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ADVENTURES IN AUTOPHARMACOLOGY: A BIOGRAPHIC VIEW WITH DIGRESSIONS INTO OTHER MATTERS

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INTRODUCTION

I have not had the opportunity, and perhaps I lacked the ability, to achieve the dream of most pharmacologists; that is, to play an instrumental role in the development of a therapeutically useful drug. By chance, as I will relate, my main research has been in autopharmacology, which may be defined as the pharmacological study of the natural constituents of the body which have regulatory roles; thus, it is in the borderland between physiology and pharmacology. Autopharmacology has its own rewards and provides essential basic information to those who are in the business of developing new drugs.

Following the example of several earlier writers of prefatory chapters, I opted for an autobiographical approach. But the more cogent reason for an autobiographical approach is that the directions of research are determined not only by the logical progression of scientific accomplishments, but by more mundane circumstances.

Haphazard Induction into an Academic Career

I had no family background or connections that steered me into any of the professions or an academic career. The Second World War began two weeks after my twelfth birthday in 1939 and ended a few days before my eighteenth

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birthday in 1945. Through most of my teenage years, I had thought only about joining the army and had no other career aspirations or indeed knowledge of any other options. If there were career advisers at that time, I either missed seeing one, or have completely suppressed the memory of any such advice. My secondary schooling came to an end in December, 1945 (in Australia, the academic year corresponds to the calendar year). I applied to join the British Commonwealth Occupation Force (of Japan) and I also applied for admission to the University of Melbourne. The papers for enlistment in the army and permission to enroll as a student in the University of Melbourne arrived in the same mail. I tore up the army papers and duly began what turned out to be a lifetime in academia. I still wonder sometimes whether I made the wiser choice.

When I began my undergraduate studies, I had absolutely no idea about any of the biomedical sciences, or of the possibility of training for any of the health professions. However, progression into biochemistry and physiology was only a matter of following the lead of other students, and did not require any mental effort that interfered seriously with involvements in left-wing student politics, the free-thought movement, or the lighter side of undergraduate student life in Melbourne in the postwar period.

Almost at the end of my undergraduate course, we were required to devise and carry out a small research project instead of going through yet more formal laboratory exercises. I devoted myself so enthusiastically to my project that I neglected my routine studies and did not do well in the final examinations. Nevertheless, I was accepted as a candidate for a Master of Science (M.Sc.) degree and was offered some part-time teaching as a demonstrator in practical classes.

POSTGRADUATE RESEARCH TRAINING

George Reid, a Pioneer of Serotonin Research

I could not have been more fortunate than to have had George Reid as my M.Sc. supervisor. His main research interest was in the vasoconstrictor activity that was released from platelets into serum during the clotting process. The substance responsible for the activity was known as serum vasoconstrictor, thrombotonin or thrombocytin: it was of course serotonin or 5-hydroxytryptamine, but this was long before these names were prevalent in the pharmacological literature. What Reid had done was to characterize the pharmacological profile of serum and of crude extracts of platelets in a wide range of tests (1).

A method for concentrating a vasoconstrictor principle from serum had been published by Page and his colleagues (2), and my task was to follow

their procedure and to determine whether or not the concentrated vasoconstrictor had the same pharmacological profile as native serum prepared from platelet-rich plasma or crude extracts of platelets. The task was daunting. Each batch started with 50–200 liters of cattle blood collected at the abattoirs. Finally, after some ten days work, about one gram of material was available for pharmacological study.

The active principle isolated by Page's group was identified as a 5-hydroxytryptamine creatinine sulfate complex and given the trivial name serotonin (3). In 1951, serotonin was synthesized (4, 5). Reid obtained a sample of synthetic serotonin from the Upjohn company in Kalamazoo, and we quickly established that it had identical activity to the serum vasoconstrictor, and published the first account of its pharmacological actions (6). At about the same time, the Italian pharmacologist Erspamer showed that enteramine, which he had extracted from rabbit intestine, was identical to serotonin (7). Erspamer's papers in Italian and German journals in the 1940s on enteramine and a similar substance in some marine invertebrates were hard to get because of the disruption of the war years, and when we finally obtained copies and laboriously translated them, we failed to appreciate their significance because of our preoccupation with the cardiovascular actions of the serum vasoconstrictor.

Learning the Trade

The testing of the various batches of crude extracts of serotonin entailed not only determining vasoconstrictor activity on various isolated preparations of blood vessels and effects on other smooth muscle-containing tissues, but also a wide range of studies in anesthetized, decerebrate, and spinal cats with measurements of arterial and venous pressures, regional blood flow and plethysmography of hindlimbs, spleen and kidney, and intra-arterial injections (8). Under Reid's guidance, I was thoroughly trained in all these techniques.

In addition, my work as a demonstrator required the preparation of up to ten spinal or decerebrate cats a week for use by medical students in physiology classes. As I became adept at these somewhat grisly exercises, the task could be completed in a little more than one hour with the assistance of the Chief Technician, who was fearless in his handling of the sometimes fierce, half-wild cats that were supplied.

Training in the techniques of physiological pharmacology in those days involved not only mastering quasi-surgical skills, but also a repertoire of tasks necessary for recording the observations, using the available technology that dated from the end of the nineteenth century, now fortunately obsolete. These tasks included the preparation of smoked kymograph paper, using the soot from a benzene flame, and the varnishing of the paper to preserve the records. The pointers that scored the traces on the smoked paper had to be delicately

adjusted and were actuated by the movements of floats on the surface of mercury or water U-tubes for measurement of pressure, by tambours or bellows for measurement of volumes, and by systems of thread and pulleys for measuring changes in length, with the addition of springs for measurement of changes in tension. A measuring cylinder and stop-watch were used for detecting changes in blood flow. Electrical stimulation of nerves was applied from induction coils.

Those who learned the trade of experimental pharmacology in the last twenty or so years will probably not even recognize some of the above-mentioned terms, let alone envisage how experiments were conducted.

The Impact of Reid's Illness and Death

Reid suffered from severe hypertension that developed into malignant hypertension. At that time, radical sympathectomy offered some hope for delaying the inexorable progression of morbidity and death. He underwent this heroic surgery, but to no avail, and died in 1952 at the age of 37, before the publication of his pioneering paper on the cardiovascular pharmacology of serotonin (9). Had he been treated with hexamethonium, which was just coming into use following the clinical studies of Horace Smirk in New Zealand demonstrating its effectiveness in halting and reversing the pathogenesis of malignant hypertension (see 10), he would probably have survived for many years and the history of the pharmacology of serotonin would have been altogether different. Reid had suggested that I study medicine, but I had become so enthusiastic about research and had such an antipathy to didactic study that this path had no appeal. However, had Reid lived, he would probably have persuaded me to follow his advice, and, no doubt, my life under his continued guidance would have followed a different course.

The Second Stage: Sydney (1953–1956)

The first full Department of Pharmacology in Australia was founded in the University of Sydney. I think that George Reid had been offered the Chair, but declined it because of his hypertensive illness. In the event, an Englishman, Roland Thorp, who had been with the Burroughs Wellcome company, became the foundation Professor in 1949.

Thorp had maintained his connections with Burroughs Wellcome and was offering a Fellowship that allowed the pursuit of a Ph.D. but entailed a certain amount of work for the Australian branch of the company in assaying locally manufactured ampoules of insulin, oxytocin, and vasopressin for conformity to the standards of the British Pharmacopoeia, which is still mandatory in Australia. I applied for and was granted the Wellcome Fellowship in Sydney.

The possibility of studying for a Ph.D. degree in Australian universities had only been established in the late 1940s, and enrollments for this degree

in Departments of Physiology (or Pharmacology) were still uncommon. When I set out to enroll in Sydney, I discovered to my dismay that I was not qualified because I had not formally been awarded my B.Sc. in Melbourne—because I had not paid the graduation fee. Even when that oversight had been remedied, I could not submit my thesis for M.Sc. on the work I had done with George Reid until two years from the formal date of graduation as a B.Sc. Notwithstanding, I began work in Sydney on the bioassay of batches of insulin, oxytocin, and vasopressin and undertook as my Ph.D. project a study of the interactions between cardiac glycosides and adenyl compounds.

My experience with the pharmacological actions of adenyl compounds such as adenosine, AMP, ATP, and nicotinamide adenine dinucleotide (11, 12) was relevant to the theme of autopharmacology. The pharmacological actions of adenyl compounds were not well known then, and I subsequently suggested them to Burnstock as possible candidates for the transmitter of what became known as purinergic nerves (see below). Compounds such as ATP and coenzyme I, as nicotinamide adenine dinucleotide was then called, were not easy to come by, and we isolated some samples ourselves from rabbit tissues.

Embarking on Postdoctoral Studies

Thorp had solicited contributions from the pharmaceutical industry to invite eminent British pharmacologists to Australia. The first of these, Frank Winton, who was then Professor of Pharmacology at University College London, visited in early 1956. I was appointed as his personal aide and came to know him quite well. I am still indebted to him for his kindly advice and encouragement, which opened up new perspectives of ambitions for pursuit of a career in pharmacology. Before then, I had not dared to hope for a postdoctoral position overseas. However, Winton convinced me that this was not only reasonable, but also achievable.

Soon after his visit to Australia, Winton served as external examiner for J.H. Burn's Department of Pharmacology in Oxford. Burn had in his gift a post known as a Departmental Demonstrator. This post had just been vacated by Ulli Trendelenburg, who had completed an Oxford D.Phil. and taken a position with Krayer at Harvard. Winton suggested me as a successor to Trendelenburg, and Burn duly invited me to take on the Departmental Demonstratorship. Recognizing the eminence of Burn, I construed his invitation as a command. The premier position of the Oxford Department of Pharmacology at that time and the importance of Burn's influence on those who worked in his Department have since been pointed out by Vane in his address at the memorial service for Burn in 1982 (13).

Burn wanted me to start almost immediately, but I sought to delay commencement of duties from September 1956 until January 1957, to which

Burn somewhat reluctantly agreed. In the meantime, I had to submit my Ph.D. thesis and raise the money for the trip to England, by boat.

OXFORD WITH J.H. BURN (1957–mid-1959)

Life as a junior member of Burn's staff was a far cry from my previous experience in the more easy-going atmospheres of Melbourne and Sydney. One of the first things I learned was that it was not wise to arrive later or to depart earlier than Burn. I soon established a good relationship with the Laboratory Manager, Harold Ling, who instructed me about the various unwritten house rules.

My first task was to prove myself capable of performing the various laboratory exercises that I had to demonstrate to the medical students. Thanks to my previous experience, this posed no difficulties.

My first serious research in Oxford involved mastering a preparation of rabbit isolated atria with the vagal nerve supply attached. I had the feeling that Burn thought that this was beyond my capacity. My somewhat paranoid attitude was engendered by the curt manner in which he issued his instructions, usually followed by an expression of doubt about whether I would be able to accomplish the tasks he set. When I did, his reaction was more one of surprise than commendation, at least for my first six months in Oxford. In the event, two publications arose from work with isolated vagally innervated atria (14, 15).

Despite the initial absence of rapport with Burn, I greatly enjoyed the challenges and the successes of research under his direction, and I never lost sight of the privilege of being able to work with him. His contributions to pharmacology were immense (13, 16).

Equally important was the stimulation of being in what was then one of the most active pharmacology departments in the world, and particularly the company of the many postgraduate students and postdoctoral research workers from various parts of the world, including another Australian, Mollie Holman, who was then a D.Phil. student under the supervision of Edith Bülbring. Relationships with the senior members of Burn's staff were cordial from the outset. These comprised Harold Ing, Hugh Blaschko, Edith Bülbring, Miles Vaughan Williams, and John Walker. I did have a minor problem with Blaschko and Bülbring: they were of German origin and spoke with a slight accent although in impeccable English, but they sometimes had difficulty in understanding my Australian accent and idiomatic usage.

In the latter half of 1957, my relationship with Burn, or perhaps my attitude to him, improved considerably, but it was also clear that he did not appreciate my commitment. On one occasion, I was given a peremptory note concerning the fact that I had not appeared at lunch, which was served daily in the library:

it went on to suggest that I was lunching outside with my lady friend and, since lunch was a mandatory part of the corporate life of the department (see ref. 13), I either joined in or worked elsewhere. In fact, I had been so engrossed in our research that I started a new experiment as soon as the first one for the day was completed, preferring to forgo lunch. When I explained this to Burn, he was momentarily taken aback, but then I was severely criticized for neglecting my nutritional status.

His concern about the well-being of his colleagues, however junior, was genuine. When I returned days later than originally scheduled from a touring holiday in Europe that included a visit to the then USSR, I discovered him on the point of making official inquiries as to my whereabouts and assurances about my safety, thinking that I had run foul of the Soviet authorities.

In 1958, the award of a Fellowship of the Australian & New Zealand Life Insurance Medical Research Fund enhanced my financial status, by a factor of more than three. My salary as Departmental Demonstrator had barely covered the cost of living in Oxford. The freedom from the worry of running up debts was an important factor not only in increasing research productivity but in allowing greater recourse to the pleasures of life in England, including visits to continental Europe in vacation periods. The award was extended beyond the usual twelve-month duration to the date of Burn's pending retirement in July, 1959. These eighteen months were one of the most enjoyable and productive periods of my life.

Indirectly Acting Sympathomimetic Amines and the Burn-Rand Hypothesis

Burn had returned from a visit to Krayer's laboratory in Boston in the summer of 1957 full of enthusiasm for studying reserpine, which had been shown to release noradrenaline from a dog heart-lung preparation into the blood in the circuit. I became his main assistant in this new line of research, which was immediately rewarding, and many new concepts about noradrenergic mechanisms and the functions of sympathetic nerves flowed from it.

The least controversial hypothesis was that some sympathomimetic amines acted indirectly by releasing noradrenaline from a store at sympathetic nerve terminals (17). This concept at once accounted for the old paradoxical observation that denervation abolished the response to tyramine whereas it enhanced the response to noradrenaline. A similar paradoxical difference was produced by cocaine (18), and this was explained by the proposal that cocaine blocked the uptake of tyramine at sympathetic nerve terminals, and hence prevented the displacement of noradrenaline from its stores (19).

The most controversial outcome from our experiments was that the release of noradrenaline from sympathetic nerve terminals was secondary to the release of acetylcholine (20–24). This became known as the cholinergic-link

or sometimes as the Burn-Rand hypothesis. To the best of my recollection, the idea started as a sort of fantasy that arose from pushing some of the consequences of our new observations to extremes, but it then developed into a serious hypothesis that could accommodate many earlier observations.

Burn supported the concept of a cholinergic link in noradrenergic transmission with an almost religious zeal. But enthusiasm for new ideas had always been one of his characteristics, and indeed enthusiasm is an essential element of all but pedestrian research. This is not the place to deal in detail with the evidence for the hypothesis or that which eventually led to its demise. However, it did provide the stimulus for a great deal of research that led to many new discoveries, and it weakened the stranglehold that the then current dogma about neurotransmitter mechanisms imposed on new ideas.

Scientific Meetings

Burn attached great importance to the communication of research findings to meetings of the British Pharmacological Society and the Physiological Society. There were always rehearsals for these occasions, even if Burn himself was delivering the paper. For inexperienced people, there was rigorous drilling, not only on the scientific aspects of the communication, but also on the technique: he was not satisfied until it could be delivered fluently, with clear diction, integration between slides and words, and well within the time limit of ten minutes. The standards of presentation required by the Societies were high, but Burn demanded that papers from his department exceeded the standards. Attendance at these meetings was one of the highlights of periods I spent in the UK at Oxford and later at London.

A Place in the History of Pharmacology

I take great pride in being able to trace my scientific lineage directly to the beginning of the era of scientific pharmacology, at least within the British tradition, which can be regarded as starting with H. H. Dale. Burn was launched into his career in pharmacology by Dale, and I first became fairly widely recognized in pharmacology because of my association with Burn. In addition, there was another link. An Australian, C.H. Kellaway, had worked on anaphylaxis with Dale in the early 1920s. Kellaway then became Director of the Walter and Eliza Hall Institute of Medical Research in Melbourne, and W. S. Feldberg, another of Dale's colleagues, worked with Kellaway on the pharmacological actions of snake venoms in the period 1936 to 1938. My first mentor, George Reid, worked for eighteen months in 1940–1941 with Kellaway.

Although Sir Henry Dale had long retired from active research by the time I arrived on the scene, he continued to follow all the latest trends. I was greatly honored when I was summoned to his presence in the office of the

Wellcome Trust to give a first-hand account of some of the research findings that Burn had told him about.

ENTR'ACTE

My Fellowship provided for an additional year of support on return to the Department of Pharmacology in Sydney. However, I was granted leave to attend the 21st Congress of the International Union of Physiology (IUPS) in Buenos Aires, and then to spend a period of 3 months in the USA, where I was based at the Department of Pharmacology at the University of Vermont. I finally returned to Sydney in time for Christmas in 1959.

Return to Sydney

My consuming interest at this time was the cholinergic link in noradrenergic transmission, and I resumed research on that topic as soon as the necessary equipment could be acquired. I was fortunate in having three talented students join me: Victor Chang and Kevin Brandon, who were undertaking a year of research for a Bachelor of Medical Science degree before completing the clinical years of their medical course, and Helen Boyd, who had completed a B.Sc.

Chang worked with the isolated preparation of the guinea-pig vas deferens with the hypogastric nerves attached. The story of the development of this preparation by Seid Hukovic in Oxford has been told elsewhere (25). Chang not only mastered it immediately, but greatly refined many of the details, and showed that hemicholinium abolished the contractions elicited by stimulation of the sympathetic hypogastric nerves (26, 27). This finding was construed at the time as evidence supporting the cholinergic link hypothesis but, as it transpired, the effect was largely due to impairment of cholinergic transmission at ganglionic synapses close to the vas deferens. Chang's ambition was to become a surgeon, and the flamboyant manual dexterity he displayed in my laboratory was prognostic of his ensuing success in that vocation: in preparing the vas deferens, he would tie knots in the cotton threads one-handed, using either his right or left hand, and occasionally tied two knots simultaneously. After completing his medical degree and postgraduate training in thoracic surgery in the UK and the USA, Chang performed the first heart transplant in Australia, and went on to perform many more before his untimely and tragic end in 1991; he was murdered by extortionists when he refused to accede to their demands for money.

In other experiments with the vas deferens, Chang, Boyd, and I studied the effect of anticholinesterases in enhancing the contractions elicited by hypogastric nerve stimulation (28), which we construed as further evidence for the cholinergic-link hypothesis. In addition, we made the surprising finding

that several of the drugs then available with adrenoceptor-blocking activity also enhanced contractions of the vas deferens in concentrations lower than those that produced the expected effect of reducing them on the then accepted grounds that neuroeffector transmission was adrenergic. It is now known that disruption of the feedback inhibition of transmitter release largely explains the effect, but we attributed it to the anticholinesterase activity that we showed was a property of the adrenoceptor blocking agents we had used. The paper contained strange but readily verifiable observations, and explanations in the Discussion that did not fit well with the accepted dogma. It might never have been published had not Blaschko been the referee: his view was that if the observations were correct (and he did not doubt that they were), their interpretation was up to the authors providing it was coherent, even though it was unorthodox. I think it is a pity that he did not write a guide to referees, too many of whom attempt to impose their interpretations of data on authors.

Brandon worked with me on the role of acetylcholine in the spleen. We showed that acetylcholine was present in the cat's spleen and, like the noradrenaline content, it was depleted after sympathetic denervation. We concluded that it was present in the sympathetic nerve terminals and that it served to provide the cholinergic link in noradrenergic transmission (29). On the assumption that there is no cholinergic link, the role of the acetylcholine in the spleen remains as obscure today as it was to Dale & Dudley in 1929 when they isolated acetylcholine from the spleen of cattle and horses in quantities sufficient for chemical identification (30).

In addition to research with graduate students, I also worked with a member of the staff of Thorp's department, Jocelyn Pennefather, on the restoration of the noradrenaline content of the cat's spleen and kidney by infusions of noradrenaline and its precursors after depletion of noradrenaline from the sympathetic nerves by treatment with reserpine (31). We did this the hard way by measuring the noradrenaline content in extracts of the organs by bioassay. At about the same time, Axelrod and his colleagues at the US National Institutes of Health were doing similar work with the then newly available tritium-labeled noradrenaline, but the costs of ^{3}H-noradrenaline and the necessary equipment for scintillometric radio-assay were prohibitive for us, and most other investigators.

After a Postdoctoral Fellowship: What Next?

Since my Fellowship was coming to an end, I had to find a job. By now, I had been in research in pharmacology for ten years, and had every intention of continuing for as long as possible. Somewhat prematurely, and unsuccessfully, I applied for the newly created Chair of Pharmacology in Perth.

At the time, the best opportunities for a person in my position were in the

USA. This was in the period of the so-called brain-drain, when scientists were attracted to the USA mostly from the UK and other European countries, but also to a significant extent from Australia.

A Hiccup

Of the numerous attractive possibilities for positions in the USA, I chose one at the University of Vermont. Since this was a State University, the regulations (at least, at that time) required that I became a candidate for US citizenship. This procedure entailed submitting a twenty-page application form soliciting detailed information from the age of sixteen about residences, occupations, associations, and many other matters. I completed it as conscientiously as possible, and eagerly awaited the next phase of my life.

As my departure time approached and I still had no visa, I called the US authorities in Sydney and was at first reassured that the delay was purely bureaucratic in nature. At that juncture, I packed my few possessions, sold my car, and purchased my ticket to the USA, fortunately via London. On the eve of my scheduled departure date, the US authorities informed me that I was not eligible for the visa I had requested. No official reason was forthcoming, but many years later I was told that the problem was my membership of the Melbourne University Student Labor Club in the late 1940s. Apparently, this had been declared a communist-front organization in the McCarthy period, although the membership actually included a wide range of left-wing political views from Fabian socialists through social democrats to militant communists. In retrospect, I am rather proud of being in the same category as Charles Chaplin, Dashiel Hammett, Paul Robeson, and the pharmacologist Mark Nickerson, to name only a few, who were victims of McCarthyism.

I was momentarily nonplussed by the frustration of my plan to work in the US, but having prepared to leave Sydney, I flew to London, cashed the remainder of the ticket, and set out to find a place where I could get on with some research as soon as possible. My plans fell quickly into place when I went to see Gladwin Buttle at the School of Pharmacy. He arranged laboratory space for me immediately and, with two telephone calls, procured a Wellcome Research Fellowship in less than two hours. Naturally, I jumped at the opportunity.

SCHOOL OF PHARMACY, LONDON

The School of Pharmacy evolved from the College of the Pharmaceutical Society of Great Britain. The Pharmacological Laboratories of the College had been established in 1926 with J.H. Burn as the first Director. In 1937,

the College was incorporated as the School of Pharmacy of the University of London, and Burn took up his Chair in Oxford in that year. He was succeeded as Professor of Pharmacology at the School of Pharmacy by J.H. Gaddum. Then the Chair was filled by Gladwin Buttle from 1946 to 1966. The output of pharmacological research and of pharmacologists from the Pharmacological Laboratories and the Department of Pharmacology of the School of Pharmacy have made a significant impact on the development of pharmacology (32).

Despite my obsession with a cholinergic link in noradrenergic transmission, my knowledge of cholinergic mechanisms was somewhat limited. Fortunately, one of my new colleagues at the School of Pharmacy, W.C. Bowman, was rather expert in this area. It had come to my attention that the toxicity of the triethyl analogue of choline (triethyl choline, TEC) was mitigated by choline, and this suggested that TEC might have the property in common with hemicholinium of interfering with cholinergic transmission. If so, I would have another tool for probing the cholinergic link. In discussing these thoughts with Bill Bowman over a few pints in a local pub one evening, it became clear that we must first determine what effect TEC had on orthodox cholinergic transmission. We quickly established the fact that TEC caused a gradual failure of neuromuscular transmission when motoneurones were stimulated rapidly, but not when they were stimulated at low frequencies; furthermore, the failure of transmission after prolonged high-frequency stimulation was corrected by choline. Our interpretation of these and other findings was that TEC was utilized in place of choline and converted to acetyltriethylcholine when biosynthesis was stimulated by exhausting the reserves of transmitter and, since acetyltriethylcholine was inactive on cholinoceptors, transmission failed (33).

Thus, we regarded acetyltriethylcholine as a false transmitter or surrogate transmitter. As far as we are aware, this was the first time the concept of a false transmitter had been expounded, although it is commonly believed that the idea came from studies on false transmitters in noradrenergic mechanisms. In fact, Michael Day and I subsequently explored the possibility that a false noradrenergic transmitter, methylnoradrenaline, could be formed by metabolism of methyldopa along a path parallel to that followed by the normal precursor dopa (34, 35).

Until my period at the School of Pharmacy, I had paid little attention to the teaching of pharmacology, except for my work as a Demonstrator in my early days in Melbourne and in my initial position at Oxford. Since most of my new colleagues had extensive teaching commitments, I was inevitably drawn into this aspect of pharmacology and joined in their discussions. Then, after a year as a Wellcome Research Fellow, I was invited to take up a lectureship in the School of Pharmacy. I soon found that involvement in teaching undergraduate pharmacology was almost as stimulating as research.

Textbook of Pharmacology

Experience as a teacher in pharmacology disclosed the fact that there are deficits in most textbooks. In the School of Pharmacy, in London, the deficit in existing pharmacology texts was particularly apparent since they were written generally for medical students and assumed a good deal of biochemical and physiological knowledge. However, the basic biomedical sciences were part of the teaching of pharmacology. Consequently, when Bill Bowman, Geoff West, and I set out to write a Textbook of Pharmacology, the first part of the book dealt with what we perceived as the biochemical and physiological background to pharmacology (36). In the second edition (37), Bowman and I carried this even further, and attempted to integrate the more basic sciences with pharmacology, and we also paid more attention to the pathophysiological states at which therapeutic drugs are aimed. To judge by the feedback we got from students and teachers, demand for this approach was wider than we had originally envisaged. Our third edition will, in addition, deal more extensively with the relationship of the new molecular biology to pharmacology.

RETURN TO MELBOURNE

In 1964, I was granted leave from the School of Pharmacy to spend a few months with Geoff Burnstock in Melbourne. At that time he was a Reader in the Department of Zoology, and shortly after became the Professor. (He is now Professor of Anatomy and Developmental Biology at University College, in London.) We had first met in Oxford where Burnstock had a postdoctoral position with Edith Bülbring, and became good friends. Burnstock had assembled a talented group of graduate students in Melbourne, many of whom subsequently rose to important positions. These include Graeme Campbell (who succeeded Burnstock as Professor of Zoology), Max Bennett (Professor of Neurobiology, University of Sydney), John Furness (Professor of Anatomy, University of Melbourne), Marcello Costa (Professor of Physiology, Flinders University), and Chris Bell (Reader in Physiology, University of Melbourne). All have made substantial contributions to autopharmacology although, since they are not primarily pharmacologists, would probably not see their work in this light.

Burnstock and his colleagues played a major role in throwing new light on autonomic neuroeffector transmission. (See refs. 25, 38).

My work with Burnstock and Campbell clearly established that transmission from nerve terminals to smooth muscle in the taenia of the guinea pig caecum was neither adrenergic nor cholinergic (39). Subsequently, Burnstock and his colleagues suggested that the transmitter was ATP, and so began the purinergic theory of transmission.

During my leave from the School of Pharmacy, I also worked for a short time in the Department of Physiology and Pharmacology in Adelaide, with two successful accomplishments. The first, with Ivan de la Lande, was to develop an isolated preparation of the central artery of the rabbit ear and to characterize its responses to sympathetic nerve stimulation (40). This publication was recognized by the Science Citation Index for its frequent quotation in the literature. The second, with Bob Whelan and other colleagues, dealt with a vasodilator action of nicotine injected intra-arterially into the human forearm (41): the explanation for this unusual finding remains to be elucidated.

On Becoming a Professor of Pharmacology

The prospect of returning to my alma mater to succeed Frank Shaw, the founder in 1956 of a separate Department of Pharmacology, was too appealing to resist. In 1965, however, the features of the Department were that the morale of the staff was at a low ebb, accommodation was squalid and unkempt, and the equipment was either obsolete or inadequate in quantity. When I accepted the position, the Vice-Chancellor pointed to a fine new building and said that the Department would be housed in it, along with the Departments of Anatomy, Pathology, and Physiology; three months later, when I took up the position, the same Vice-Chancellor told me that there had been an overrun on costs, and some other accommodation would be found for the Department of Pharmacology. Four years later, some better but still temporary and inadequate accommodation was provided: nothing has changed since then.

For the first couple of years, I carried a very high teaching load while I actively sought new recruits to the department. I was determined to continue with research, but this was a daunting task under the circumstances. Fortune favored me with the addition to the department of Colin Raper from the School of Pharmacy in London, Jeff Wilson, a fellow Ph.D. student in London, who was granted a Research Fellowship, and Marian McCulloch, who had just completed her Ph.D. in the department. We were thus able to maintain some research productivity and to take on a number of graduate students.

This initial impetus was important for the development of the department: the standard of our teaching and research, and morale, all improved greatly over time. I have to acknowledge the support and encouragement through this difficult period of Geoff Burnstock, R.D. (Pansy) Wright (who had been the Professor of Physiology for many years), and Austin Doyle (a Professor of Medicine).

As Professor I was also the Head of Department, and thus administration made a major demand on my time. Internal matters such as the organization of teaching and research were pleasant enough and usually fruitful, but involvement with University committees and the administrative bureaucracy

was usually excessively time-consuming, frustrating and unproductive, no doubt because of my ineptitude.

Modulation of Neuroeffector Transmission

My interest in autonomic neuroeffector transmission was carried out mainly in collaboration with two greatly esteemed colleagues, Marian McCulloch and David Story. The major theme of research that developed was the feedback inhibition of noradrenergic transmission (42), which evolved into the more general area of modulation of transmitter release (43–49).

One ramification of an earlier interest in surrogate transmitters was the concept that the incorporation of adrenaline into transmitter stores for noradrenaline led to activation of a positive feedback when the adrenaline released by nerve impulses acted on prejunctional β-adrenoceptors (45–47, 50–53). We incorporated this concept into the hypothesis that adrenaline released during stress was taken up into transmitter stores of sympathetic nerves, and the resultant increase in sympathetic drive to the cardiovascular system played a part in the development of hypertension (50–53).

Nitrergic Transmission

My current interest is with the most recently discovered transmitter, nitric oxide (NO). This interest began with a graduate student, Chun Guang Li, when we studied modulation of transmission at neuroeffector junctions where the nature of the transmitter was not known, in particular, the transmitter that produces relaxation of the rat anococcygeus muscle.

Evidence for reduction of transmitter release by activation of prejunctional cholinoceptors was forthcoming (54), but lack of knowledge about the nature of the transmission process stimulated our attention. Almost all the previous work directed to elucidating the nature of the inhibitory transmitter of the anococcygeus muscle had been done by Gillespie and his colleagues, and he had pointed out its similarity to that of EDRF, the endothelium-derived relaxing factor (55). When Moncada and his colleagues showed EDRF was NO derived from arginine, and that the synthesis of NO could be inhibited by the N^G-monomethyl derivative of L-arginine, L-NMMA (see 56), the opportunity had arrived for testing whether the inhibitory transmitter was also NO.

Salvador Moncada provided a sample of L-NMMA, and we immediately found that it did indeed block inhibitory transmission in the rat anococcygeus muscle (57). Of course, the idea had occurred to others, naturally including Gillespie, and no less than four groups published papers in the last few months of 1989 showing that inhibitors of NO synthesis blocked inhibitory transmission in the anococcygeus muscle (see 58). This and other evidence indicated that the inhibitory transmitter was NO, or perhaps a NO-yielding substance, and we coined the term nitrergic to describe this mode of transmission.

Nitrergic transmission was soon demonstrated at many other neuroeffector junctions in the gastrointestinal tract, genital organs, lungs, and blood vessels (for reviews, see 58, 59). In the rat gastric fundus and in guinea-pig trachea, Li and I showed that both NO and vasoactive intestinal polypeptide mediated nerve stimulation-induced relaxation (60, 61).

Ventures in Toxicology

In Australia in the mid-1960s, there were few pharmacologists and even fewer toxicologists available to serve on expert committees advising government. For this reason, I was appointed to Committees of the National Health and Medical Research Council dealing with the scheduling of poisons, the evaluation of pesticides and agricultural chemicals, and the acceptance of food additives. In addition, by virtue of my academic position, I was a member of the Poisons Advisory Committee of the Victorian (State) Department of Health. My responsibilities to these committees demanded that I broadened my horizons to encompass a reasonable working knowledge of toxicology.

In the international scene, I was appointed as a member of the Expert Advisory Panel on Food Additives and Contaminants of WHO. This membership led to my selection to several Joint FAO/WHO Expert Committees on Food Additives (JECFA), the first being in 1969 and the most recent in 1992. The role of JECFA is the toxicological evaluation of food additives and contaminants to arrive at safe limits for their ingestion in the diet (62). To do justice to this task, many other matters need consideration, such as the technological needs for additives, dietary intakes and nutritional requirements, commercial practices in the manufacture, distribution, and marketing of foods, and national and international food standards. My limited academic background was sufficient to cope with the purely toxicological aspects of evaluations, but I have to confess to almost complete ignorance of the other factors. Fortunately, another member of all the JECFAs on which I have served was Herb Blumenthal, who until his recent retirement was a senior official in the section of the US Food and Drug Administration dealing with food additives and contaminants. We became close friends and during the evenings over dinner he enlightened me about all those parts of the deliberations of committees that I had found obscure.

In 1991, the complicated and unwieldy regulatory procedures that had previously existed in Australia for arriving at Food Standards, including the acceptance of food additives, were rationalized by the creation of a National Food Authority (NFA). The Authority consists of a full-time chairperson and four part-time members, of whom I am one, and is serviced by a staff of experts in all the relevant areas. Thanks to my experience as a member of JECFAs, and particularly to Blumenthal for instruction in the wider perspectives, I can meet the challenge of my responsibilities to the NFA adequately.

INTERNATIONAL AFFAIRS

I have already mentioned the large number of visiting pharmacologists from all over the world who were attracted to the Oxford Department of Pharmacology by the eminence of Burn and his senior colleagues. In fact, Burn had no fewer that 160 co-workers in his 32 years in Oxford (13, 16). In the period I spent in Oxford, there were at least twenty overseas visitors. My association with them gave me a lasting sense of belonging to an international community of pharmacologists. The special fellowship among those who had worked in the Oxford Department of Pharmacology extended to those who had worked there previously, and even extended to those who worked there in the post-Burn era. My attitude to the importance of internationalism in pharmacology was further strengthened when I attended the Buenos Aires meeting of IUPS in 1959, at which it was decided that there would be International Congresses of Pharmacology (see 63).

I attended the First IUPHAR meeting organized in Stockholm by Börje Uvnäs in 1961 and the Second in Prague in 1964, which was particularly memorable because of the special kindness and hospitality extended to me by Helená Raskovác. The pressure of duties in Melbourne prevented me from attending the Third (Sao Paulo) or Fourth (Basle) Congresses, and I thought it prudent not to apply for a visa to attend the Fifth (San Francisco) IUPHAR Congresses. Since then I have attended regularly.

Tenth International Congress of Pharmacology, 1987

At the Sixth IUPHAR Congress in Helsinki, a group of the Australian participants made a bid for a future Congress. This was not successful, but signaled our intention to make future bids. At the Eighth IUPHAR Congress in Tokyo the Australian bid for the Tenth Congress was successful.

This was an important event for all Australian pharmacologists, and particularly so for me since I had the honor to be chairman of the National Organizing Committee. Planning for the Tenth Congress in Sydney was practically a full-time job for most of those involved in the organization, but we were rewarded by the success of the Congress. A special issue of Trends in Pharmacological Sciences was published to coincide with the Congress: my article in it dealt with the development and current position of pharmacology in Australia (64); most of the other articles were by Australian pharmacologists.

Southeast Asian/Western Pacific Regional Meetings of Pharmacologists

In the early 1970s, I met a kindred soul in respect of enthusiasm for internationalism in pharmacology in the late Koroku Hashimoto, then Profes-

sor of Pharmacology at Tohoku University in Sendai (65). He pointed out that pharmacology was well developed in Japan and Australia, but was struggling in most of the countries in our region; he suggested that we could help our colleagues in these countries by organizing regional meetings, and he had no difficulty in enlisting my assistance in putting this idea into effect. Regional meetings were held in Singapore (1976), Jogjakarta (1979), Bangkok (1982), Penang (1985), Beijing (1988), and Hongkong (1991), and the next is scheduled for Manila. Not only did these meetings bring together pharmacologists from the region, and many from outside the region, they also stimulated the organization of pharmacology since at least five national societies from within the region affiliated with IUPHAR.

CONCLUSIONS

In reviewing some aspects of my career, the question inevitably arises: would I choose a different path if I could live my life again? This question presumes the impossible, that hindsight should be become foresight, but had I known at the outset what I have since learnt by experience, I would probably have followed a different path. In particular, I would have given more serious consideration to working in the pharmaceutical industry, which offers a realistic opportunity to be involved in the development of therapeutically useful drugs. However, despite some setbacks, I have no regrets about the course I followed as opportunities arose. I have greatly enjoyed the camaraderie of pharmacology and the special pleasure that comes occasionally from teaching. Can anyone ask for more than to have as a job what one would willingly do as a hobby?

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