated, simply as "Vagusstoff" and "Acceleransstoff", and avoiding any mention of

[1] Autobiographic Sketch, loc. cit. 1960.

their suggestive similarities to acetylcholine and adrenaline respectively. The matter of real importance, however, was that the further experiments, as reported in some 19 publications in all, on these phenomena, by LOEWI and his colleagues, in the period from 1921 to 1938, were largely directed to demonstrating properties of the vagus-transmitter, so closely corresponding to those of acetylcholine, as practically to establish its identity. And of very special importance, for further developments, was the evidence which they produced, that the remarkable evanescence of the action of the vagus-transmitter, as of acetylcholine, was due to its rapid destruction by a specific cholinesterase; and, further, that the long known action of physostigmine (eserine), in specifically intensifying responses to the stimulation of parasympathetic nerves, was due to its antagonism to the action of this cholinesterase, and to the consequently longer survival of the liberated acetylcholine, and the corresponding persistence of its effects.

LOEWI's first experiments in this series, published in 1921, had already changed the status of chemical, neurohumoral transmission, from that of an interesting, but apparently intangible hypothesis, to that of an experimentally demonstrable phenomenon, at least for the peripheral, neuroeffector transmission, from autonomic nerve-endings in the amphibia. I think, however, that it should also be emphasized, that it was the later experiments of the same series, made by LOEWI with a succession of his colleagues, and dealing with the identity of the vagus transmitter, with cholinesterase and the protective effect of eserine, which opened the way, first to further developments by a number of investigators, extending the evidence for neuro-effector transmission from peripheral, autonomic nerve endings, to the warm-blooded, mammalian types; and then, yet further, to investigations, primarily by workers in my own research department, of the possible significance, for its transmitter function, of the other, "nicotine-like" actions of acetylcholine, on ganglion cells and voluntary motor end-plates. With regard to the likelihood of this last extension of the transmitter function of acetylcholine, LOEWI himself shared the sceptical attitude of some other distinguished physiologists; and he was even, as it seemed to me, incautious enough, to make a public profession of his incredulity, in a lecture. But he readily accepted, of course, when it came, the experimental evidence for these additional cholinergic phenomena; one of the essential conditions for the production of this evidence having, in fact, been the protective action of eserine, which his own experiments had revealed. And thus, in effect, LOEWI's trial in 1920, at the bidding of an impulse so strangely engendered by a dream, of so simple and direct a method for testing the chemical transmission hypothesis, and his publication in 1921 of the unquestionable evidence for it, must in fact be regarded as having provided the starting point for new research enterprises in the whole of this field, extending now to the evidence for chemical transmission, not

only at all the junctions of the peripheral nervous system, but more recently, largely through the initiative of Sir JOHN ECCLES and his team collaborators, at those of the formidable synaptic complexities of the mammalian central nervous system.

The appropriateness of the award of a Nobel Prize to OTTO LOEWI, in 1936, for his researches in this field, was widely recognized. To me it was a matter for special pride and satisfaction, to be associated with him in this award; and, when we met again in Stockholm for the impressive ceremony, we both welcomed this as a new link in our scientific and personal friendship.

### Personal and Family Life. Exile and Resettlement

Reference has already been made to OTTO LOEWI's early interests, retained throughout his long life, in a wide range of the arts. He seems to have found Marburg rather restricted in such cultural opportunities; but these were lavishly at his disposal, of course, when he moved with HANS MEYER to VIENNA. While there he formed the habit of spending an annual holiday in Switzerland, and formed a special affection for the Engadine, which his memory always retained; and this feeling was further confirmed when at Pontresina, in 1907, he met Dr. GUIDO GOLDSCHMIDT, then Professor of Chemistry in Prague and later in Vienna, with his wife and their daughter GUIDA, who became OTTO LOEWI's wife in 1908, and was able to share with him all the details of their removal, in 1909, to their new and attractive home in Graz. There they were to be happily established for the next 29 years — the major part of LOEWI's scientific career — and to bring up their family of three sons and one daughter. GUIDA LOEWI, devoted wife and constant companion to her husband and her children, mistress of a charming household and perfect hostess to their many friends, was to share in all her husband's interests and experiences, happy and successful, tragic and adventurous, until she died with a tragic suddenness in New York, in 1958, fifty years after their marriage, at a time when they had been about to leave together, on a first visit to Europe since their exile.

In every way, the tenure of the Chair of Pharmacology at Graz had seemed to give LOEWI, and his family, the kind of opportunities which they could most desire — admirable conditions for teaching and research in his chosen range of the sciences, and therewith the social life and friendships and the cultural privileges which they could all enjoy. I was particularly impressed by the fact that even the first world war, beginning 5 years after he became Professor in Graz, had appeared to leave LOEWI free to continue his academic researches, practically unhindered by demands to meet war-time emergencies; by contrast with the experience of his envious colleagues, myself among them, in other belligerent countries.

By MARCH 1938, LOEWI might presumably have begun to think of plans for his normal retirement, a few years later. With the Nazi occupation of Austria, however, he and his two younger sons found themselves suddenly arrested and thrown into prison, together with a large number of other Jewish residents in Graz. After two months of this deprivation and ill usage, LOEWI was released; and in September he obtained permission to leave Austria, but only at the cost of signing an instruction to a Swedish bank, to transfer property, which was there being held for him, to a German bank under State control. A cable informed me that he was flying to me in England; and, in welcoming him, we were relieved to find that his arrival had not coincided with the outbreak of a war, which had then appeared to be imminent, but, in the event, was postponed till the following year. After staying with us for a few weeks, during which he was able to make and to renew English contacts, he received, and accepted, a welcome invitation from the Belgian Fondation Franqui, and left us for Brussels, where he was installed as a Research Professor, in Professor HEYMANS'S Department of Pharmacology. Being in England again, however, in the next year, for a holiday with friends in the country, he was caught by the outbreak of the second world war, and could not return to Belgium. He found harbourage, however, and renewed opportunity for some months, in the late Professor GUNN'S Department of Pharmacology at Oxford. And then, in the middle of 1940, he was finally able to accept an invitation from the Medical School of the New York University, to become a Research Professor of Pharmacology in Professor GEORGE B. WALLACE'S Department. LOEWI arrived in New York on June 1st 1940, two days before he became 67 years of age, and was fortunate thus to resettle himself in the further and final stage of his career; for the generosity, which had provided him with this attractive research appointment, was extended to enable him to hold it to the end of his life. It was not to be expected that, at that stage of his long career, he would be able to resume his full activity in research. He was concerned mostly to tidy a number of "loose ends"; but his daily visits to Professor WALLACE'S Department were warmly welcomed, for the inspiration which contacts with his ripe and varied experience, and with his still enthusiastic interest, gave to the younger research workers and to the students.

LOEWI'S wife and the members of their family were all able to join him in New York in 1941, where they readily and gratefully adapted themselves to the new conditions and associations. He became an American citizen in 1946, and he soon acquired, thus late in life, so good and natural a style, as well as so ready a fluency, in the English language, that he was still for a number of years in wide demand, as an effective and eloquent lecturer in his own extensive range. His tireless zest for knowledge, his eager brilliance in discussion and reminiscence, made him widely known, and brought him many friends during this long and happy evening of his career, which was to last for

more than 21 years. He and his wife soon formed the habit of going for the hot months of each summer to Woods Hole, on the coast of Massachusetts, where the world famous Research Station for Marine Biology gave them opportunities for making contact with additional aspects of scientific research, for forming new scientific friendships, and for renewing others already established. Loewi had already been suffering for some time from asthma, and from other physical troubles, which caused some concern to his friends. And this was accentuated when, not long after the sad death of Mrs. LOEWI, he had a fall which fractured his pelvis, and left him with a severe and lasting physical disablement. When I was able to visit him, however, in New York, in the autumn of 1959, his brain had evidently retained all its familiar activity and alertness, and he was still as eager for reminiscence, for argument and humorous comment, spiced with quotations from his favourite Goethe, and for new mental enterprise. In each of his remaining summers there were friends ready to give him careful transport to Woods Hole, where he continued fully to enjoy the conditions and the company. In the last letter which I had from him, dated from Woods Hole on July 2nd, 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 of him thus, eased and refreshed by the Atlantic breezes, where, as recently described by friends in the U.S.A.[1], "he became a legend to the students of the Marine Biological Laboratories" — their "Uncle Otto" in fact; and where "On summer afternoons and evenings he was usually seen sitting in front of the house where he lived, at his feet on the lawn a small knot of people listening to an ever animated discourse". OTTO LOEWI, indeed, enjoyed good conversation as he enjoyed all the good things, material and spiritual, which life had to offer; and he was himself an irrepressible talker, though never a wearisome one. His family realised that, when the end came, it came in a form which he might himself have desired. On the morning of December 25th, Christmas Day, 1961, he suddenly stopped speaking, in the middle of a sentence; and it was found that his life had flickered out.

On August 17th, 1962, Dr. PHILIP B. ARMSTRONG, the Director of the Marine Biological Laboratory, in conjunction with Professor STEPHEN KUFFLER of the Harvard University Medical School and other friends of OTTO LOEWI, arranged for the reinterment of his ashes at Woods Hole, where he had been so happy in so many summers, and for a commemorative celebration in connexion therewith. To my deep regret I was prevented, by a minor accident, from accepting a generous invitation to be present on this occasion and to take part in the proceedings. My friend and former colleague Sir G. LINDOR BROWN, however, now a Secretary of the Royal Society, was fortunately able to be present, and to represent OTTO LOEWI's many British friends and admirers.

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[1] KRAYER, DAVIS and KUFFLER: The Pharmacologist, pp. 47—49. Spring 1962.

It was mostly in his later years, when he had become a citizen of the U.S.A., that OTTO LOEWI received honorary degrees from many universities, and was honoured by many Scientific Societies. He thus became Honorary Sc. D. of New York and Yale, Honorary Ph. D. and M. D. of Graz, Honorary M. D. of Frankfurt. He was made a Foreign Member of the Royal Societies of London and of Edinburgh, of the Accademia dei Lincei of Rome, of the Bavarian and Austrian Academies of Science; an Honorary Member of the Academies of Medicine of New York and of Belgium, of the American Society of Pharmacology, and of the British and German Societies of Physiology and of Pharmacology.

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