Victor Whittaker
Sir William Dunn Reader in Biochemistry, 1966-1973

This prestigious readership had been held since its inception in 1924 by Joseph Needham. Soon after his appointment Needham deserted biochemistry but was well known for his pioneer work as a sinologist. He was left-wing and admired Chairman Mao and when, on his retirement in 1966, I was appointed as his successor, I was sometimes asked what oriental language and culture I intended to specialize in! There was no laboratory space of his that I could inherit, so I was allocated the small lab and office vacated by Malcolm Dixon, who was also retiring.

Frank Young, then the Sir William Dunn Professor of Biochemistry and head of the Department, had ambitious plans for its development. He envisioned its division into four sub-departments: microbiology, plant biochemistry, endocrinology and neurochemistry (now more often called molecular neurobiology because some of its leading protagonists were not initially trained, as I was, in chemistry and/or biochemistry). Microbiology had come into being under Professor Gale, Dr Northcote directed plant biochemistry, Young himself, endocrinology; only a neurochemist was now needed to complete Young's plans. These developments would become possible thanks to the University's successful application for government funding for two new buildings, for Biochemistry and the Cavendish physics department.

I do not know how I came to be offered the Readership. I was then a Senior Principal Scientific Officer (SPSO) at the Agricultural Research Council's Institute of Animal Physiology (now the Babraham Institute), initially a member of Sir Rudolph Peters' Biochemistry Department then, on Peters' retirement, under his successor, Guy Greville, formerly of the Cambridge Biochemistry Department. I had a research unit and adequate laboratory space. The research policy of the Institute under its Director, Sir John Gaddum, was a liberal one and I had acquired international recognition, initially by my work on the specificity of the cholinesterases and then by my successful bulk isolation, by homogenization and centrifugal fractionation, of detached central nervous system pre-synaptic nerve terminals and the synaptic vesicles which they contained. The isolated nerve terminals I called 'synaptosomes'. I showed that synaptosomes were sealed structures which behaved like miniature cells on incubation in a suitable medium, releasing their content of transmitter in a calcium-dependent manner when appropriately stimulated. They were thus an excellent model system with which to study in detail the mechanisms involved in synaptic transmission. Fractions were identified and assessed for homogeneity by electron microscopy; I had to persuade the editors of the Biochemical Journal to allow me to include electron micrographs in my first paper! Gaddum had to retire in 1965 due to ill health, dying shortly afterwards, and Richard Keynes, head of Physiology, became Director of the Institute. He came under pressure from the Research Council to redirect the Institute's research policy, liberal under Gaddum, on more agricultural lines and made it clear that neurochemistry was not a priority. A move to Cambridge would give me greater freedom and, with a retirement age of 65 instead of 60, five more years of professional life.

Shortly after I was offered the Readership another offer came from the New York State Department of Mental Hygiene to head up a department of neurochemistry in a new institute for research in mental retardation they had built in Staten Island. The laboratories and finance were excellent and the salary was about three times that of the Readership; however, I had to consider the interests of my wife and my three teen-age children. I consulted Young. He told me that until the new department was forthcoming he would agree to my spending four to six months per year in the US using long vacations and my right to sabbatical leave. The director of the New York Institute welcomed an association with Cambridge and agreed to the arrangement. There followed an immensely stimulating, strenuous but ultimately insupportable life-style.

Incorporation and college membership

I was an MA, DPhil and DSc of Oxford but had no Cambridge degree. To become a member of Cambridge University and a voting member of the Senate, I had to acquire a Cambridge degree. As a member of Oxford University I was, however, entitled to be 'incorporated' into Cambridge University at the level of my highest Oxford degree. I was presented to the Vice-Chancellor by Professor Young, wearing a resplendent gown of red and ermine. I swore in Latin to uphold the statutes of the University and not behave corruptly when serving on committees. I also learned that were I to be remiss in my duties or to behave scandalously, I could be brought before the Septemviri – a council of seven wise men – for judgement. I was now a Cambridge ScD by incorporation and entitled to full membership of the University. Fortunately, I managed to avoid judgement by the Septemviri during the seven years I was a Reader!

The next formality was the acquisition of a college fellowship. Whereas full professorships were linked to professorial fellowships in the older colleges, this was not so for readers. Caius might have been the obvious one to join, since my predecessor, Joseph Needham, was now its Master, it was the sister college of my Oxford college (Brasenose), it had a medical tradition and Sir Rudolph Peters, with our Oxford and Babraham links, was a Fellow. But no invitation came. Instead, a newly founded graduate college, University (now Wolfson) College, offered me a fellowship which I gladly accepted. I greatly enjoyed the friendliness and informality of the college (no high table!) and have continued to do so as a senior member since my return to Cambridge in 1993.

Teaching

I was given to understand that the readership was primarily a research appointment and that teaching duties would be light and broadly confined to one's own area of expertise. Young was particularly keen to have an authoritative course of lectures on cell biology which would include cell and molecular neurobiology; this would be for Part II students specializing in biochemistry and would be given during the Long Vacation term. I welcomed this assignment as the subject was one I felt I was well qualified to teach and covered much the same ground as a lecture course for the students of the City University of New York that I was giving when over there for the Staten Island appointment. What I did not expect was to be so heavily involved in first and second year medical and Tripos teaching. Young had delegated the responsibility for this to another member of staff, Mrs ('the Newt') Newton. To my surprise, this lady asked me to do quite a lot of demonstrating in the first year practical classes and to lecture on nutrition – something I had not done since my Oxford days. However I loyally worked up a series of lectures on aspects of nutrition, as in the past developing the subject historically and on the basis of scientific evidence, but I had overlooked a new form of political correctness – 'history is bunk'. I was advised to lecture systematically not historically and get to the received body of facts as quickly as possible. It reminded me of the demand for 'the cold dope' by my Cincinnati students when, during 1948-1952, I was an Assistant Professor of Physiology in the University of Cincinnati's College of Medicine but was unexpected in Cambridge.

This relatively heavy load of teaching made it difficult for me to get to international conferences if they took place in term-time, as they not infrequently did. I remember one particularly unfortunate clash – the meeting was a 'must' for me, but to the chagrin of the organizing committee, I had to cut short my stay so as to be back in time for yet another lecture on nutrition. On my return, I was annoyed to find that the lecture schedule had been altered during my absence; I had no immediate teaching duties and I could have stayed on! I suspect that my status as an outsider, well-known abroad, often invited to international meetings, running a fairly large group and spending much of my time in New York may have evoked a desire in some of my colleagues to 'cut me down to size' by loading me with junior teaching duties. Also I found myself out of sympathy with the prevailing left-wing sympathies of some of my colleagues. However I tried to perform my teaching duties faithfully and enjoyed most of them. Just how onerous but how rewarding they could be is shown by a development which occurred during my readership.

Senior members of staff were worried by the neglect of the third-year practical classes by the students. It was decided to abandon set experiments and instead to devise projects in which students would be asked to investigate a simple project as though they were doing research. My project involved comparing the density-gradient fractionation of crude mitochondrial fractions from liver and brain tissues and noting that the latter gave myelin and synaptosome fractions as well as mitochondria whereas the former contained only mitochondria. A large classroom was set aside for the project and stocked with the glassware, chemicals and apparatus needed for the projects. There was no fixed time-table. The results were highly successful; apathetic students (often the brightest) became motivated and work went on until late in the evening. We had to establish a rule; all out by 10 p.m.! A rota of teaching staff was established to enforce it.

The Faculty Committee

I soon found myself on the Natural Sciences Faculty Committee. The third-year project practicals were only one of several new ideas. What struck me was the relative conservatism of student suggestions; the staff were much more radical. I was also surprised by the hostility that several members of staff felt towards the Research Council Institutes, Babraham included. 'We let them lecture here and then they take all our best students!' 'Our teaching load prevents us doing the sort of high-powered research they have time for, so the students prefer them to us!' As someone with inside experience of a research-council institute, I tried to counter this attitude. 'You should realise that there are dozens of scientists in these institutes who would only be too pleased to help with the teaching here. This would reduce your load and give you more time for research. More of our ablest students would then want to work in your departments.' I was listened to but I saw no changes and suspected that some of them used the teaching load as an excuse not to do research, for which they had little motivation.

Examining

Another duty that I became involved in was serving as an internal examiner of the Part II biochemistry students. As the examinations took place in June, I would often work in the rose garden of my house in the Huntingdon Road at a table piled with examination papers. The garden had been designed by the eminent physiologist, Fellow of Clare and amateur garden-designer Nevill Willmer for the original owner, Harold Taylor, also a Fellow of Clare. Willmer liked to divide his gardens, as you can see in another of them, the Fellows' garden at Clare, into several 'rooms' at different levels and separated by hedges. The handwriting of the papers was often appalling and the answers were sometimes in note form. Marking was necessarily rather subjective but, remarkably, the examiners were generally in agreement as to the overall class. Students on the borderline between classes were given a *viva voce* examination. To allow for nervousness, a student could pull him- or herself up by a good viva but couldn't lower the class by a poor one.

I was also involved in the examination of applicants for the PhD as both internal and external examiner, the latter usually of Oxford candidates. The theses were interesting to read and I tried to make the examination a constructive and relaxed opportunity for a young scientist to discuss his or her work with a couple of experts. Sometimes, when I pointed out a defect, the student would reply, 'Oh, my supervisor told me to do it that way', I would respond, 'Much as I would like to, I am not here to examine your supervisor, but you; tell me how *you* would have done the experiment. This sometimes elicited a good answer but more often confusion; the attempt to blame the supervisor for a badly designed experiment had not worked. I never failed a PhD thesis. We had the option to defer and our victims left the exam feeling that after all it *had* been a constructive experience.

Research

As my group enlarged with post-docs from abroad, Young tried to improve my accommodation. In addition to Dixon's small first-floor office and laboratory, I was given another small lab along a corridor littered with discarded apparatus, and eventually, a hutted lab in the Department's yard. The Department possessed an electron microscope but I was denied access to it; however a joint application for another one by Nick Hale, an endocrinologist, and me was successful. It was housed in a small room on the floor below and my ultracentrifuge was placed in a cold-room I shared, at times, with forty Part II students. The stairs up and down which samples had to be carried consisted of worn marble and on one occasion I slipped, fortunately without serious injury. The Department's financial contribution was minimal - the salary for one technician and a few hundred pounds for consumable supplies - but I managed to secure a Programme Grant from the MRC. My group was typically about ten strong, with one to two PhD students, four post-docs and three to four technicians. During my seven years as a Reader fourteen post-docs and seven technicians passed through my group; of the scientists, the US provided the largest contingent (five), the UK was next with three, Italy and Germany provided two each and Sweden and Venezuela, one each.

My account of our research will of necessity be brief. Among the problems I was interested in was to find out how the neurotransmitter acetylcholine was stored within the nerve terminal and which compartment, cytoplasmic or vesicular, provided the acetylcholine released during synaptic transmission. We used anaesthetized cats and guinea-pigs. Subcellular fractions were labelled by allowing radiolabelled choline and homocholine to diffuse into the tissue of the occipital lobe from small cups placed on its surface. The lobe neurones were then stimulated via the lateral geniculate body, the transmitter released by stimulation was collected, stimulated tissue was excised, synaptosomes isolated and from them synaptosomal cytoplasm and two fractions of synaptic vesicles were derived. The ratio of labelled acetylcholine to homocholine was measured. The fraction of mono-disperse synaptic vesicles took up little of the labelled transmitter and its homologue and was identified as containing reserve vesicles already replete with unlabelled transmitter. The other fraction of vesicles was associated with plasma membranes. It had become highly labelled as had the cytoplasmic fraction and the released transmitter. However, the ratio in which the transmitter and its analogue were released was different from that of the cytoplasmic fraction but close to that of the released fraction. This showed that the specificity of the choline acetyltransferase of the cytoplasm was different from that of the vesicular uptake mechanism and that the source of released transmitter was not the cytoplasm but the vesicles in close contact with plasma membranes. The mono-dispersed vesicles were evidently reserve vesicles replete with transmitter and thus unable to take up newly synthesized transmitter from the cytoplasm.

At Babraham I had begun to work on an unusual model system, the electric organ of the electric ray *Torpedo marmorata.* The electrocytes of this organ develop from myocytes and are thus phylogenetically related to muscle cells; their innervation is thus purely cholinergic. However, their innervation is about 1000 times greater than the low level in muscle, making investigation by subcellular fractionation feasible. Although synaptosomes can be prepared from the electric tissue in low yield, the morphology of the terminals does not favour their formation; instead, the terminals are torn open and the synaptic vesicles released. Extensive work with this model system has made it possible to obtain a full understanding of the mechanisms involved in the vesicular storage and release of the transmitter in cholinergic synapses.

My departure for Göttingen

It had long been accepted that the new Department would be built on the part of the old Addenbrooke's site facing Lensfield Road and would be ready for occupancy in 1972. £150 000 was spent on architects' fees. Clearing the site would involve demolishing a row of listed buildings. Young appeared before the planning committee and won his case. Has the University acted promptly all might have been well, but it procrastinated; a new government came into power late in 1967 and decided that the law protecting listed buildings needed strengthening and that all planning decisions affecting such buildings not implemented by December 1967 should be reviewed. A second public hearing took place and Young lost his case. The University's Land Department moved into the buildings, raising the suspicion that this had been their aim all along and explaining why they had not started demolition before the deadline. Worse was to follow. The new Government decided that it only had enough money to pay for one department, not two and the University must choose which. Young argued his case before the Council of the Senate but lost. The Cavendish would be re-housed, not Biochemistry! This was a severe blow and Young became depressed.

Just at this time the building housing Colloid Science became vacant. Nick Hales and I suggested that this, if remodelled, would make an excellent home for a sub-department of cell and molecular biology which we could share. Other possibilities were also discussed. Young's response was negative; he feared that if the Department's needs could be met without re-housing the entire Department, he would never get his new building. He never did! I respected Young; I shared his vision for the new Department and fully understood his disappointment that it was never built during his professorship.

I now began to consider leaving Cambridge. I had no guarantee of continued support after the end of my five-year MRC Programme Grant in 1974 but had received offers from the US and, surprisingly, Germany. A multi-departmental institute had been built in Göttingen by the Max-Planck Society and I was invited to head up a proposed Department of Neurochemistry. Although the salary was only twice that of my readership in contrast to the threefold offered by US institutions, staff salaries, equipment and supplies were all on hard money; grants were merely icing on the cake. The retirement age was 68, not 65 and there was the possibility of further work as an emeritus. We would be nearer Britain and our offspring, now adults and living their own lives, would be nearer for visits. My group accompanied me on a visit to the Institute and all wished to come. I accepted all but two of them, a married technician whose husband worked in another department and a Canadian girl who was *fière de ses charmes* and the shortness of whose miniskirts had attracted the attention of the male members of the Biochemistry Department.

I decided to accept the Göttingen offer and spent seventeen years there, fourteen as Director and five as an emeritus. I was warmly welcomed, had superb conditions for my research, never felt like a foreigner and acquired a knowledge of the language, history and culture of another European country which had made an amazing recovery from disaster. I experienced at first hand the unification of east and west Germany in a university city only 15 km from the fortified frontier which had previously separated them. The city's and university's link with Britain during the Hanoverian period (the university was founded by our George II as Elector of Hanover) made us feel at home One of my PhD students, Thomas Südhof, went on to win the Nobel Prize in a field I introduced him to. I returned to Cambridge in 1992.