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JOHN HILTON EDWARDS

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John Edwards was a human geneticist who pioneered the development of clinical genetics in Birmingham. His name is known to all in the field for his discovery in 1960 of trisomy 18, the second trisomic condition to be described in humans after trisomy 21 in Down syndrome in 1959. He was an astute clinician and recognized that if other human chromosome aberrations were to occur, they would be associated with a similar pattern of multiple malformations and handicap. His observation of a nine-week-old child with the provisional diagnosis of Ullich–Turner syndrome suggested this possibility, which was confirmed in samples taken by Edwards at autopsy. His early interest in genetic aspects of disease is evident from his study of Peutz–Jegher syndrome published in 1957. These and similar experiences led him to a varied career in genetics, which at that time seemed to have little place in the practice of medicine. His clinical interests were complemented by his research in population genetics, statistics, genetic linkage, gene mapping and comparative genetics. He was appointed Lecturer in Social Medicine in Birmingham in 1956 and almost all of the next 23 years were spent there as Senior Lecturer, Reader and, from 1967, Professor of Human Genetics. In 1979 he moved to Oxford to become Professor of Genetics in the Biochemistry Department. He retired in 1995 and continued to work on comparative genomics in collaboration with colleagues in Australia and New Zealand. He died in 2007 and is remembered as a kind physician and an outstanding diagnostician. An exceptional scientist, he had a most original mind and a keen wit and was a critical commentator on developments in science.

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Biographical Memoirs

FAMILY HISTORY AND EARLY YEARS

John Hilton Edwards was born on 26 March 1928, when his parents lived at Ingleborough Lodge, Dulwich. He was the elder son of Harold Clifford Edwards (1899–1989), later Consulting Surgeon at Kings College Hospital and Dean of Kings College Hospital Medical School, and his wife Ida Margaret Atkinson née Phillips (1900–81). His younger brother, Anthony William Fairbank Edwards FRS (b. 1935), was Professor of Biometry at Cambridge University until his retirement in 2003. Their paternal grandfather, William Evan Edwards (d. 1948), was a professional piano teacher in Newport, Gwent, and part-time lecturer in music at the National University of Wales, Cardiff. Ida Phillips was a pupil of William Edwards and a nurse before her marriage to Harold Edwards in 1923. She was the only surviving child of Arthur and Margaret Phillips, who had moved from Abertillery to Newport when Ida was a child. Arthur Phillips was an ironmonger and the family were originally from Pembrokeshire.

John’s early years were spent in London where his father was establishing a practice in surgery. In 1934 John, aged seven, was sent as a day-boy to the preparatory section of the Queen Anne School for Girls in Harley Street and he recalled spending most of his time there helping to look after an aquarium containing various reptiles. A grass snake given to John at Christmas 1935 kept escaping and had to be transferred to a zoo. It seems that Julian Huxley FRS was involved somehow and was responsible for arranging for John’s subsequent visits to Regent’s Park Zoo and his introduction to friendly reptile keepers who allowed him to handle non-venomous species. By the following year (figure 1), with difficulty in reading, John was transferred to Doon House preparatory school in Westgate-on-Sea, which was evacuated in 1940 to Falmouth and later to Peterchurch. In December 1938 his mother was diagnosed with tuberculosis and was moved five months later to a Swiss sanatorium at Montana-Vermala for treatment. At the end of August 1939, just before the outbreak of World War II, Ida Edwards returned home urgently and continued her treatment at Wonersh, near Guildford. Harold was appointed in charge of emergency medical services at King’s College Hospital, London, and Anthony, aged four, was sent to a dormitory school that was evacuated to Woolacombe, North Devon. Ida’s condition required surgery and following this, she moved to Woolacombe to be close to Anthony. Harold joined the Royal Army Medical Corps in 1941 and the family remained separated until the end of the war.

John records visiting Woolacombe during school holidays and notes that he enjoyed exploring rock pools by the sea and visiting a local farm. His interest in marine life extended on one occasion to dissecting a dogfish. This may have influenced an early interest in a scientific career. John left Doon House for Uppingham in 1942. After two years in the classics section, where he enjoyed Greek but not Latin, he moved to the science section and in 1946 left school with a distinction in physics at the Higher School Certificate level. He had joined the OTC Air Section at school, which enabled him to take a course in gliding (figure 2) and to experience flights in Lancaster bombers and military gliders. Despite an unsuccessful attempt at a scholarship, he gained admission to Trinity Hall, Cambridge. His tutor was initially under the impression that he was reading classics and so John studied the *Odyssey* while taking the Natural Sciences Tripos *en route* to a pre-clinical degree. The University Gliding Club featured prominently during his time at Cambridge and this, together with some uninspiring lectures, he believed were probable reasons for his graduating with a third class degree. However, he attended and enjoyed some zoology classes that were not part of the pre-clinical syllabus and spent time reading about vertebrates and invertebrates in the zoology library. In the few notes
that he left us he mentions that he enjoyed lectures at the Scott Polar Research Institute. He was keen to join the University Air Squadron and disappointed to fail the medical because of unilateral myopia, so he joined the Gliding Club and became its secretary and instructor. A second attempt to join the Air Squadron was successful and for a year he was happy to fly Tiger Moths until his unilateral myopia was rediscovered and he was grounded once again.

John left Cambridge in 1949 and moved to London for his clinical training. He chose not to join King’s College Hospital Medical School, where his father was currently Dean, and instead...
decided on the Middlesex Hospital. As he found the introductory course boring, he wrote to Regent’s Park Zoo and offered his help with autopsies, claiming an expertise in zoology. He spent many pleasant coffee mornings at the zoo, but no mammals died during his time there. He soon moved to the more interesting environment of the Central Middlesex Hospital and spent most of three years there, influenced by Avery Jones, Richard Doll, Walter Pagel and Horace Joules who were on the staff. He joined the Territorial Army (Artists Rifles) taking part in training weekends, camps and courses including a parachute course. He graduated MB BCh in 1952, but failed to obtain a pre-registration House Physician post, which he regarded later as a stroke of luck as he was offered a position as ship’s surgeon, with an interest in zoology, on board the MV *John Biscoe* (figure 3) of the Falklands Islands Dependencies Survey (FIDS). His National Service was deferred and he spent nine months in the South Atlantic, partly at Port Stanley where he had the company of an experienced German refugee physician, Fritz Hillenbrand, who was Chief Medical Officer in the Falkland Islands and who succeeded him on the *John Biscoe*. They worked together on outbreaks of scarlet fever, mild diphtheria and severe rubella. His main problems during his time with FIDS were with dentistry and psychiatry patients, plus an unsuccessful attempt to persuade his superiors to supply him with reagents for the Dick test that he hoped to use for determining susceptibility to scarlet fever among the ship’s crew. Much of his time was occupied in reading.

**LONDON, 1953–56**

Once back in London John married Felicity Clare Toussaint (b. 1927) on 18 July 1953 at the parish church of East Harling, Norfolk. Felicity was a fellow medical student and the daughter
of Charles Hugh Christie Toussaint, Consulting Chest Physician at the Central Middlesex Hospital. His first job in London was as Junior House Physician in neurology with Douglas MacAlpine at the Middlesex. This was interrupted by the chance discovery of a tuberculous lesion in one lung during his medical examination for National Service. John was treated for six months with isoniazid and streptomycin and used the enforced bed rest to read up on statistical methods, most probably from M. G. Kendall's *The Advanced Theory of Statistics*, and works by R. A. Fisher. As noted earlier, John's mother had been seriously ill with the same condition, as had a paternal aunt. Following his recovery in February 1954, John took a second six-month job as Junior House Physician, this time in gastroenterology with Francis Avery Jones. After this he was advised to follow a career that was less physically demanding. He therefore chose a Senior House Officer post in psychiatry at Knowle County Asylum. He found the experience of looking after patients with severe mental illness rewarding and, as he had the opportunity to undertake a few autopsies, he became interested in brain pathology. The apparent normality of the brain in schizophrenia seemed to impress him and so he returned in February 1955 to the Central Middlesex Hospital to a Senior House Officer appointment in pathology. This provided the opportunity to record, with Thomas H. Dormandy, a family with Peutz–Jegher syndrome, a condition in which oral pigmentation is associated with gastrointestinal polyposis. Its publication in 1956 was John’s first paper on a Mendelian disorder (1). However, two prior publications are also of interest. The first was a letter to *The Lancet* in April 1956, on the antenatal detection of hereditary disorders (2). In it he predicts the use of genetic markers in amniotic cells to determine the risk of sex-linked recessive and autosomal dominant disorders by genetic linkage. This was probably suggested to him by recent work on the management of Rhesus incompatibility based on amniocentesis.
The procedure became established 15 years later for the fetal diagnosis of Down syndrome. The second paper, on tea-drinking and gastritis, which appeared in The Lancet five months later, was written jointly with Felicity Edwards (3). A group of 155 patients with severe indigestion requiring gastric biopsy were given cups of tea and the temperature recorded at which it was drunk. A significant association between higher temperatures and abnormality of the gastric mucosa was observed. John notes that this was the only time he ever used a ‘t’ test!

**BIRMINGHAM, 1956–58**

In 1956 John passed the examination for membership of the Royal College of Physicians and successfully applied for a lectureship in epidemiology at Birmingham University to work with Thomas McKeown in the Department of Social Medicine. He was interviewed for the post by Lancelot Hogben, Professor of Medical Statistics (and previously Zoology), for whom he had a great respect. John’s next two years were spent mainly working on the epidemiology of dislocation of the hip and of neural tube defects. He established clinical contact with Douglas Hubble at the Department of Child Health and joined in ward rounds once a week at the Birmingham Children’s Hospital. John regarded Hubble as his mentor during his early years in Birmingham.

His epidemiological work resulted in a remarkably detailed paper with Reginald G. Record on the aetiology of congenital dislocation of the hip (5). It was concluded that the stability of the hip joint is determined by multifactorial inheritance and by factors in the prenatal and postnatal environment. The risk of recurrence in a subsequent child was estimated to be about 5%. The findings reinforced data in previous reports. John also made a detailed study of the aetiology of neural tube defects based on the reports of the Registrar General for Scotland in 1950–56 (6). This revealed no suggestion of an important genetic effect but instead a strong effect of environmental factors and a steep trend in incidence associated with social class; a seasonal trend was noticeable, with a higher incidence in the winter months. There was no evidence of inadequate nutrition as a possible factor. The findings are of interest in the light of the finding some 20 years later of folic acid deficiency as the main cause of these malformations, an explanation entirely consistent with the results of John’s study (Smithells *et al.* 1980). Another paper makes a critical examination of the reputed primary influence of ABO phenotype on fertility and sex ratio (4). He points out that the various authors responsible for making these claims took little account of the 5% non-paternity rate and the over 10% of group AB children that are known to be erroneously grouped as B. The results, corrected for these and other errors, were not statistically different from expected and so refuted the earlier claims.

**OXFORD, 1958–59**

In 1958 McKeown suggested that John should join the recently established MRC Unit in Population Genetics at Oxford. The Unit was directed by Alan Stevenson, who was distinguished for his work on congenital malformations. John was at the Unit from 1958 to 1960 but kept regular contact with Douglas Hubble and the Children’s Hospital in Birmingham.
This was a most important time in John’s career as it coincided with the early development of human cytogenetics and the discovery of the additional small chromosome 21 in Down syndrome by Gautier and Lejeune in 1958 (Lejeune et al. 1959) and the discovery of human sex chromosome aberrations by Charles Ford FRS, Patricia Jacobs FRS and others in 1959 (Ford et al. 1959; Jacobs & Strong 1959) (figure 4). Non-disjunction was the cause of trisomy 21 and John read up the literature on the subject, including the paper by Blakeslee
on non-disjunction in the Jimpson weed, *Datura stramonii* (Blakeslee 1934). Trisomy had been described for each of the 12 chromosomes of this plant and this suggested that trisomy 21 might not be the only trisomic disorder to occur in humans. He appreciated that the characteristic of Down syndrome was the diverse pattern of multiple malformations of the heart, gastrointestinal tract and limbs together with the unusual dysmorphic features of the head, face and hands, and the associated learning difficulties. He concluded that if other trisomies of the autosomes were viable in humans they would be characterized by similar, if not more severe, patterns of abnormality.

In the summer of 1958 John had attended the International Congress of Genetics at Montreal. On the voyage to Canada he shared a cabin with J. Maynard Smith, E. C. R. Reeves and James H. Renwick and they had joint meals with Bette Robson and Sylvia Lawler from the Galton Laboratory. John notes that he learnt more genetics from them during the voyage to and from Montreal than at the Congress. However, he must have had his first introduction to clinical cytogenetics there, as this was when Lejeune announced (at a peripheral meeting) the discovery of the extra chromosome in Down syndrome. Afterwards John maintained close contact with the human geneticists he met at the conference.

Shortly after the discovery of trisomy 21 John decided that he would also set up facilities for tissue culture and chromosome analysis. He received advice on this from Ford at the Atomic Energy Research Establishment at Harwell. Ford had been the first to confirm the correct human chromosome number from testis material (Ford & Hamerton 1956) and he helped John and George Clarke, a senior technician at the Unit, to set up fibroblast cultures from skin biopsies. John developed a comparatively painless skin biopsy technique that involved pinching a tiny fold of skin with forceps and slicing off the exposed part with a scalpel blade. He practised this on himself, producing tiny scars on his knees. The method, published in a note to *The Lancet* (1960), was to prove completely acceptable to his patients (9).

On one of his monthly visits to the Birmingham Children’s Hospital John observed a severely handicapped infant with the characteristics he thought might qualify for a trisomic condition. The child died at four months of age and John obtained tissue samples for cell culture at the autopsy. The following day (a Saturday) he took half of the samples to Harwell, and Charles Ford’s postdoctoral assistant, David Harnden, was persuaded to come in at the weekend to set up the cell cultures. The other half failed to grow at the Unit. Chromosomal analysis by Harnden revealed an extra chromosome in the E group (16–18), identified as chromosome 17 but later corrected to chromosome 18. The results were published in *The Lancet* in April 1960 (7) back to back with a paper reporting a one-year-old child with an extra D group (13–15) chromosome and a different constellation of malformations from trisomy 18 (Patau *et al.* 1960). The two trisomies became known at first as Edwards’ and Patau’s syndromes, respectively, but, with improvements in chromosome identification, are now identified as trisomies 18 and 13, respectively. No other viable non-mosaic autosomal trisomies have been discovered since then in humans, although all except trisomy 1 have been described in pregnancies that have miscarried early in gestation (Carr & Gedeon 1977).

John wrote another important cytogenetics paper, with Victoria Smallpiece, while at the MRC Unit. This was about an intelligent child that had some clinical features, including palm prints (examined by Lionel Penrose FRS), characteristic of Down syndrome. Chromosome analysis by Constance Clarke at Harwell demonstrated a mixture of normal cells and cells
with trisomy 21. This was the first reported case of trisomy-21/normal mosaicism in which it was evident that the presence of normal cells was responsible for modifying the Down syndrome phenotype (10).

John was not only helping to pioneer cytogenetics at the MRC Unit but was also working on two other aspects of genetics. The first was concerned with genetic susceptibility to such common diseases as diabetes and coronary artery disease. The aim was to distinguish the effect of single genes of low penetrance from the combined effect of a multiplicity of genes and environmental factors. His paper in 1960 is entitled ‘The Simulation of Mendelism’ and is widely considered to be one of his most original contributions to the literature (8). He contended that the apparent segregation of phenotypes did not necessarily mean the segregation of only a few genes and, because of familial aggregation, environmental factors as varied as nutrition and tuberculosis could sometimes simulate single gene defects. The genetics of common complex diseases remained his major theoretical interest throughout his career, as shown in his publications of 1969 and the 1990s. It was not until genome-wide scans using DNA markers became available 20 years later that genetic loci of small effect could be shown by association studies to influence susceptibility to a few common diseases, including diabetes.

A single gene defect was the subject of a second study. John investigated four pedigrees in which 28 males were shown to have X-linked hydrocephalus due to stenosis of the aqueduct of Sylvius (11). He described the unusual appearance of the thumbs, which were short and in-turned into the palms. This and other clinical features were characteristic of the condition and useful in the differential diagnosis of hydrocephalus of uncertain origin. He later came to regard this as his most interesting study in clinical genetics.

**Philadelphia, 1960–61**

John’s move to the MRC Unit in Oxford proved to be difficult for him in several respects. When he arrived there the building work for the Unit was unfinished, the accommodation provided for him proved unsatisfactory and colleagues he expected to work with (especially Jim Renwick) had moved elsewhere. The problems with facilities and personalities at the Unit did not improve and John resigned his position at the end of 1959. He decided to take up an offer to become a consultant in genetics at the Children’s Hospital of Philadelphia. He spent the academic year of 1960–61 there working with Peter Nowell and David Hungerford to establish a diagnostic cytogenetics laboratory. This coincided with the period when Paul Moorehead, also in Philadelphia, had developed an important technique for chromosome analysis from short-term cultures of peripheral blood samples (Moorehead *et al.* 1960). While in the USA, John took the opportunity to visit Victor McKusick in Baltimore and attended the second Short Course in Medical Genetics at Bar Harbor, Maine, that McKusick organized in conjunction with The Jackson Laboratory. He made regular visits to the New York Blood Center to discuss blood group research and population genetics, where he had contact with Howard Levene, and he also made important contacts with James German at Cornell University and Alex Bearn at the Rockefeller Institute. The two years, 1959–61, were probably the most productive of his career.

When John returned to Britain in 1961 he was invited by McKeown to resume his previous lectureship in social medicine at Birmingham, which had been kept vacant since he left it in
1958. This time the position was offered with a half-time attachment to Hubble’s department at the Nuffield Institute of Child Health. He was provided with a large room in the Institute which served as office, laboratory and conference room. With his new expertise in chromosome analysis from blood samples, John was quick to set up a small cytogenetics laboratory in a converted lift shaft at the Institute and to initiate the beginnings of an informal clinical genetics service with his paediatric colleagues. As the demand for diagnosis of genetic disorders grew, John set about organizing additional genetic clinics around Birmingham and the West Midlands. The earliest monthly clinics were at Warwick, Coventry, Stoke, Shrewsbury and Northampton. He soon developed a reputation as an outstanding diagnostician as well as a kind and courteous clinician. Most often he held his genetic clinics jointly with a local paediatrician who helped put into practice the genetic advice offered to the family. He contributed regularly to the weekly paediatric meetings of the Special Care Baby Unit at Queen Elizabeth Maternity Hospital.

Two single-author epidemiological papers were published in 1961 from the social medicine department arising from John’s earlier interests in cyclical trends and seasonal incidence of congenital malformations. The first of these short papers concerns the pros and cons of various statistical methods used in examining data for cyclic trends (12) and the second paper, published alongside the first, provides evidence for seasonal variation in the number of births in Birmingham affected by anencephaly, hare lip, patent ductus arteriosus, congenital dislocation of the hip, hay fever and asthma, each showing a seasonal pattern at the 5% level of significance (13).

The research output during the next few years was comparatively low as John became increasingly engaged in diagnostic cytogenetics and genetic counselling. It seems that he provided this service virtually single-handed and it was not until 1964 that he had the assistance of Jack Insley, both in the clinic and in the cytogenetics laboratory. Others came between 1963 and 1966, including Tessa Dent, research associate in cytogenetics, and Ian Rushton, registrar in paediatric pathology. John did much of the microscopy and karyotype analysis of patients himself and one of the studies he worked on was the analysis of a series of Down syndrome patients born to young mothers in the Birmingham region (29). The aim was to determine to what extent inherited translocations and maternal mosaicism contributed to the recurrence of the syndrome in future pregnancies. He found only one inherited translocation in a series of 128 families and rightly concluded that routine parental karyotyping caused unnecessary distress and was unwarranted (29). When prenatal diagnosis was introduced in the 1970s, the recurrence of Down syndrome in a woman with one affected child was found to be less than 0.5%, although the option of prenatal diagnosis gave the reassurance necessary for couples to contemplate further pregnancies. John recognized the value of prenatal diagnosis and, as mentioned above, had drawn attention to the use of amniotic fluid cells in the diagnosis of fetal genetic disorders in 1956.

The clinics and laboratory occasionally produced patients with unusual features worthy of research and publication. One of these was a child with Down syndrome of unusually mild expression in which the extra chromosome was approximately half the size of the normal chromosome 21 and similar in size to the Philadelphia chromosome described in chronic myeloid leukaemia (14). No conclusion about its origin was possible due to the technical limitations of analysing structural chromosome aberrations. The next cytogenetic paper of special interest from John’s laboratory concerned a pair of twins, one of whom had Turner syndrome with XO/XY mosaicism (15). The remarkable finding was that the twin brother
of this 15 year-old girl had an XO karyotype from lymphocyte cultures without evidence of mosaicism for XY cells. Blood and serum groups confirmed that they were monozygotic twins. The complete male development in one of the twins was explained by undetected XY cells in key tissues, such as the endocrine cells of the testes, implying that both twins were derived from an XY zygote, the XO cell line in both arising by mitotic non-disjunction in the early embryo.

John was part of a joint study with Hugh Cameron and June Wingham on placentation and zygosity in twins born in the Birmingham area between 1964 and 1965. He took this opportunity to test for genetic linkage between the locus for placental alkaline phosphatase and the loci for 10 other blood groups using Penrose’s sib-pair method applied to the non-identical twins from the Birmingham study (17). The results showed no evidence of close linkage between placental alkaline phosphatase and any of the blood groups, but the results were of interest as an important demonstration of a useful approach to genetic linkage analysis. Other aspects of the Birmingham twin study based on high resolution placental pathology were published subsequently by the group.

Among handicapped patients with multiple malformations and dysmorphic features there was one distinct group with a condition known as de Lange syndrome, which seemed particularly suitable for chromosome analysis. Some 69 patients had been reported when John added 20 more, of which most had been referred to him for chromosome analysis (18). The chromosomes appeared normal in all these cases although a small undetectable structural abnormality was thought to be possible; however, John was able to make a detailed and useful clinical characterization of the syndrome and these results were reported with R. G. MacArthur in 1967. Since 2004, spontaneous gene mutations at three separate loci have been found to cause de Lange syndrome.

With Catherine Yuncken, Ian Rushton, Susan Richards and Ursula Mittwoch (from the Galton Laboratory) John discussed mechanisms at fertilization responsible for triploidy in a 1967 report of three cases, one terminated and two that had miscarried (19). Digyny was found to be a more likely explanation than diandry. In the following year he reported (with Alan McDermott, Jack Insley, Margaret Barton, Pamela Row and Hugh Cameron) on a child with arrhinencephaly and a short arm deletion of chromosome 18 (22) and, in another report (with Alan McDermott, Jack Insley and Ian Rushton), on two familial reciprocal translocations in which offspring with an unbalanced product of the translocation had various developmental malformations; in the latter it was possible to confirm the translocation in meiotic studies in one of the carrier fathers (21). The findings reflect the difficulties of chromosome identification in a period before the introduction of chromosome banding techniques. Meanwhile, John had joined with his social medicine colleagues in two further studies on the epidemiology of congenital malformations, both published in 1964.

In a study with D. J. P. Barker in 1967, John reported on the relationship between obstetric complications and school performance as measured by a verbal reasoning test taken at the time of the 11-plus examination (16). Birth and examination records of over 50 000 children were linked by computer and the results showed mild but significant impaired performance for short gestation, prolonged gestation, toxaemia, occipito-posterior presentation and delivery in an ambulance. Twins showed a marked impaired performance.

Promotion to Senior Lecturer in the Department of Social Medicine and Honorary Consultant in Paediatrics at the Birmingham Children’s Hospital in 1965 was quickly followed by promotion to Reader in Human Genetics in 1967. This undoubtedly came in response to
John’s valuable contribution to the development of research and diagnostic services in clinical genetics in the West Midlands. In 1965 he was invited to become consultant investigator to the Genetical Committee of Iceland to assist in developing the programme to link civic and medical records of the Icelandic community (20). All births in Iceland from 1840 were to be included in a computerized database, a nationwide pedigree described by John as ‘a vast crystal of about half a million individuals bonded by links to parents, spouses and children’ (58). The idea was conceived by Luca Cavalli-Sforza and partly funded by what became the Department of Energy in the USA and partly by the Icelandic Government. John saw himself as a catalyst between Iceland and the USA. On two visits, he and his family took their campervan by sea and, in 1972, they came to Reykjavik with their travelling chess sets and enjoyed watching the Fischer–Spassky chess match. His contributions to the national database were recognized by his election as Corresponding Fellow of the Visindafélag Islandinga (Scientific Association of Iceland). His Icelandic colleagues say that he had more influence on the development of human genetics in Iceland than any other person. He contributed to the research on consanguinity (in more than 100 cousin marriages) and on familial susceptibility to cancer, but was sceptical on the possibility of finding genes of low effect in common multifactorial diseases. He noted that the database has failed to find the ABO blood group and peptic ulcer association reported in the 1950s or any of the HLA and disease associations known since the 1970s (58). Despite this, the anonymized database has been used subsequently by deCODE, a company registered in Delaware, that aims to exploit the resource in research for the identification of disease genes. John was critical of the science behind deCODE and of the ethics related to the security of personal data or the patenting of natural events (58).

SABBATICAL YEAR IN THE UNITED STATES, 1967–68

In 1967 new building works in the Institute of Child Health meant that John had to give up his small cytogenetics laboratory in the converted lift shaft. As the work load was becoming greater than could be reasonably undertaken by John and his small staff at the Institute, a decision was taken to move diagnostic cytogenetics to the Infant Development Unit at Birmingham Maternity Hospital, with proper support from the NHS hospital under the direction of Hugh Cameron. John saw this as an opportunity to have a break from chromosome analysis and so took a year’s sabbatical as a Senior Research Associate at the New York Blood Center and Visiting Professor of Pediatrics at the Cornell Medical Center, New York.

At the New York Blood Center, with Fred Allen, John could concentrate on developing his computer programs for genetic linkage in families using blood groups and other protein polymorphisms (20). This fitted well with his interest in the Iceland record linkage programme and his other interest in the association of HLA tissue types in susceptibility to disease. He also wrote notes on the nature of the variable antigenic sites at the Rhesus blood group locus and on the value of twins in genetic studies (24). With the programmer, Karen Glen, and visiting students, including Gilbert Côté from Canada and Eleida Chautard-Freire-Maia from Brazil, John worked on linkage analysis of pedigrees with many genetic disorders and variants using punched cards (figure 5) and modifications of his program specially designed for a variety of computers. The program was shared widely with other researchers and used, for example,
to demonstrate the linkage between the loci for phenylcarbamide tasting and the Kell blood group (Chautard-Freire-Maia 1974).

In a study with Ian Leck, John returned to the survey of the incidence of malformations in Birmingham that he first reported in 1964. This now included 190,236 births during 1950–59 of which 94,474 from 1950–54 had been followed up to age six (23). The incidence of malformations was 26.7 per 1000 births and the eight most common were clubfoot, cardiac malformations, anencephaly, spina bifida, clefts of lip and palate, Down syndrome and hiatus hernia. The study was one of the most comprehensive to be recorded in the literature at the time.

John never shirked from criticizing statements in the scientific press that he judged incorrect or misleading. Under a section in *The Lancet* headed ‘Dogma Disputed’, John took exception to the advice of a committee of the World Health Organization (to which he was consultant geneticist from 1972–95) that diabetics should not marry one another (25). He demonstrated with a little algebra that it made not much difference to the number of affected children if diabetics married one another or married non-diabetics. On the other hand, he drew attention to the dangers of encouraging meetings of families with identical recessively determined disorders. Such opportunities were increased by societies for specific disorders that combine social with fund-raising activities. He noted that it would be unfortunate if these ‘well-meaning activities should increase the numbers of those eligible for membership’.

Three papers published in the *Annals of Human Genetics* in 1969–70 with R. G. Record and McKeown reflect the interest of the Department of Social Medicine in studies of intelligence in relation to maternal factors (birth order, maternal age, birth weight, gestation and twinning) at the time of birth and are based on records of nearly 49,000 Birmingham births in the five years 1950–54 (26–28). As in their 1965 study on obstetric complications (15), the measurement of
intelligence was made from verbal reasoning tests in the 11-plus examination. Most findings could be attributed to the postnatal environment. The mean intelligence scores were once again lower for twin births than for single births, confirming postnatal influences.

One of John’s undoubted skills was explaining complex issues in simple terms, often using analogies to illustrate a point. During a lecture, John’s diffident manner meant that sometimes the point was lost on the audience, or perhaps was missed due to the interjection of an amusing anecdote. However, the written version of his lecture invariably demonstrates the care and skill with which the content was crafted. An example is provided by his talk on the ‘Genetical Background of Therapy’, given in April 1969 to the International Symposium on Pharmacogenetics (30). His theme is the inherited variability of enzymes and the metabolic map that provides the basis of rational medical therapy. He describes metabolic disease in terms of extreme variation and suggests (and dismisses as unrealistic) that the variable response to drugs, including their side effects, might indicate the need to provide specific therapy for each patient ‘in the same way as the blood banks provide labelled bottles matched to the recipient’. This was well before personalized medicine became fashionable.

In a contribution to a symposium in 1969 celebrating the fiftieth anniversary of the formation of the Genetical Society (the world’s oldest), John gives an excellent summary of the application of genetics to man, emphasizing its limited achievements in medicine and its lack of influence on the frequency of genetic disease (31). Writing almost another 50 years later, there has been dramatic change, with the map of the human genome (to which John made important contributions) and its draft DNA sequence now providing the basis for genetic disease and the driving force in medical science. His 1969 snapshot of human genetics considered the practice of fetal sexing with its possible future impact on the sex ratio at birth. Forty years later it was evident that this practice had had alarming consequences in South East Asia and India (Madan & Breuning 2013). John stressed the importance of the historical record of advances in genetics and deplored the tendency of others to neglect to give credit to the findings of early investigators.

John’s continued interest in blood groups is indicated in a short paper on MNSs frequencies in 3895 Swiss blood donors in Vox Sanguinis (1970) in collaboration with the Blood Transfusion Centre in Zürich (32). Dosage effects of anti-M and anti-N sera were used to identify rare variants and their frequencies were generated by computer. The observed genotype proportions agreed closely with those expected. The findings confirmed the reliability of the grouping procedures. The XG sex-linked blood group locus was also of interest to him as it could be used to determine the parental origin of non-disjunction in human sex chromosome aneuploidy. The distribution of Xg phenotypes among those affected was open to interpretation and John helped to clarify the issues raised (34).

The 1970s saw major developments in cytogenetics and genetic counselling services, first with the introduction of chromosome banding techniques that greatly improved the identification of structural chromosome abnormalities and, second, with the introduction of prenatal diagnosis in the late 1970s that allowed the fetal diagnosis of metabolic disorders and neural tube defects in addition to fetal chromosome aberrations. The demand for genetic counselling grew rapidly with the need to provide advice to couples contemplating prenatal diagnosis on the grounds of maternal age and familial chromosome abnormalities. The number of genetic clinics increased in the West Midlands, with new clinics set up in Stafford, Burton-on-Trent, Rugby, Nuneaton, Wolverhampton and East Birmingham Hospital. Sarah Bundey joined the clinical team in 1973 to work on neuromuscular and eye diseases. She helped with
the muscular dystrophy patients and later organized the 1987 birth study of 5000 Birmingham newborns. In addition to his other responsibilities, John took on a part-time role as Director of the West Midlands Regional Cytogenetics Laboratory at the Birmingham Maternity Hospital in 1975 and this continued until 1979.

While John’s cytogenetics research continued during this period in which medical aspects of genetics were beginning to flourish, he started several new areas of investigation. Tissue typing was one of these and John worked on the linkage relationships of HLA loci and the association of HLA types with susceptibility to disease. Working with colleagues in Iceland, Newfoundland, Norway and Britain, they defined close linkage between the HLA-B locus and Bf, the locus for properdin factor B (of the alternative complement pathway). Haplotypes carrying the HLA-B8 allele and the Bf-S allele were found in all individuals in large samples from the four populations, a phenomenon John called ‘allelic association’ (39). The lack of recombination in such large samples indicated very close linkage.

John collaborated with Pauline McIntosh at the Blood Transfusion Service in developing a computer program to simplify the procedure to match donor kidneys to HLA-compatible recipients on the waiting list for transplants. The HLA work with McIntosh continued for several years, culminating in a valuable paper (1980) in *Tissue Antigens* on 1000 HLA haplotypes in which the proportion of each haplotype was shown in graphical form in a group of 500 healthy British individuals (43). The diagram used was the forerunner of the famous Oxford Grid designed by John to indicate the chromosome homologies between human and mouse (see below). Another project involved collating the blood groups of Icelanders and linking these with the genealogical details in the massive record linkage programme that involved the entire population of Iceland (35). This project had several aims in addition to the possible detection of genetic linkage between the various blood group loci, and these included a search for association with disease (such as ABO and gastric cancer) and an investigation into the geographic origins of the Icelandic population. Analysis of the distribution of the ABO and secretor groups suggested that a substantial proportion of the population are descended from the people of Scotland and Ireland.

When the first International Human Gene Mapping Workshop was held in New Haven in 1973, John made important contributions in genetic linkage analysis using the computerized linkage program he had developed in Birmingham (36). This was only the second human computerized linkage program and followed closely the one that had just been published by Jim Renwick. John reported on genetic linkage with centromeric markers at the second Human Gene Mapping Workshop (HGM) in Rotterdam the following year. From then on, he was a regular participant at all the HGMs concluding with the eleventh in 1991. In each HGM he took responsibility for assembling the current data on unassigned linkage groups. He continued his responsibilities for linkage at several of the ‘Single’ Gene Mapping Workshops that were held from 1991 to 1999, including those relating to chromosomes 9, 12, 14, 17 and 19. He organized highly successful linkage workshops for geneticists in India and elsewhere during this period and promoted the rule that all original data on which conclusions (such as lod scores) were based should be made available, so that their reliability could always be assessed (56).

Work on comparative mapping between human and mouse was initiated about this time with Thomas Roderick and colleagues at The Jackson Laboratory, Bar Harbor, Maine, and homologies of several genetic linkage groups were identified between the two species and reported at the HGM Workshops. His collaborative work on HLA, population genetics and
gene pools (40) led to his appointment as Visiting Professor of Human Genetics at the Memorial University of Newfoundland in 1977, resulting in regular visits to St John’s over the next few years during which he initiated the allelic association study on HLA and properdin factor B (40).

The possibility of assigning gene loci to the chromosome involved in trisomy was developed in several papers by John and Gilbert Côté in 1975. Common blood group and serum markers were typed in trisomic patients and their parents to determine if the proportion of heterozygotes in trisomics was greater than expected in disomics (37). None of the loci showed evidence of assignment in trisomies for chromosomes 13, 18 or 21. This strategy was another example of John’s innovative and ingenious approaches to gene mapping that, in this case, sadly proved unfruitful.

Towards the end of his time in Birmingham, John was greatly concerned about improving genetic services to the population. One anxiety related to the use of serum creatine kinase (CK) levels in the identification of the carrier status of women in families with X-linked Duchenne muscular dystrophy (DMD). Sarah Bundey undertook an extensive study of CK levels which revealed a marked decrease with age and in pregnancy. Several of their papers address the various problems, including the difficulty posed by the common occurrence of new mutations among affected males. John’s survey of 18 clinical geneticists in the UK revealed a serious lack of precision in interpreting risk based on CK levels (41). This problem remained unresolved until the X-linked locus for dystrophin was mapped in 1986 and, later, when DNA analysis enabled its many mutations to be identified. Ian Craig and Yvonne Boyd in Oxford, supported by John, made important contributions to mapping the dystrophin locus through the analysis of X-autosome translocations in females affected with DMD (Boyd et al. 1986).

**OXFORD, 1979–95**

In 1978 John was invited to apply for the Professorship of Genetics at the Biochemistry Department at Oxford University, recently vacated by Walter Bodmer FRS on the latter’s appointment as Director of the Imperial Cancer Research Fund in London. John was duly elected and took up the post, attached to a Professorial Fellowship at Keble College, in October 1979. The same year he was elected to the Fellowship of the Royal Society ‘for contributions to human cytogenetics and genetic epidemiology including elucidation of the threshold model for multifactorial traits and pedigree linkage analysis’. A part-time appointment as Honorary Consultant in Genetics to the Oxford Area Health Authority was provided for him belatedly in June 1980, after he had undertaken clinical work for eight months without the cover of a contract. The bulk of the genetics teaching in the Department continued to be given by David Roberts and Ian Craig as John’s undergraduate lectures proved hard for students. His informal supervision of them, however, was very helpful and highly appreciated. He was also highly instrumental in attracting able DPhil and postdoctoral recruits, which he shared unselfishly with others in the Department.

On moving to his new position John continued to see patients with genetic disorders at the Department of Medical Genetics at the Churchill Hospital and at Swindon. Genetic clinics were also held at High Wycombe, Northampton, Banbury, Slough, Reading, Aylesbury, Kettering and Milton Keynes. His clinical colleagues included Dick Lindenbaum, Garry Brown and Patricia Boyd. He no longer had responsibility for laboratory diagnostic services
including cytogenetics, but worked on the investigation of his patients closely with Jon Jonasson and Margaret Fitchett at the regional clinical cytogenetics laboratory at the Churchill Hospital. Susan Huson was appointed Consultant in Administrative Charge of Clinical Genetics in 1989. John was influential in ensuring that facilities for prenatal diagnosis were available as a possible option for patients in the Oxford region. His firm views on the distinction between disease prevention and the avoidance of genetic disease by prenatal diagnosis are indicated in a 1988 paper (51). Among his other duties, John was appointed in 1987 to membership of the National Radiological Protection Board and this involved him in discussions on the effects of the Chernobyl disaster and four visits to the Soviet Union. A visit to Moscow and Leningrad in 1991 led to an agreement on collaboration between his department and the USSR Ministry of Health, the purpose of which was to exchange information on the DNA diagnosis of DMD, Huntington’s disease and myotonic dystrophy. This involved technology transfer and the exchange of material such as restriction enzymes from Moscow and computing expertise from Oxford.

John was responsible for encouraging computing in the Oxford Genetics Laboratory and was much occupied in developing his computer programs for genetic linkage and gene mapping. This activity was evident in the publication of a series of papers in which he developed novel methods for improving the reliability and interpretation of genetic data. These articles usually appeared in the *Annals of Human Genetics* or in reviews, and covered many aspects including linkage detection, the two locus problem, exclusion mapping, gene order, sib-pair analysis, allelic association and haplotype analysis. John’s linkage data exclusion map in 1987 aroused the interest of clinical geneticists as it correctly predicted the location of the neurofibromatosis gene on chromosome 17 (47), a result confirmed when the NF1 gene was identified three years later. He continued his collaborative work on the ordering of loci within the major histocompatibility complex with attention given to the detection of DNA polymorphisms in the group of loci that included genes for the three components of the serum complement system that are associated with susceptibility to autoimmune disease (49).

Elizabeth Thompson, Professor of Statistics at the University of Washington, Seattle, and a former friend and colleague of John, has kindly given her assessment of his contributions to human gene mapping and population genetics. She writes as follows:

Professor J. H. Edwards made significant contributions to the interpretation of linkage lod scores and to the understanding of the information content of alternative family study designs. He proposed summarizing the information in terms of the equivalent numbers of informative meioses [33, 38]. Using these measures, he promoted the importance of three-generation families for linkage detection and mapping, and was a leader in the Human Gene Mapping endeavours of the 1970s [36, 45]. As data became available at multiple markers across the genome, the ordering of markers became a problem; early framework marker maps had errors in ordering that distorted efforts to map disease genes. Edwards used his methods for quantifying inferred recombinant counts in informative meioses to address this locus ordering problem [50].

One of his key interests was in recessive disease, where the impact of ascertainment on recurrence risk strongly suggested to him that embryonic recessive lethals underlie the genome sharing in sibs [59]. These ideas led to his major contribution of exclusion mapping [48] where, using Cystic Fibrosis as an example, he showed how under assumptions of locus and allelic homogeneity of a recessive disease, a small number of affected individuals can convincingly exclude the causal locus from large portions of the genome.
Edwards was a very early contributor to ideas of haplotypic ancestry, and association mapping. Before the formal development of coalescent theory, he considered the numbers of meioses ancestral to a current sample of alleles and the expected half-life of a local haplotype. The associations maintained by the limited number of opportunities for recombination led to some of his developments of association mapping [39]. These ideas were further explored and developed in an important paper in 1980 [42]. This paper is much less well recognized by more recent researchers than it deserves, probably for two reasons. First the paper is in a conference collection rather than in a regular journal and second, Edwards uses the term *allelic association* rather than the more prevalent *linkage disequilibrium*; he detested the latter term as a cause of much misunderstanding and misleading inference. Many of his ideas both of haplotypic ancestry, allelic association, and the mapping of causal genes for recessive traits are brought together in his chapter *Recessive disease and allelic association* [57]. The final section on the observed frequencies of disease-allele bearing haplotypes across diverse countries shows echoes of his first association mapping in the context of frequencies of HLA haplotypes [39].

The research work during his time in Oxford for which John is perhaps best known relates to his studies on chromosome homology and genetic conservation between human and other mammals, especially the mouse. The Human Gene Mapping Workshops from 1973 documented an increasing number of gene assignments to the chromosomes of the laboratory mouse in addition to assignments to human chromosomes. Mouse geneticists had been building the mouse genetic map earlier from linkage data using translocation breakpoints, and work on man-mouse somatic cell hybrids was responsible for much of the new work on the human gene map. It was evident that many genes that mapped to the human X chromosome were also on the mouse X and homologies to human autosomal linkage groups were soon found to be located on mouse autosomes. John, together with mouse geneticists Anthony Searle, Mary Lyon, Jo Peters and their colleagues at Harwell, made a point of assembling these homologies and, in 1981, published a comparison of the maps of mouse and human in which the homologues of 47 autosomal and 9 X-linked loci were tabulated (44). In a following paper in 1984, he showed that 27 homologous chromosomal segments containing two or more loci could be mapped to both species (46). In an inspired diagram the homologies are presented in the form of a square divided into rows of human chromosomes in numerical order from top to bottom, and columns of mouse chromosomes in order from left to right (figure 6). The sides of each rectangle in the resulting grid are proportional to the relative size of each chromosome, and each rectangle represents the region of homology between the respective mouse and human chromosomes. The chromosomal location of each homologous gene thus finds its place in a rectangle in the appropriate row and column. Genes clustered in the same rectangle are syntenic even if separated by 50% recombination. The appearance of genes from the same chromosome in one species in rectangles from two chromosomes in the other species indicates an interchromosomal rearrangement during divergence of the two species. The concept is ingenious and in the 1984 grid (figure 6) it is immediately apparent that there are 27 conserved regions with at least two homologous loci and, on the other hand, that some human chromosomes have genes on more than one mouse chromosome and vice versa (46). In fact, the mouse genome was later shown to be highly rearranged compared with that of humans and most other mammals.

The value of this simple diagram was quickly apparent to the comparative genetics community and it was dubbed by Victor McKusick as the Oxford Grid in 1988 in his eighth edition of *Mendelian Inheritance in Man*. The name stuck. In the 1987 version, the number
of conserved autosomal segments had increased to 40 with only human chromosome 13 lacking a conserved segment. By 1989 all chromosomes in both species were shown with conserved regions, 50 within autosomes and five on the X chromosome, comprising a total of 322 homologous loci (52). Of the five conserved segments in the mouse X, one was inverted relative to the human X and the order of others indicated intrachromosomal rearrangement. This is an early illustration of a mechanism common in evolution and important for speciation in which karyotypes from separate species differed in the order of conserved segments within and between chromosomes while maintaining an essentially conserved genome. John expands on this theme in his 1991 paper, now entitled “The Oxford Grid”, and discusses mutation rates and the role of translocations and centromere repositioning in evolution (53).

The last of this series of papers with John as a co-author deals with mouse homologues of human hereditary disease and the value of the map position of human disease loci in identifying and characterizing mouse homologues that could be of interest in studying the natural history of the disease, including the role of genetic imprinting and possible strategies for therapy (54). This is an early view of the opportunities afforded by mouse models of human disease and a forerunner of the huge efforts to generate mouse mutants and to engineer specific disorders by transgenesis.

Perhaps the most important result of the comparative mapping studies in human and mouse was a better appreciation of the remarkable level of genome conservation in the animal kingdom. The extent of this conservation was well illustrated in the late 1990s by the comparatively few large chromosomal blocks of DNA that make up the karyotypes of all
species (Ferguson-Smith & Trifonov 2007), a finding revealed by cross-species fluorescence hybridization using chromosome-specific paint probes and confirmed by genome sequencing in the early years of the twenty-first century. John’s early review in 1994 of the value of ‘Comparative Genome Mapping in Mammals’ in advancing human genetics is an excellent account of one of the most important developments in biology and is another example of his great ability to describe a subject, both simply and entertainingly (55).

After retirement in 1995 (figure 7), John continued to help construct Oxford grids for dog and several farm animals, increasing the resolution by mapping the order of a greater number of loci along each chromosome. With Jo Dicks he developed simple computer programs for storing and presenting chromosomal homologies in databases and was a keen supporter of the Location DataBase introduced by Newton Morton. The extension of the Oxford Grid to sheep was first initiated during a sabbatical to New Zealand in 1993 with Tom Broad (Palmerston North) and Diana Hill (Dunedin). His regular visits to two of his children living in Australasia over the next few years provided the opportunity to strengthen these useful collaborations. A particularly important collaboration that continued until a few months before his death was with Frank Nicholas and colleagues at the Faculty of Veterinary Science, University of Sydney, with whom he helped create a web-based resource, the Oxford Grid Project hosted by the Australian National Genome Information Service (http://oxgrid.angis.org.au). In addition to human and mouse, this website now shows grids for many species, including cattle, sheep, pig, horse, dog, cat, opossum and tammar wallaby. Regular online additions to this database have rendered hard copy publications unnecessary so that most of John’s later contributions to this field are included only in the material available on the web. John was appointed Visiting Professor at Sydney University in 1998 in view of his close collaborations with Nicholas. He continued to travel widely and, in 2002, was in Bangalore with Sue Povey and Oliver Mayo organizing another workshop on linkage. His computer programming continued in Oxford and he enjoyed discussing work with Anthony Edwards in Cambridge (figure 8).

John had a quick wit and was a delightful and stimulating colleague. His sense of adventure was always evident in both his research and in his way of life. He was active in skiing, gliding and walking. A bench at Wengen in the Swiss Alps, dedicated to John by his children, commands his favourite view across the Lauterbrunental to the Schilthorn. He read widely and enjoyed browsing in second-hand bookshops. His absent-mindedness was legendary. Well-known examples include twice turning up at Heathrow without a passport and posting Christmas cards in a New York litter bin. Once, while baby-sitting his first child, she was nowhere to be found until it was discovered that she was asleep on his lap under an open Encyclopaedia Britannica.

John seemed always to have an apt analogy to emphasize a point. Ian Craig remembers: ‘The genius of the man came in thinking laterally, diagonally and all other ways except in a vertical direction. His clinical knowledge and insight, combined with a deep understanding of genetic principles, provided a robust backdrop to our mapping work. My memories are of kindness combined with eccentricity.’ Elizabeth Thompson felt that ‘his mind was so quick that his speech could not keep up, necessitating the elimination of half sentences, or even more’. David Weatherall FRS considered him ‘One of the nicest and cleverest of our field’. Oliver Mayo writes: ‘... no one else in my scientific world combined insight, keen humour and capacity to confuse and illuminate simultaneously.’ Walter Bodmer FRS notes: ‘He had a fine feel for human genetics, including a historical perspective, and always an original way of looking at problems and presenting them.’ Ed Southern FRS comments: ‘He had a
brilliant mind; lesser intellects had difficulty following his reasoning and, in my case, it would often take months for the penny to drop. But what pennies!’ Tom Roderick recalls: ‘He had a marvellous brain that short-circuited so many esoteric concepts with each other. A vivid memory I have of him is his arched back bending over the computer with face close to the keyboard.’ His clinical and scientific staff found him invariably helpful and supportive and he was a kind and generous supervisor of his graduate students, who remember him with great respect (figure 7). He had a talent for inspiring his students and staff and it is agreed that this, and his pioneering clinical work, were his most important legacies of his time as professor and head of department in both Birmingham and Oxford. He was always sociable while indifferent to public opinion and personal advancement.

In a two-page apology written in March 2006, found among his Birmingham papers, John notes that he had no excuse for failing to leave an autobiographical record. However, he acknowledges his good fortune to have met Sewall Wright, Haldane, Fisher, Newcome, Lederberg and Lejeune and to work with Cavalli-Sforza, Neel, Frezal, Sharat Chandra and McKusick. He indicates his indebtedness to Lancelot Hogben, to his collaborators at The
Jackson Laboratory, to those at Harwell and at the Galton Laboratory, and to his colleagues in Birmingham and Oxford, and for the numerous conversations with Lionel Penrose and Cedric Smith. The impact of these scientists on John’s research is evident in his publications but, unfortunately, he left no account of his personal interactions with them.

Each year, in the last week of January, John organized a seminar, held in the old library of the Genetics Laboratory at Oxford, to which he invited colleagues with backgrounds in cytogenetics, statistics, clinical, population and molecular genetics from other UK centres to contribute short talks on a theme that John felt was ripe for discussion. Those who chose to use 35 mm slides competed with inadequate blackout curtains and a temperamental projector, while others lounged on decaying leather sofas and armchairs. But the output was some original and stimulating discussion and the company always returned home refreshed with new ideas. This is just one example of John’s great ability to make one think constructively, and for this, and for his many other gifts, he will be remembered with great affection.

John died of prostate cancer on 11 October 2007. He is survived by Felicity and their four children, Vanessa, Conrad, Penelope and Matthew, and eight grandchildren.

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archives and Peter Harper made available transcripts of his interviews in 2004 with John. Garry Brown, Patricia Boyd, George Fraser, Ian and Sally Craig provided comments on the activities of the Genetics Laboratory at Oxford during John’s tenure. My thanks are due to Elizabeth Thompson for her assessment of John’s contributions to human gene mapping and population genetics. Birmingham University Library granted access to John’s archives (US99), which are deposited in the Cadbury Research Library Collection (http://www.birmingham.ac.uk/crl). Figures 3, 4 and 5 were copied, with permission, from the US99 archive. The frontispiece shows John shortly after his retirement from Oxford University in 1996, and was provided by Anthony Edwards.

AUTHOR PROFILE

Malcolm Ferguson-Smith

Malcolm Ferguson-Smith is Emeritus Professor of Pathology at Cambridge University where he works on genome and karyotype evolution at the Vet School using gene mapping and chromosome-specific sequencing. He graduated in medicine from Glasgow University in 1955, trained in pathology and took a Fellowship in Medicine from 1959–61 with Victor McKusick at Johns Hopkins Hospital, where he set up a chromosome diagnostic service and studied human sex chromosome abnormalities. He then joined Guido Pontecorvo’s Genetics Department in Glasgow, worked on chromosome identification and gene mapping before taking a joint appointment at the Royal Hospital for Sick Children to establish the West of Scotland Regional Genetic Service. His friendship with John Edwards dates from 1961 when they met at McKusick’s Bar Harbor Course in Medical Genetics. Both he and John have parallel careers starting with a common interest in human cytogenetics. John became Professor of Human Genetics in Birmingham in 1967 and he followed suit in Glasgow in 1973 on his appointment as Burton Professor of Medical Genetics. John moved to the Oxford chair in 1979 while he became head of Pathology in Cambridge in 1987. At each location, both directed regional clinical genetic services and, in retirement, both took up comparative genetics. Their close interactions lasted 46 years.

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