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David Weatherall


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INTRODUCTION

Cyril Clarke was an outstanding physician, medical scientist and lepidopterist. His career was unusual in that he developed a serious interest in medical research only after many years in clinical practice, a change of direction from the life of a busy consultant physician that was undoubtedly stimulated by his lifelong interest in butterflies. This remarkable transition was to result in his leading the team in Liverpool that developed a method for preventing rhesus haemolytic disease of the newborn, one of the major advances in preventative medicine of the second half of the twentieth century.

EARLY LIFE AND FAMILY

Cyril was born in Leicester on 22 August 1907 to Astley Vavasour Clarke (1870–1945) and Ethel Mary (Poppy) Clarke, née Gee (1872–1966). His father and paternal grandfather were both doctors in Leicester. His grandfather was shot by a deranged patient in 1900 and died a year or so later. His father, a physician at Leicester Royal Infirmary, was one of the first in the UK to use diagnostic X-rays. During his period as President of the Leicester Literary and Philosophical Society, in about 1911, he suggested that a university should be established in the town and, later, he was one of the founding members of Leicester University. He was also a city councillor and Deputy Lieutenant of the County of Rutland. Cyril’s maternal grand-
father, Henry Simpson Gee, founded the boot and shoe firm Stead and Simpson, and at one time was Chairman of the Midland Bank.

Cyril had two sisters, Ethel (born in 1900) and Helen (born 14 months after Cyril). The family lived in Landsdowne House, Leicester, together with several maids and a chauffeur, Powell, who had been the family coachman in the days when they travelled by coach and horses. In 1917 Cyril’s father developed the bizarre notion that Germany was about to bomb Leicester from its Zeppelins and hence Cyril and Helen were evacuated to a small village, Houghton-on-the-Hill, about six miles away. During their brief stay in Houghton their education was continued by a 16-year-old governess, Margaret Foster. Cyril recalled later that it was ‘Fossie’ who introduced him to the joy of collecting butterflies and moths, an obsession that, except for the period during which he boarded at Oundle, remained with him for the rest of his life.

Before he left home for Oundle, Cyril spent several years at Wyggeston Grammar School in Leicester, where he came under the influence of a ferocious headmaster, Jimmy Went, a classicist. His report for the winter term, 1918, aged 11, shows an ‘excellent’ for Latin, while the section on science is left blank. There were, however, signs of his curiosity and potential as a scientist, even at this early age. In the same year he kept his first scientific journal, recording the transactions of the Leicester Entomological Society. Together with a close friend, his first cousin Harry Gee, he built a laboratory at his home and acquired a balloon-filling apparatus. Between 1923 and 1926 Cyril and Harry sent up over 1000 different-coloured balloons with a label attached, requesting that the finder return the balloon remnants and answer various questions regarding location, date, time, etc. Two hundred and twelve balloons were returned, 48 of which covered more than 50 miles, a few reaching mainland Europe. In 1923 Cyril and Harry went to the Bagworth Colliery, owned by Harry’s father, and investigated the work of the miners; two small pieces of coal are preserved in their minute book.

In September 1921 Cyril left home to board at Oundle. He was later to write:

… at Oundle the butterfly nonsense was soon knocked out of me. I spent most of my early days at the school endeavouring to hide from my contemporaries that I had previously attended the ‘local grammar’ and had not been sent away to a prep school. Contrary to the belief of many that I benefited from the teaching given at Oundle in science, I was usually bottom of my class in that subject and top in classics.

Indeed, Cyril’s reports from Oundle show that in the Michaelmas term, 1923, he switched from the ‘classical side’, where his reports tended to be very good or excellent, to the ‘science and engineering side’, where he was rated ‘good’ or ‘satisfactory’, though ‘weak’ when it came to exams.

UNIVERSITY, MARRIAGE, AND EARLY DAYS AS A PHYSICIAN

Cyril left Oundle in 1926, and after a brief visit to Strasbourg University to improve his French and German he was admitted to Caius College, Cambridge, to read Natural Sciences with the objective of pursuing a career in medicine. Although this seems to have been an obvious choice for somebody who was brought up in a medical atmosphere, Cyril wrote later that he and his sisters became strongly ‘anti-medical’ over the years. However, he felt that this had been of great value to him subsequently because it helped him to understand a patient’s point of view! He left Cambridge in 1929 with a second-class degree in Natural Sciences and a
Cyril Astley Clarke

scholarship to Guy’s Hospital Medical School. After qualifying in medicine in 1936 he held house physician posts with Dr John Ryle, who was one of the major influences on his future career. He also worked with Dr J.J. Conybeare and Dr C.P. Symonds, whose efficiency and speed of work also impressed him greatly. While a medical student at Guy’s he was the British Medical Association prize essayist in 1933.

Like many doctors who have completed their first junior hospital posts, it seems that Cyril was not clear where his future in medicine might lie. And so, after brief periods in dermatology and physiology, from 1936 to 1939 he worked in a life insurance practice in the City. Although this apparent lack of ambition did not please his father, Cyril seems to have been happy enough in insurance medicine, not least because it gave him the opportunity to indulge his other great love, sailing, at the weekends. He recalled that his major claim to fame at this time of his career was to examine Winston Churchill, who smoked a cigar throughout his medical examination.

However, a closer examination of Cyril’s career during this period suggests that he was far from unambitious. He passed the examination for Membership of the Royal College of Physicians of London in 1935 and obtained the MD degree of the University of Cambridge in 1937. And like everything he did, sailing was no idle pastime. Because of recurrent seasickness he diverted to dinghy racing; 12-square-metre Sharpies before the war, and Fireflies and the bigger dinghy classes afterwards. He has written that he regarded himself as a competent club helmsman but that when he was selected for the Olympic trials at Torbay in 1948 he was soon sorted out!

Cyril’s love of sailing was also responsible for an event that, as recounted later, was to play a major part in his success as a scientist. In 1934, when visiting the Itchenor Sailing Club in Chichester harbour, he met Frieda M.M. (Feo) Hart. They were engaged three months later and were married on 27 December 1935 in the chapel of the Savoy. Their eldest child, Miles, was born in 1936. Miles David Astley was also educated at Oundle, and after a period working with a Trinidad asphalt company he established his own business, Miles Macadam Surfacing Limited, in Cheshire. Their second son, John Stephen Astley, was educated at Rugby and Oxford and obtained a first-class honours degree in Greats. His career in journalism began as a member of the news team in Times Newspapers, after which he joined the BBC television team in Panorama and later moved to Granada Television, among other things to work on the programme World in action. Their youngest son, Charles Richard Astley, was educated at Rugby, Caius College, Cambridge, and Guy’s Hospital Medical School. He later became a consultant neurologist at St Bartholomew’s Hospital, London, and was a member of the Himalayan expedition in 1969 and several other major international climbing expeditions.

NAVAL SERVICE AND FIRST CLINICAL RESEARCH

Cyril was starting to get bored with insurance work, and war was threatening. Hence, in June 1939 he joined the Royal Naval Volunteer Supplementary Reserve and was called up on 3 September 1939. He spent the first six weeks of the war improving his snooker at Chatham and was then posted to H.M. Hospital Ship Amarpooora, which was being fitted out in Liverpool. He sailed for Scapa Flow in November, where he was stationed for over two years; his ship acted as a base hospital because there was only a sick bay on shore. Cyril recalled how, just before they arrived in Scapa, H.M.S. Royal Oak had been sunk by the German
submarine-commander Prien, which had crept into the Flow. It was a particularly tragic episode; the losses on the battleship were terrible, largely because the warning had been given erroneously as an air attack so that all the crew went below decks. Although most of the patients that Cyril dealt with on the *Amarapoora* had common, day-to-day ailments he saw a number of patients with meningococcal septicaemia, some quite atypical, who responded to sulphonamides, which had just become available (1)*.

In 1942 Cyril left Scapa and sailed to North Africa via Gibraltar, where he was severely ill for two weeks with infectious hepatitis. His next voyage took him from Gibraltar to Algiers, where his ship took on board many sick and wounded to be moved home, and also some mentally deranged American soldiers. He recalled later how he was put in charge of the latter and how terrifying they were to look after, although he seems to have managed to sort them out. The journey home to Avonmouth was fairly uneventful except when a Luftwaffe plane flew straight over the mast; some German prisoners of war (POWs) reassured Cyril, saying that there was nothing to be frightened of because not even the British bomb hospital ships! After returning to Avonmouth Cyril left the *Amarapoora* and was appointed as a medical specialist at the Royal Naval Hospital, Seaforth, Liverpool. There he met several consultants in the Liverpool hospitals who were to play a major role in his future career.

In October 1944, after spending a period of leave with Feo in the Lake District, Cyril returned home to find a telegram that read ‘proceed to Royal Naval Hospital, Sydney, Australia’. And so, in November 1944 and for the second time, Cyril sailed from Liverpool, this time aboard a large liner that had been christened the *Empress of Japan* but which, for obvious reasons, had been renamed; it was now the *Empress of Scotland*, although all the notices in the cabins were still in Japanese. He arrived in Sydney via the Panama Canal in 28 days and found that the town was lit up for Christmas. After some delay the Naval Hospital was finally established and he spent his time looking after patients with a wide variety of illnesses, interspersed with dinghy sailing with Ian Sneddon, the Sheffield dermatologist, in Botany Bay.

Shortly after the defeat of Japan a large number of British POWs from Hong Kong were moved to the Naval Hospital in Sydney. It was in defining the extraordinary array of neurological problems from which these troops suffered that Cyril had his first experience of clinical research. The syndrome that he described was remarkably constant, both in presentation and time of onset. Within three months of imprisonment they developed swelling of the ankles followed by weakness and paraesthesia (tingling) of the limbs, difficulty in walking, and failure of vision and hearing. About a year later skin lesions suggestive of pellagra developed, together with a painful dermatitis of the scrotum. At this stage nearly all of them experienced a characteristic burning sensation involving the feet, a condition which had become known in the POW camps as ‘electric feet’. Most of them had lived on a daily ration of less than one pound of rice and Cyril thought that the condition must represent some form of nutritional neuropathy, although the response to improved diet and vitamin therapy was poor. Cyril and Ian Sneddon published a clinical description of these patients in 1946 (2). Unknown to them, a paper describing a very similar syndrome in German prisoners of war had been reported by Spillane & Scott (1945). Seven years later Cyril followed up some of these patients and found that many of them were still severely disabled (3). Although it seems likely that this was a dietary-deficiency disorder its aetiology remains obscure.

* Numbers in this form refer to the bibliography at the end of the text.
Cyril returned from Australia on a P&O troopship in 1945 and arrived in Southampton at Christmas-time in the pouring rain. After staying with his family at Leicester for a while he applied for a registrar’s post at the Queen Elizabeth Hospital, Birmingham. The major problem that he had in obtaining this post was to prove, unequivocally, that he was medically qualified; it turned out that his predecessor, classified as the best registrar the hospital had ever employed, had been an unqualified physiotherapist! However, his stay in Birmingham was short and, after encouragement from some of the physicians and surgeons he had come to know in wartime Liverpool, he was appointed to a consultant physician’s position post there in 1946.

**LIVERPOOL**

When Cyril moved to Liverpool as consultant physician to the David Lewis Northern Hospital he was already close to 40 years old and had no track record in academic medicine. Indeed, it is unlikely that he had ever dreamt that he might end up as a professor of medicine. Remarkably, his extraordinary successes as a physician scientist were nearly all achieved during the last 20 years of his career.

After he had settled down in Liverpool, and established a beautiful home in Caldy on the Wirral peninsula, Cyril directed his extraordinary energy into building up his clinical practice and in pursuing his all-absorbing interests in butterflies and sailing.

**Butterflies**

Cyril’s interest in butterflies had been rekindled during his spell in Australia, where he became fascinated with monarchs and swallowtails. Now armed with a large greenhouse in his new home he started to study the swallowtail butterfly, *Papilio machaon*. Because male and female butterflies rarely mate spontaneously in a cage, and need space for courtship flights, Cyril’s first task was to devise a technique to persuade them to mate; ‘hand-mating’ as he later christened it (4). Although he became reasonably proficient at this unlikely activity, there is no doubt that it was the more delicate, feminine touch of Feo, who soon took over from him, that was the reason for so many later successes. Using this method they were able to mate the black North American swallowtail, *Papilio polyxenes*, to a male *P. machaon*. Much to their surprise they were able to produce F1 hybrids and then backcrosses that were either yellow or black. Cyril interpreted these findings as indicating that there is only a single gene difference between the two ‘species’ (15).

In October 1952 Cyril answered an advertisement from a young geneticist, Philip Sheppard (F.R.S. 1965), who was at that time working in the department of E.B. Ford, F.R.S., in Oxford, asking for some *P. machaon* pupae. Shortly afterwards Cyril met Philip and they agreed to collaborate, first to study the genetics of swallowtails generally and later to analyse the mechanisms of mimicry in swallowtails and other tropical butterflies. During its early days this work was performed by correspondence but in 1956 Philip obtained a senior lectureship in genetics in the Department of Zoology at Liverpool. He later became Reader in the Sub-Department of Genetics and was appointed to the first professorship of genetics in Liverpool in 1963. Until his death in 1976 he and Cyril continued to collaborate on many aspects of butterfly genetics.

Their investigations of mimicry used three classical Batesian mimics: *Papilio dardanus*, *Papilio polytes* and *Papilio memmon*. The general principles on which they worked were to
try to analyse genetic differences between the various forms, first within one race and then between races, and in particular to try to obtain crosses in which a mimic found in one area was not found in another (13).

Work on *P. dardanus* suggested that perfection of mimicry is dependent on the whole genome, and where such a co-adapted gene complex was modified by hybridization to a race in which a particular mimetic form was rare or absent, the pattern of the mimic became either less perfect or imperfect as the appropriate modifiers became fewer. This was particularly well demonstrated in *P. dardanus meriones*, the race from Madagascar where mimicry of any kind in this butterfly is non-existent. The results of the various cross-breeding experiments strongly supported the views of Sir Ronald Fisher, F.R.S., and E.B. Ford with regard to the evolution of mimicry, namely that a mutant, dominant in effect, gives some resemblance to the model and that perfection is obtained by the gradual accumulation of modifiers (6). Cyril and Philip also found that a combination of several characters was responsible for the various wing patterns and suggested that what seemed to be a multiple allelomorphic series of about 12 units was, in effect, a supergene with a limited number of alleles at several closely linked loci. Within this region, crossing-over could occur; on this assumption it was possible to explain some of the rarer forms and also those that, although non-mimetic, were strikingly dissimilar from the primitive male-like form. These results were confirmed and expanded by studies of *P. polytes* and *P. memmon*.

Cyril and Philip extended their studies of the genetic mechanisms for the mimetic properties of butterflies to a variety of other types, including *Papilio glaucus* and the nymphalid butterfly *Hypolimnas bolina*. The latter, which they studied in Sri Lanka in 1974, turned out to provide a striking contrast to the papilios. The female is monomorphic and had been considered to be a good Batesian mimic of various species of *Euploea*. However, uncharacteristically, where it becomes polymorphic, in the east of its range, it is non-mimetic. Although they were not able to account for the large excess of females, studies in collaboration with Miriam Rothschild (F.R.S. 1985) and Neville Marsh showed that *H. bolina*, when its larvae feed on sweet potato but not when reared on other food plants, contains cardioactive substances. It therefore seemed that *H. bolina* is a Müllerian or Batesian mimic according to the larval food-plant.

After Philip’s death in 1976 Cyril continued many of the studies that they had initiated together. One of these involved a large-scale analysis of the reasons for the morphological variability of the scarlet tiger moth, *Panaxia dominula*. This moth had been found principally in colonies in the south of England, where three genetically controlled forms were observed. The reason for the variation in distribution of these forms had been a subject of considerable controversy between Ford and Fisher, revolving around the question of whether their relative proportions were due to selection or drift. Philip had conceived the idea of starting colonies in regions in which *Pan. dominula* does not occur naturally and where there would be no contamination from other colonies. In 1961 he had put down a number of newly hatched caterpillars obtained from Cothill, near Oxford, on a disused railway line on the Wirral, close to Cyril’s home. Cyril rediscovered this colony in 1988 and analysed the proportions of forms annually until 1995, finding that their patterns were compatible with random mating, suggesting that particular forms had not come under any local selection (16).

Another long-term series of investigations that were performed by Cyril with the earlier help of Philip concerned the problem of industrial melanism and the peppered moth, *Biston betularia*. Before 1840 the peppered moth occurred in only one form, a pale variety, *f. typica,*
though there was a very occasional black mutant, *f. carbonaria*. However, with the coming of the Industrial Revolution the latter form prospered and by the end of the nineteenth century the moths were nearly all black around large cities, the explanation being that *f. carbonaria* was protected from birds by its camouflage when resting on the polluted bark of trees. Cyril’s home was on the edge of the Wirral peninsula, close to Liverpool and hence to one of Britain’s worst areas of industrial pollution. However, a variety of clean-air acts were being passed and, encouraged by a visit to his home by Bernard Kettlewell in 1956, Cyril decided to conduct a survey of the different forms of *B. betularia* on the Wirral peninsula. Starting in 1959, and continuing every year up to 1994, with the help of his friends he caught moths each night in June and July by using a mercury vapour lamp. This was not as easy as it sounds. Having had one of Cyril’s moth traps in my garden I remember well the annoyance it caused to our neighbours when it lit up the sky every night just as they were retiring. But despite these social irritations, between 1959 and 1994 Cyril was able to catch no less than 17 648 *B. betularia*, nearly all males. During the early part of these studies there was an extremely high proportion of the black mutant, *f. carbonaria*. Interestingly, in about 1975 the proportion of *f. carbonaria* started to decline, and by 1994 it had been reduced to 18.7% from the figure of 94% in 1959, a change that might at least in part reflect attempts at decreasing industrial pollution in Merseyside over that period. Cyril wrote extensively about these studies and some of the important unanswered questions that this work left behind (14, 16).

There is a memento to the work of Cyril and Philip Sheppard in the form of the Clarke–Sheppard–Gill collection of butterflies and moths in the Natural History Museum. This was started in 1982 and contains some 5000 specimens in 132 drawers, together with reprints of the papers that they wrote together.

**Human genetics, blood groups and disease, and the prevention of rhesus haemolytic disease**

In the early 1950s Cyril was a busy general physician who was spending most of his spare time breeding butterflies and learning about the complex genetic mechanisms of mimicry. Although at that time genetics had very little place in clinical practice it is not surprising that he began to wonder whether the two halves of his life might be in some way connected. As he recalls later (15) he was motoring on the Norfolk broads with Philip Sheppard and asked him for his opinion. Philip’s view was that studies of human blood groups and disease might be a good starting point. This is not surprising. In the early days of human genetics blood groups were the only well-defined genetic markers and offered the only possibility for linkage studies. Furthermore, geneticists such as E.B. Ford of Oxford, in whose department Sheppard had worked, were already raising the possibility that factors such as disease might have been responsible for maintaining the polymorphisms of the ABO and other blood-group systems.

Merseyside, with its high-density population and relatively small area, seemed an ideal region for human population-genetics studies. Cyril started to gather round him a small team of young doctors at the David Lewis Northern Hospital to study the relationship between different diseases and blood groups. He was encouraged in this direction by a paper by Ian Aird and his colleagues at the Hammersmith Hospital (*Aird et al. 1954*), which suggested that there was a strong association between blood group O and peptic ulcer. Guided by Philip Sheppard, who provided invaluable advice about the methodology and statistical approaches to population studies of this type, Cyril’s group demonstrated an association between group O and duodenal ulcer, and later found that this was particularly strong in those with group O who were also non-secretors of blood group substances (5). At first this work was criticized by several
geneticists, including L.S. Penrose, F.R.S., who thought that the findings might reflect racial stratification and suggested that the studies should be repeated with unaffected siblings as controls. After about 500 sibships had been obtained, the previously noted association between peptic ulcer and group O became non-significant, although it still seemed to go in the right direction. Although this result shook Cyril, Philip remained unperturbed and suggested that more data were required. When these were finally obtained and were combined with similar data from the USA, the association was shown to be real, although the mechanism has never been determined.

While this work was evolving, a paper had appeared from the USA suggesting a strong association between duodenal ulcer and a particular rhesus blood group genotype and also with the MN blood group. When these findings were discussed with W.T.A. (‘Bill’) Donohoe, the technician who played such a vital role in all Cyril’s work on blood groups, Donohoe suggested that the American results might be an artefact caused by temporary changes invoked by blood transfusion. Cyril’s team repeated the American work and found that this was indeed so, and that when non-transfused patients were tested the association vanished (8).

Cyril’s next studies of the relationship between blood groups and disease, and those that led to his most important work, were also directed at the rhesus blood group system. In all his later writing about this period, Cyril insisted that the study of the rhesus blood group system was a direct extension of his work on mimicry in butterflies; he likened the closely linked Rh loci on chromosome 1 to similar sets of linked genes responsible for mimicry in swallowtail butterflies (16). Although the analogy stretches the imagination, regardless of the reasons Cyril decided to look again at some older observations on the relationship between the maternal ABO blood group system and the likelihood of rhesus sensitization and the development of haemolytic disease of the newborn.

In the late 1950s, young doctors often approached Cyril to ask for advice about research projects that they might perform to obtain the degree of MD by thesis. In 1957 Cyril suggested to one such doctor, Ronald Finn, that it would be interesting to re-examine the observation that foeto-maternal ABO blood group incompatibility protects against the development of rhesus haemolytic disease of the newborn. Finn’s studies confirmed this. Furthermore, while he was finishing off this work two important papers appeared. First, Kleihauer and his colleagues in Germany demonstrated that it is possible to identify foetal cells in adult blood by a simple acid-elution slide-staining technique (Kleihauer et al. 1957). This method was applied by Alvin Zipursky and his colleagues in Canada to demonstrate that it is possible to identify foetal erythrocytes in the maternal circulation (Zipursky et al. 1959). Finn used this technique to analyse the frequency of the cross-placental passage of foetal cells in pregnancy and found that they are present in the blood of nearly 12% of women post partum. He also noted an association between the development of Rh antibodies and the size of these foetal bleeds into the maternal circulation. Furthermore, foetal cells were never found in maternal blood when the foetus and mother were ABO incompatible. It therefore seemed that circulating Rh-positive foetal cells in an Rh-negative mother might be similarly eliminated by the administration of anti-D, thus preventing Rh sensitization of the mother. A preliminary set of experiments in male volunteers suggested that this might be so (7).

These early successes suggested to Cyril and his colleagues that there might be a genuine possibility of preventing rhesus haemolytic disease of the newborn, at that time the cause of many thousands of deaths of newborn babies. The team that worked on this project consisted of Ronald Finn and Cyril’s long-standing friends and collaborators Richard McConnell and
Philip Sheppard; it was later joined by John Woodrow, a clinical immunologist and rheumatologist, and Shona Towers, an obstetrician. All the laboratory work was led by Bill Donohoe, and the group obtained considerable help on the blood transfusion aspects of the programme from Dermot Lehane of the Liverpool Blood Transfusion Service.

The next set of studies set out to confirm and refine these preliminary results. Experiments in male volunteers analysing the clearance of Rh-positive cells by giving predominantly complete (19 S) anti-D serum suggested that immunization was enhanced rather than prevented. However, using a different approach, namely giving incomplete (7 S) anti-D the results seemed to be much more promising. Furthermore, the team was able to obtain some Ortho anti-D γ-globulin and this was found to be much more effective than the high-titre serum that they had been using. A further set of studies, this time on female volunteers, suggested that they were on the right line, and sequential analyses of the blood of pregnant women indicated that the major transplacental passage of foetal cells probably took place either just before or just after delivery. After seminal papers, which summarized these results (9, 10), Cyril’s team felt that they were now ready to perform a clinical trial for the prevention of rhesus sensitization in pregnant women.

The first trial was conducted jointly between several centres in England and in Baltimore, Maryland, and it demonstrated that the injection of anti-D, given shortly after delivery, resulted in no case of Rh immunization in 78 treated women; 19 women showed immunization in a similar number of controls (11). By 1971 the authors of the combined trial published a follow-up of the women who had been treated in the first study and found that the failure rate was only 2.3%, whereas 30.7% of the controls were immunized after their second Rh-positive baby. The reason for this high immunization rate in both groups was undoubtedly because the women were at a high risk of immunization, as judged by the number of foetal cells found in their circulation after delivery of their first baby. Indeed, Philip Sheppard had insisted that the first trial should recruit only women at high risk of immunization.

The work of the Liverpool group was confirmed by the New York team of Freda, Gorman and Pollack, which had set out to tackle the same problem quite independently but along the same lines. Work performed shortly afterwards in Germany also confirmed the findings of the Liverpool group. By now it was apparent that it would be possible to prevent the bulk of cases of Rh haemolytic disease of the newborn. Although a great deal more work was required by Cyril’s team and many others to determine the ideal time at which to administer anti-D antibody and the appropriate dosage required, over subsequent years there was a steady decline in the numbers of babies with haemolytic disease of the newborn; in 1977 there were 18.4 deaths per 10 000 live births, and by 1992 the figure had fallen to 1.3. Overall, the work of Cyril’s team had been a remarkable success story and was undoubtedly one of the major advances in public health of the second half of the twentieth century. All the key papers relating to this work, with commentaries by Cyril, are reproduced in a monograph (12).

However, although von Dungern (1900) had shown that active immunization to an antigen can be prevented by the presence of passive antibody against that antigen (see Woodrow 1970), and the Liverpool group found that the injection of anti-Kell antibody largely prevented Rh-negative volunteers from becoming immunized to the Rh antigen after being injected with D-positive cells, the precise mechanisms of protection are still not absolutely clear. John Woodrow, the member of Cyril’s team who thought most deeply about this problem, writes:

I remember puzzling as to what exactly happened when the antibody-coated Rh(D) positive red cells were taken up by macrophages in the spleen. There was already evidence of the need to ‘process’ antigen and so
what determined whether a macrophage destroyed an antigen or ‘processed’ it? The B-cell epitopes are largely conformational and so presumably do not survive uptake by macrophages. We do not know whether, when IgG anti-D prevents the antibody response, the T-cell response still goes ahead. It should be possible now to test for this in protected mothers (an experiment on male volunteers would not be acceptable today).

The reduction in Rh haemolytic disease has made it more difficult to obtain appropriate antisera. Hopes that monoclonal antibodies might be valuable in this respect have not come to fruition and so the source of appropriate antibody for the control of this disease in the future remains a problem.

Cyril turned his lively mind to a variety of other research topics during his later period in Liverpool. With Richard McConnell he became interested in familial cancer of the oesophagus and he later described the association between this condition and the skin disorder tylosis. He also had brief excursions into studies of the pathogenesis and genetics of spina bifida, asthma and schizophrenia, although with less spectacular success.

The development of academic medicine in Liverpool

When Cyril settled down as a consultant physician at the David Lewis Northern Hospital in Liverpool, his life revolved round his clinical and teaching work at the hospital, an increasingly busy private practice, and his first special interest in internal medicine, the management of asthma, a condition from which Feo suffered for many years. Following the lines of a psychiatrist he had known at Guy’s, he started an asthma clinic for children, and because he believed that maternal tension was often a major factor he organized a programme whereby they slept away from home, in hospital for example, and went to school daily from their new environment. He and Feo also ran a children’s play clinic once a week with a similar objective.

Academic medicine in Liverpool in the 1950s and early 1960s was at a low ebb. Lord Cohen, the Professor of Medicine, although a brilliant physician, had not established any form of research programme and, indeed, the Department of Medicine had only one lecturer! As Cyril’s genetics research developed in the 1960s he started to attract around him a set of extremely able young clinical scientists. Not surprisingly, therefore, Lord Cohen invited him to accept the post of Reader in Medicine. In 1958 he left the Northern Hospital, not without a few regrets, and moved to the Department of Medicine, where his clinical sessions were based at the Liverpool Royal Infirmary and Broadgreen Hospital. On the retirement of Lord Cohen in 1965 he was appointed Professor of Medicine, a post he held until his retirement in 1972.

Under Cyril’s direction the Department of Medicine started to flourish. It soon became internationally recognized for its work on rhesus haemolytic disease and started to attract a variety of young clinicians who were interested in the evolving field of medical genetics. David Price Evans, who was to follow Cyril as Professor of Medicine, worked on pharmacogenetics, I returned from the USA to establish a team working in haemoglobin genetics, and several other young people, including Marcus Pembrey, Rodney Harris and Peter Harper, trained with him and ultimately established departments and held chairs of clinical genetics elsewhere in the UK. Cyril led his department with a light touch, preferring to let bright youngsters go their own way, but always being 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 reason for Liverpool’s influence on the development of medical genetics in Great Britain.

In 1963, as the result of a grant from the Nuffield Foundation and with the support and encouragement of E.B. Ford, Cyril established the Nuffield Institute of Medical Genetics,
which he directed from 1963 to 1972. This provided invaluable space for the increasing numbers of young people who wished to come to work in clinical genetics in Liverpool and, of equal importance to Cyril, allowed him to build a large facility for his butterflies on the roof!

The recognition of Cyril's work by the Nuffield Foundation was mirrored by many other tributes to the importance of his contributions, including the Gairdner Award, the Albert Lasker Medical Research Award (jointly), the Gold Medal of the Royal Society of Medicine, and many honorary degrees, fellowships and memberships of learned societies. Not surprisingly, in view of his broad interests, he became increasingly in demand to serve on national and international bodies and editorial boards. Although these included Chairman of Council of Bedford College (1975–85), Chairman of the British Heart Foundation Council (1982–87), Chairman of the British Society for Research on Ageing (1987–92), President of the Royal Entomological Society of London (1991–92) and Editor of the *Journal of Medical Genetics* (1970–85), Cyril confided to his close friends that the post that gave him the greatest pleasure, and which, incidentally, prepared him best for high office in the medical establishment, was his chairmanship of the Council of the British Mule Society.

When Cyril retired in 1972 the Presidency of the Royal College of Physicians became vacant and he was elected to this post in the same year. The election was a remarkable occasion. At that time Fellows of the College who wished to vote for a new President had to attend the College in person. There was enormous support in Liverpool and the northwest for Cyril; College Fellows from London were amazed to observe the arrival of large numbers of charabancs, full of northerners who had never before been seen at the College!

**THE ROYAL COLLEGE OF PHYSICIANS AND RETIREMENT**

Although Cyril was never deeply interested in medical politics, and was essentially a shy man, he held the post of President of the Royal College of Physicians of London with great distinction and flair from 1972 until 1977. In his early days his shyness and stammer had made it difficult for him to be an effective public speaker, but by then he had more or less overcome both these problems and his wicked sense of humour and eye for the ridiculous allowed him to preside over College meetings and dinners with enormous success. Michael Tibbs, who was College Secretary during Cyril’s time, recalled how he took enormous trouble to get to know the staff. During his period at the College he was responsible for important new developments for the training of physicians, including long-overdue improvements in the M.R.C.P. examination and the instigation of the Joint Committee on Higher Medical Training, and a variety of programmes directed at increasing the College’s input into the education of clinicians in the medical sciences. But although he was an extremely successful President, and despite the efforts of the College officers to persuade him to stay longer, after five years he decided that he had done enough and was anxious to get back to his genetics work in Liverpool.

After his retirement as President he continued to work with the College, first as Director of its Medical Services Study Group and then, from 1983 to 1988, as Director of its Research Unit. While at the Unit, he became interested in the causes of longevity and contacted centenarians who had received congratulatory letters from The Queen, almost 90% of whom turned out to be women. But this was the only factor that Cyril was able to relate to longevity and, at the age of 88 years, he wrote that he would very much like to know why his pet animal, the...
butterfly, has the 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 (16).

Feo (figure 1) had provided Cyril with enormous support throughout his career and was an integral and irreplaceable part of all his research and academic activities, not to mention his sailing. It was a remarkable partnership and, after her death on 13 August 1998, he never fully recovered. He spent his last year in a nursing home at Red Rocks, West Kirby, Merseyside, and died of pneumonia on 21 November 2000. Cyril and Feo are buried in Grange Cemetery, West Kirby, overlooking the Dee Estuary, which they both loved so dearly.

POSTSCRIPT: THE MAN

As a person, Cyril was a remarkably complex mixture of a lifelong public-school boy, constantly bubbling with enthusiasm and new ideas, and yet, at the same time, seeming to be rather distant so that his students and junior hospital staff sometimes found him difficult to approach and a little terrifying. This was, in part at least, a reflection of his innate shyness; those who came to know him well appreciated his warmth, loyalty and, not least, his impish sense of humour. He never appeared to be entirely comfortable with the transition from a full-time physician to an academic clinician and clinical scientist. Throughout his short academic career he always described his clinical colleagues as ‘proper doctors’, clearly finding it difficult to believe that somebody could combine the career of a physician and research worker. He always referred to himself as a ‘dilettante’, and described his work as ‘fun’, apparently never wishing any of his colleagues to realize how seriously he took it. His approach to clinical science was Churchillian; he was always more interested in the broad picture and happy to leave the details to others. Yet it was undoubtedly his remarkable flair for spotting impor-
tant areas of clinical research, and his extraordinary ability to pick out and collaborate with able colleagues, that was the basis for the great success of the Liverpool Medical School under his leadership and his work that led to the prevention of rhesus haemolytic disease.

However, reflecting his family background and the early part of his career, there is no doubt that Cyril’s first priority in life was always his patients. He was an extremely caring if slightly eccentric clinician and teacher, 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 Hospital, who, as he grew older, restricted his personal pharmacopoeia to morphia and sodium bicarbonate. ‘And’, he would add, ‘he was not too liberal with the bicarbonate’. But unlike many senior figures in academic medicine, patient care always came first, right to the end of his career. Michael Tibbs recalled one particular day when Cyril insisted on doing a teaching clinic in Liverpool at 8.00 a.m., travelling to London for a working lunch at the Royal College of Physicians, returning for a departmental meeting in Liverpool and returning to the College to preside over a dinner, after which he caught the night train back to Liverpool.

Possibly because of his educational and family background, combined with shyness, Cyril often seemed unwilling or unable to display the warmth and kindness that undoubtedly underlay his relationships with his friends and colleagues. In 1962, shortly after returning from the USA to work in his department, I was invited back to the USA to continue my research. My colleagues told me that this would be a disastrous move for my career. Seeking Cyril’s advice, I went into his office and told him of my predicament. Without looking up from the manuscript on which he was working he asked me what I wanted to do. I told him I would like to go back to the USA. Still not looking up, he replied in his delightful stammer, ‘well, b-b-bugger off then’. I subsequently discovered that for many years after that episode he went to great pains to support my career, and those of many of my Liverpool colleagues, yet at the same time taking the most extraordinary and often devious steps to make sure that we never found out what he was doing!

Perhaps it is better not to try to delve too deeply into the personalities of highly gifted polymaths like Cyril Clarke, but simply to celebrate their remarkable lives and achievements, not asking how or why.

**PRIZES AND MEDALS**

1973 *James Spence Medal, British Paediatric Association*
   *Addingham Medal, University of Leeds*
1974 *PB Fernando Lecture Medal, Sri Lanka*
1976 *John Scott Award, Philadelphia*
1977 *Fothergillian Medal of the Medical Society of London*
   *Gairdner Award*
1979 *Ballantyne Prize, Royal College of Physicians of Edinburgh*
1980 *Albert Lasker Medical Research Award (jointly)*
1981 *Linnean Medal for Zoology*
   *Artois-Baillet Latour Health Prize*
1984 *James Blundell Award, British Blood Transfusion Society*
   *Nuffield Medal, Royal Society of Medicine*
1986 *Gold Medal, Royal Society of Medicine*
DEGREES AND DIPLOMAS

1973  F.R.A.C.P.
      F.F.C.M.
      Member Federation of Hungarian Medical Societies
1974  Honorary Fellow of the Ceylon College of Physicians
      F.R.C.P.I.
1975  F.R.C.P. Edinburgh
1976  F.A.C.P.
1977  F.R.C.P.(C.)
1981  Hon. F.R.C.P. Edinburgh
1982  Hon. F.R.C.Path.
      Honorary Fellow of the Royal Society of Medicine
1984  Honorary Fellow of the Faculty of Occupational Medicine
1985  Fellow, Bedford College, University of London

HONORARY DEGREES

1971  ScD, Leicester
      DSc, Edinburgh
1973  ScD, East Anglia
1974  ScD, Birmingham
      ScD, Liverpool
      ScD, Sussex
      Honorary Fellow of Caius College, Cambridge
1977  ScD, Hull
1979  ScD, Wales
1980  ScD, London

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Many of the details of Cyril's family life were obtained through the kindness of his sons, Stephen and Charles, some
in the form of an album that they had prepared about his life, and also in a compilation of tributes to Feo Clarke that
were read at her funeral. Information about other aspects of his life and work was obtained from two articles that Cyril
wrote about his career, published in the Proceedings of the Royal College of Physicians of Edinburgh in 1995. Some
aspects of his Liverpool days are recorded in a newsletter that was published by the Association of the Liverpool
Medical School in honour of his 90th birthday in September 1997, in which many of his clinical colleagues and
friends paid tribute and wrote personal reminiscences. I am particularly grateful to John Woodrow for discussions and
reprints regarding the scientific basis of the rhesus programme. Finally, I was fortunate enough to have kept all Cyril's
personal correspondence with me, covering more than 40 years of his life.

The frontispiece photograph was taken in 1976 by Godfrey Argent, and is reproduced with permission.
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