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Some reflections on those who taught me —a personal view

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It was a good summer in 1947, until the middle of August, that is. The eager daily scanning of the local evening paper was suddenly over. The results of the School Certificate Examination were out but one name was missing. It was no mistake. I had failed in biology, chemistry, physics—and Latin. My complacent expectations of reading medicine at Oxford were rudely shattered—if only I had passed in Latin! There was no mercy. Within hours the holiday was over and I was employed by a local pharmacist. Sweeping, dusting, unpacking and running messages between his three shops, I became aware of a sterner discipline than that of home or school. I was frightened—perhaps I should have to spend my life doing what I was told. How I treasured those precious moments of freedom delivering the private prescriptions by bicycle—one little wheel at the front with a huge wicker basket.

Eventually I came to terms with a change in aspirations and after six weeks persuaded both parents and headmaster to allow a return to school. I was determined to become a pharmacist now and in due course found myself waiting outside Harry Berry's office at No. 17. The lesson had been learnt the hard way—some effort is required no matter how good the memory or intellect. And so I became an undergraduate at the 'Square' in October 1951.

Few memories remain of the first term but one is clear enough. It is of Gladwyn Buttle pacing up and down the absurdly small platform in the small lecture theatre (now a museum/reception hall) talking of teeth, enzymes and constipation. Introductory physiology, I suppose, but having discovered that he was professor of pharmacology, that subject became my new career ambition. At that stage, it cannot have been the course content which was so appealing. For me it was an intense personal magnetism for the man which the passage of 25 years has done little to dim.

Intending pharmacologists suffer a distinct disadvantage by reading their first degree in pharmacy in that the instruction in physiology and biochemistry is lacking in volume and scope. On the other hand the pharmacy course provides a much better basis in both physical and organic chemistry in contrast to today's degree schemes in pharmacology. On balance I feel fortunate to have had the early chemical input. The exacting laboratory standards imposed by Louis Sharp and Alan Glenn, although irksome at the time, provided a sound basis for subsequent excursions into quantitative biological chemistry. Added to this was an enlivening introduction to Perkin & Kipping's *Organic Chemistry*—a work in three slim volumes which I still consult—by Wilfrid Linnell. In a way which I wish I could emulate, Linnell managed to unfold the magic of organic chemistry which gave me a permanent interest in twisting the tail of chemical science for potential therapeutic advantage.

Many 'Square' graduates owe (I suspect) an unacknowledged debt to Monica Mann (now Butterworth) who patiently instilled the skill and persistence so necessary for competent biological assay. As with B.P. volumetric assays, the course in 1951–54 required competence in virtually all B.P. biological assays each of which was tackled in the final year. Against this highly practical background the need for and the use of statistical procedures was self evident. Thus the mysteries of Student's *t*-test and linear regression analysis, the advantages of 4 or 6 point assays, the importance of parallelism *etc.* were seen as work-a-day friends rather than something else to learn. These classes were held in the laboratories of the Royal Veterinary College and added to once a week by a practical tutorial/demonstration from Eleanor Zaimis. Little, if any, concession was made to those not decided on a pharmacological career by the demands made on anticipation, memory and embryo powers of reasoned deduction. These were the high spots of my undergraduate days kindling a two-fold interest in the recognition of the pharmacological properties of an uninvestigated compound and the mechanisms by which drug responses are produced. Zaimis's enthusiasm for the elucidation of pharmacological mechanisms was infectious and if I had any doubts about post-graduate research this brief, but telling apprenticeship dispelled them.

I cannot recall a conscious decision to become a research student. Nor do I remember anyone actively seeking to recruit me, quite the reverse I fear. My first supervisor was George Somers and my subject of research (largely self-selected) was the pharmacology of chlorpromazine. At that time (October 1954) relatively little was known about the substance and it seemed a sound choice on a number of counts. It was a disastrous mistake. Without the wit to recognise that the important investigations lay in the central nervous system, I floundered about in a peripheral autonomic context, finding nothing in particular and doing it rather badly. Near despair at Christmas, I was rescued by J. R. Hodges who offered to supervise me but in a different topic area. Whilst I had enjoyed his lectures as an undergraduate, no special interest had emerged in pituitary adrenal relationships. But here was the gift of a clearly thought-out project employing methods that were well established in the Department. Although somewhat sceptical of the validity of using DOCA to suppress endogenous ACTH release, it soon became evident that results with meaning could be obtained. Slowly, by encouragement and example Hodges restored self-confidence leading to a personal participation in experimental design. Now, however, it was based on the firm security of a mastered methodology. In addition to learning this fundamental basis of all research work, I also discovered from Bob Hodges the importance of writing with clarity and that a polished verbal performance requires both planning and rehearsal.

After two years with Hodges at No. 17, the opportunity arose to spend some time with George Sayers, one of the pioneers of pituitary physiology, in his laboratory in Cleveland. Sayers was kind about my results (Barrett & Hodges, 1956a, b) which had failed to support his earlier observations (subsequently proved correct) that adrenalectomy was followed by ACTH overproduction. He was quite adamant, however, that DOCA blockade was no substitute for hypophysectomy and that I should have to learn how. Amidst protests that acquisition of the technique would absorb a disproportionate time, Sayers retorted that I had two weeks to learn and that such defeatist attitudes were unwelcome. Two weeks and a hundred rats later, and with the help of a chiropodist who was blissfully unaware of the existence of the Circle of Willis, I was reasonably proficient. I did not realize it at the time, but there was something typically American about this episode. Unlike many British investigators, our North American colleagues are less often prisoners of their own methodology. Having defined the relevant question, they seem more ready to utilize the most appropriate technique even if this means going elsewhere to learn it. There was also less pride in the possession of technical skills, a trait which has virtues but which can become counter productive.

On arrival in Cleveland with my 'superior' British Degree and near postdoctoral status, it was a shock to discover that my knowledge of biology in general and of pharmacology in particular was poor by comparison with that of my American contemporaries. Although there are many arguments against course work during the Ph.D. period, it seems to me that present day accusations of narrowness amongst British postgraduates are not without some justice. Perhaps it was particularly a feature of the Square in the post-war period with its self-governing status and the extensive in-breeding reflected in staff appointments.

Clearly I had failed to retain an elementary knowledge of radioactivity or renal physiology. We were injecting dogs with [^{35}S]cysteine in the course of following vasopressin biosynthesis. At night I used to take the dogs for exercise until one escaped my control, disappeared into Earl Sutherland's laboratory across the corridor and relieved itself on a bench. The anger occasioned by the unhygenic aspect was trivial compared with that following recognition of radioactive contamination! Few were slow to see this situation as evidence of immaturity and irresponsibility on my part. The intense sense of purpose of my fellow students was sometimes hard to live with but also a reminder that despite a common language, the United States is a foreign country.

My principal research had concerned the specificity of action of putative corticotrophin releasing factors *in vitro* in anterior pituitary homogenates (Barrett & Sayers, 1958). It was my task to prepare the first draft of this paper and then take it to Dr. Sayers. All went well until we reached the 'discussion'. My original was dismissed as being re-iterative of the earlier sections and then, rather as a concert organist selects stops, Sayers plucked pertinent references from his impressive memory (and to me an astonishing range of journals) and proceded to construct an argument of both strength and interest. Each selected reference had then to be checked, not only for accuracy of citation but also that the evidence and arguments adduced therein were truely relevant and substantiated. Nothing angered him more than attempting to bolster one's own conclusions by quoting statements from elsewhere which were

themselves unjustified by evidence. It was the first time I learned the real meaning of critical analysis.

The time spent in Western Reserve was probably the most significant period in the shaping of my career. Most importantly it broadened horizons and opened up the possibility of achieving independence as a research investigator. Being in a large department with a variety of interests, enforced contact with all kinds of influence and attitudes. The standards were high and survival depended on more than personal competence and effort. To the left, Sutherland and Rall were uncovering the role of cyclic-AMP, to the right Berne was discovering the role of adenosine in the coronary circulation. It was a good place to grow up and try to discard the excesses of childish exuberance.

In the autumn of 1958 I became an Assistant Lecturer at the 'Square', the Pharmacology Department at last being united in the new buildings in Brunswick Square. At long last my Ph.D. Thesis was submitted and it was my turn to face Dr. Marthe Vogt as examiner. As many will testify this prospect was more daunting in anticipation than reality and the retained memory is one of kindly, if stern, criticism and sympathetic encouragement. From subsequent experience, I am sure that the sense of occasion which always accompanied an examination by Dr. Vogt, and which affected the whole Department, brought a fitting climax to a doctoral candidate not always achieved by others and often to the later disappointment of the doctorand.

With the departure of Bob Hodges, Pat D'Arcy and Gerald Cox elsewhere I was left as the only endocrine pharmacologist in the Department. A period of self-doubt followed once described by Bill Bowman as the completion of cross-word puzzles which were capable of solution simply because one had set them oneself. Geoffrey West was a great help at this time providing sensible pragmatic advice during the difficult transition from the tying up of loose ends of the Ph.D. work to something more original and independent.

So far I have made little mention of the ever present influence of Professor Buttle whose constant advice and support had enabled me to get this far. It was Buttle who backed me at the beginning and gave me the chance of a research studentship. Even earlier it was he who suggested that fewer extramural activities would help in obtaining a degree. But it was the manner in which he advised people that distinguished him from others. It was above all his obvious sincerity in caring about people which shone like a beacon. One suspects that his absent-minded eccentricity was not entirely uncalculated, perhaps an instinctive management technique, but it was so natural and unaffected that he was loved by everyone. Of course there were irritations. It was little consolation, for example, to be told that £300 a year should be plenty for a postgraduate to live on and in the same breath be advised on the tax advantages of maintaining a £10,000 overdraft.

Buttle was never an inspiring leader of a major research effort at the 'Square' but he created and sustained an environment into which research workers from all over the world gravitated: an environment in which most prospered and many emerged to make substantial contributions to the development of the subject. His generosity of mind (and sometimes of pocket) and time for those in difficulty is legendary. As with his friend, the late Lord Rosenheim, contact with Gladwyn Buttle enriched the lives of those who made it. His own enthusiasm for hard work was exemplary and he could be chidingly severe on those who didn't try.

One last enigma which only fell into place for me quite recently was his tendency to mention jobs in other places. One never knew whether this was an honorable career opportunity or the hint of the boot —or so we thought! In retrospect one can see it as part of a training to make one's own decisions—one of so many things for which his students and associates will remain for ever grateful.

As the result of one of these 'tips' I visited and joined the laboratories of ICI in Cheshire where I met two men, Garnet Davey and J. W. Black—from whom I was subsequently to learn a great deal. Charles Code once defined genius as the ability to equate 2 + 2 with 5—and be right! If so then Davey has that quality—'don't bother him with facts because he's already made up his mind'—and more often than not he *was* right. It was, for example, evident early in the development of β-adrenoceptor antagonists that unwanted effects of bronchoconstriction could possibly deter their use in patients with concomitant angina and obstructive airways disease. Davey believed that it would prove possible to dissociate cardiac and bronchial β-blocking activity. I didn't believe it but by covertly instituting a search of previous test results Davey 'discovered' practolol. And when it was published (Barrett, Crowther & others, 1968) his name was not on the paper! There was an important lesson here, self-evident but often ignored, that nothing is wholly clear-cut in pharmacology. Davey taught me two other important lessons, particularly applicable in large institutions, which I failed to learn until I had

left ICI. The first is to avoid telling a fool he is foolish since you only make him an unhappy fool. The second is that few fortresses are gained via the main gate. If you believe in your objective, choose the means most likely to succeed irrespective of personal pride or subsequent recognition. Garnet Davey's recent retirement will leave a vacuum of high degree. No matter how effective the use of the retrospectroscope by those who are left, much of the credit for ICI's innovative record is his, not least by his willingness to back people with ideas.

It was Jim Black's influence which finally wed me to the notion that chemistry could be twisted to therapeutic advantage. From him I learned that an identified target coupled with an appropriate biological screening procedure and enthusiastic chemical support could be one of the most exciting branches of experimental pharmacology. After excursions into the control of adiposity, gastric secretion and atherosclerosis I found my niche amongst the β-adrenoceptor antagonists. From a synthesis by David Le Count, the 'perfect' β-blocker emerged—potent, cardio-selective, no membrane stabilizing activity, no partial agonist action and a long half-life—atenolol (Barrett, Carter & others, 1973). I wonder!

And now, if you please, I'm ready to start my career in pharmacology.

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