OBITUARY

Wilhelm Feldberg, CBE, FRS (1900–1993)

We had looked forward to celebrating Wilhelm Feldberg's 93rd birthday on 19th November this year. He died on 23rd October, assured of a permanent place in the history of medical science by his outstanding work on neurochemical transmission and the actions of drugs on the central nervous system.

Feldberg was born in Hamburg. He studied medicine in Heidelberg and Munich. During his holidays he worked with E. Schilf at the Institute of Physiology in the University of Berlin and qualified M.D. Berlin in 1925. In the same year, he married Katherine, daughter of the art critic, Karl Scheffler and the next two years, which he fondly described as a prolonged honeymoon, were spent in England. He was inspired by Langley's book, *The Autonomic Nervous System*, which Schilf had translated into German and Schilf arranged for him to work with Langley in Cambridge. Langley died 6 months later and was succeeded by Joseph Barcroft. During the last 6 months of his stay in England, Feldberg worked with Dale in the National Institute for Medical Research which had been established in Hampstead. He acknowledged the formative influence of this early period on his approach to research and was particularly influenced by Dale who stressed the importance of first perfecting a method over months or years, if necessary, before carrying out the definitive experiment. 'Die methode ist alles' was in fact one of Feldberg's favourite aphorisms and underlies the whole of his work.

Feldberg returned to the Institute of Physiology in Berlin but in 1933, in a general purge of Jews in German universities, he was summarily dismissed. He had met Dale again at a meeting in Wiesbaden during the previous year and this prompted an invitation to work with him in his laboratory at Hampstead. There he met Gaddum, to be joined later by Marthe Vogt and G.L. Brown. He left Hampstead in 1936 to take up a 2 year scholarship with Kellaway in Australia and then returned to Cambridge where he was appointed Reader in Physiology. His distinguished career with the Medical Research Council began in 1949 with his appointment as Head of the Division of Physiology and Pharmacology in the National Institute for Medical Research. The Institute was then in the process of moving to its present site in Mill Hill but the Division was affectionately referred to as 'F4' in memory of the room which Dale had occupied in the old Institute at Hampstead. Feldberg retired as Head of Division in 1966 and a Laboratory of Neuropharmacology was set up for him. This was closed in 1974 but he continued to be supported by grants from the Council. Sadly in 1990, he encountered fierce opposition from Animal Rights activists and this led to unfavourable publicity and his finally retiring from the Institute. He had completed 65 years of continuous research with an output of 355 publications, revealing a capacity for work and self-discipline which few could hope to emulate.

It is instructive to trace the historical background to Feldberg's work on the identification of acetylcholine as a neurotransmitter. In 1904 Elliot, a student at Cambridge, was impressed by the similarity of responses to injections of adrenaline and stimulation of sympathetic nerves which he suggested might act by releasing an adrenaline-like substance. By similar reasoning, Dixon in 1907 proposed that parasympathetic nerves released a muscarine-like substance. In 1914 Dale published his classical paper on 'certain ethers and esters of choline', described acetylcholine as parasympathomimetic and predicted the existence of a choline esterase in blood. From 1921 to 26 Loewi carried out his

Professor Wilhelm Feldberg

famous experiments on the release of vagusstoff and acceleransstoff from the vagosympathetic nerve terminals in the perfused frog heart.

In Berlin, Feldberg had decided to investigate the release of acetylcholine by nerve stimulation but the problem was to obtain a sufficiently sensitive method of bioassay. He adopted Fühner's preparation of the eserinated dorsal muscle of the Hungarian leech. The principle was to stimulate the nerve supply to an organ in the eserinated animal and to allow the venous outflow, after cooling, to pass over the leech muscle in an organ bath. Working with Krayner and Minz, Feldberg demonstrated release of acetylcholine from the tongue on stimulation of the chorda tympani in the lingual nerve, from the coronary sinus in the heart-lung preparation on stimulation of the vagus and from the adrenals after splanchnic stimulation. Feldberg introduced his leech muscle preparation to Dale's laboratory and in the following 3 years there followed a prodigious output of 24 papers or communications in the *Journal of Physiology*, in all of which he was a co-author, extending chemotransmission to the nicotinic action of acetylcholine at autonomic ganglia and the neuromuscular junction. Using the method devised by Kibjakow, Gaddum and Feldberg perfused the superior cervical ganglion and demonstrated the release, after stimulating the cervical sympathetic, of a substance which they identified as acetylcholine by the method of parallel

quantitative assay introduced by Gaddum and Chang. With Dale, the release of acetylcholine was demonstrated from skeletal muscle in a perfused leg preparation after stimulation of anterior spinal nerve roots. A crucial experiment was to produce contraction of skeletal muscle after close-arterial injection of acetylcholine. Brown introduced a new electrophysiological dimension into the work and added convincingly to the theory that acetylcholine was the transmitter at the neuromuscular junction by demonstrating the potentiating effect of eserine on motor nerve twitches. Dale and Feldberg demonstrated the cholinergic nature of the vagal innervation of the stomach and of postganglionic sympathetic fibres to sweat glands.

When Feldberg moved to Cambridge he and Fessard showed that the motor endplate in *Torpedo* had a cholinergic innervation and they produced an electric discharge on close-arterial injection of acetylcholine. Feldberg then turned his attention to the synthesis of acetylcholine. He defined the factors required for the action of choline acetylase, as it was then known, in cell-free extracts of acetone-dried brain and used the distribution of choline acetylase activity to define cholinergic nerve tracts. With Vogt he discovered an alternation of cholinergic and non-cholinergic neurones in certain systems, for example in afferent sensory and motor pathways. Feldberg showed that the synthesis of acetylcholine in the gut occurred largely outside the nerve plexus and that glucose was required not for its synthesis but as a source of metabolic energy for muscle contraction. He was embroiled in an argument with Ambache, rebutting his contention that contraction of the gut by small doses of acetylcholine was due to an action on the ganglia rather than a direct action on smooth muscle. The discovery of the ganglion blocking action of hexamethonium at this time by Paton and Zaimis was opportune.

Feldberg's work on the pharmacology of the CNS started at Mill Hill in 1950 and involved a succession of co-workers from F4 and abroad. To circumvent the blood brain barrier and to avoid peripheral effects, drugs were injected centrally. Feldberg conceived the brain as a hollow organ which could be approached from its inner surface by injections into the cerebral ventricles and from its outer surface by topical application of drugs. Intracerebroventricular (i.c.v.) injections are recorded as early as 1922 but Feldberg greatly refined the technique. A special cannula for i.c.v. injections was devised by Collison, his redoubtable Chief Technician whom he had inherited from Dale. The use of the Collison cannula was first described with Sherwood in 1953 and the characteristics of penetration and peripheral absorption of drugs injected i.c.v. were defined. A wide variety of effects was produced by drugs injected into a lateral ventricle. Among the most dramatic were sleep, anaesthesia, analgesia, loss of consciousness, convulsions, tremor, catatonia, scratching movements and fever. Experiments with dye distribution showed that a drug injected into a lateral ventricle passes into the third ventricle, through the cerebral aqueduct into the fourth ventricle and then through the lateral recesses of the fourth ventricle to reach the subarachnoid space surrounding the ventral and dorsal surfaces of the brain stem.

Feldberg devised techniques to localize the site of action of drugs and so discover the physiological function or pathological dysfunction of the underlying structures. Tubocurarine provides a good example. In contrast with its peripheral neuromuscular blocking action, tubocurarine injected into a lateral cerebral ventricle of the cat acted as a central stimulant, producing convulsions with an abnormal spike discharge in the electrocorticogram, accompanied by autonomic and motor effects. It was inactive when injected into the cisterna magna, from which access to the ventricles is excluded by the absence in the cat of the foramen of Magendie at the end of the IVth ventricle. It was still effective, however, when injected into a lateral ventricle after cannulation of the central aqueduct which prevents access to the IVth ventricle and subarachnoid space. By regional per-

fusion of the drug, the spike discharge was finally localized to the inferior horn of the lateral ventricle and the underlying hippocampus but the autonomic motor effects, which could be dissociated from this discharge, were shown to be elicited from structures in the IIIrd ventricle. This has an obvious bearing on the spread of an electrogenic focus in clinical epilepsy. Other central actions of tubocurarine were localized to different sites – scratching movements to the upper part of the dorsal cervical cord and release of vasopressin to the ventral surface of the brain stem.

Feldberg became interested in the mechanism of fever and this proved to be a contentious field. In the cat, on i.c.v. injection, 5-hydroxytryptamine (5-HT) caused a rise, and adrenaline a fall, of body temperature but species differences raised doubts about their significance in fever and the amines were supplanted in this role by prostaglandins. Prostaglandin E_2 (PGE_2) injected i.c.v. caused fever, it appeared in the CSF during fever induced by bacterial pyrogens and lipid A and disappeared when the fever was lowered by antipyretics which inhibit prostaglandin synthesis. A new area of study arose from an analysis of the hypotensive response to sodium pentobarbitone and glycine injected into a lateral ventricle. The site of action was traced to the ventral surface of the brain stem which Feldberg described as a 'scarcely explored area of pharmacological sensitivity'. The topical application of the drugs through perspex rings revealed a bilateral circumscribed zone from which the fall in blood pressure was elicited, revealing a possible physiological function of the underlying structures in the maintenance of normal blood pressure. A second area, the 'nicotine-sensitive zone' was discovered from which topical application of nicotine caused the release of vasopressin without oxytocin. This zone is now thought to be coincident with the A1 group of noradrenergic neurones on the ventral surface which selectively innervate vasopressin-secreting cells in the supraoptic and paraventricular nuclei. γ -Aminobutyric acid (GABA) applied to this zone blocked the physiological release of vasopressin in response to carotid occlusion and it was suggested that this zone acts as a relay station for afferent neural pathways to these nuclei which are relayed by the nucleus of the tractus solitarius from peripheral receptors in the cardiovascular system. Hypertonic saline injected i.c.v. in the cat also released vasopressin without oxytocin but the site of action was traced to the dorsal surface of the brain stem in the region of the obex, possibly revealing the presence of osmoreceptors in the area postrema. The obex and the NTS were found to be involved also in the action of morphine on the cardiovascular system. Topical application to the obex caused a fall in heart rate and blood pressure due to a selective inhibition of sympathetic tone to the heart and blood vessels, an action which could be important in the therapeutic use of morphine in left ventricular failure.

Feldberg's last experiments at Mill Hill were on hyperglycaemia. This had first been observed in response to morphine and adrenaline injected i.c.v. in the conscious animal. The effect of adrenaline was due to peripheral absorption from the fossa interpeduncularis. Morphine acted by central sympathetic stimulation of the adrenal medulla and the site of action was traced once again to the ventral surface of the brain stem in a region caudal to the trapezoid bodies. With a touch of serendipity, experiments with antagonists revealed an unexpected hyperglycaemic response to i.c.v. injection of naloxone, phentolamine and propranolol. The hyperglycaemic response to all these drugs was abolished by i.v. chloralose but, curiously, when injected i.c.v. in one hundredth of the i.v. dose, chloralose itself produced hyperglycaemia as well as anaesthesia. GABA i.c.v. acted similarly. It was suggested that GABA and β -endorphin could act at synapses on the ventral surface in the central regulation of normal blood sugar levels and this has relevance to the aetiology of non-insulin dependent diabetes. One outcome of this work was the controversial suggestion that the chief physiological function of adrenaline in low concentrations is

to regulate the blood sugar level rather than the cardiovascular system.

An absorbing and continuing interest in histamine started from Feldberg's earliest days in Berlin with E. Schilf. With Kellaway, he worked on the release of histamine from the perfused lung by snake and bee venoms and bacterial toxins. It was shown that the perfusate contained not only histamine but another substance termed SRS or Slow Reacting Substance. This led subsequently to the discovery of SRS-A, the Slow Reacting Substance of Anaphylaxis and offered already at that time an explanation of the ineffectiveness of antihistamines for the treatment of bronchial asthma. The release of histamine by morphine, 5-HT, 48/80 and horse serum was investigated as well as its distribution within the skin and gut.

Feldberg was respected as much for his humanity as for his scientific achievement. He was a warm and generous man who worked tirelessly to promote both the personal and scientific interests of his staff in F4. He was a great wit and raconteur who collected a repertoire of inimitable jokes and stories for his after-dinner speeches. His good humour was unfailing to the end. His reputation attracted a large number of visiting workers from all parts of the world. Those who had worked with him were invited to contribute to a commemorative album presented to him on his 90th birthday. There were 71 contributors. He loved entertaining at 'Lavenham', his home in Mill Hill, educating his friends and colleagues in fine wines, surrounded by his collection of books, paintings and antiques. His particular joy was a complete set of Toulouse-Lautrec's 'Elles' series of lithographs which he had borrowed money to acquire as a young man.

Feldberg's reputation was international. He was awarded the CBE in 1963, elected FRS in 1947 and FRCP in 1948. He received honorary doctorates from many universities at home and abroad – MD from Freiburg, Berlin, Cologne, Liège, Würzburg and Heidelberg; DSc from Bradford and London and LLD from Glasgow and Aberdeen. He was awarded the Royal Medal of the Royal Society in 1983. His work was recognized in Germany by the award of the Grand Cross, Order of Merit of the German Federal Republic in 1961 and the Schmiedberg Plakette in 1969. With typical generosity, he used his restitution money and the pension he received as an Emeritus Professor in Germany to establish the Feldberg Foundation for exchange lectureships in medical research between England and Germany. It is most fitting that, 4 years before his death, the British Pharmacological Society paid our tribute to him by the award of the Wellcome Gold Medal.

Feldberg's first wife, Katherine, a literary scholar, translator and anthologist, died in 1976. In 1977 he married Kim O'Rourke, the secretary of the division who contributed so much to its efficiency and to the publication of his work. Tragically she died only 4 years later. Those who knew Feldberg were infected by his never failing excitement for his science; this shines out from the XVIth Sherrington Lecture in which he chronicled his extraordinary breadth of interests. He dedicated this lecture to Katherine and Kim. His son died in 1960. His daughter is a paediatric cardiologist in Seattle.

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