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FIRST W.D.M. PATON MEMORIAL LECTURE

An F4-vescent episode: Sir Henry Dale's laboratory 1919–1942[1]

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Introduction

In 1992 Sir William Paton donated his Wellcome Gold Medal Prize money, matched by the British Pharmacological Society, to establish a fund to encourage and facilitate the historical study of pharmacology. His death a short while later led to the creation, by the Society, of the Paton memorial lecture, and it is immensely flattering to be invited to give this inaugural address. This paper will describe the laboratory, and early pharmacological work performed there, of Henry Dale, in the National Institute for Medical Research (NIMR) in Hampstead, North London. This lab, F4, described by Paton as 'one of the classic laboratories' was where Paton began his own research career in 1944 (Paton, 1986).

The NIMR

The NIMR was the first, and only laboratory of the Medical Research Council (MRC) for many years. The MRC itself was created as a consequence of the National Insurance Act of 1911. The original Bill, pushed forward by the then Chancellor of the Exchequer, David Lloyd George, was directed towards the medical and social care of working men, and included the provision that one penny per insured person should go towards sanatorium care for TB sufferers. In time that clause was modified to provide research funding for TB, which became translated into medical research in general (Thomson, 1973). In 1913 a Medical Research Committee was created to advise on and supervise the disbursement of the monies raised by the Act, and in 1920 it was this body that was reconstituted as the Medical Research Council (the abbreviation MRC will be used for both).

The MRC first met in July, 1913 and an early decision was to establish their own central institute for medical research, in which salaried medical and scientific staff would be employed to pursue full time medical research, unencumbered by the demands of teaching or medical practice. The MRC soon acquired Mt Vernon Hospital, a former private TB hospital in Hampstead, North London, for conversion into their institute. They began to consider the creation of departments and appointment of staff, and after considerable discussion, agreed that the institute should contain departments of bacteriology, statistics, applied physiology, and the focus of this paper, a department of biochemistry and pharmacology. The Cambridge biochemist and MRC member, Frederick Gowland Hopkins, proposed that Henry Dale should be invited to head this latter department.

Henry Dale

Henry Dale was then the Director of the Wellcome Physiological Research Laboratories, a unique research institute established in 1894 by the pharmaceutical manufacturer Henry Wellcome. Dale had worked there for ten years, his research work having principally been the physiological and pharmacological analysis of chemicals derived from the fungus, ergot of rye. From ergot Dale had already discovered acetylcholine, tyramine, and histamine, and his ergot work had suggested the possibility of chemically related substances exerting similar physiological effects. He coined the word 'sympathomimetic' for such chemicals that mimicked sympathetic nervous stimulation. Ergot also provided Dale with clues about the mechanisms of anaphylaxis, and directed him towards discovering the oxytocic principle of the posterior pituitary gland. A major component of his success was his collaboration with the chemists, George Barger and Arthur Ewins, both of whom joined Dale in accepting employment with the young MRC in 1914.

So it seemed likely that Dale, who had just become the first person associated with the pharmaceutical industry to be elected to Fellowship of the Royal Society, would continue, and expand, his work on the physiology and pharmacology of biologically active chemicals. But the first world war intervened. Mount Vernon Hospital was handed over to the War office for use as a military hospital, and the scientists already offered MRC employment were housed in a variety of temporary accommodations across London. Dale's department was established in two small rooms at the Lister Institute on the Chelsea Embankment, where studies of deficiency diets, gas gangrene, anaphylaxis, and wound shock were undertaken, and a particularly major responsibility was the supervision of the production and testing of replacements for the German produced anti-syphilitic, Salvarsan.

It was not until the beginning of 1919 that the MRC regained control of Mount Vernon Hospital as the site for their institute. The pre-war aim of the MRC had been for the Institute to have a Director and approaches had been to Sir Almroth Wright, the designated head of the department of Bacteriology. At the end of the war, much to the relief of many members of the MRC who had found it difficult to negotiate with the demanding bacteriologist, Wright asked to remain in his department at St Mary's Hospital. A replacement was not sought, and from 1919 until 1923 the Heads of all four research departments of the NIMR were directly accountable to the MRC and exercised equivalent authority. This clearly became impracticable as the Institute expanded and acquired its intended levels of staffing, and by 1923 it was apparent that, for the smooth running of the Institute, a recognised and authorative Management Committee be established. This was chaired by Dale until 1928, when the MRC finally reverted to their original intention, by appointing Dale as Director.

F4

The physical creation of the NIMR was met by vociferous protest from anti-vivisectionists who mounted a campaign against the MRC and the principle of state supported animal experimentation in general and the Institute in particular (Tansey, 1994). Undeterred however, the MRC started converting the hospital wards, one of which is shown in Figure 1, into research labs, the same room in the late 1920s is shown in

[1] Based on a lecture, delivered at the BPS meeting in London, January, 1994.

Figure 1 A ward of the Mount Vernon Hospital for Consumptives, Hampstead, c. 1900. From the Archives of the NIMR, reproduced courtesy of the Wellcome Photographic Library.

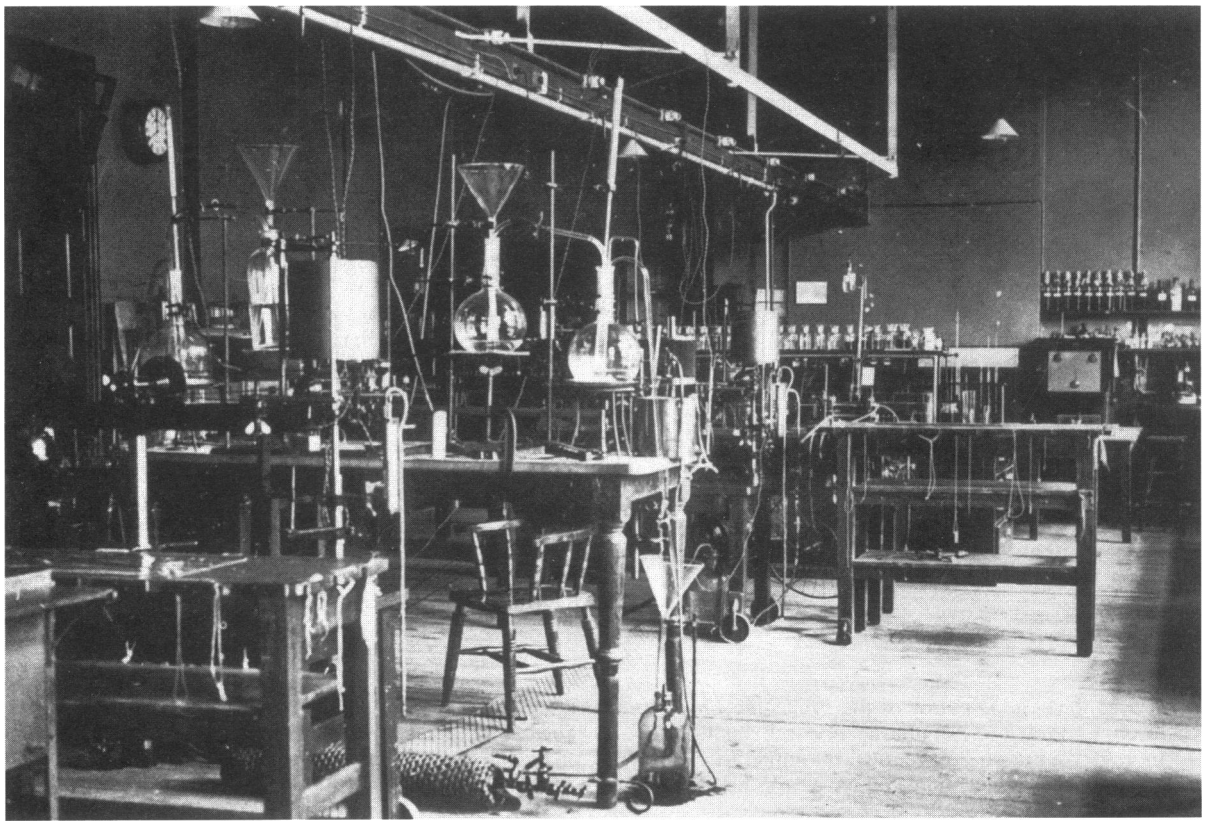

Figure 2 The same room as shown in Figure 1, after conversion into F4, the research laboratory of Henry Dale, c. 1925. From the Archives of the NIMR, reproduced courtesy of the Wellcome Photographic Library.

Figure 2. This is F4, the fourth room on the first floor, Henry Dale's large open plan research lab. A glance at the apparatus indicates the kind of experimental investigations in use: anaesthetic and surgical equipment for *in vitro* and *in vivo* preparations; and recording instruments such as the plethysomograph and kymograph. Directly below was the Georgian-style library, from which protests would come as gas cylinders were rolled from one end of the lab to the other; directly above was an organic chemistry lab, the frequent leakages and spillages of which stained F4's ceiling. These two labs with small ancillary rooms and an office constituted the department of Biochemistry and Pharmacology.

The permanent establishment of the NIMR allowed Dale to recruit staff and encourage visitors to his laboratory. In April 1920 he finally moved into F4, and just a few weeks later was visited by an American who noted that the lab 'was quite completely equipped and installed' (Miles, 1920). He was followed by a glittering array of research workers and collaborators, and some measure of Dale's success can be assessed from the numbers who became distinguished scientists: Fellows of the Royal Society or equivalent national academies; professors or research directors; knights of the realm; and at least four who later became Nobel Laureates. One of Dale's first appointments was J.H. Burn, who had been a pre-war colleague at the Wellcome Physiological Research Laboratories. Burn, later professor of Pharmacology at Oxford, spent the greater part of his period at the NIMR engaged upon developing biological standarization methods and assay techniques. During the five years he worked at NIMR, Burn and Dale collaborated closely, their efforts culminating in the adoption in 1925 of the first international biological standards by the League of Nations' Health Organisation (Bülbring & Walker, 1984). Several other recruits also came from the Wellcome labs. One was J.H. Gaddum who arrived in F4 in 1927, and almost immediately became associated with the then ongoing work on acetylcholine, especially in ascertaining its role at sympathetic ganglia (see e.g. Chang & Gaddum, 1933). He also discovered Substance P, working in collaboration with one of the many foreign visitors to F4, Svente von Euler. In 1936, Gaddum published an account of contemporary work on endogenous vasoactive chemicals, much of it done in F4. The book appeared only in German, the translation being done by W.S. Feldberg. On its 50th anniversary in 1986, a new English translation was finally produced. With its original introduction by Dale and modern annotations by F.C. MacIntosh, another F4 old-boy, the book provides a splendid account of the state of this branch of pharmacology before the Second World War and of its subsequent development (MacIntosh, 1986).

In addition to Burn, Gaddum, Ewins, Barger and Dale himself, other staff to move from the Wellcome Laboratories to the NIMR during those early years include J.B. Buxton, P.P. Laidlaw, Harold Dudley, Harold King, G.S. Walpole, and Percival Hartley. The exodus was such that at one point the Director of the Wellcome labs wrote to Dale, 'I am getting a bit scared about raids on the WPRL staff' (O'Brien, 1923). The importance of the Wellcome laboratories to the early MRC has never been properly analysed, but it is remarkable that so many talented scientists came from the same laboratories, an establishment unique in the history of British physiology and pharmacology (Tansey, 1989). Dale's recruiting technique became well-known and a particularly amusing incident is recalled by the endocrinologist (Sir) Alan Parkes, for whose services University College, represented by Lovatt Evans, and the NIMR led by Dale, competed in 1932. The 'game of academic poker' that Parkes describes was evenly balanced, as each institute increased their offer – a higher salary, better equipment, a bigger laboratory, more animals. Dale was then told by Lovatt Evans that Parkes' long experiments in reproductive physiology and endocrinology were facilitated by the provision of a bed-study. Dale matched that easily – the NIMR could provide Parkes with such a room. Evans retaliated: Parkes got tea in bed in the morning. 'Look Evans', Dale retored, 'he can have breakfast in bed in the Institute!'. Parkes duly moved to Hampstead for several 'happy and productive years' (Parkes, 1985 pp. 49–50).

Parkes was not alone in acknowledging Dale's inspiration and encouragement. One American visitor, Dickinson Richards recalled how, in 1927, Dale combined all his external duties and affairs with the conduct of experimental work.

> Dale was primarily an experimenter and continued this through almost all his active years ... the laboratory door would fling open, and Sir Henry (Dr Dale as he was then) would come charging in, often in morning coat and striped trousers, grab a lab coat off the hook, and be with us in seconds. What is more, he would stay until the experiment was finished, whether at tea time, dinner time, or later (Cournand, 1989).

Throughout his time with the MRC Dale was heavily burdened with external responsibilities. From 1925 to 1935 he was Biological Secretary of the Royal Society; in 1936 he was appointed a Founder Trustee of the Wellcome Trust, becoming Chairman in 1938; from 1940 to 1945 he was President of the Royal Society and secretary to the Scientific Advisory Committee to the War Cabinet; and he served on and chaired, numerous national and international professional committees (Feldberg, 1970).

Another regular overseas visitor was the American Professor of Pharmacology, A.N. Richards, who collaborated with Dale on studies of the complex physiology and pharmacology of histamine – a substance that Dale had first discovered, in an extract of ergot, and became interested in whilst working at the Wellcome labs. But, like noradrenaline and acetylcholine, there were then no reliable reports of its natural occurrence in the animal body. Dale and his chemist colleague, Harold Dudley, undertook a systematic search for histamine in the body's tissues. They finally found histamine in the mammalian spleen. But they also made an unexpected discovery – they found acetylcholine (Dale & Dudley, 1929). This was an immediate and powerful stimulus to investigations of the role of acetylcholine in the nervous system.

F4 and acetylcholine

More visitors began to arrive in F4, many of them supported by the Rockefeller Foundation, the Beit Trustees, the Royal Society and personal grants from the MRC. One such visitor was Heinz Schild, later Professor of Pharmacology at University College, London who recalled

> 'Arriving in Dale's laboratory in October 1932, I was struck by its marvellous organisation and, more important, its powerful flow of ideas. Its exterior atmosphere was that of a typical old-fashioned physiological laboratory, with the smoked drum as mainstay. The laboratory consisted of an oblong room with two or three operating tables. It formed part of the building of the National Institute for Medical Research, of which Dale was the overall Director. The technical organisation of the legendary F4 lab centred on Collison, the chief technician. Collison had to be informed the evening before of any experiment planned, which was then set out to perfection next morning, but it was not advisable to change one's mind. It would be difficult to disentangle how many of the basic ideas emanated from the master himself – who was kept rather occupied, though by no means exclusively, by his administrative duties, and how much by such outstanding co-workers as Feldberg and Gaddum ... I can remember Dale and Feldberg carrying out the experiment that proved that sweat secretion was cholinergic, although anatomically sweat glands are innervated by the sympathetic' (Schild, 1979).

The 1930s were indeed exciting times for pharmacology, although increasingly troubled politically. The first volume of the General Minutes of the British Pharmacological Society illustrates the former: 'In June 1931 a circular letter ... was sent out to about 30 people who were in charge of departments for teaching pharmacology or of institutions for pharmacological research, in Great Britain' (Bynum, 1981). That letter suggested the creation of the Society, which was formally established in the Summer of 1932. A few months later, Adolf Hitler became the German Chancellor, and Jewish scientists became immediately expendable. One such was Wilhelm Feldberg, instantly dismissed from his Institute in Berlin. By a set of fortuitous incidents and with the support of the Rockefeller Foundation, Feldberg arrived in Britain and went to work with Dale in F4. He brought with him the acetylcholine-esterase inhibitor, what has been called the 'key' to unravelling the acetylcholine story – he brought eserine, and the leech muscle bioassay for acetylcholine (Feldberg, 1979).

Feldberg's sensitive assay technique, combined with the physiological, pharmacological and chemical expertise already in the lab, facilitated the accumulation of a substantial body of evidence about the synthesis, release, activity and metabolism of acetylcholine at the neuromuscular junction, in autonomic ganglia and in postganglionic parasympathetic fibres. Between 1933 and 1936, the staff of F4 published 14 research papers in the *Journal of Physiology*, each one adding substantial evidence to the role of acetylcholine as a neurotransmitter (Tansey, 1991).

However, one of the most significant contributions at that time from F4 was not a report of new experimental results. It was a communication to the Physiological Society on the nomenclature of fibres in the autonomic nervous system, in which Dale introduced the terms 'cholinergic' and 'adrenergic' to designate nerve fibres by the nature of the chemical that they used, or might possibly use, as a transmitter, rather than by their anatomical classification. The prescient final sentence reads 'I think such a usage would assist clear thinking, without committing us to precise chemical identifications, which may be long in coming' (Dale, 1934).

In 1936, Dale shared the Nobel prize with the Austrian pharmacologist, Otto Loewi, for his work on chemical neurotransmission and in particular the elucidation of the role of acetylcholine. To a large extent this marked the end of Dale's direct practical involvement in research, although he did perform some experiments again during the Second World War. One unusual assignment that came his way was a request to analyse several unidentified pills found in the pockets of Hitler's deputy, Rudolph Hess, after his bizarre flight from Berlin to Scotland. The combined chemical and physiological examination was undertaken by James Walker, one of the staff chemists, and Dale. The tablets included amphetamines and several homeopathic remedies. The composition of one tablet was difficult to determine, until Dale tested the effect of a small drop of a dilute solution on the pupil of a cat, which immediately dilated: the active principle was atropine, commonly used in travel sickness pills (Walker, 1979). The official MRC report, presumably written by Dale, records,

> 'It seems quite clear from the remarkable collection of drugs that Captain H was intent on protecting himself against all assaults of the devil so far as his flesh was concerned, and if he knew the action of all the drugs he carried, he has obviously missed his vocation and ought to have made a very handy general practitioner' (Rees, 1947).

Dale was due to retire in 1940, and towards the end of his career became deeply involved in plans to expand the NIMR. The site selected was at Mill Hill in North London, which had been acquired in 1920 by the MRC, on Dale's personal recommendation and was popularly known as 'Dale's folly'. Here the NIMR already had field laboratories and animal accommodation. Dale was closely associated with the design of the Institute, being particularly keen to promote as much individual and departmental interaction as possible, and to provide no opportunity 'for people skulking in private laboratories' (Parkes, 1985, p. 62). The approach of war and the resultant disruption of plans eerily reminiscent of the situation when Dale began with the MRC in 1914, meant that he was asked to stay on to oversee what were anticipated to be difficult times.

An immediate difficulty was the stream of calls upon his time and laboratory space by refugee scientists. From the mid 1930s onwards, F4 provided space for, *inter alia* Wilhelm Feldberg, Marthe Vogt, Edith Bülbring, and Otto Loewi. Dale, as a member of the Academic Assistance Council (AAC, later the Society for the Protection of Science and Learning), a body established by British academics to assist overseas colleagues, was also instrumental in finding other laboratories for refugees and in obtaining funding. As the political situation worsened in Europe, these funding sources became vital, and Dale's correspondence reveals numerous letters on behalf of refugee scientists. It is noteworthy that the first ever scientific grant awarded by the embryonic Wellcome Trust (established 1936) was in 1938 to the AAC to enable Otto Loewi to leave Austria to work in F4.

In 1942 Dale finally retired and was presented with a commemorative album of photographs of those who had worked in F4, its very creation being no mean achievement in the middle of war. More than 160 scientists from around the world are recorded there, including the Nobel Laureates, Herbert Gasser, Dickinson Richards, Macfarlane Burnet and Albert Szent-Gyorgi.

F4: 1942–1949

After Dale's retirement, the electrophysiologist G.L. Brown became head of the lab, and he and the staff of F4 were heavily engaged in military medical research, especially problems associated with conditions for submariners and other military personnel. Once the war was over, much of the lab's work returned to the physiology and pharmacology of neurotransmission, especially at the neuromuscular junction. Others then working in F4 included J.A.B., now Sir John, Gray, who became Professor of Physiology at University College before returning to the MRC as its Secretary, and W.D.M. Paton who left F4 to establish the pharmacology department at the Royal College of Surgeons, before becoming Professor of Pharmacology at Oxford (see Figure 3).

Most participants in these events regard the end of the F4 era as the move of the NIMR from Hampstead to Mill Hill in 1949. This coincided with G.L. Brown's departure to become Professor of Physiology at University College, London, and the transfer of F4 to Wilhelm Feldberg's Headship. To commemorate that event a dinner was held at the London Zoo, to which all who had worked in F4 at some stage of their careers were invited. Many of course could not attend, but those who did lined up for the ritual photograph (see Figure 4). Some of the diners were still working in F4, and had been collaborating on a special celebratory project for the occasion, a spoof film of life in F4. This was shot in the lab on two consecutive Saturday mornings, then a normal part of the working week, and with the formal permission of the Director of the NIMR, Sir Charles Harington. The script, such as it was, had been written by W.D.M. Paton. The cameramen were J.L. Malcolm and B.D. Burns, both the proud owners of new 8 mm ciné cameras, put into large corrugated dustbins mounted on casters, borrowed from the Animal House, and pushed around so that they could 'zoom' into and out of shots.

(At this point during the original lecture, the film was projected. Shot in black and white, the silent film is constructed around a series of captions, some of which are reproduced in bold in the summary given below).

The film is called **LET'S GET AN EFFECT**, which was a favourite saying of Henry Dale's whilst doing an experiment, and subtitled **AN EF-FOUR-VESCENT EPISODE**, an ob-

Figure 3 An informal snap-shot of life in F4, c. 1947. From left to right, the feet of G.L. Brown, J.A.B. Gray, W.D.M. Paton. From a photograph given to the author by the late Sir William Paton. Reproduced courtesy of the Wellcome Photographic Library.

Figure 4 The F4 dinner, London Zoo, 1949. Front row: N.K. Dutta, J.H. Burn, ?, G.L. Brown, H.H. Dale, C. Lovatt Evans, E.J.H. Schuster, Eleanor Zaimis, W. Feldberg. Back row: W.D.M. Paton, hidden (probably M. Vianna Dias), W.A. Bain, ?, P. Hartley, H.O. Schild, J.L. Malcolm, W. d'A. Maycock, F.C. MacIntosh, B.D. Burns, H. King, Edith Bülbring, J.H. Gaddum, J.A.B. Gray, L.W. Collison, C.B.B. Downman, F. Dickens, W.L.M. Perry, H.B. Barlow. From a photograph given to the author by the late Sir William Paton. Identifications by W.D.M. Paton and F.C. MacIntosh, reproduced courtesy of the Wellcome Photographic Library.

vious pun. The principal 'actors' in the drama are then introduced. G.L. Brown, who had succeeded Dale as head of F4 is shown making a 'close arterial injection' into frog muscle. The arterial ligature allows blood, and its cholinesterase, to drain out of the muscle before an injection of acetylcholine (see MacIntosh & Paton, 1974). The Canadian, F.C. MacIntosh, about to return to McGill University as Professor of Physiology is seen performing **EXQUISITELY ACCURATE EXPERIMENTS**, which refers to the most sensitive and classical test for ACh, the eserinized leech muscle. MacIntosh was outstandingly rigorous in doing control experiments and is shown completing his 13th and 14th controls. The third main performer is L.W. Collison, who had been Dale's head technician, the caption making reference to **COLLISON'S ARTISTRY**. Here Collison places a second pair of spectacles on top of his own, and 'prepares' a kymograph trace for publication, by blacking out an artefact. Apparently the error was deliberately drawn in and Collison was heard during the filming 'What, you want me to draw it in and then black it out? Sir Henry would never have done it like that'. The film then provides a tour around the lab and its staff, paying reference to **F4'S SUPERB EQUIPMENT**, in which a Dale-Schuster pump from the early 1920s, one of the oldest pieces of equipment in the lab, was shown; and a **PLENTIFUL SUPPLY OF MATURE EXPERIMENTAL ANIMALS**, is illustrated with a tank of tadpoles. **LITTLE WONDER THAT F4 IS THE MECCA OF THE PHYSIOLOGICAL WORLD** refers to the constant stream of visitors F4 received, re-establishing pre-war contacts and creating new ones. The scene shows an inquisitive visitor interrogating MacIntosh, still performing control experiments, during the course of which the kymograph trace is wiped clean, and a sooty MacIntosh returns unhappily to his experiment. The availability of facilities and resources **HAS ENABLED 'ONE OF US'**, a phrase frequently used in Dale's papers, and a paper is alleged to have appeared with the footnote 'The publication of this paper has been delayed by the death of one of us'. **TO PLAN THE EXPERIMENT TO END ALL EXPERIMENTS GIVING CAREFUL CONSIDERATION TO: MEMBRANE RESISTANCE**, Paton is seen exploding a condom, used as a source of thin rubber for respiratory valves during the wartime diving and submarine work that had occupied much of F4. He had recently purchased the lab's supply in King's Cross Road; after demonstrating their strength the shopman had asked 'plain or teat ended, Sir?' Paton's reply 'It doesn't really matter - I always cut the ends off,' has been the basis of several stories; **CAPACITY** shows Brown eating an immense pile of sandwiches, whilst μ was intended as a pun, the Institute's cat being filmed; **SPACE CONSTANT F4** was filled to capacity, and a congested scene is shown; **TIME CONSTANT** shows the lab clock moving towards opening-time, before the scene shifts to the local pub 'The Hollybush'; **AND STATISTICAL ERROR** W.M. Perry (now Lord Perry) is shown working frantically with a calculating machine; **AND WITH CAREFUL REFERENCE TO THE LITERATURE** refers to major scientific players in the debates about chemical neurotransmission; and to others whose work was not highly valued in the lab. **HE HAS BROUGHT HIS WORK TO ITS CLIMACTERIC:** Laboratory scene along the long window bench crowded with people and equipment. To the left of the door can be seen the water centrifuge and balance with Collison's notice 'Near enough is not good enough'. Brown enters, picks up a baton and 'conducts' the experiment. Some mysterious experiment than passes down the line – there are gas and water spirometers, an oscilloscope, cannibalized RAF equipment and an old calculating machine. The answer to the experiment is patiently calculated and rushed to the exhausted maestro: **NEUROMUSCULAR TRANSMISSION IS ELECTRICAL.** This devastating news causes Brown to collapse **AND LEAVES US FOR 'ANOTHER PLACE'**, carried away like an exhausted gas cylinder, on his chest a picture of Dale and tied around his feet a label 'Empty. To University College. C.O.D.' The final scene shows Collison walking through the empty lab, shaking his head, and muttering what was apparently a constant refrain **'SIR HENRY WOULD NEVER HAVE DONE IT LIKE THAT'.**

I hope this paper has given a brief taste of how Sir Henry did do things, and why F4 was such a significant laboratory in the recent history of pharmacology.

I am very grateful to the Director of the NIMR, Dr John Skehel FRS, for the provision of research facilities at the National Institute for Medical Research, and for allowing me to consult and quote from Institute Archives. I am particularly indebted to the Institute's Librarian, Mr R.J. Moore, and his staff, for their assistance. I also thank the Wellcome Trust for their financial support, and Mrs W Kutner for secretarial help. Personal recollections of F4 used in this paper were generously provided by the late Professor W.S. Feldberg FRS, Sir John Gray FRS, the late Professor F.C. MacIntosh FRS, professor J.L. Malcolm, Lord Perry FRS, and the late Sir William Paton FRS. I would like to dedicate this paper to the memory of Sir William, in gratitude for his encouragement and advice in pursuing the recent history of pharmacology.

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