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THIRD W.D.M. PATON MEMORIAL LECTURE

Burn Oxford for a start[1]

A.S. Milton

Department of Pharmacology, University of Cambridge, Tennis Court Road, Cambridge, CB2 1QJ

Introduction

It is a great honour to be invited to give this, the third William Paton Memorial Lecture. I trust that the title of my lecture will become clear in due course.

Bill Paton was passionately devoted to the subject of pharmacology and felt very strongly that the history of the subject and its development should not be forgotten. This is particularly important today when we see the subject under threat, with Departments of pharmacology being merged with other subjects for 'mega' departments with such anonymous titles as Biomedical Sciences. Indeed there is one university where the word pharmacology has been proscribed. Professor Paton generously donated his Gold Medal prize to the Society to further the history of pharmacology, a direct result has been the establishment of these historical lectures in memory of him.

I find it particularly interesting to learn how people become pharmacologists, and, in this lecture I wish to reminisce about the careers of three pharmacologists who played a great part in the development of pharmacology in this country, and personally in my own career.

In the first Paton Memorial lecture, Tilli Tansey showed a photograph of Sir Henry Dale with those who worked with him in F4 (Tansey, 1995). J.H. Burn and W.S. Feldberg both appear in that photograph as does Laurence Malcolm.

But to begin at the beginning. My own career as pharmacologist came about quite by accident; on leaving school I had six months to fill in before going up to Oxford, and so I started looking for a job. About a mile from my home there was a gateway leading to a long drive, and on the gateway was a small sign which read 'Langley Court, Wellcome Research Laboratories'. I had no idea what went on there, however, one day I cycled up there to see whether I could get a job, and on the next day I found myself a very junior technician come 'bottle washer'. This in the Microbiology Section.

It was during that summer that I met my first pharmacologist, J.W. Trevan, though I didn't know he was a pharmacologist, or even what pharmacology was. Trevan was, at that time, Director of the Wellcome Research Laboratories in Beckenham. I shall say a little more about him later on in my lecture. The following summer, in the long vacation, I was again looking for a job, so on by bicycle again, and back to the Wellcome Research Laboratories. This time I found myself as a technician in the Pharmacology section headed by A.C. White, working with Alan Green who was aiming to repeat for 5-hydroxytryptamine (5-HT, serotonin) what Wellcome had done for histamine in the discovery of mepyramine, that is to find an antagonist to it. I spent the summer testing every chemical compound I could get my hands on from the Wellcome Chemical Research Laboratories, including designing a few drugs myself, as 5-HT antagonists, using the oestrus rat uterus preparation. All to no avail, but it was my introduction to pharmacology, and it was because of this that during my third year at Oxford I took the course in Chemical Pharmacology given by Raymond Ing and Hugh Blaschko. It was also why my tutor suggested that I go and see J.H. Burn who was Professor of Pharmacology at Oxford, to see whether he would take me on as a postgraduate student, which he did, and so you could say that my career as a pharmacologist started with Burn at Oxford. This was in 1957.

But to go back over twenty five years to 1931. If we remind ourselves of the very first meeting of this Society you will note that three of the pharmacologists I have already mentioned were there.

Programme of First Meeting of the
British Pharmacological Society Oxford, 4th July 1931.

(1) J.H. Burn: 'Is cocaine a sympathetic stimulant?'.
(2) J.A. Gunn: 'The pharmacological action of harmine and some of its derivatives'.
(3) A.D. Macdonald: 'The estimation of the toxicity of local anaesthetics'.
(4) E. Mellanby: 'Convulsive ergotism'.
(5) A.C. White: 'The fatty infiltration of the liver in rabbits produced by injection of large doses of pituitary extract'.
(6) J. Trevan: 'Demonstration of a light frog lever suitable for class and research work'.

You will also note that Burn gave the very first communication to the Society, so you could say that the meetings of this Society were started by Burn at Oxford.

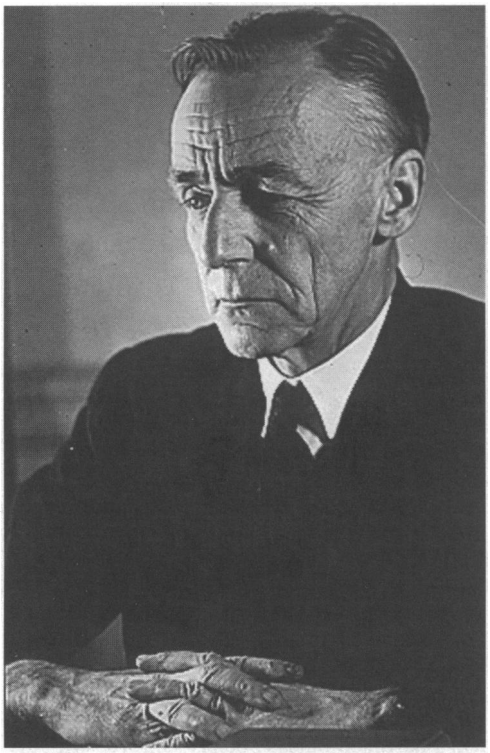
Trevan

However, before I come to J.H. Burn, a few words about Trevan (see Gaddum, 1957). J.W. Trevan was born in 1887 in Bodmin in Cornwall. He was a medical student at Bart's, where as well as qualifying in medicine he also obtained a B.Sc. degree with honours in physiology. He was never really interested in clinical medicine, and, as well as being a casualty physician for six years, he was also a demonstrator in physiology. However, he was most impressed with F.A. Bainbridge, later a F.R.S. who was lecturer in pharmacology. Trevan was also particularly interested in making gadgets. For example, he used the screw of a lathe to drive the piston of a syringe in order to give a constant infusion of digitalis to a cat: a refined version of this was to become the micrometer syringe. His contribution to that first meeting of the Society was the very first demonstration, where he described a frog lever which he had invented.

In 1920 he was appointed a pharmacologist at the Wellcome Physiological Research Laboratories at Langley Court where he was to spend the rest of his research career, in 1941 becoming Director, and in 1952 Research Director of the Wellcome Foundation. When he became Director, A.C. White was appointed Head of the Pharmacological Department.

Trevan's greatest contribution to pharmacology, was the introduction of the use of *Statistical Methods in Pharmacology*. I quote from his own writings 'In the early days Burroughs Wellcome insulin was tested not only at Beckenham but also in

[1] The Paton Memorial Lecture, given by the author at the meeting of the British Pharmacological Society at Brighton, December 1995



Dr J.W. Trevan (courtesy of Glaxowellcome)

the National Institute for Medical Research. Some batches of insulin which I had passed for potency were rejected by the Institute. This touched my pride (besides getting me into trouble with B.W. & Co.). In actual fact neither the Institute nor Beckenham was right; neither of us had really done an adequate assay. So I got out an old *Encyclopaedia Britannica* and spent several weekends 'mugging up' statistics from Edworth's article on the subject. This eventually resulted in a publication which brought some sort of order into the existing chaos of biological assay to the rank of a science'.

At that time people were only vaguely aware that animals of the same species did not always give exactly the same response to drugs. It was, however, tacitly assumed that the differences between animals of the same species were small and could be ignored. The toxicity of drugs was therefore determined by giving a series of different doses each to one animal and recording the 'minimal lethal dose'. It was generally believed that this dose would kill all 'normal animals' and that smaller doses would kill none.Discrepancies were explained by assuming some animals were not 'normal'. Trevan eventually proposed that toxicity should be defined in terms of the dose causing a percentage mortality. He used the term LD_{50}, to denote the dose killing fifty percent of the animals, and it has been used ever since. Trevan also introduced the idea of log dose curves. In one remarkable experiment to assay insulin, 27,000 mice were used (Trevan, 1927). These assays provided the data for the calculations which showed that the use of a Standard Curve gave accurate assays and that the errors observed in practice agreed well with those calculated theoretically.

Burn

Joshua Harold Burn was born in 1892 and came from Barnard Castle in County Durham (see Bülbring & Walker, 1984). He was very proud of his birthplace, particularly its history and the Castle itself, built by Bernard of Balliol in the 12th century. How gratifying it was to him that the Chair of Pharmacology at Oxford should be attached to Balliol College. The college had been founded by the wife of John of Balliol. (The Chair has now, I believe, been transferred to a women's college.) In his retirement Burn was to write a small book on the Balliol family.

Professor Joshua Harold Burn

He went up to Cambridge in 1909 to read chemistry. When he arrived there he discovered that for his first two years he had to study physics and two other subjects. His tutor, who was F.G. Hopkins, suggested botany and physiology.

'I discovered that, compared with those who taught physiology and physics, the chemists were an unattractive lot, particularly those who demonstrated in the practical classes. These seemed very undistinguished, had cheerless faces and wore rather shabby clothes. The physiologists and physicists had far more personality. In physics I heard lectures given by J.J. Thompson, who seemed to be not of this world. In physiology the Professor was Langley, always well dressed, who rode to hounds and spoke to no one as far as I could see'. (see Burn, 1969).

He spent most of his first two years in debating and in the discussion of politics, the results of his exams at the end of his second year were a disaster. Hopkins wanted him to continue reading chemistry, Burn resisted and chose physiology. He obtained first class honours and was awarded a Scholarship to work with Barcroft and, for a short time, with his former tutor Hopkins.

On January 1st, 1914 he went to work with Sir Henry Dale at the Wellcome Physiological Research Laboratories, which was his first introduction to pharmacology and where he was introduced to such techniques as isolated organ baths and spinal cats. Dale left the laboratories at the end of June to take up his new appointment with Barger, at the newly established Department of Biochemistry and Pharmacology for the Medical Research Committee. War started in August and Burn went off to active service in the October; however, not before Dale had suggested he should take a medical degree; he registered as a student who had done part of the course (i.e. his studies at Cambridge). In 1917 he was able to leave the army to complete his medical studies first at Guy's Hospital before taking his finals in Cambridge in the summer of 1920.

In 1920 Burn rejoined Dale, at what was now called the National Institute for Medical Research, where his responsibility was to study methods of biological standardization.

It was this interest in biological standardization which led Dale to suggest that Burn set up a laboratory for the Pharmaceutical Society to standardize the increasing number of biological preparations such as insulin, pituitary extracts, digitalis etc. (I also suspect that Dale realized that Hampstead was not big enough for both of them!). In 1926 Burn became director of the Pharmacological Laboratories of the Pharmaceutical Society of Great Britain. Burn at this time collaborated with Trevan, who as I have already mentioned had opened out the field of bioassay and biological variation. Eventually these laboratories would become part of the College of Pharmacy, with Burn becoming the first Professor of

Pharmacology, and subsequently in 1933 Dean of the College of Pharmacy. The college was renamed the School of Pharmacy of London University in 1937.

As well as being involved in standardization, Burn really started on his pharmacological investigations at this time. Perhaps the most interesting research from this period was his work, particularly with Edith Bülbring, on a comparison of the effects of tyramine and adrenaline, and on the uptake of adrenaline into sympathetic nerve endings; this eventually led to our understanding of the mechanism of action of indirectly acting amines (Burn, 1932). Burn was also puzzled by the vasodilatation which occurred when sympathetic postganglionic nerves were stimulated. Was there a possibility of cholinergic sympathetic fibres? In a collaboration with Edith Bülbring, in a series of experiments which were to continue for some twenty years, they investigated this and many related problems. Their first major finding was in 1935 when they showed that the vasodilator response to sympathetic stimulation in the dog's hind limb was augmented by physostigmine (eserine) and abolished by atropine (Bülbring & Burn, 1935).

In 1937 Burn succeeded Gunn at Oxford and remained there until his retirement in 1959, with the exception of the war, when he acted as liaison officer between the Medical Research Council and the corresponding scientific officers in Canada and the U.S.A.

When, in 1944, Burn returned to Oxford he made two important decisions, one was to develop Biochemical Pharmacology and the other to create a post in organic chemistry in the Department. He wrote to Sir Edward Mellanby '....since my stay in America I realize more than ever how closely pharmacology and enzyme chemistry are linked. I have therefore secured Blaschko....and now that I have got him I must pay him....' (see Burn, 1969). At about the same time he persuaded Raymond Ing who had previously been Reader in Pharmacological Chemistry at University College, and was then a member of the chemical research group in organic chemistry in Oxford to join the Department.

Burn continued to work on the autonomic nervous system for the rest of his life. When I joined him he was interested in rhythmicity, particularly in ciliated epithelium and in the heart. He had an idea that acetylcholine acted as a local hormone on these tissues causing the beating. It was on this that I was to work for my D.Phil. However, his main interest at this time, something which would in a way bother him for the rest of his life was 'the cholinergic link' in which he maintained that in sympathetic nerve endings acetylcholine and noradrenaline were present together and that noradrenaline release was always subsequent to acetylcholine release. In other words acetylcholine was really the only true transmitter throughout the peripheral nervous system. The work at that time was carried out with Mike Rand. Burn used to get very upset that this idea was not universally accepted, particularly by Sir Henry Dale. I remember long after Burn had retired, that each year enclosed with his Xmas card were details of published papers from the previous year which he thought supported his view.

One of Burn's great strengths was his ability to attract scientists from all over the world to come and work in the department. This harks back to Sir Henry Dale and F4, and was something started by Burn when he was at the College of Pharmacy, where between 1926 and 1937, Burn had 44 coworkers of whom no fewer than 30 came from overseas. In Oxford the number was 162.

Looking at the photographs I have of the members of the department taken in the summers of 1960 and 1961 I see, as well as the permanent members of the department, namely J.H. Burn, Hugh Blaschko, Raymond Ing, John Walker and Miles Vaughan-Williams, many who have made their contributions to pharmacology and will be known to you. Among those are M.J. Rand (Australia), T. Cruschiel (Poland), O. Hornikiewitz (Austria), V.M. Varagic and S. Hukovic (Yugoslavia), T. Axelsohn (Iceland), N. Kurki (Finland), T. Godfraind (Belgium), and many others.

People used to go and work with Burn for a variety of reasons, the usual ones: the reputation of the department, of Burn himself, perhaps wanting to live in Oxford. One of the most amusing concerns a young chemistry student from Birmingham. At that time experimentation was sadly lacking in the chemistry course at Birmingham. The student concerned was an experimentalist by nature, he had as a child, in his first experiments with his chemistry set, completely demolished his mother's kitchen. When asked by Professor Stacey who was Professor of Chemistry in Birmingham at that time what he wanted to do on leaving University he replied 'Anything but chemistry'. This was in 1957, and it so happened that Burn had recently written to Stacey, saying that he was looking for a young chemist who would train in pharmacology. Professor Stacey told the student about the offer from Burn, the student accepting the offer on the spot, and then in his own words 'rushed off to the university library to find what pharmacology was'. The student in question was John Vane, and that is how John became a pharmacologist!

On one occasion an American was coming to the department, so Burn decided to go down to Southampton to meet him off the transatlantic liner at the Ocean Terminal. Burn had never met the person concerned. But here again Burn was ahead of his time. Nowadays we are all used to being met at airports by people with little signs. Burn did just that, except that instead as is customary nowadays to show the name of the person being met, Burn gave his own name, and, so was seen walking up and down the quay side with a notice which read 'Burn Oxford'. I must thank my daughter, Mrs Imogen Adamson, for drawing the cartoon.

What are my own memories of Burn. My first was learning that he thoroughly disliked men with beards. Before joining the department I had spent the summer as a guide at a walking centre in the Lake District, where wishing to appear older than my years I had grown a beard. A few days after joining the department, a letter appeared on the table in the hall addressed to me 'Dear Milton, If I had known you were going to grow a beard I would not have offered you your present position. I

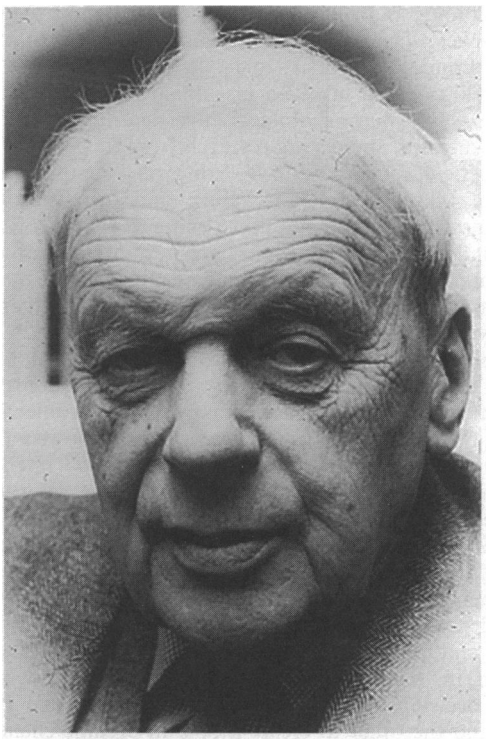
suggest it goes. Yours sincerely, J.H. Burn'. As he was paying my salary out of departmental funds, indeed he signed my monthly pay cheque, what could I do?

He was also very anti-smoking. He didn't like the telephone, and the only one in the department was in a large wood and glass box, which looked rather like a greenhouse in the middle of the entrance hall to the department, and could be seen by everyone. He would have to come out of his office when called to the phone. When doing an experiment he would not come to the phone.

His method of writing a paper was quite extraordinary. When he thought you had done enough experiments he would ask you into his office with your research notebook, and would sit down with his old fashioned dipped pen and write the manuscript in longhand. When it was finished he would give it to the secretary to type, would get Long, the photographer, to do any diagrams and off it would go to the journal. No revision or second draft or anything. This was a great advantage if you were a graduate student, for when you came to write your thesis, the chances were that most of it had already been written for publication if not already published.

He was interested to see that his protégés did well. He insisted for example that my first paper was published in the proceedings of the Royal Society (Milton, 1959).

He retired from Oxford in 1959, but for the next nine years he would spend several months in the Department of Pharmacology of Washington University in St Louis, in which city he had a married daughter. He continued to attend meetings and give lectures for many years.



Professor Hugh Blaschko (courtesy of the Oxford Mail)

Blaschko

I have already mentioned Hugh Blaschko who appears in the photographs of the Oxford Department when I was there.

Hugh Blaschko's childhood and early life makes fascinating reading, his father was a doctor and many of his friends were well known doctors and scientists, among the latter were the physicist Max Born, father of Gustav Born, who later worked with Blaschko in Oxford. As a result of the family's friendship with Max Born, Hugh met such famous physicists as Albert Einstein and Enrico Fermi. Anyway that is another story. How did he become a pharmacologist?

Studying medicine in Berlin, Hugh recounts 'I am afraid I was not a model student, I used to go to lectures that interested me, but would skip those that I found unprofitable....' (see Blaschko, 1980). For instance, instead of attending medical lectures he went to a course of popular lectures given by Albert Einstein. Anyway, eventually he qualified in medicine in 1922. He had decided by this time that he was most interested in research, particularly as he says 'In the borderline between physiology and biochemistry'. Three years later on 1st January, 1925 he started work at Dahlem in Berlin in Otto Meyerhof's laboratory. Meyerhof had received the Nobel Prize two years earlier, jointly with A.V. Hill. It was through Meyerhof that Blaschko came to work for a year with A.V. Hill from 1929 to 1930. A year which was to have great importance in the future.

During his younger days Hugh Blaschko suffered several bouts of pulmonary tuberculosis. It so happened that in 1933 when the Nazi regime came to power, he was in hospital in Freiburg im Breisgau, where strangely, Hans Krebs was one of his attending physicians. It was whilst convalescing that he joined Krebs, who also had his research department in Freiburg (they had first met in Freiburg in 1919, when Hugh had spent a summer there). Whilst in hospital he received an invitation from A.V. Hill to come back to London, which he did in May 1933. A year later Krebs and Hill decided he should leave London and an invitation came from Joseph Barcroft, who was Professor of Physiology in Cambridge, which he accepted.

His first research in Barcroft's Department was with catalase and catalase inhibitors. However one day Barcroft asked him 'How is adrenaline destroyed?'. Barcroft had seen some differences in the time course of the pressor response to adrenaline in mother and foetus. As Hugh says, 'I knew nothing about adrenaline, but I promised to look it up in the library. However, when I went to the Biochemistry Library, I soon discovered to my surprise that the fate of adrenaline was not known'. All that was said about it was that it was auto-oxidized. This auto-oxidation of adrenaline was inhibited by cyanide; however, when Blaschko incubated adrenaline with tissue homogenates, the inactivation was not inhibited by cyanide and this oxidation used half a molecule of oxygen for each molecule of adrenaline. It had the characteristics of an enzymic reaction and that is how the action of monoamine oxidase on adrenaline was discovered. Blaschko had been joined by Hans Schlossman and Derek Richter and they soon established that noradrenaline and dopamine were oxidized similarly to adrenaline (Blaschko *et al.*, 1937). Hugh Blaschko's lifetime work on amine-oxidase had started.

As I recounted earlier, Burn, on a visit to America had seen the upsurge in Biochemistry there and realized the contributions it could make to pharmacology, so in the autumn of 1943 Burn invited Blaschko to join him in Oxford, and there Hugh Blaschko consolidated his position as one of the fathers of Biochemical Pharmacology in the U.K.

I first met Hugh Blaschko when I joined the Department in Oxford. I suppose what most struck me about him, and I am sure all those who met him, was his kindness. He was always willing to listen, to give advice, and because of his encyclopaedic memory would always be able to put one on the right track.

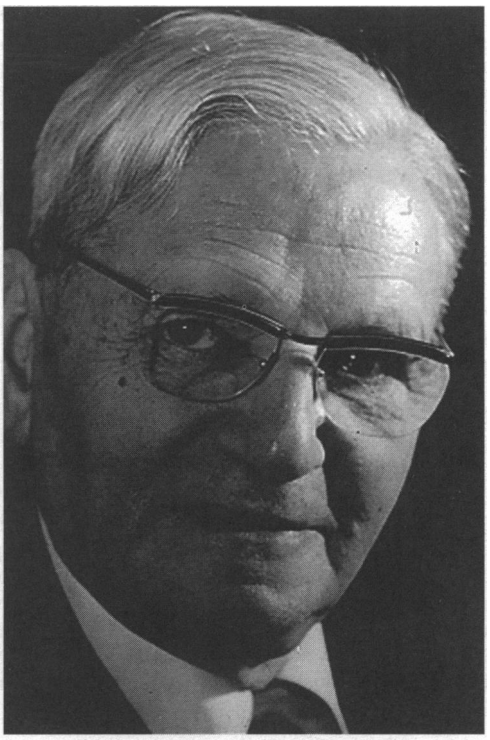
When he came to the U.K., Hugh had made a point to remember everything he read and learnt here in English. He appeared to have complete recall of everything he had said, read or done since 1933. However, he once told me that inspite of all this, he still couldn't do arithmetic in English, and had to revert to German to add and subtract, to divide and multiply.

He was always willing to listen to people's ideas. During the time I was in Oxford he was completing his survey of the presence of amine oxidase throughout the animal kingdom. I remember how excited he was on receiving a sample of tissue from a mermaid (a dugong is I believe its proper name).

Interestingly he had been unable to find amine oxidase in

molluscs. It so happened that I had recently been appointed to a junior lectureship at Dartmouth Medical School in the U.S.A. where I was to go immediately I had finished my D.Phil. Bob Gosselin with whom I would be working maintained that ciliary activity in invertebrates was controlled by 5-hydroxytrytamine. Thinking about this I said to Hugh, 'Have you ever tried 5-HT as a substrate in molluscs?'. He said that he hadn't, only his usual substrates for MAO, which, if I remember correctly, were phenylethylamine, and tyramine. He immediately got out the Warburg apparatus, homogenized some gill plates of the edible mussel *Mytilus edulis*, which I had asleep in the cold room, and we confirmed that the homogenate would not oxidize phenylethylamine, but low and behold it oxidized 5-HT, so in the space of a day we had discovered a new enzyme. This we subsequently called hydroxy-indole oxidase at it oxidized other OH-indoles as well as 5-HT (Blaschko & Milton, 1960). This enzyme is now long forgotten but it was exciting at the time.

A friendship which started in the department when I was just a graduate student lasted for the rest of his life. I shall never forget the occasion when during a meeting of another society in Oxford, Betsy who was with me, together with our son Nathaniel, who was only a few months old at the time, went to see Hugh in his office, he was absolutely charming with the young baby and spent most of the time we were with him playing with the baby.



Professor W.S. Feldberg

Feldberg

Wilhelm Siegmund Feldberg was born in Hamburg on the 19th November, 1900.

His very name is of interest. Until late in the nineteenth century Jews in Germany did not have family names. When the law was changed, Jews were required to register a name. At that time Feldberg's ancestors, who were itinerant peddlars, were in the Black Forest in Southern Germany, not far from the highest point, a mountain known as Feldberg. And so they took the name of that mountain as their name.

In talking of his scientific career, he recounts how his first experiment was a complete failure (see Feldberg, 1982).

'My first experiment, in which I tried to confirm a previously successful one, was a complete failure, though I thought I had rigidly adhered to the method described in the original publication. At the time I was five years old. I know, because my brother, who was a year older than I, had just begun school, and coming home one day, told us of his first scripture lesson in which he had learned how God had formed man from, as my brother said 'a lump of clay, and then breathing the breath of life into its nostrils'. Deeply impressed, I went into the garden, took some clay, formed a kind of doll, and then breathed and blew with all my might into its nostrils. I still remember my disappointment when nothing happened. And I could not understand why everyone laughed when my mother told them at tea, how I had come up from the garden, with clay all over my face, having tried to wipe away the tears and complaining bitterly between sobs that I had not succeeded, however hard I had blown, to bring my man to life. Later, my experiments became less ambitious. But in principle we are all doing the same kind of experiment I was doing then. Either we try to repeat His experiments, or we try to find out how He did them. But how many of the beautiful 'new' ideas that excite us when they hit us for the first time turn out to be right?'

Feldberg graduated in medicine in Berlin in 1925 and then came to England where he worked as a visiting scientist with J.N. Langley and Joseph Barcroft in Cambridge and with Henry Dale at the National Institute for Medical Research in Hampstead. Thus began his scientific career in medical research, a career which he pursued for the rest of his life. On returning to Germany in 1928, he worked with E. Schilf on the role of histamine in allergic reactions, research which led to our understanding of the pathology of asthma; together they published a book in 1930 on histamine, which they dedicated to Dale (Feldberg & Schilf, 1930). In an essay which he wrote in 1977 on the early history of acetylcholine transmission, Feldberg recounts how he came back to work with Dale in the 1930's, how one day in 1933 shortly after Hitler came to power, the director of the Institute in Berlin where he was working sent for him and informed him that he had been dismissed, that he must leave the Institute at the latest by midnight that day and that he was not allowed to enter it anymore (Feldberg, 1977). It is a measure of the man that he continued to carry out experiments by working during the night when no-one was around and knew that he was there. Some weeks later he met a representative of the Rockefeller Foundation whom he asked whether there was anything that the Foundation could do to get him out of Germany. Professor Feldberg recounted this episode saying that the representative although being sympathetic told him that there were so many scientists wishing to leave Germany that there was very little that he could do (remember Feldberg was only 32 years old at the time). The representative then asked Feldberg for help, as he was looking for a person called Feldberg, as he had a message for him from Sir Henry Dale in England, who had told the Foundation that they had to get Feldberg to England. Feldberg told him that he was that very person, and that is how it happened that on the 7th July, 1933 Felberg landed at Harwich with his wife Katherine and their two young children. Feldberg brought with him to Dale two techniques which were the keys which resulted in the first direct experimental evidence for the role of acetylcholine, both in ganglionic and neuromuscular transmission. As he says himself 'Perhaps it was that I had brought with me a key that would open the doors'.

These two keys were physostigmine (eserine) which prevented the breakdown of acetylcholine by cholinesterase, and the Hungarian leech muscle for the estimation of acetylcholine, the most sensitive method available at that time. In the three years in which Feldberg worked with Dale, his name appears on twenty four separate publications in the *Journal of Physiology*, this research in collaboration with Dale, J.H. Gaddum, Marthe Vogt and G.L. Brown provided the final proof for chemical transmission. With no permanent position available in the U.K., Professor Feldberg and his family departed on the 15th April, 1936 to Australia where he worked in

Melbourne for two years, continuing his research into the release of histamine, studying the effects of venoms and bacterial toxins, before returning to Cambridge in 1938 as University Reader in Physiology. He stayed in Cambridge until 1949 when he was appointed head of the Division of Physiology and Pharmacology at the National Institute for Medical Research which by that time had moved from Hampstead to Mill Hill. When he reached retirement age he stayed on at Mill Hill firstly as Head of Neuropharmacology and then as an honorary research worker, finally retiring in 1990.

It was in the early 1950's that Feldberg started on his research on the inner surface of the brain where he devised a series of cannulae which could be implanted into the cerebral ventricular system to allow the direct administration of drugs into the brain. An account of this research is published in a book which he wrote in 1960. A part of this initial research was on tremor, particularly that produced by the injection of tubocurarine into the ventricular system. In a paper written with Laurence Malcolm in 1959 (Feldberg & Malcolm, 1959), who was later to become Regius Professor of Physiology in Aberdeen and who was still in Aberdeen when I was appointed to the Chair of Pharmacology there in 1973, Feldberg observed that the tremor produced by tubocurarine could be abolished by adrenaline and he also mentions in this paper that he makes no distinction between tremor and shivering. At no time in these early experiments did he record body temperature, yet these techniques were the trigger for so much of what was to come.

In 1963, he was joined by R.D. Myers from Purdue University in Indiana. Myers, working with Villablanca, had carried out experiments in which they had injected bacterial pyrogens into cerebral ventricles and showed that the animals developed fever. Myers persuaded Feldberg that he should monitor body temperature during their intra-cerebroventricular experiments. As Feldberg said many times later, though perhaps jokingly, this was one of the greatest mistakes of his life. Within a very short time, Feldberg and Myers had shown that in the conscious cat, intracerebroventricular injection of 5-hydroxytryptamine produced a rise in deep body temperature, whereas adrenaline and noradrenaline produced a fall. In 1964, they published a paper in the *Journal of Physiology* entitled 'Effects on temperature of amines injected into the cerebral ventricles, a new concept of temperature regulation' (Feldberg & Myers, 1964). This paper opened a new chapter in the physiology and pharmacology of temperature regulation which has continued to this day.

This research on body temperature and the monoamines was continued by Feldberg for many years with a variety of distinguished visitors to his laboratory. It was in the late 1960's that I came to collaborate with Feldberg. I was at the School of Pharmacy in London at the time, and had become interested in temperature regulation, in particular the antipyretic actions of the aspirin-like drugs. I had previously been interested in the i.c.v. effects of nicotine. I had wondered whether the tremor produced by nicotine was in fact a shivering response. I was joined by Sabine Wendlandt, an East German who had recently graduated in Psychology from McGill University in Canada. We decided to investigate Feldberg's monoaminergic theory of fever and attempt to fit into this concept the mode of action of the antipyretic agents. Our observations led us to suggest that a prostaglandin was the central mediator for fever, that pyrogens cause the release of these substances and that antipyretic drugs somehow interfered with this release (Milton & Wendlandt, 1970).

The first time I met Professor Feldberg was at a meeting of the Physiological Society at Mill Hill in 1957, I was a young graduate student at Oxford and I remember being introduced to him and Sir Henry Dale by my supervisor J.H. Burn. It was many years later at the International Physiology Congress in Washington when I bumped into the Feldberg having a beer with Keith Cooper, he poked his finger at me and said 'Look here Milton, why is it we only meet at international meetings, when we only work a few miles apart?'

It was a result of this encounter that Professor Feldberg kindly invited Sabine Wendlandt and myself to spend one day a week in his laboratory, collaborating with him to investigate the role of prostaglandin. In 1971 Feldberg and Saxena had confirmed our experiments on prostaglandin E_1 (PGE_1) and showed that an infusion of PGE_1 into the ventricles could produce a sustained fever (Feldberg & Saxena, 1971). They also were able to find a biologically active substance in cerebrospinal fluid collected from the third cerebral ventricle. Saxena had returned to India by the time Sabine Wendlandt and I joined Professor Feldberg; however, we were joined by another scientist from India, K.P. Gupta. We developed a method for perfusing the cerebral ventricle system from the lateral ventricle to the cisterna magna and collected the perfusate. We were able to show that in control situations no prostaglandin could be detected in the perfusing fluid whereas during fever the levels were elevated. When we administered a variety of antipyrtic agents, not only did the fever reduce, but also the levels of prostaglandins (Feldberg *et al.*, 1973).

This research was communicated to this Society at the Bradford Meeting in 1972 (Feldberg *et al.*, 1972). The minutes of that Meeting, written by John Vane who was general secretary of the Society at that time, record:

'There were several newcomers nervously giving their first-ever communication to the Society. One of these was outstanding for his clarity and lucidity and I predict a very bright future for him. His name, in case you wish to note it, is Wilhelm Feldberg. Yes, believe it or not, Professor Feldberg, a member since 1934, a Trustee since 1965, an Honorary Member since 1967, and host to the Society at Mill Hill in 1956, 1959 and 1967 presented his first paper to us in Bradford in 1972! Rumour has it that he has given a multitude of papers to another more senile Society, but now that he has seen the light, we hope to hear from him many more times'. Sadly this was not to be, or so I believe, as I haven't been able to trace any subsequent communications.

The reasons for what happened at Bradford was that in all previous communications to the Society bearing Feldberg's name, the communications had been given by one of the co-authors; just as with Burn, Feldberg liked to give his young workers, particularly if they were from abroad, a chance to be seen and heard. At this meeting, I was giving the previous communication, and couldn't present two consecutive communications to the Society, Sabine Wendlandt was too shy, and Gupta felt (quite wrongly) that his English was not good enough. So Professor Feldberg had no option.

In mentioning his many co-workers, Feldberg once showed me the thesis he had submitted to London University for his Ph.D. The thesis consisted of a copy of all his publications up to that time, bound together. London University rejected the submission, and Feldberg received a letter from the university register, informing him that the thesis had been turned down, because he was not the sole author of any of the papers. Apparently Feldberg wrote back saying that he hoped he would never live to see the day when he had to publish a paper with his name being the only one on it. Amusingly it was London University who gave Feldberg the title of Professor, in recognition of his teaching, because of the many Ph.D. students he had supervised at Mill Hill, and for the many occasions he had acted as a Ph.D. examiner for London University.

In the early 1970's as well as working on temperature regulation he worked on the hypotensive effects of clonidine, applying it to the undersurfaces of the brain and spinal cord. I remember one paper which he wrote with Guertzenstein which came back from the Journal with a referee's comment, 'Had Professor Feldberg done any statistics on the blood-pressure changes?'. Professor Feldberg replied 'If I do ten experiments and the blood pressure goes up, and I repeat those ten experiments in the presence of a drug and the blood-pressure falls, I do not have to do any statistics to tell me that there are differences'. The paper subsequently appeared without any further comments. In his final years in the laboratory he returned to an earlier interest, that of morphine and blood sugar.

His final communication (with D.A. Pyke and W.A. Stubbs; Feldberg *et al.*, 1988), 'Hyper- and hypoglycaemia produced in anaesthetized cats by phentolamine' was presented in 1988, at the meeting of the Physiological Society in Cambridge. At that time, he was approaching his 88th birthday. This was the last time that I saw Professor Feldberg, and it obviously sticks in my memory, because I sat next to him at the official dinner, together with my son, Nathaniel, who was attending his first Physiological Society meeting.

All of those who worked with Professor Feldberg will have their own individual memories of him, and their own collection of stories. Two stories stick in my mind. The first was the occasion when he was invited by the British Pharmacological Society to be the guest of honour at an official dinner of the Society at a meeting in London. I was in his office when he received this invitation, he turned to me and said that he was taking his grand-daughters to see 'Cosè fan tutte' at Covent Garden the same evening and that Mozart was far more important than the British Pharmacological Society. The second occasion was when he came to Aberdeen to receive an honorary degree from the University. This was after the death of Katherine and he was accompanied by Kim O'Rourke, his faithful secretary for so many years and who was soon to become the second Mrs Feldberg. Indeed they first publicly told of their engagement while in Aberdeen. They were staying at the Station Hotel and I was commanded to have breakfast with them as Professor Feldberg maintained that the Station Hotel served the best kippers in Britain. Of memories, who can forget dining at 'Lavenham' with the collection of signed Toulouse-Lautrec lithographs encircling the drawing room walls, which Professor Feldberg and Katherine had purchased in Paris in happier times and then brought to England?

Professor Feldberg was the only person I have known who on the day that he failed his driving test, was given a full licence. It was soon after driving tests had been introduced in the U.K. and he had gone to take his test accompanied by Heinz Schild, Schild being the qualified driver who had to accompany a learner. At the end of the test the examiner failed Feldberg; if any of you here ever had the experience of travelling with Feldberg driving, I am sure you will not be surprised. Anyway, on the way back from the failed test, Schild suddenly asked Feldberg 'Didn't you drive when you were with Dale in the early 30's'. At that time there were no driving licences. Feldberg said that he had, and Schild told him that everyone who had driven before the introduction of licences was given a license automatically. So Feldberg went off to whatever office it was, told them that he had just failed his test, and asked whether in fact he had needed to take the test as he had driven before licences had been introduced. He was told that he didn't and was promptly given his licence.

I have given you, I hope, some insight into the lives of just a few of those who helped develop British Pharmacology. I would like to end my lecture by quoting once again from Professor Feldberg (1982), because here he sums up not just his own life, but I think also many others, including those I have talked about today.

'Looking back and being listened to. What pleasure it gives! Dwelling only on what one wants to remember but with full confidence in this unconscious choice which is the most personal one. That is its justification. And after having looked back I like to leave you with one final thought: How fortunate are those who can do research their whole life. For however long they live, they die young'.

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