

A Service of Thanksgiving  
for the Life of

## John Hilton Edwards

26<sup>th</sup> March 1928 – 11<sup>th</sup> October 2007



2:30 pm  
19<sup>th</sup> April 2008

Keble College Chapel  
Oxford

**Address**

Malcolm Ferguson-Smith, Cambridge

Thank you, Felicity, for asking me to join in this service of thanksgiving for John's life, and for his achievements in medicine and science. I was his colleague in human genetics for 47 years and will try to give you a necessarily brief account of him from the viewpoint of someone in the same field and much the same age who worked in Glasgow and Cambridge, rather than in Birmingham and Oxford where John served in each as Professor of Human Genetics.

John entered academic medicine in 1956 as a young Lecturer in Epidemiology at Birmingham University. While working on the congenital malformation register he became interested in the genetic aspects of malformations. At that time, you will appreciate that genetics played virtually no part in the practice of medicine. The molecular structure of DNA had been solved only three years earlier, and the discovery that we had 46 chromosomes and not 48 was made the same year that John was appointed Lecturer. Today, genetics is at the heart of medicine and DNA is the basis of diagnostic pathology. John was one of the pioneers that helped to make this remarkable transformation possible. The late Jerome Lejeune was another pioneer, and his

contribution was to discover in 1959 the extra chromosome 21 responsible for Down syndrome. One year later John, working with David Harnden, discovered the next chromosome disorder due to an extra chromosome 18. This condition became known as Edwards Syndrome. The discovery was no chance observation. It was due to sound clinical intuition. He appreciated that the pattern of multiple minor malformations and mental handicap in Down syndrome could be the clues that could lead to other chromosomal syndromes. Other less astute clinicians were looking at the chromosomes of Mendelian disorders and major malformations and finding nothing. Chromosome analysis in those days depended on bone marrow or testis samples, both requiring invasive and traumatic procedures. John developed a “painless” skin biopsy method instead, which involved pinching a tiny fold of skin with forceps and slicing the exposed part with a sharp scalpel blade. He practised this on himself, producing multiple tiny scars on his knees. The method proved completely acceptable to his young patients.

In the years that followed John continued his interest in chromosome abnormalities and described patients with mosaic trisomy, triploidy and various translocations. He established a small laboratory for this work in the Nuffield Institute of Child Health in Birmingham. In one important study he analysed personally the chromosomes of 128 patients with Down syndrome born to young mothers in order to determine to what extent inherited translocations and maternal mosaicism contributed to the frequency of the condition. Only one inherited translocation was found and he rightly concluded that routine analysis of affected children caused unnecessary distress and was unwarranted. When prenatal diagnosis was introduced later in 1970, the recurrence of Down syndrome in women with an affected child was found to be less than half a percent. The option of prenatal diagnosis, however, gave couples the reassurance necessary to contemplate further pregnancies. John’s laboratory was one of those that were early in the field in providing prenatal diagnosis. Indeed, as early as 1956, he had written to the *Lancet* drawing attention to its possible use in the diagnosis of fetal genetic disorders.

John’s contribution to the development of cytogenetics was very important, but he also made outstanding contributions to other aspects of human genetics including linkage mapping, genetic susceptibility to common disease, and comparative genomics. He attended all eleven Human Gene Mapping Workshops from 1973 to 1991. These workshops provided the chromosome maps that led eventually to the human genome project and the complete DNA sequence of the human genome in 2001. John’s contribution was to provide novel computing methods for assigning and ordering genes onto their specific chromosomes. He was an expert in statistics and mathematical genetics and wrote his own computer programmes. He insisted that his colleagues make their primary data freely available and was an early advocate for openness in human genetics. At the time when few human genes were mapped to chromosomes, John developed the novel idea of exclusion mapping using negative linkage which determined the chromosomal regions that could be excluded by the data.

From the beginning of his career John was interested in how to determine genetic susceptibility to common diseases such as diabetes and heart disease. His aim was to distinguish the effects of single genes of low penetrance from the combined effects of a multiplicity of genes. His ideas are encapsulated in a paper entitled “The simulation of mendelism” published in 1960. This paper is considered one of his best. He returned to this theme on many occasions up to the last year of his life with many critical papers on the proper use of sib-pair analysis, on haplotype mapping, and on various aspects of allelic association. He was an undoubted leader in this complex field.

John’s interest in the conservation of linkage groups between species led in the 1980s to a series of papers with Mary Lyon, Tony Searle and other mouse geneticists at Harwell, comparing the chromosomal homologies of mouse and human. He designed a graphical representation of homologies based on comparative mapping that became known as the Oxford grid. The grid revealed in simple form the large blocks of chromosome in which groups of genes are conserved between the two species. With the help of Frank Nicholas, a database has now been created in which the genomes of many species, including farm animals has been created. As you will hear from Frank, these grids are very valuable for evolutionary studies, as well as being a demonstration of the extraordinary conservation of chromosome structure within the animal kingdom.

Among clinical geneticists, John was an outstanding diagnostician and his clinical experience led to notable papers on the characterisation of X-linked hydrocephalus due to stenosis of the aqueduct of Sylvius, and on the delineation of the Cornelia De Lange and Peutz-Jeghers syndromes. He ran genetic counselling clinics

throughout his professional life and I know from several sources that he had an excellent rapport with his patients. They greatly admired him and appreciated the time and care he devoted to them. He was always extremely helpful to his clinical and scientific staff and was a kind and generous supervisor of graduate students. He had a particular talent for inspiring his students and staff and it is agreed that this was one of his most important legacies of his time as Professor and Head of Department in Birmingham and, from 1979, here in Oxford. Other appointments included Consultant to the University of Iceland from 1967, where he helped to establish record linkage of all Icelandic births from 1840. He was also Visiting Professor of Human Genetics at the Memorial University of Newfoundland from 1977, Consultant in Human Genetics to the World Health Organisation from 1972, and Visiting Professor at the University of Sydney in relation to his work on comparative mapping. He was elected to the Royal Society in 1979. John acknowledged how he was greatly influenced in his career by mathematical geneticists including Lancelot Hogben, Lionel Penrose, Cedric Smith and Jim Renwick.

It was always great fun to be with John. His conversation was full of amusing anecdotes and he always had an apt analogy to emphasise a particular point. For example, he suggested that “reduced penetrance allows a mutant gene to advance like a wolf in sheep’s clothing”. On the decline of breast feeding, and the possible selection against human milk production, he noted “If the breast now influences selection by shape rather than function, this has no long term genetic hazards.” On another occasion, when discussing with someone the pros and cons of prenatal diagnosis, he asked “Madam, if you were a kangaroo would you look in the pouch?”

I have collected a few memories of John from those who knew him well. Ian Craig, his colleague in Oxford, 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.” Oliver Mayo writes “...no one else in my scientific world combined insight, keen humour and capacity to confuse and illuminate simultaneously.” Walter Bodmer 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.” Eleida Freire Maia, his student in the 1970s, remarks that “to study under John’s supervision was a special gift. He taught ways of solving problems not easily found.” Ed Southern 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.”

I share with Sue Povey, Andrew Read, Dian Donnai and many others, fond memories of those extraordinary annual seminars, organised by John in the last week of January and held in the old Genetics Department Library in the Oxford biochemistry building. A small group of colleagues were invited to contribute on a subject that John felt was ripe for discussion. Those who chose to use 35mm slides competed with inadequate blackout curtains and temperamental projector, while others lounged on ancient sofas and decaying armchairs. But the output was some original and highly productive discussion and we always returned home refreshed with new ideas. This is just one example of John’s great ability to make us think constructively and for this, and for many of his other gifts, we will remember him with the greatest affection.

## Address<sup>1</sup>

Frank Nicholas, Sydney

It is appropriate that I am speaking after Malcolm, who has provided such a wonderful description of John’s first three score years and almost ten. My task is to describe John’s “retirement” years.

I first met John in 1992, only a few years before his retirement. The next year he came to Sydney for the first of what turned out to be more-or-less annual visits to the Faculty of Veterinary Science at the University of Sydney; visits that continued for 13 years, until the middle of 2006, by which time flying had become too much of a burden.

Why a faculty of Veterinary Science, and why at the other end of the world? To answer the second question first (and this does help to keep things in their proper perspective): two of John and Felicity's children – Penny and Conrad – were then living in the antipodes; and that was a very important determining factor!

Why Veterinary Science? As we have seen from Malcolm's address, John's collaboration with his Harwell colleagues had stimulated an increasing interest in the comparative map of humans and mice. Whilst the mouse had (and still has) much appeal for comparative biology, it also has limitations, especially to a human clinician.

As only John could write (the following words are taken from a 1994 review): "Unfortunately, this 'homunculus', although convenient to house and cheap to feed, is too small and short-lived to be suited to the study of some human disorders. Venipuncture is difficult, organ transplantation almost impossible, lung biopsy fatal and the skin concealed by hair. This is no criticism of the mouse, which, like ourselves, has virtues and limitations; fortunately limitations in one species are largely balanced by advantages in the other. Sheep, goats, cows and pigs are of a convenient size for therapeutic trials and ~100 million of each are available and under scrutiny, their health often supervised by various inspections and their diseases well documented."<sup>2</sup>

Thus, by the time John retired from Oxford, he was hot on the trail of what he delighted in calling "the farmyard". That, then, is the reason why he alighted upon a faculty of Veterinary Science.

Why the Faculty of Veterinary Science in the University of Sydney? Because that faculty just happened to house a national bioinformatics facility.

Why was John interested in a bioinformatics facility? Well, as mentioned by Malcolm, in the early 1980s John had conceived a very simple but elegant diagram to illustrate the extent to which segments of chromosome are shared between pairs of species. Such a diagram first saw the light of day (at least in print) back in 1984<sup>3</sup>; and it was baptized "Oxford Grid" by Victor McKusick in 1988<sup>4</sup>. This diagram illustrates an intriguing aspect of John's intellect: despite his considerable mathematical skills, he was always on the lookout for simple diagrams to convey important ideas.

John realized the internet's enormous potential for the public sharing of knowledge, and for making his Oxford grids available electronically to the whole world, in such a way as to bring together the wealth of knowledge becoming available about an ever-increasing number of species. Also, it just so happened that the Sydney bioinformatics facility hosted Online Mendelian Inheritance in Animals (OMIA)<sup>5</sup>: the farmyard equivalent of Victor McKusick's catalogue of inherited human disorders.

For John, then, the comparative genomics stars were all aligned and pointing to Sydney.

At the age of 70, he was appointed a Visiting Professor at the University of Sydney, and he set to work in earnest.

On every visit, he would arrive with various pieces of hardware – dongles, discs, memory sticks – not to mention assorted instruction manuals, stuffed into the many pockets of his red coat. And always with two, sometimes three, laptop computers, each of which urgently required at best some rejigging; at worst, some major repairs. But remarkable progress was made, largely due to the services of an amazing programmer (Stefan Gregory), who happens to be a pure mathematician and who, to John's great delight, plays guitar in an alternative-rock band<sup>6</sup>. Thanks to Stefan's efforts, John's vision of electronic grids soon became a reality on what is known as the Oxford grid web site<sup>7</sup>.

How is John's vision doing today?

Well, one of John's dreams has been fulfilled: thanks to the efforts of Matthew Hobbs and Jonathan Usmar, the amazing comparative genomics information created by Ensembl (a bioinformatics joint project between the European Molecular Biology Laboratory's European Bioinformatics Institute and the Sanger Institute, hosted in Cambridge) is now turned automatically into a matrix of Oxford grids – a grid of Oxford grids that encompasses every pair-wise combination of the ever-increasing number of species for which Ensembl has developed a list of orthologous genes<sup>8</sup>. The number of grids grows as the list of Ensembl species grows, and all of these grids are freely available, just as John always wanted.

Also, in the months since John's death, in collaboration with colleagues from the University of Illinois, the first grid based on actual sequence comparisons between species has been drawn: first cab off the rank is a cattle-human grid based on 47,000 homologous segments of sequence – by far the most data-intensive grid ever created. And the picture it shows is truly beautiful!<sup>9</sup>

The point of all of this is to show the importance of John's legacy; and how his concept is continuing to flourish.

But what of the other sides of John?

In the course of more than a decade's collaboration, I received more than 1000 emails from him. These could form the basis of a most interesting book! I will share just a few with you:

"Welcome invasion [of grandchildren] starts tomorrow so not much transistorised activity next week."

“Dear Frank, Rather slow progress - Penny's internet, but not her children, inactive.”

Another quote, relating to John's long-term interest in sib pairs, as mentioned by Malcolm: “At present busy on piglets - who are well endowed with sib-pairs - one local boar has produced over 140 piglets - and the local rams should be even more productive.”

And another: “Saw Mary Lyon yesterday - first the Afghans blow up the Buddahs then Harwell remove her map of the mouse [from the Harwell website]”

And (while John was in Sydney), the somewhat alarming “setting off on coastal walk with money and a toothbrush, but expect to return tonight unless tempted by sufficient moonlight”. Fortunately, this was followed 15 minutes later by another message that requires the background knowledge that when Charles Darwin visited Sydney in 1836, he rode a horse 120 miles into the Australian interior: “Dear Frank, Just in case you think I am trying to emulate Darwin's horse, or otherwise venturing into the unknown, I am merely taking the boat to Manly and turning left.” Somewhat consoling, but even so, the thought of John catching the ferry to Manly and then “turning left” was a worry. And in the end, he did have somewhat of an after-dark adventure that day. But that is a story for another time.

John's absent-mindedness is well known. But I have two stories that go against that image.

The first involves a very special necklace, bought in Turkey by our daughter Hannah, then studying here in Oxford, as a birthday present for her mother - my wife, Jan. Possibly with some hesitation, Hannah entrusted the necklace to John on his next trip to Sydney. On our very first meal together in Sydney after John had arrived, he proudly produced a tiny red box from his coat pocket, handed it to Jan and said, with a chuckle, "Felicity would be very proud of me!"

And then there was the dinner invitation that went badly wrong. Jan and I had invited John to dinner one evening with some other colleagues. The plan, as carefully explained to John, was that he should catch the ferry from Circular Quay – a very pleasant journey – and should phone me when he arrived at our local wharf. I would then drive down to pick him up. Our other guests arrived; we worked our way through all the crisps and peanuts, and still no phonecall from John. And no answer from his college room. Eventually, we dined without him, very worried at his non-appearance. First thing next morning, I phoned the college again, and John answered, very worried about us! He had caught the ferry as instructed, and, as also instructed, had phoned on arrival at our local wharf, only to be greeted by a recorded message. Fearing that some disaster had befallen us, and with no other way of contacting us, he had caught the next ferry back to the city, eaten a pizza alone in a wharf-side café, and then caught a bus back to the college. I couldn't understand how he could have got a recorded message, until the penny dropped: I had mistakenly given him my work phone number rather than our home number!

John was very forgiving, and was rather amused that someone else could have got things so muddled!

In closing, I would like to return to John the scientist. Where does his scientific legacy fit into the overall scheme of things?

One way to answer this question is in the context of the many celebrations that will be held next year to mark the 200<sup>th</sup> anniversary of Charles Darwin's birth and the 150<sup>th</sup> anniversary of the publication of *Origin of Species*. This is a particularly pertinent context, given that today actually marks another Darwin anniversary: Darwin died on this day – April 19<sup>th</sup> – 126 years ago. And there is a direct connection between Darwin and John: immediately after graduation, they both spent time on board a British survey vessel in the Falkland Islands: in Darwin's case, on the *Beagle*; in John's case, on the *John Biscoe*.

If Darwin were alive today, what current knowledge of genetics would really excite him? If he were today writing the 50<sup>th</sup> edition of *Origin of Species*, what modern genetics knowledge would he include? In the lead-up to next year's celebrations, this is a question that needs to be asked.

I freely admit to being hopelessly biased, but I reckon one of the things Darwin would include is an Oxford grid!

Why? Because, with the possible exception of Malcolm's zoo-FISH diagrams<sup>10</sup>, an Oxford grid based on sequence homology provides by far the best simple illustration of the amazing conservation of segments of chromosome through evolution. Furthermore – and this is an important point - the hierarchical nature of the variation in the extent of conservation is consistent only with the evolution of species; it is entirely at variance with the separate creation of each species.

So, there we have it. John was a very special scientist; one who, over and above the many achievements of his “working” life described by Malcolm, has left a substantial “retirement” legacy that will flourish and expand into the future.

He was also a very special person. My wife Jan and I thank Felicity for allowing us to share some of John's retirement life (and for the wonderful hospitality at the Union Club in Sydney). Like his many colleagues here today, I count it as a great privilege to have been able to work with John.

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<sup>1</sup> This is a lightly-edited version of the actual address delivered during the memorial service.

<sup>2</sup> Edwards, J.H. (1994) Comparative genome mapping in mammals. *Current Opinion in Genetics and Development* 4: 861-867.

<sup>3</sup> Buckle, V.J., Edwards, J.H., Evans, E.P., Jonasson, J.A., Lyon, M.F., Peters, J., Searle, A.G. & Wedd, N.S. (1984) Chromosome maps of man and mouse II. *Clinical Genetics* 26: 1-11.

<sup>4</sup> McKusick, V.A. (1988) *Mendelian Inheritance in Man. Catalogs of Human Genes and Genetic Disorders*. (8th edition) Baltimore: Johns Hopkins University Press, p. cxvi.

<sup>5</sup> <http://omia.angis.org.au/>

<sup>6</sup> <http://www.faker.com.au/>

<sup>7</sup> <http://oxgrid.angis.org.au/>

<sup>8</sup> [http://oxgrid.angis.org.au/oxg\\_table.html](http://oxgrid.angis.org.au/oxg_table.html)

<sup>9</sup> [http://oxgrid.angis.org.au/btau4\\_vs\\_hsa36/500\\_index.html](http://oxgrid.angis.org.au/btau4_vs_hsa36/500_index.html)

<sup>10</sup> <http://www.chromhome.org/>