Obituary

Cyril Astley Clarke

The passing of Cyril Clarke marks the end of the era of great medical all-rounders. His career as a clinician ranged through life insurance practice, medical specialist in the navy, consultant physician, and later Professor of Medicine in Liverpool, and, finally, President of the Royal College of Physicians of London. His research contributions were equally broad based, spanning his classical work on mimicry in swallowtail butterflies to his enquiry into longevity by tracing and studying the lifestyles of centenarians who had received congratulatory messages from the Queen. He was one of the first in this country to appreciate that medical genetics, far from being a discipline which focuses on rare and esoteric diseases, has a major role to play across every aspect of day to day clinical practice. This led him to establish the Nuffield Unit of Medical Genetics in Liverpool, which became a stable for many who went on to develop this field throughout the United Kingdom and elsewhere.

But Cyril Clarke’s most important contribution to medicine, and one that reflects his flair and willingness to chance his arm in problems which were often outside his field of expertise, was his inspiring leadership of the Liverpool team that discovered how to prevent rhesus haemolytic disease of the newborn, one of the major advances in preventive medicine of the last half century. This work typified his unwillingness to be deterred by the gloomy prognostications of experts in their fields, who often told him that his thinking was way off the mark, and his instinctive gift for what Peter Medawar called “the art of the possible”, reflected in his ability for sensing the quality of his younger colleagues and the science that they were pursuing.

Cyril Astley Clarke was born in 1907. His father, Astley Vavasour Clarke, was a physician at the Leicester Royal Infirmary and one of the first to use x-rays in this country; his grandfather was senior surgeon to the same hospital. He was educated at Oundle, Caius College, Cambridge, and Guy’s Hospital Medical School. After three years in life insurance practice, which allowed him time to indulge in his passion for sailing and offered him the opportunity to examine Winston Churchill, he enrolled as a medical officer in the RNVSR and served throughout the war in the navy, ending his service by writing one of his first papers, on the neurological complications of malnutrition that he observed in British prisoners of war in Hong Kong.

After the war Cyril moved to Liverpool where he became Consultant Physician at the David Lewis Northern Hospital. Despite busy hospital and private practices he, together with his long time friend and collaborator P M Sheppard, began a series of classical experiments on the genetics of swallowtail butterflies, work which later stimulated his interest in medical genetics. The success of the team of young clinical research workers that built up around him left him less time for his clinical practice, and he was appointed Reader in Medicine at the University of Liverpool and, in 1963 on the retirement of Henry Cohen, he became Professor of Medicine, a post that he held until 1972. He founded the Nuffield Unit of Medical Genetics, which he directed from 1963 to 1972. On the year of his retirement he was elected President of the Royal College of Physicians of London, a post he held with great distinction and flair until 1977. From 1977 to 1983 he served as Director of the College’s Medical Services Study Group, and from 1983 to 1988 was Director of its Research Unit. Among his many other activities he served as President of the Royal Entomological Society and, much to his delight, President of the British Mule Society. He spent his later retirement in Liverpool continuing his work on the genetics of butterflies and in a characteristically broad range of medical research.
Cyril’s interests in butterflies, which started as a childhood hobby, was reawakened while he was serving in the navy and visited Australia. He had a childhood ambition to breed the swallowtail butterfly, *Papilio machaon*, and he developed a technique for making them mate by hand. By chance, he obtained a North American swallowtail, *Papilio polyxenes*, and was able to mate this with *P. machaon*. He produced F₁ hybrids, and then backcrosses, and hence discovered that their colouring reflects only a single gene difference between the two species. Philip Sheppard read of this work and contacted Cyril and thus started a long standing and extremely productive collaboration on the genetics of mimicry in tropical butterflies. The two of them also became interested in moths and industrial pollution and followed up the observations of Bernard Kettlewell on the adaptive changes in the colouring of moths in relationship to pollution. Starting in 1959, and working every year up to 1994, Cyril and his colleagues caught moths in June and July using a mercury vapour lamp. Overall, they collected 17,648 *betularia* and were able to relate the proportion of carbonaria to the level of pollution.

There seems little doubt that Cyril’s interest in medical genetics was stimulated by his work on butterflies. It was Philip Sheppard who suggested to him that blood group genetics might be a productive way into this field. Cyril started by examining the relationship between blood groups, secretor status, and duodenal ulcer and then turned his attention to rhesus haemolytic disease. After his student Ronald Finn confirmed the observation that ABO incompatibility between mother and fetus is protective against haemolytic disease in the newborn, and hearing of the transplacental passage of red cells from the fetus to the mother, Cyril and his colleagues evolved the notion of an XX chromosome complement in the newborn, and hearing of the transplacental passage of red cells from the fetus to the mother, Cyril and his colleagues evolved the notion of injecting mothers with anti-rhesus antibody (anti-D). Studies using male volunteers were initially unsuccessful because they were carried out with complete anti-Rh. But, at the suggestion of Ruth Sanger, they were able to prevent immunisation in a further set of volunteers by using incomplete anti-D. The story of this success was heralded in a local Liverpool newspaper with the headline “Men of Merseyside Mothers To Be”. The rest of this story is well known.

Cyril was a caring if slightly eccentric clinician, very much of the old school, who believed in minimal intervention. His advice to his new house staff on the use of drugs came, he claimed, straight from the mouth of one of his teachers at Guy’s, who, as he got older, restricted his personal pharmacopoeia to morphia and sodium bicarbonate, and was not too liberal with the bicarbonate.

As Professor of Medicine he led his department with a light touch, preferring to let bright youngsters go their own way, but always around if they needed support. His remarkable flair and enthusiasm, and his ability to sniff out talent and to pick research areas of importance, was undoubtedly the major factor which led to the wonderful achievement of the rhesus team, and to the success of the Department of Medicine at Liverpool and its major influence on the development of medical genetics.

As a person, Cyril was a complex mixture of a life long schoolboy, constantly bubbling with enthusiasm and new ideas, and yet at the same time he could appear to be rather distant, so that his students and junior staff sometimes found him difficult to approach and not a little terrifying. This was undoubtedly a reflection of his innate shyness; as they got to know him better he revealed his extraordinary warmth became apparent. He was extremely loyal to his staff and supported them throughout their careers, usually behind the scenes and often without their knowledge. In 1935, he married Frieda, or Féo as she was always known. Féo became an integral part of all Cyril’s work and his many other activities, which ranged from crewing for him in his annual small boat racing (not a relaxing pastime since Cyril had been an Olympic trialist and hated losing) to breeding swallowtail butterflies in captivity. It was a remarkable partnership; Cyril never fully recovered after Féo’s death in 1997. They are survived by three sons.

Cyril’s work was widely recognised. He was elected FRS and received many national and international awards. At the age of 88 years, still busy at his research, he wrote that he would very much like to know why butterflies have an XX chromosome complement in males and XY in females, yet the latter live much longer than the tempestuous XX males. “God moves in a mysterious way” he concluded. Certainly there can have been few more mysterious phenomena than the multifaceted talents, flair, and complexity and warmth of character of the man who wrote these words.

DAVID WEATHERALL

(This is an extended version of an obituary which appeared in *The Guardian*.)
Cyril Clarke, *Journal of Medical Genetics*, and the foundation of clinical genetics

Cyril Clarke became editor of *Journal of Medical Genetics* in 1969, five years after its inception, and he continued to edit it for the next 15 years. A glance at both the content and the editorial board members of the Journal in those early years shows the range and quality of its content and the calibre and diversity of those he enlisted in running it. Basic science and clinical expertise were well balanced, setting the pattern for the future. When I succeeded him as editor in 1985, it was indeed a hard act to follow.

Cyril’s great age (93 at his death) means that most people working in the field now will have little direct (or perhaps even indirect) knowledge of his key role in founding and shaping what is now the specialty of Medical Genetics. His natural shyness and reticence have added to this, and while his autobiographical notes, written at the age of 88 and published as “88 years of this and that” are a delight to read, they are typically unassuming and light hearted.

Like most people of true genius, he was far ahead of his time; I have only recently come to realise how far ahead. He believed passionately that genetics should form part of all medical practice and thinking; only now, with the understanding of the genetic component of common diseases, is this beginning to happen and still only to a limited extent.

As an adult general physician he saw genetics as applying equally to all age groups, not just as a paediatric interest. A direct result of this has been the development of UK Clinical Genetics as a balanced specialty with recruits from both adult and paediatric medicine, in sharp contrast to most of continental Europe and Australia. Most of those who worked with Cyril (“trained” would not be quite the right word) and who went on to found departments in the UK and North America came from and kept links with adult medicine, the value of which is now being appreciated. The close link with Victor McKusick’s Baltimore department reinforced this.

Equally ahead of his time was Cyril’s recognition that “model organisms”, as they are now considered, could be used directly to gain insights into human disease. Although a number of the pioneer geneticists were keenly interested in both human disorders and basic genetics, none was a practising clinician. Many of the insights to be found in his book “Genetics for the clinician” remain as relevant today as when it was written almost 40 years ago. His Lepidoptera may not have been the most orthodox choice for model organisms, but at that time their population genetics and evolutionary biology were much better documented than that of *Drosophila* (and he would undoubtedly have commented that they were much more fun to work with!). His partnership with Phillip Sheppard, whom he persuaded to move to Liverpool from the Oxford School of Evolutionary Genetics, was crucial in developing this basic work and in ensuring that it kept a vigorous scientific basis.

Cyril’s lasting scientific reputation will rightly rest on the prevention of rhesus haemolytic disease by immunological approaches, work of remarkable originality that should logically have come from basic scientists, paediatricians, or obstetricians rather than from a clinician quite unconnected with the field. Again, this immense success of “genetic therapy” was far ahead of any other applications, to the extent that it is often no longer regarded as a “genetic” success and is increasingly taken for granted. The book in which he brought together all the key papers deserves to be better known.

How Cyril Clarke managed to achieve all of this from a background of “ordinary” general medicine and in a provincial university academic base is to me both extraordinary and inexplicable. Anyone who had the pleasure of working in the David Lewis Northern Hospital in Liverpool (whose initial impressions in the 1960s could be best described as Dickensian) would agree that it was not the natural nurturing ground for academic genius. Furthermore, Cyril only switched to academic medicine at the age of 50 and undertook all his key research over the next 15 years, a “late developer” if ever there was one.

An equal puzzle is how he was able to remain part of the “medical establishment”, becoming President of the Royal College of Physicians on retiring from the Liverpool Chair of Medicine. It would be good to imagine that this in some way reflected success in persuading the College that genetics was important in medicine, but sadly I do not think that was the case. They certainly recognised his scientific talent and his Rh work, but few of his contemporaries there understood his ideas, even to a limited degree, and his “butterfly work” was, I suspect, tolerated as the pastime of an otherwise great man rather than appreciated for its scientific merit.

Anyone who, like myself, had the privilege of working in Liverpool with Cyril Clarke, was fundamentally influenced by the experience and also by the friendship and support that characterised his whole department. In my own case, both friendship and scientific contact continued over the next 30 years (in late 1997 I received with a note his latest reprint on population genetics’ written aged 90!). Only after losing his dearly loved wife Feo, two years ago, did his own health rapidly decline. Cyril Clarke’s death does indeed, as David Weatherall states, mark the end of an era. Fortunately, though, his influence lives on in the field of Medical Genetics today with its vigorous combination of clinical and scientific
Persisting memories of Cyril Clarke in Baltimore

The passing last Fall of Cyril Clarke brought back memories of pleasant and productive interchanges between Liverpool and the Johns Hopkins Hospital over a 20 year period or more beginning in 1957. Cyril was a central figure in those transatlantic collaborations in training and clinical research.

Medical genetics was institutionalised at Johns Hopkins on 1 July 1957, when the multifaceted chronic disease clinic created by Dr J Earle Moore became the base for a medical genetics programme, the Division of Medical Genetics. The Moore Clinic very quickly became synonymous with medical genetics at Johns Hopkins. Although the Medical Genetics Division was a section of the Department of Medicine, its purview encompassed all ages and all specialties, with clinical care, research, and teaching, as in other specialty divisions.

The first visitor to the Moore Clinic from Liverpool was Richard McConnell, who spent a time there during a grand tour in Iowa and elsewhere in the United States, pursuing his interest in ABO/secretor polymorphism in gastric cancer and peptic disease.

Anne and I first met Cyril and Féo in 1956 at the first World Congress of Human Genetics in Copenhagen. The friendship was solidified and the exchange with Baltimore established in our visit to Liverpool in early September 1958, which included a visit to the butterfly laden Clarke ménage. Cyril and Féo had been in Montreal to attend the International Congress of Genetics in August 1958. Cyril confessed serious withdrawal symptoms requiring him to go to the Royal Vic to see outpatients! On that visit, arrangements were firmed up for the first visit of Liverpudlians to come to the Moore Clinic, to acquire a BTA (Been to America) degree. That was David A Price Evans, who during his stay in the Moore Clinic did much to initiate the field of pharmacogenetics, by defining the genetics of isoniazid metabolism. Price Evans was Cyril Clarke’s successor as Professor of Medicine at Liverpool. During our visit to Liverpool, Malcolm A Ferguson-Smith came down from Glasgow to make arrangements for his sojourn in the Moore Clinic which began in February 1959. At that time, he started what may have been the first hospital based cyto genetics laboratory in the United States.

Over the next 20 years or so, the large number of Liverpudlians who were fellows at Johns Hopkins included Peter Brunt, J Michael Connor, Brian Hanley, Peter S Harper, F Michael Pope, Brian Walker, David Weatherall, and J C Woodrow. Ronald Finn and “Johnny” Woodrow worked particularly with Julius R Krevans pursuing the brilliant hypotheses of Cyril concerning the mechanism and prevention of erythroblastosis fetalis. David Weatherall worked first with Ned Boyer in the biochemical genetics section of the Moore Clinic before establishing clinical connections with Dr C Lockart Conley in the study of haemoglobinopathies and with others in the department of Howard Dintzis in the study of basic mechanisms in the thalassaemias.

In 1976, while Cyril was President of the Royal College of Physicians, Anne and I stayed in his flat at the College. During that time I gave the Lilly Lectures and acquired an honorary MD from the University of Liverpool. It was a rare privilege, in 1977, to receive a Gairdner Award in Toronto at the same time as did Cyril.

In a few words it can be stated that Cyril left his mark on medical genetics by his penetrating and inquisitive mind and by his encouragement of a whole generation of students. Extending from his study of butterflies, he was thinking and speaking about the role of polymorphisms in multifactorial disorders, what we now call complex traits, far ahead of his time.

We at Johns Hopkins are much indebted to Cyril for the able protégés he sent to Baltimore in the formative years of medical genetics here.

VICTOR A McKUSICK