CONTRIBUTORS TO MEDICAL SCIENCE

Sir George Pickering (1904 – 1982)

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I first met George Pickering when I was a medical student in the Anatomy Department at St Mary’s Hospital Medical School. He brought an amputated leg which had arteriovenous anastomoses within it, leading to overgrowth of the limb and subsequently to amputation to try and correct the high cardiac output and failure which it caused. He had injected the arteries with a barium paste and wanted someone to try and find the connections by simple dissection. As I liked dissection, I volunteered, and though I was unable to show any major connections, which were presumably at arteriolar-venular level, it was to mark the beginning of a very long apprenticeship.

My next encounter was during my clinical course at Harefield Hospital, to which the School had been evacuated during the war, and there are two vivid memories. The first is of the small man with hair blown in the wind, piercing blue eyes, talking over the side of a battered Morris Minor Tourer known as Cur, after its registration number; and the second is of the revelation of his teaching at the bedside. I had never before encountered anyone who so inspired the true spirit of critical scientific enquiry and, as I was later to learn, combined this with the qualities of a great physician. It took fortitude to withstand some of the fierce criticism of clinical histories painstakingly assembled, and woe betide those who used words loosely or inaccurately. His subsequent views on education derive much from his consuming interest in the use of English and the precision of mind required for its mastery. This of course showed when he was the sole editor of Clinical Science, as well as in many of his writings on education.

What then was the making of this clinical scientist and the nature of his contributions to medical research?

He showed his natural curiosity at an early age and it was through his interest in his native Northumbrian countryside that his original intention to study for a degree in agriculture was formed, but R. A. Peters persuaded him to read for a degree in biochemistry or physiology. He was awarded a scholarship at Pembroke College, Cambridge, and after a successful period in the basic sciences, his thoughts inclined towards medicine. He went to St Thomas’s Hospital with a clinical fellowship and after qualification was house physician to Sir Maurice Cassidy, a most observant cardiologist who first described the association between carcinoidosis and right-sided valvular heart lesions. Pickering wanted to combine scientific work of a physiological nature with the study of clinical problems, and by happy chance one of his famous Cambridge teachers, Joseph Barcroft, had a major effect on his future. Barcroft arranged a visit to Thomas Lewis at University College Medical School, then the founding home of clinical science in this country, and by good fortune a position had fallen vacant by reason of an incompatibility of temperament, which was not uncommon, but with the courage of self confidence, Pickering accepted the post.

His work at University College Medical School

The School was then at its zenith and there could not have been a better place for the development of clinical science than the environment provided by Wayne and Grant in Lewis’ Department, and T. R. Elliott’s Department of Medicine, where Himsworth, Smirk and McMichael were busy. This was the same Elliott who in 1904 had first proposed the adrenaline hypothesis of sympathetic transmission’ while working in Langley’s Department at Cambridge. In the Department of Pathology and Biochemistry, Boycott, Harrington, Cameron and Payling-Wright were all formidable intellects and their future careers were to represent a major portion of the broad base of medical research in this country. Pickering often liked to quote from the works of Wilfred Trotter,
that most unusual neurosurgeon whose philosophic essays relay the penetrating insight into human nature which undoubtedly attracted Pickering. In the next eight years Pickering developed some of the ideas and concepts to which he returned very frequently during the long course of his research career. The training he received from Lewis with its weight on accurate observation on subjects and patients, with a heavy emphasis on the simplest possible type of experiment, never left him. Lewis liked to work alone or at most with one other worker, and if you could stand up to his strong personality, and oppose his lucidly argued views, it was possible to survive. Pickering was one who could and did, but like all young men who wish to make their own mark, he left, but with respect and not acrimony.

Here it was that Pickering learned how to investigate the peripheral circulation by early studies on Raynaud's phenomenon, and the use of simple plethysmography and hand blood flow using calorimetry formed the basis for his very early papers on the mechanism of vasodilation and vasoconstriction in the hands. These were some of the earliest observations in the literature, which suggested not only sympathetic vasoconstrictor fibres but vasodilatory fibres to the forearm. He was to return to this later in patients with arterial hypertension when he made use of the knowledge that body warming removed sympathetic tone to the hand, and showed that the increased vascular resistance in the hand was not due to excessive sympathetic activity in most forms of arterial hypertension. At the same time he quite characteristically turned his curiosity about clinical phenomena into clear-cut investigations wherever he thought that the problem was of sufficient importance. So, for example, with Wayne he described the angina and intermittent claudication which came with anaemia and was corrected by a return to a normal haemoglobin level. Similarly he analysed the headache following injections of histamine and showed that it occurred at the nadir of blood pressure and cerebrospinal fluid pressure, and attributed the pain to the throbbing vasodilatation of the vessel wall with possible traction on the meninges. This recalls his later investigation of headache in high blood pressure, where he showed that it correlated with a high cerebrospinal fluid pressure only in the really severe grades of hypertension, the malignant phase.

He made three other approaches to which he was to return in a major way later and which came about because his interests had been aroused by the problems of causation in arterial hypertension. In 1936 he transfused blood from patients with essential hypertension into other subjects and failed to demonstrate a rise of pressure. Then by simple compression of the carotid sinus with measurement of the effects on blood pressure and pulse rate, he showed that there was very little difference in the response between normal subjects and those with hypertension. Then finally, just before he left University College Medical School, and was influenced, as were so many, by the striking demonstration of a rise of pressure produced by renal artery constriction, the Goldblatt experiment, together with Prinzmetal he rediscovered renin in extracts of rabbit kidney, where it had been described 40 years before in 1898 by Tigerstedt and Bergman. This led him to try and reproduce the Goldblatt experiment in the rabbit and, at about the same time in collaboration with Clifford Wilson, to study the acute arterial lesions produced by experimental renal hypertension. Once more he was to return again to the subject of arterial disease in his later years at Oxford.

His work at St Mary's Hospital

In building up clinical research work, Charles Wilson as the Dean, later Lord Moran, selected Pickering in 1939 as a likely leader, and when the Medical School was moved to Harefield Sanatorium at the outbreak of war, he continued, although on a reduced scale, to develop his experiments. His observations both on renin and its assay, and the type of hypertension produced by renal artery constriction in the rabbit, were probably the most important. He showed that partially purified preparations of renin infused intravenously in the rabbit consistently produced a diuresis and natriuresis, and he also developed a pressor assay for renin using the indirect method of measuring blood pressure with the Grant capsule on the central artery of the ear. At the same time he was beginning to marshal his thoughts on the quantitative description of hypertension by consideration of the relationship between benign and malignant hypertension. It has to be remembered that the term benign did have the connotation at that time of a process which did little damage, whereas everyone knew that malignant hypertension was a killing disease. Many also believed that it was a completely separate disease process in which the level of blood pressure was not accorded primacy. Pickering saw, however, that on the whole it was the level of pressure which was of great importance and that the degree of vascular damage was closely related to the level. It can be seen that these thoughts would lead naturally to his later well formulated
views on blood pressure as a continuous variable without arbitrary division into normotension and hypertension.

Influenced as always by the problems presented by his patients, he found time to start his observations on the nature of the pain due to peptic ulcer and this was when there was still support for the view that contraction of muscle around the bed of the ulcer might be a major cause. It was clearly established that the origin of the pain was acid acting directly on the bed of the ulcer and not due to sensations from the abdominal wall. Later, on his return to London after the war, it was clearly established that there were different patterns of acid secretion in gastric as opposed to duodenal ulcer. While at Harefield Sanatorium, intrigued by cases of constrictive pericarditis, he was able to show that most were probably due to tuberculosis, and this was a most important contribution since most people had been concerned with the end stage of the disorder, which had proved difficult to classify aetiologicaly. He always had a keen interest in the mechanisms of fever and his main influence there was to stimulate others to work on the problem after helping to start the investigations on a proper footing. From this, however, has flowed a considerable body of work on the nature of naturally occurring pyrogen and its site of action, and the ten years at St Mary's after the war marked perhaps the most productive time of his research career, since he was surrounded by young people from home and abroad who responded to his bubbling enthusiasm by working all the hours that were possible, and from it came the isolation of angiotensin and its investigation in man and animals, some initial thoughts on transient ischaemia of the brain and retina which allowed him to inveigh against the concept of spontaneous arterial spasm, and finally, probably the most important of his contributions, his studies on the inheritance and environmental factors in high arterial pressure. The sight of him in the laboratory with his sleeves rolled up and what was frequently known as his thoracotomy shirt, due to tears which he seemed secretly to delight in, was enough to carry all these projects along since everyone recognized they were in the presence of an elemental force.

The clear demonstration from his studies that there was not a sharp dividing line between normotension and hypertension has had an enormous influence on medical thinking, since it was allied to a quantitative approach which set standards of the greatest importance in this area of epidemiological medicine. He has left the concept of polygenetic inheritance with a marked environmental interaction as his major contribution, and this led to the famous Platt-Pickering controversy which at times raged with the fury of Huxley and Wilberforce over Darwinism in the last century. The attempt to demonstrate or deny biomodality in distribution curves of blood pressure occupied what may seem to many at this distance a disproportionate amount of mental energy, but out of it came a much greater appreciation of numeracy in medicine.

Strangely, he was not initially interested in the therapeutic revolution represented by the introduction of hexamethonium into the treatment of hypertension by the work of Paton and Zaimis, and he viewed the efforts of his younger colleagues to master its use with amused tolerance as they spent much of their time picking their unfortunate patients up from the floor, on to which they had collapsed, owing to the unpredictable nature of the oral absorption of the early ganglion blockers. Causation and mechanisms were always his greatest loves, which leads naturally to the final phase of his research.

Oxford

He was appointed to the Regius Chair in 1956, and proceeded to build up a completely new department devoted to clinical research. Here he returned to vascular disease and a reminder of one of his early observations, together with Lewis, in which they showed that a patient with gangrene of the finger tips did not have 'Raynaud's disease', but multiple recurrent embolization of the digital arteries from organic disease in the wall of the brachial artery as it crossed an elevated first rib. This had been reinforced by his thoughts on transient ischaemic attacks in the brain and retina which he believed were of the same nature, namely emboli arising commonly from the major arteries in the neck. His surgical colleagues, expert in vascular surgery, removed the more obvious source in patients, the atheromatous stenosis at the origin of the internal carotid, with apparent great success, even though the subject remains controversial. This and the subsequent work on the retina, with excellent observations on the way in which what were probably platelet emboli could be observed to come, to obstruct, and then to disappear, have had a very great influence on the clinical approach to stroke, and the prevention of so-called transient ischaemic episodes. This led him to return to the views of Virchow and of Duguid, who both felt that many atheromatous plaques in the walls of arteries were due to deposition of platelets, and subsequently of fibrin, and their ultimate incorporation in the wall. He used this opportunity once more to
attack the concept of vascular spasm and it would have been of great interest to hear his views on the subject of coronary artery spasm, while clearly it matters a great deal to know whether there is local pathological change in the region of a variable constriction.

A return to his original work on baroreceptors showed him that a more direct method of measuring arterial pressure was needed, and this led to the development of intra-arterial recording which could be maintained for days with full activity. Quite apart from the important studies which it led to on the physiology and pathology of the baroreceptors, he took an impish delight in demonstrating those tracings of blood pressure taken during all the many and various activities of which man is capable.

Assessment of his influence

It would be impossible to achieve this without giving due weight to his other contributions that had considerable influence on medical research. Editors of scientific journals had great influence in times when they largely carried the burden single handed, which was the case with Lewis and Pickering in respect of *Heart*, subsequently *Clinical Science*. Many authors had cause to thank him for improving their clarity of expression. It was appropriate that he gave one of the papers at the first meeting of the Medical Research Society, and together with his colleagues of like mind, he helped to make this Society of enormous importance in developing the spirit of scientific clinical research. For a young man to present a paper before the formidable group of research workers who were often given to trenchant critical enquiry, not always delivered in the most kindly spirit, embodied all that was implied in baptism by fire. Pickering was always a good questioner as well as an excellent analyst of ideas coming from description of work presented at the Society, which met with a regularity which of course is now regarded with disbelief. It did mean that all the promising young men in the land were seen and heard, and as an extended selection committee, played a very important part. Of his other writings I believe that his book on *High Blood Pressure* is the last great individual synthesis that was possible in the subject, ranging as it did over the history, current research, and the concepts resulting from research. It had a flavour that completely expressed all that I have attempted to describe about George Pickering.

His most important contribution I leave until the last. His ability to attract the young by his infectious enthusiasm for everything he did is my abiding impression of him as a young man, but with it there was a fierce passion for the truth as he saw it, which was embodied in his conversation, his use of English, both spoken and written, and in his assessment of people. He could always be roused, even as he grew older, by anything which smacked of loose thinking, and he had a turn of phrase which did not reject even coarse vulgarity as a weapon in his attack upon an alien creed. He divided people up firmly into black and white. There were no greys in George's world. If you were white, it was difficult to lose his regard even when disagreeing with him, but if you were black, it was almost impossible to come out of the shadow. His attitudes attracted research workers from the world at large, and the emphasis he placed on clarity of thought, on honesty of purpose, allied to a tendency to burst into Rabelaisian laughter, made the question at research meetings if he was not there the natural one of "How is George and what is he up to?". His biggest influence was the inculcation of attitudes which have stayed in the memory of so many of his pupils, and influenced their actions in research as well as the practice of medicine.