

## **The Department of Pharmacology at University College London, 1905 – 2007. A short history.**

The Department, the first of its kind in England, was founded in 1905 and was to remain in existence until 2007. University College London (UCL) was founded in 1826 as a secular institution to provide education for all who could benefit by it, irrespective of creed, personal wealth, race or social class. It was part of the radical opposition to the hegemony of Oxford and Cambridge that arose in the early part of the 19<sup>th</sup> century. Even in these very early years, medical sciences, as we have now come to know them, were prominent and the first Professoriate at UCL included A.T.Thompson as Professor of Materia Medica and Pharmacy (later termed Materia Medica and Therapeutics). A subsequent holder of this post included Sydney Ringer (1878-87), who was most noted for his work on the isolated beating heart and the systematic design of salt solutions able to prolong its viability together with his seminal 'Handbook of Therapeutics' which eventually saw 13 editions between 1869-1897

In 1905. Pharmacology was established as a distinct discipline within basic medical sciences. Arthur R. Cushny, FRS (1866-1926) was the first holder of the newly instituted Chair of Pharmacology. After graduating in medicine from Aberdeen, Cushny had studied in Berne, Würzburg, and Strasbourg, where he became Assistant to the famed Oswald Schmiedeberg. In 1893, at the age of 27, he was appointed Professor of Pharmacology at the University of Michigan, Ann Arbor. Eight years later Cushny came to the Chair at UCL where he soon expanded the Department from the single room he had been given. Indeed he was able to raise the funds for the excellent building which the Department still occupies. His main interests were in the heart and kidney. His work on the involvement of calcium in the action of digitalis was prescient. He was interested in optical isomers and his data from an early clinical trial using hyoscyne isomers was used by W. S. Gossett (1908) in the pseudonymous paper that described Student's t test (The probable error of the mean). He published book a *Textbook of Pharmacology and Therapeutics* (eighth edition 1924). He introduced the Cushny myograph, an ingenious arrangement of counterbalanced levers that allowed the faithful recording of the rate and force of contraction of the rapidly beating animal heart. It was still in use in practical classes at UCL, and elsewhere, in the 1960s.

Cushny left UCL in 1918, to become Professor of Materia Medica and Pharmacology at Edinburgh. He was succeeded by A.J. Clark, FRS (1885-1941). After qualifying in medicine, and serving as a field medical officer throughout the First World War, Clark had been appointed Professor of Pharmacology at the University of Cape Town where he remained until accepting the Chair of Pharmacology at UCL in 1920. His influence on the subject was profound. The distinguished physiologist and Nobel laureate A.V. Hill had begun the quantitative study of the action of agonists on an isolated tissue (frog skeletal muscle) some

years earlier. Clark took this much further and extended it to examine the actions of antagonists. The data he gathered on the exact relationship between agonist concentration and response, and on how this changed in the presence of a competitive antagonist, were published in two classic papers in the Journal of Physiology in 1926. His contribution amounted to the transition of pharmacology from a descriptive subject to the quantitative science that it is today - this emphasis on quantitative approaches has remained strong throughout the subsequent history of the department. Clark's book '[The Mode of Action of Drugs on Cells](#)', (Williams & Wilkins, 1933) is a classic and the following quotation from it set the tone for the department for many years.

*...”In the first place, there is no advantage in fitting curves by a formula unless this expresses some possible physico-chemical process, and it is undesirable to employ formulae that imply impossibilities. It is a question of finding a few systems so simple that it is possible to establish with reasonable probability the relation between the quantity of drug and the action produced”.....*

While at UCL Clark wrote the first edition of his textbook 'Applied Pharmacology' in 1923, a book that was to be updated by two of his successors as Head of Department, H.O. Schild and H.P. Rang, and is still extant in the form of the widely used textbook 'Pharmacology' by H.P Rang, M.M. Dale, J.M. Ritter and P.K Moore (7th Edition, 2012).

In 1926 Clark followed his predecessor in moving to the University of Edinburgh. E.B. Verney was appointed to succeed him and continued Cushny's interest in kidney function. While at UCL Verney discovered the antidiuretic hormone and also the mechanism by which structures in the brain sense minute changes in blood osmotic pressure. Both findings were of profound importance for the understanding of water and electrolyte balance. Verney was also instrumental in arranging for Otto Kraymer to come to the Department, albeit for only a short period, following Kraymer's exclusion from all academic positions in German universities because of his objection to the expulsion of Jewish scientists from their posts. Kraymer was later to head the Department of Pharmacology at Harvard with the greatest distinction. In 1934 Verney vacated the Chair to take up an academic post at the University of Cambridge where he later became the first Sheild Professor of Pharmacology.

A year later J.H. Gaddum, FRS was appointed to succeed Verney at UCL. Like Clark, he had a profound interest in quantitative methods. He extended A.J. Clark's work on competitive antagonism, and applied the law of mass action to describe the relationship (the Gaddum equation) between receptor occupancy and the concentrations of an agonist and a competitive antagonist at equilibrium with the receptors in a tissue (the theory had been known since Michaelis & Menten 1914, but Gaddum was the first to apply it in a pharmacological context) He was also a master of bioassay which was then the preferred and often the

only way to determine the concentrations of biologically active molecules such as the more labile neurotransmitters and the neuropeptides.

On moving to the School of Pharmacy, Gaddum was succeeded by F.R. Winton. His main scientific interest was in the control of blood flow to the kidney. Winton stewarded the Department through the difficult war years when the Medical School was evacuated to Leatherhead and he also worked hard and successfully to ensure that pharmacology had an appropriate place in the preclinical curriculum. He also oversaw the extension of the Department, including the Pharmacology Lecture Theatre (now the Schild Theatre). He was the author, with Leonard Bayliss, of a widely used Textbook of Physiology.

The Department's tradition of interest in quantitative and mechanistic pharmacology was consolidated by Winton's successor, H.O. Schild FRS (1906 – 1984) who was to hold the Chair from 1961 to 1973. He had qualified in medicine in Munich and then worked with Straub, the leading German pharmacologist of the time. By good fortune, Schild had been accepted as a visiting worker by Sir Henry Dale and was in England when the National Socialists came to power. He decided to stay in Britain and became an assistant in the Department of Pharmacology in Edinburgh, then headed by A.J. Clark. When J. H. Gaddum was appointed to the Chair at UCL, he invited Schild to join him as a Demonstrator. So began his long association with UCL, interrupted only by his bizarre internment on the Isle of Man as an 'enemy alien' at the outbreak of the Second World War. Following his release (greatly aided by F.R. Winton's and Sir Henry Dale's appeals to the Home Office) he returned to his work in the Department, then based in Leatherhead, and in 1961 became Winton's successor as Head of Department and Professor of Pharmacology.

Schild was remarkable in the range of his pharmacological interests. He made major contributions to receptor pharmacology, to the understanding of the mechanism of histamine release and to bioassay. Like Gaddum, he used quantitative approaches whenever possible. He extended Gaddum's and Clark's work on competitive antagonism, and starting from the Gaddum equation, derived the relationship (the Schild equation) that should hold between the concentration of a competitive antagonist and the factor by which the agonist concentration had to be increased in order to restore a given response in the presence of the antagonist. This provides an estimate of the affinity constant for the combination of the antagonist with its receptor which is not dependent on the nature of the agonist.

Schild was also an effective yet generous and kindly Head of Department. He oversaw the planning and introduction of a three year B.Sc. course in Pharmacology which began in 1967 and continues to this day. Medical students were able to enter its final year and Schild, who never lost sight of the roots of the subject in medicine, was delighted that many took this opportunity.

Schild was succeeded by J.W. Black. FRS, an appointment that greatly pleased Schild. The two had come to know each other well when Schild had acted as a consultant to the then Smith, Kline & French at the time when Black was leading the team that developed the histamine receptor antagonists which were to transform the treatment of duodenal ulcer. The quantitative methods that Schild had pioneered were crucial for this work. Black was to introduce many changes in the Department. Perhaps the most important was the introduction of a BSc course in Medicinal Chemistry. His long experience in the pharmaceutical industry had convinced him that organic and physical chemists working on drug development with pharmacologists and biochemists would benefit greatly from a substantial knowledge of biology, certainly enough to allow them to understand and assess the kinds of measurements that their biological colleagues undertook. Though the students were based in the Department of Chemistry, they took also courses in physiology and pharmacology, particularly its molecular aspects. This BSc course, like that in Pharmacology, also flourished and continues today. Another important change was a sharp reduction in the number of experiments with animal tissues undertaken by medical students during their course in pharmacology. At the same time, the emphasis on the importance of observations on human subjects was increased. Regrettably, Black's appointment coincided with the onset of the straitened circumstances that all UK universities were to experience and that have continued in one form or another ever since. The changes he made helped the Department to adjust to these harder times. In the event, and to the regret of his Departmental staff, Black found that only the pharmaceutical industry could provide the facilities needed for the work he wished to pursue, and in 1978 he left to join the Wellcome Foundation.

Sir James Black, as he was to become, was succeeded by H.P. Rang FRS who had studied medicine at UCL and had also worked in H.O. Schild's laboratory while a medical student. Rang had previously been the Professor of Pharmacology at Southampton. He brought with him David Colquhoun who was also returning to the Department, having been appointed to the teaching staff by H.O. Schild before periods spent in Yale and then Southampton. These appointments greatly strengthened the interests and achievements of the Department in fundamental aspects of pharmacology, particularly the study of ion channels and receptors. In collaboration with Maureen Dale (also appointed during Schild's Headship), Rang prepared the first edition of *Pharmacology*, the successor to Wilson & Schild's *Applied Pharmacology*.

In 1983 Rang was offered and accepted the Directorship of the Sandoz Institute of Medical Research, a division of Sandoz, then an independent pharmaceutical company. The new Institute was located in UCL and developed a close relationship with the Department, both in teaching, to which members of the Institute contributed, and in research. As the Chair of Pharmacology had become vacant, an interregnum of four years followed during which the Department was headed by D.H. Jenkinson, yet another member of staff who had been invited to

join the Department by Schild. This period saw the first of the nation-wide Research Assessment Exercises, in 1986. The Department headed the list as indeed it was to do in each of the four others that followed in 1989, 1992, 1996 and 2002. Another important event was the merger of the Middlesex Hospital Medical School with UCL. A single Department of Pharmacology was formed with the academic and technical staff from the Middlesex moving to the UCL site. The merger coincided with the retirement of Professor F Hobbiger, holder of the Astor Chair of Pharmacology at the Middlesex.

David Colquhoun FRS was appointed to the established chair in 1985. It was subsequently dubbed the A.J. Clark chair, in honour of Clark's role in the establishment of quantitative pharmacology. His work, with statistician Alan Hawkes and Bert Sakmann (Nobel prize 1991) established the department as the world leader in the theory and experiment of single ion channels. He used these methods to solve the basic pharmacological problem of measuring separately the affinity and efficacy of agonists (also known as the binding-gating problem). On Colquhoun's retirement in 2004, this work was continued and extended by Lucia Sivilotti. Papers that she published in 2004 and 2008 constituted the first substantial advance in the understanding of partial agonism since cel Catillo & Katz (1957). In 2014 she was appointed to the A.J. Clark chair, after it had been vacant for 10 years. Her work is in the quantitative tradition that has been associated with the chair.

After Rang's reign the traditional role of Heads of Department was replaced by rotating headships that were no longer were associated necessarily with an established chair.

In 1987 D A Brown FRS was appointed as head of department with the title Astor chair (a title inherited from the Middlesex medical school). His is renowned for his discovery of the acetylcholine (muscarinic)-sensitive potassium channel (M channel). The growing importance of molecular biology led Brown & Colquhoun to apply to the Wellcome Trust in 1990 and they funded the establishment of the Wellcome Lab for Molecular Pharmacology which Colquhoun directed until 2004. He had previously held the same position at the School of Pharmacy. Brown's tenure saw a second merger, this time with the Department of Pharmacology at the Royal Free medical School.

Trevor Smart succeeded Brown to become head of department in 2002. In 2007, after 201 years of distinction, was destroyed in an exercise that saw the formal separation of teaching and research. Smart then became head of a huge merged unit, the Research Department of Neuroscience, Physiology and Pharmacology. This separation proved to be a failure, especially for teaching, but also because the morale that resulted from working in a world-famous department was lost. There is now widespread acceptance that if you offer degrees in a subject, there should be a department to back it up, to ensure that teaching is done in a

collegiate way, and to ensure that new appointments have the expertise to teach advanced courses.