BIOGRAPHICAL MEMOIRS

Sir Robert Geoffrey Edwards CBE. 27 September 1925 — 10 April 2013

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SIR ROBERT GEOFFREY EDWARDS CBE
27 September 1925 — 10 April 2013
Robert Geoffrey Edwards was fiercely proud of his Yorkshire origin. After a faltering start to his academic career, he developed an extraordinary aptitude for original research, which he pursued with energy, enthusiasm and dedication that very few could match. He pioneered the most significant advance in the history of treating human infertility, established proof of principle for preimplantation diagnosis of genetic disease, and was the first to advocate the use of spare embryos as a source of stem cells for regenerative medicine. He not only promoted a better understanding of early human development, but he also provided invaluable insight into the many ethical issues raised by such work. Moreover, he played a key role in establishing both an international learned society and serving as editor of several journals devoted to the study of human reproduction and embryology.

FAMILY HISTORY AND CAREER

Since he was known almost universally as Bob rather than Robert I have chosen to refer to him thus throughout this memoir. Bob’s paternal grandfather, a coal miner named Emmanuel Edwards, was born in Portobello, Staffordshire, in 1860. In 1885 he married Eliza Boobyer, who was two years his junior. According to the 1911 census, they had 16 children during the intervening 28 years, with 13 surviving to adulthood. The 15 for whom records are available were born in Ibstock, Leicestershire, and most of the sons became miners. Bob’s father, Samuel Edwards, was born in 1896, and in 1920 married Margaret (née Street), who was born in Ardwick in Lancashire in 1893. At the time of their marriage Samuel and his wife lived in Levenshulme in the Greater Manchester area. However, Bob’s elder brother, Samuel (Sammy), was born in 1922 in the village of Ibstock, Leicestershire, and by the time of Bob’s birth on 27 September 1925 the family was based in the ancient West Yorkshire mill town of Batley in the Metropolitan Borough of Kirklees. Bob’s younger brother, Harry Raymond, was also born in Batley on the very same date two years later. The name Batley is of Danish origin,
meaning either valley or homestead, and is recorded as ‘Bateleia’ in the Domesday Book. Coal mining in the area goes back to the sixteenth century. The last pit was closed in 1973. In the nineteenth century the town was the centre of development of what was known as the ‘shoddy’ trade, in which wool, rags and clothes were re-woven into blankets, carpets and uniforms. Bob’s mother, Margaret, worked as a machinist in one of the local mills, and his father was employed as an engineer’s labourer. An earlier celebrated ‘scientific son’ of Batley was Joseph Priestley (FRS 1776), who was born in the nearby village of Birstall.

While Bob, then known as ‘Geoff’, was still a youngster, the family relocated to Gorton in Greater Manchester. The three boys were clearly academically able, because all were awarded scholarships to Manchester Central Boys’ High School (now the Central Grammar School for Boys). Among the school’s earlier distinguished alumni were Sir John Alcock, who, with Arthur Whitten Brown, was the first to fly the Atlantic non-stop, the Oscar-winning actor Robert Donat, and James Chadwick (FRS 1927), who was awarded the 1935 Nobel Prize in Physics for discovering the neutron.

Apparently to his mother’s annoyance, Sammy refused to take up his scholarship, which resulted in irresistible pressure on Bob and Harry to do so. However, the education of the two younger brothers was interrupted by the war, with the entire school being evacuated to Blackpool. This proved to be such a miserable experience for the children that Bob and Harry returned home after six months, by which time Sammy had joined the Royal Air Force. Their parents decided that the two younger boys should be sent for safety’s sake to a farm near Chapel-le-Dale in the Yorkshire Dales. For an entire year they remained on the farm full-time because the nearest school, which took only day pupils, was too distant for them to attend. Although teaching inspectors tried hard to get the boys back to school in Manchester, their mother altogether resisted such a move while the city was still being bombed. However, during this hiatus in their formal education, the two boys learnt a great deal about farming, particularly the husbandry of sheep and cattle. This experience resulted in Bob’s lifelong love of the Yorkshire Dales, to which he would return regularly in later years for family holidays. Although their mother remained in Manchester throughout the war, the two boys saw their father very regularly during their year on the farm because he was engaged nearby, working on the Settle to Carlisle railway’s Blea Moor tunnel.

Despite the loss of a year’s study, Bob gained his A-levels three years later. On leaving school in 1943, he was immediately recruited into the Army and sent to Fort George in Scotland to train as a driver-mechanic. After selection for training as an officer he was relocated to Kent, where he gave instruction on how to drive tracked vehicles. His army service was, however, interrupted by nine months of compassionate leave to help a sick friend run his farm in the Yorkshire Dales. Subsequently, Bob was sent to the Middle East, where his duties took him to Palestine, Jordan, Egypt, parts of Iraq and Lebanon. It was during this period that he developed an enduring sympathy for the plight of Palestinian Arabs. On being demobilized in 1948, he returned to ‘smokey’ Manchester and thence enrolled at the University College of North Wales in Bangor to read agriculture. Although obviously inspired in this choice of subject by his earlier farming experiences, he soon reached the conclusion that he had made a grave mistake (17)*:

Now, in 1951, I had decided that I was not particularly interested in seeds of wheat, seeds of oats or seeds of barley—certainly not in how many of them needed to be sown, for efficiency’s sake, into one acre of land. I was on the wrong road and it was a costly error.

* Numbers in this form refer to the bibliography at the end of the text.
His decision to switch to zoology in the final year, the department of which was then headed by the distinguished reproductive biologist F. W. Rogers Brambell FRS, came too late to salvage more than a pass degree. This was a mortifying experience for Bob that threatened to spell the end of all hope of pursuing a career in science. Nonetheless, despite having little expectation of a positive response, he was encouraged by John Slee, a fellow student who became a lifelong friend, to follow his example in applying to C. H. Waddington FRS, head of the Institute of Animal Genetics at Edinburgh University, for admission to the postgraduate diploma course in Genetics. To his surprise and delight, and much to the credit of Waddington, he was accepted. However, this still left him with the headache of raising the necessary funds, which were quite beyond the means of his parents to provide. Thus, in the intervening summer he undertook whatever menial jobs he could secure, from helping farmers with their harvest and portering bananas in Manchester docks and heavy sacks in flour mills, to serving as a general dogsbody in a newspaper office. This enabled him, by the time he started the course, to have amassed sufficient funds to cover his tuition fees, books and the first three months’ lodging in Edinburgh.

Under Waddington’s leadership, the institute provided a very stimulating environment for an embryonic scientist, with other such notables on the staff as Lotte Auerbach (FRS 1957) and Douglas Falconer (FRS 1973). Bruce Cattanach (FRS 1987) was among the PhD students, and Mary Lyon (FRS 1973) was one of the young postdoctoral researchers. Waddington was sufficiently pleased with Bob’s performance in the diploma course to invite him to stay on to do a PhD. For this he chose as his supervisor Dr Alan Beatty, whose research was on fertilization and early development in the mouse. What particularly interested Bob was Beatty’s ideas on how the genetic constitution of the mouse embryo might be modified because he had become convinced that many anomalies of development were rooted in the mal-segregation of chromosomes during oocyte maturation. Bob therefore decided to explore the consequences of modifying the chromosomal constitution of mouse embryos as the principal thrust of his PhD work, and devised or adapted a wide range of procedures for achieving this end. During the course of these studies he gathered an impressive amount of data on the timing of events during oocyte maturation and fertilization and during the initial stages of mouse development in both normal and chromosomally abnormal situations. Initially, to gain access to all relevant stages, he had to spend endless night-time hours in the animal house making observations. According to Mary Lyon, his extraordinary dedication and determination, such vital hallmarks of his later work, were already evident at this early stage in his career. Mary had approached him with the aim of seeking his help in improving her understanding of murine reproductive physiology, which, with characteristic generosity, he was more than happy to do. She notes that while Bob spent many nights in the animal house, she had only to visit for a few to benefit from his generous tuition. But, as Mary wryly observed in a recent letter to me, ‘My Scottish landlady did not believe that scientific research took place in the small hours and I prefer not to speculate on what she thought I was doing at the nocturnal visits!’

This extraordinarily gruelling routine undoubtedly prompted Bob’s interest in exploiting reproductive endocrinology as a way of making the various stages of oogenesis, fertilization and early development conform to more social hours. Specifically, it encouraged him to question the then prevailing wisdom that, unlike immature mice, adults were not responsive to induction of ovulation with exogenous gonadotrophins. His collaborator in showing that ovulation in adult mice could indeed be induced thus was his future wife, Ruth Fowler, who deserves equal credit for what has remained a mainstay procedure to the present day.
Bob and Ruth became engaged during the course of their collaboration in Edinburgh and married in 1954 before finally leaving the city for a year in California. After they started going out together, Bob discovered that one of his four greatest scientific heroes, Ernest Rutherford FRS (PRS 1925–30), was his future wife’s grandfather, the other three ‘heroes’ being Gregor Mendel, Dmitri Mendeleef and Luke Howard FRS, a pioneer of meteorology. Sir Ralph Fowler (FRS 1925), Plummer Professor of Mathematical Physics in the University of Cambridge, married Ernest Rutherford’s only child, Eileen, and they had four children, two sons and two daughters, of which Ruth was the youngest. Sadly, Eileen died in 1930, shortly after giving birth to Ruth. The very difficult situation that this posed for Ruth’s father was resolved by family friends, Phyllida and Derek Cook, who moved into the Fowler home in Trumpington with their own three daughters, where they happily raised a family of seven! Following in father’s footsteps, one of Ruth’s brothers, Peter Fowler (FRS 1964), became a distinguished cosmic ray and particle physicist on the staff of the University of Bristol, where he held a Royal Society Research Professorship from 1964 until his retirement in 1981. Ruth was herself a very able scientist and was the lead contributor to the endocrinological aspects of Bob’s work.

Bob’s five years in Edinburgh were extremely productive, as is evident from the number and diversity of original papers that resulted from the research he undertook during that period. As these formative years in his research career were drawing to a close, his interest in the possibility of separating sperm bearing an X chromosome from those bearing a Y chromosome prompted him to contact Albert Tyler, who championed the view that sperm–oocyte interaction was akin to that between antibody and antigen. The outcome was that, accompanied by Ruth, and with support from the Population Council of New York, he spent a year with Tyler at the California Institute of Technology, where his growing interest in reproductive immunology was further stimulated. On returning to England he took up a five-year postdoctoral appointment in the Experimental Biology Division of the National Institute for Medical Research (NIMR) at Mill Hill, which was headed by Sir Alan Parkes FRS. Here Bob’s role was to explore immunological aspects of reproduction, particularly the antigenicity of sperm and its possible implications for infertility and contraception. Although primarily engaged with work in this area, he was recurrently drawn back to embryology, and in particular to the question of whether oocytes could be persuaded to complete their maturation in vitro. Having achieved success in this regard with the mouse, rat and hamster, among other mammals, Bob decided to press on with corresponding studies on human oocytes. Aided by contacts of the distinguished immunologist Sir John Humphrey FRS, a senior colleague at the institute, he was able to obtain freshly excised ovarian material from various London obstetricians, most notably Molly Rose at the Edgeware General Hospital. However, once the Director of the NIMR, Sir Charles Harington FRS, learned that Bob was working with human oocytes, he forbade him to continue to do so. His words, according to Bob, were: ‘I do not want any human eggs fertilised here.’ By then, Parkes was no longer at hand to support Bob, having moved to Cambridge in October 1961 to take up the newly founded Mary Marshall and Arthur Walton Chair of Reproductive Physiology in space on the top floor of the Physiological Laboratory. Although Harington’s successor, Sir Peter Medawar FRS, was entirely happy for Bob to continue the human work, it was then too close to the end of his five-year contract for him to take advantage of the new Director’s more enlightened attitude.

Parkes invited Bob to join him at Cambridge on a Ford Foundation Fellowship but, because this was not available until 1963, he passed the intervening year at the Beatson Institute for
Cancer Research in Glasgow, whose Director, John Paul, was a widely respected pioneer in the field of cell and tissue culture. This meant weekly commuting from north London, where Ruth and their growing family were still based. Working with John Paul and Robin Cole, Bob sought to isolate cell lines from blastocysts of the rabbit and thus gained experience in cell and embryo culture that was to prove invaluable for his future research.

The move to Cambridge was one for which Bob initially had very mixed feelings. On the one hand he found the life of privilege he observed around him even more difficult to reconcile with his strongly held egalitarian principles than he had the Officers’ Mess in his Army days. On the other hand, he was struck by the beauty of the city and, most particularly, by the extraordinary intellectual vibrancy of the university. The positive aspects of the move clearly won him over because, apart from limited sabbatical spells elsewhere, he remained a member of the university until he retired and continued to live and work near Cambridge thereafter. He also maintained his association with Churchill College, where he had been a Fellow since 1984.

Bob’s extensive work on mammalian oocyte maturation in vitro had by then fully confirmed that release of oocytes from Graafian follicles enabled their maturation according to a predictable species-specific schedule, and provided detailed timing of the successive stages leading up to second meiotic metaphase, the normal point of arrest before sperm penetration. However, his findings on the timing of events in human oocyte maturation were clearly at variance with those reported in a much earlier study by Gregory Pincus, a pioneer of oral contraception. As a young ‘turk’ Bob had no qualms about publicly telling Pincus he was wrong. The resulting hostile relations were eventually repaired, with Bob later observing that Pincus ‘would have made a fine Yorkshireman’.

By the time he was established at Cambridge, Bob was firmly committed to obtaining the fertilization of human oocytes in vitro, but from the literature he was aware of serious challenges confronting him in his efforts to do so. An immediate problem was that human ovarian tissue for realizing this aim was not forthcoming in Cambridge, a situation that, with prompting by Ruth, stimulated Bob to write to Victor McKusick, who, presumably through his work on inherited disorders in humans, had evidently shown interest in Bob’s research. This resulted in Bob’s visiting the Division of Medical Genetics at Johns Hopkins University in Baltimore for six weeks in the summer of 1965, where McKusick introduced him to Howard and Georgeanna Jones, a husband and wife team working in the field of gynaecology. They provided Bob with sufficient ovarian tissue to enable him amply to confirm his preliminary finding on the timing of human oocyte maturation in vitro. However, attempts to fertilize the matured oocytes consistently failed, despite exposing sperm to a variety of different treatments designed to enable them to acquire fertilizing ability. The following summer was spent at Chapel Hill in North Carolina, where, in a further attempt to address this problem, Bob prepared small Millipore chambers loaded with sperm that were then inserted overnight in the uteri of women, a procedure for which there seems to have been no shortage of volunteers. However, despite prolonged exposure of the sperm to secretions of the female tract through such a semi-permeable membrane, fertilization was still not achieved.

Hence, progress with in vitro fertilization (IVF) of human oocytes seemed, for a time, to have reached an impasse. However, never at a loss for ideas on projects to pursue, Bob turned his attention to two other topics. One was the possibility of controlling the sex ratio of offspring. Many unsuccessful attempts to this end had been made using various procedures
designed to achieve the separation of sperm bearing an X chromosome from those bearing a Y chromosome. Bob’s thoughts turned to typing preimplantation embryos at a stage when they could be transferred selectively to the uterus as an alternative to amniocentesis and abortion in cases in which male offspring were at risk of inheriting serious X-chromosome-linked diseases. The publication of this work caused a considerable stir at the time because it was portrayed as offering choice of the gender of offspring rather than avoiding the inheritance of serious genetic disease.

The second topic reflected Bob’s persisting conviction that certain developmental anomalies such as Down syndrome, which showed an age-related increase in incidence, were rooted in errors of chromosome segregation during oogenesis. His hypothesis was that oocytes were ovulated in a sequence dictated by their time of entry into meiosis in the fetal ovary. Those entering earlier were held not only to be ovulated before those entering later but also to have a higher frequency of chiasmata and, in consequence, a lower risk of chromosomal mal-segregation.

By the mid 1960s it had become very clear to Bob that he needed the services of a clinician based in the UK who was not only in sympathy with his aims but also wholeheartedly committed to helping him realize them. He found such a person in Patrick Steptoe (FRS 1987) (16), an obstetrician who had not only long been acquainted with the human misery caused by infertility but, like Palmer in France and Frangenheim in Germany, was engaged in pioneering the development of vitally relevant laparoscopic surgical procedures. These entailed passing a light source, a viewing scope and surgical instruments through the navel under general anaesthesia with the abdomen inflated with gas so as to separate organs sufficiently to enable them to be seen clearly. Bob’s initial thought was that Patrick’s expertise might help him realize the fertilizing capacity of human sperm. However, he soon appreciated that laparoscopy would allow maturing follicles in the ovary to be viewed clearly enough for aspiration to recover oocytes before ovulation. But Patrick brought more than just his surgical skills to a committed working partnership that was to endure from 1968 until his death 20 years later. Before they met, Bob’s interest in achieving fertilization in vitro was firmly focused on exploring the origin of genetic, particularly chromosomal, disorders of development. It was undoubtedly Patrick who raised to the fore its potential in alleviating infertility. Early on, the media clearly regarded Patrick as the senior partner in their joint endeavour, even though he openly acknowledged that his role was that of facilitator of the scientific initiatives that were due to Bob. Bob’s scientific leadership was evident from the nicknames they were given by the staff of Bourn Hall Clinic, namely ‘Steppy’ and ‘The Boss’.

Through the efforts of Patrick and certain other obstetricians, sufficient excised ovarian material was made available to Bob to enable him to embark on a serious further attempt to obtain fertilization with oocytes matured in vitro. Particularly relevant was the work of a research student in the Marshall Laboratory, Barry Bavister, who, in attempting IVF in the hamster, found that raising the pH of the medium in which the sperm were suspended was sufficient to enable them to acquire fertilizing capacity. Applying this simple adjustment to the medium in which human oocytes matured in vitro were brought together with recently ejaculated, washed sperm enabled the early stages of human fertilization to be obtained unequivocally outside the body for the first time. This study, which was supported by critical photographic evidence that various earlier claims of success had consistently failed to provide, was published in *Nature* on 15 February 1969. It immediately placed Bob and Patrick enduringly in the limelight in a way that was hardly helpful for the future progress of
their work. The problem was exacerbated by Bob’s strongly held view that scientists had a duty to engage with, and inform, the public about what they were trying to achieve in areas of research that had obvious implications for society at large. This view was shared by very few scientists at that time and, indeed, is still commonly regarded as outside the responsibility of those engaged in such research. The fact that Bob had already taken every opportunity to explain his aims and aspirations with articles in both tabloid and broadsheet newspapers was widely misconstrued, both within the Physiological Laboratory and more generally among the scientific community, simply as publicity seeking. His actual aim in this regard is very clearly set out in an article based on a lecture and discussion he held at George Washington University in Washington DC in December 1968 that was published in *Nature* in 1971 with David Sharpe, a lawyer from that university, as co-author (11):

*When scientists clearly foresee potential conflicts with existing rules of society arising from their work, paradoxically both human progress and scientific freedom may hang on their activism in arenas generally regarded as social or political. Scientists may have to make disclosures of their work and its consequences that run against their immediate interests: they may have to stir up public opinion, even lobby for laws before legislatures, in the hope that attitudes of society as evidenced in its laws will mature at a rate not too far behind the transition of scientific discovery into technological achievement. The lobbyists for reform in the laws of drug and alcohol addiction, abortion and sexual behaviour have achieved much public approval in their areas of concern: can biologists in experimental embryology expect so much more by doing any less?*

Once fertilization *in vitro* had become a reality rather than just a prospect, Bob and Patrick faced enduring and extraordinarily hostile reactions from many quarters. What must have surprised them was the strength of opposition within both the medical and scientific establishments. The British Medical Association repeatedly portrayed Bob as Dr Frankenstein, which led him to sue that organization successfully for libel on several occasions. Among his most strident scientific critics were James Watson (ForMemRS 1981), Max Perutz FRS and Victor Rothschild FRS. However, Bob was not one to be cowed by such eminent persons, as is evident from the following exchange with Rothschild in the pages of *Nature* shortly after the IVF paper was published:

*Rothschild:* Without wishing to engage in semantic hair-splitting, one must observe that the ‘early stages’ of fertilization may be and, in the note by Edwards *et al.*, are so early as to raise the question whether fertilization, if the word is to have any meaning, occurred at all.

*Edwards, Bavister & Steptoe:* It should also be noted that conclusions in many papers reporting fertilization in progress have been based on the evidence of pronuclear stages. … Indeed, Rothschild is hoist with his own petard, for the frontispiece of his book on fertilization shows a mouse egg with a spermatozoon in the perivitelline space and labelled ‘A live fertilized mouse egg showing the whole spermatozoon in the cytoplasm’. This illustration shows the same early stage as in our Figure 4B which presents a human egg with a perivitelline sperm.

Aside from his involvement with Bob in work on IVF, Patrick Steptoe also suffered acutely from the very low esteem in which his pioneering work was regarded within mainstream medical circles. At that time, laparoscopy was widely held to carry high risks and be of little utility. Early on there were legitimate concerns about damage to the abdomen through the heat generated with lighting that was sufficiently intense to allow a clear view of its contents. However, this problem had been solved some years earlier through the ingenuity of Harold Hopkins (FRS 1973), innovator of fibre optics and rod-lens endoscopes. Nonetheless, Patrick
was widely regarded as a maverick among his peers, at least one of whose number strongly counselled Bob against collaborating with him.

The obvious next step was to see whether oocytes that had been fertilized in vitro could progress through preimplantation stages of development in culture. Fortunately there was no shortage of volunteers for donating oocytes in the Oldham area of Greater Manchester, where Patrick worked. Hence, less than two years after reporting successful IVF, Bob and Patrick, with the invaluable support of a fully qualified nurse called Jean Purdy, who was Bob’s technician, reported in vitro development to morula and blastocyst stages.

They were then confronted with the dilemma common to all who wish to translate experimental advances into clinical reality. Given that the embryos obtained in vitro looked normal morphologically, both in the living state and as fixed and stained preparations, was it safe to start placing them in women volunteers with the aim of treating their infertility? The wisdom at the time, based on work in other mammals, was that the further development of preimplantation stage embryos would be all-or-none, with development either proceeding normally or failing altogether. We now know that this is not strictly true because in vitro culture of preimplantation embryos can in some species lead to excessive growth of fetuses and consequent problems at parturition.

The decision to go ahead with transfer to women of human embryos generated in vitro confronted Bob and Patrick with a further set of problems. One was how to optimize conditions for IVF, embryo culture and transfer to the genital tract when, in contrast with the situation in other mammals such as the mouse, material would inevitably be available only sporadically and in very short supply. Hence, controlled studies using systematically varied conditions were out of the question and the best that could be done was to ‘tweak’ conditions in ways that were informed by intuition or work in other species.

A further serious problem was geographical, namely the considerable distance between Cambridge, where Bob was based, and Oldham in Greater Manchester, where Patrick conducted his clinical work. When a volunteer was available, Bob would have to drive north, often at short notice, for anything from one day to a week or more, which was obviously difficult to square with his research and teaching responsibilities back in Cambridge. In an attempt to circumvent this problem, the support of the Medical Research Council was sought in the early 1970s with the aim of bringing Patrick to the Cambridge area and thus consolidating the laboratory and clinical work in one place. Various options were explored, but these came to naught in the end. One was to move to the Clinical Research Centre in Harrow, but Bob had by then become so wedded to Cambridge that he was not prepared to sacrifice all that the university had to offer for working in an institution devoted entirely to research. Moreover, the general perception of what Bob and Patrick were trying to achieve was hardly very positive at that time. A major concern was the rate at which the world population was increasing, and any measure that might further contribute to it was hardly likely to be looked at favourably by the powers that be. This was a view that Bob found completely unacceptable, arguing that research should be directed to enabling people who desired children to have them, as well as making contraception more widely available and effective for those wishing to limit the size of their family. They were also confronted with the view that IVF would only be of value in addressing infertility due to blockage of the fallopian tubes, a condition that many felt could be corrected effectively by microsurgery. One prominent obstetrician even expressed the view that blockage of the fallopian tubes was overwhelmingly due to sexually transmitted disease so that IVF would simply enable women of low moral worth to bear children! There were
also ethical concerns regarding Bob and Patrick’s proposal, with Medical Research Council referees feeling it was premature to proceed with treatment of human patients until studies on non-human primates had been undertaken (Johnson et al. 2010; Johnson 2011). Concerns were sharpened by a report that rats born after IVF had a high incidence of small eyes. This defect, however, turned out to be a heritable trait in the strain used for the research rather than a consequence of the in vitro techniques employed. Bob’s view was that work on other primates would not only pose problems of choice of species but also prove to be of dubious relevance to the human situation. Hence, the way forward was beset with problems and challenges that, rather than seeming almost insuperable, served to spur Bob and Patrick on.

Indications were that preimplantation development in the culture of embryos produced in vitro was normal, so that the stage was set for transfer of such embryos to the uterus, which was usually done non-surgically via the cervix. Thus began a gruelling period of years during which numerous embryos were transferred, but among the very rare ones that implanted, pregnancy was typically not sustained. To persevere in such circumstances when other intellectually stimulating and more tractable research projects were available is a measure of Bob and Patrick’s extraordinarily dogged determination. They were almost certainly aided in this by an ardent desire to prove their many critics wrong. Success came eventually at 11.47 p.m. on 25 July 1978 with the birth of Louise Joy Brown, weighing 5 pounds and 12 ounces. Shortly thereafter, a second healthy baby, Alastair MacDonald, was born. This was soon followed by IVF births in Australia and the USA, with the procedure rapidly spreading to other countries so that a wealth of experience in improving its efficiency was rapidly established.

This eventual triumph after years of unrelenting effort and sustained criticism did not signal the end of Bob’s problems. Because it coincided with Patrick’s retirement from the National Health Service, other arrangements had to be made for continuing their collaboration. This was an obvious opportunity for Bob to discontinue his arduous travel to and from Oldham by bringing Patrick down to the Cambridge area. However, as the university could not offer the necessary facilities, and public funding for securing them elsewhere was not forthcoming, their IVF work halted altogether for almost three years while private sources of support were explored. During this interval, the ever-energetic Bob wrote a massive tome entitled ‘Conception in the human female’ (13), which was hailed by one of his erstwhile critics as the best book on obstetrics published in the twentieth century. Eventually, private funding was obtained to purchase Bourn Hall in the Cambridgeshire village of Bourn, a beautiful Jacobean house with its ancient family motto ‘Jour de ma vie’ carved in stone above the entrance. An array of Portakabins was soon assembled to provide wards, an operating theatre, and laboratory facilities. The work was then resumed in September 1980 and IVF was refined in various ways so that in December 1987 the clinic was able to celebrate the birth around the world of its first 1000 babies. While Bob provided the principal scientific expertise underpinning the clinical work at Bourn Hall, and was also involved in training others in the practice of assisted conception in vitro, he continued with teaching and research within the university.

**Principal scientific contributions**

In work for his PhD, Bob focused on ascertaining the consequences of altering the chromosomal composition of early mouse embryos by means of a wide variety of different approaches,
including exposing sperm to drugs and to ultraviolet and ionizing radiation. These studies also provided much information on the timing of events in normal gamete maturation, fertilization and early development in this species. However, the most enduringly significant part of Bob’s research in Edinburgh was the demonstration in collaboration with Ruth Fowler that adult mice could be induced to ovulate according to a predictable schedule. This was achieved by timed injection of gonadotrophins, specifically pregnant mare’s serum gonadotrophin, which has follicle-stimulating hormone activity, followed after an interval of about 40 hours by human chorionic gonadotrophin (hCG), with luteinizing hormone activity (1). Whereas low doses of the two gonadotrophins enabled the time of ovulation and mating to be controlled by overriding the natural oestrous cycle, a higher dosage induced superovulation: the production of substantially more mature oocytes and embryos than normal. These important findings were followed up by investigating the effect of such treatment on fetal mortality and subsequent fertility, both natural and in response to further ovulation induction. The effects of treatment with progesterone and oestrogen on pregnancy and embryonic mortality after superovulation were also explored. Induced ovulation soon became a vital part of the technical repertory for studies on oocyte maturation and early development in both the mouse and other mammals. Bob’s five years in Edinburgh resulted in the publication of more than 30 original peer-reviewed papers, of which he was the sole author of more than one-third.

Bob’s work on immunological aspects of reproduction, notably the antigenicity of semen and the existence of natural antibodies against sperm, started in Edinburgh and was pursued further during his year with Tyler at the California Institute of Technology and then at the NIMR. However, it did not progress far either in explaining infertility or in offering a promising approach to contraception. The most important series of studies that engaged much of his time at the institute was on the maturation of oocytes in vitro. He established that this occurred predictably in vitro in the mouse from germinal vesicle breakdown to metaphase of the second meiotic division at which oocytes normally arrest before fertilization in most mammals (2). Moreover, it progressed according to a schedule closely mimicking that in vivo. The addition of gonadotrophin to the medium proved unnecessary, with maturation occurring in a simple saline solution, suggesting that its induction depended simply on release from an inhibitory influence of the surrounding follicle. He showed that maturation in vitro occurred similarly in oocytes of the rat and hamster and various other mammals (3), before discovering that the phenomenon had already been described earlier in the rabbit, in humans and in other primates by Gregory Pincus and colleagues and, more compellingly, in the rabbit by M. C. Chang (Pincus & Enzmann 1935; Pincus & Saunders 1939; Chang 1955). This temporary disappointment did not deter Bob from continuing to pursue this line of research and finding that results in the monkey and baboon were less convincing than in rodents, with chromosomal condensation also being evident in non-cultured controls (3). This led him to suspect that the apparently very rapid maturation of human oocytes reported by Pincus and Saunders was probably a consequence of follicular atresia. Thus Bob could find no convincing evidence of maturation in vitro among 76 human oocytes from excised ovarian material that were cultured for up to 20 hours, well beyond the period during which these earlier workers had claimed that maturation took place.

Bob returned to this issue of human oocyte maturation in vitro following his move to Cambridge after an intervening year at the Beatson Institute in Glasgow, where, with John Paul and Robin Cole, he succeeded in deriving sustainable cell lines from blastocysts of both the mouse and rabbit. His visit to the Division of Medical Genetics at Johns Hopkins...
University in the summer of 1965, during which he had a good supply of human ovarian tissue from patients with polycystic ovaries or myoma, was rewarded with the discovery that germinal vesicle breakdown did not start until about 25 hours of culture, with about 36 hours being required for maturation to reach completion (4). The stage was thus set for the next step, namely to obtain the fertilization of human oocytes matured in vitro. However, attempts to fertilize such oocytes failed consistently, leading him to suppose that, as seemed to be true in the rabbit and rat, human sperm required a period of exposure to the female genital tract secretions to acquire fertilizing ability (Austin 1951, 1952; Chang 1951). Various procedures were therefore tried without success, such as placing human uterine or fallopian tube tissue in medium containing sperm, recovering sperm from cervical mucus 10 hours postcoitally, and transferring human oocytes and sperm into the rabbit or rhesus fallopian tube. Hence, in a visit to the University of North Carolina in Chapel Hill the following summer, efforts were concentrated on trying to ‘capacitate’ sperm by placing them in small Millipore chambers overnight in the uteri of women volunteers, but again without success. Having seemingly exhausted other options to explore, Bob devoted the next two years largely to establishing a proof of principle of preimplantation genetic diagnosis, and investigating his production-line model of oocyte development.

Resumption of efforts to achieve IVF were stimulated by the findings of Barry Bavister, a research student in the Marshall Laboratory, whose work in the hamster had revealed that sperm in this species could be ‘capacitated’ simply by making the medium in which they were suspended more alkaline. This finding was promptly tried with human sperm and allowed the early stages of human IVF to be obtained, as revealed by the presence in the vitellus of two pronuclei and a sperm tail (8).

In considering whether such fertilized oocytes could progress in development in vitro beyond the zygote stage, a concern was raised by a study in the rabbit which suggested that oocytes that had matured and been fertilized in vitro might be compromised in their development (Chang 1955). It was this concern that prompted Bob to secure Patrick’s expertise so that oocytes maturing in vivo might be recovered directly from the ovary. The need to recover oocytes shortly before they were ovulated required careful timing and, to this end, injections of exogenous human menopausal gonadotrophin and hCG were employed. Within 18 months of obtaining fertilization in vitro they were able to report morphologically normal development through to the morula and blastocyst stages (9, 10). It was at this juncture that the decision was made to apply the procedure to patients suffering from infertility.

However, no embryos produced by IVF using gonadotrophin injection to optimize the time of oocyte recovery showed any sign of implantation after placement in utero. Hormonal measurements indicated that these injections were perturbing the luteal phase of the cycle and might thereby be compromising the development of replaced embryos. When attempts were made to correct these luteal-phase perturbations hormonally, three cases of further development of embryos in utero were recorded. Two were so-called ‘chemical’ pregnancies characterized by a transient rather than sustained increase in hCG and thus reflecting failure of development soon after implantation, and the third was identified at 11 weeks after oocyte recovery as a tubal pregnancy (12, 15). These findings prompted the decision to focus on natural cycles using regular monitoring of urinary oestrogens and luteinizing hormone to detect the surge of the latter hormone that presages ovulation. This, of course, placed a premium on technical efficiency because it meant that only a single mature oocyte was typically available per cycle. In this context, Bob’s earlier work on the schedule of in vitro maturation of oocytes proved
helpful in determining the optimal timing for their recovery from the ovary. It was also found in these pioneering studies that all three pregnancies showing sustained normal development resulted from replacing embryos in utero in the evening rather than during the day. One of these pregnancies resulted in miscarriage of a normal fetus at 21 weeks and the other two in live births of normal babies, the first and obviously most celebrated of whom was Louise Brown.

**Preimplantation genetic diagnosis**

While work towards achieving fertilization in vitro in the 1960s was temporarily in abeyance, Bob turned his thoughts to the possibility that obtaining embryos in vitro would offer scope for typing them genetically for selective transfer to the uterus. He viewed this as offering a way of avoiding the transmission of genetic disease that some might consider more acceptable than amniocentesis and abortion. The most promising prospect at that time was to tackle serious X-chromosome-linked diseases, such as Duchenne muscular dystrophy, by selecting female rather than male embryos for replacement in utero. Bob invited me to collaborate on this project, which initially entailed examining intact rabbit blastocysts stained with DNA-binding dyes to detect the presence or absence of the sex chromatin body. This body represents one of the two X-chromosomes present in females that is inactivated in each cell of early embryos as a way of equalizing the dosage of genes on this chromosome with that of the single copy in males. It was already known that X-chromosome inactivation took place in the trophectoderm before the blastocyst implanted in this species. Perhaps unsurprisingly, the dye treatment was found to preclude further development. However, biopsying the trophectoderm of blastocysts that were up to 5 mm in diameter permitted the removal of a generous amount of tissue, which was then scored after appropriate nuclear staining for the presence or absence of sex chromatin. Blastocysts that were fully expanded, with the zona pellucida essentially intact, after post-operative recovery developed to full term when the sex of each was found to have been diagnosed correctly (7). This proof of principle of preimplantation diagnosis was first applied clinically more than two decades later (Handyside et al. 1990) and is now widely used when there is a perceived risk of transmission of genetic or chromosomal defects.

The second topic reflected Bob’s persisting conviction that certain developmental anomalies such as Down syndrome, which showed an age-related increase in incidence, were rooted in errors in chromosome segregation during oogenesis. His hypothesis was that oocytes were ovulated in a sequence dictated by their time of entry into meiosis in the fetal ovary, with those entering earlier being ovulated before those entering later. This idea was coupled with a further notion inspired by botanical findings that the number of chiasmata that were formed might decline the later that oocytes entered meiosis, so as eventually to fall below the diploid chromosome number. This process would be expected to lead to an age-related loss of pairing of sister chromosomes and the consequent generation of univalents that failed to segregate correctly during the completion of meiosis. He investigated this possibility in collaboration with Dr Alan Henderson from the Department of Genetics and found the predicted changes in ageing mice of the inbred CBA strain, which shows particularly marked oocyte depletion (6). Some years later, Paul Polani FRS produced findings that were consistent with the production-line model of oogenesis by labelling the DNA of germ cells in cultured early versus late fetal ovaries that were then transplanted to spayed adult females (Polani & Crolla 1991). However, definitive support for the interesting and potentially significant hypothesis of an associated decline in chiasmata frequency is still lacking.
During Bob’s year at the Beatson Institute in Glasgow, he collaborated with John Paul and Robin Cole on the culture of preimplantation rabbit blastocysts or of inner cell masses enriched therefrom. The stated objective was to obtain cells with extensive differentiation potential to facilitate embryological studies. This work was undertaken before reliable markers of differentiation and assays of developmental potential were available. However, the few cell lines that proved to be sustainable showed fibroblastic or epithelial morphology, with the former tending to increase in ploidy (5). It is interesting to note, however, that Bob was the first explicitly to suggest in an article published in 1982 that human embryos surplus to requirement for fertility treatment might be used for regenerative medicine (14). The first possibility he envisaged was culturing such spare embryos to a stage at which they could be used as a source of organ primordia. This option was closed in the UK by the Human Fertilisation and Embryology Act 1990, which proscribed the culturing of embryos beyond two weeks or the appearance of a primitive streak, which signals the beginning of development of the embryo proper. This left open his alternative suggestion, namely the derivation of pluripotential embryonic stem cells from blastocysts, as had then recently proved successful in the mouse. However, unaccountably, it was well over a decade before the latter suggestion was adopted.

Most interestingly, the value of IVF proved not just to be limited to overcoming infertility due to blockage of the fallopian tubes as medical authorities had initially asserted. In the great majority of cases in which IVF treatment is successful, the cause of infertility remains unknown. A further point of great interest to emerge from work on assisted conception in vitro is that infertility seems as often to be attributable to the male as to the female partner, countering a prejudice that the medical profession seemed to have sustained since Tudor times!

WIDER INTERESTS AND ACTIVITIES

Throughout his long and extraordinarily productive career, Bob’s interests extended well beyond the confines of the laboratory. Thus, early in his Cambridge days, he became engaged in politics, and served two terms as a Labour councillor in the city. Moreover, this experience seems to have stimulated him to consider standing as an MP. Fortunately for the millions of people whose lives were eventually enriched by his work, and for the many scientific colleagues in his field, this was a road not taken. Instead, his energy outside the laboratory was channelled in a very different direction that was to prove of immense significance for the development of his chosen field of research. His first foray into publishing was as editor of a news sheet entitled Research in Reproduction, which was funded by the International Planned Parenthood Federation and aimed at keeping busy clinicians informed about relevant research. It included both reviews of relevant articles and very instructive up-to-date wall charts.

Although a professional body devoted to all aspects of research and clinical work relevant to human reproduction, the American Fertility Society (AFS), now named the American Society for Reproductive Medicine (ASRM), had been in existence since 1944, there was no corresponding organization on this side of the Atlantic, despite the fact that Europe was fast becoming the source of many significant advances in the field. Moreover, European authors often claimed to experience difficulty in getting their work published in the AFS journal,
Fertility and Sterility. These and other considerations prompted Bob to solicit support for founding a European counterpart of the AFS/ASRM. In this endeavour he found a totally committed ally in Jean Cohen, a Paris-based obstetrician with whom Bob had established a very close friendship some years earlier while helping him set up IVF in France. The pair agreed at the outset that science should have equal standing with medicine in such an organization, reflecting science’s seminal role in the development of assisted conception and related procedures. The idea of forming such a professional body, which was eventually to be called the European Society of Human Reproduction and Embryology (ESHRE), was presented by Bob and Jean Cohen to colleagues at a meeting in Helsinki in 1984, at which it was enthusiastically received. ESHRE held its first Annual General Meeting in Bonn in 1985 with Bob as chairman, a role that he fulfilled with typical boundless enthusiasm and energy. To ensure that it did not, as some feared, simply become another clinically dominated obstetrical organization, a tradition was established, and maintained to the present day, that the chairmanship should alternate between clinician and scientist. To this same end, emphasis was also placed on minimizing membership subscriptions and the cost of attending annual and other meetings under its auspices. Education and training were prominent on the agenda, with numerous workshops covering good laboratory and clinical practice, and with early emphasis on guidelines and ethical issues. Membership of ESHRE has continued to grow year by year, and annual meetings now attract several thousand delegates from an impressive number of countries.

Among various matters discussed at Bonn was the establishment of the Society’s own journal, which, under the title Human Reproduction, started publication with IRL Press in 1986, which was soon to be taken over by Oxford University Press, with Bob as editor-in-chief. He was from the outset determined to publish only papers of the highest quality while greatly aiding authors who had difficulty expressing themselves clearly in English. This placed huge demands on his time in an era preceding the simple electronic editing on which all now rely. As the number of original articles increased, there was pressure on space occupied by reviews, which Bob was led to consign largely to a further journal founded by ESHRE entitled Human Reproduction Update, for which he also held the principal editorial role. Furthermore, as more relevant research at a molecular level was submitted, Bob successfully made the case for establishing yet a third journal, entitled Molecular Human Reproduction, which he also edited. By the time the five-year contract with Oxford University Press was due for renewal, all three journals had achieved very high standing in the field under his editorship, which, however, then ended both suddenly and rather acrimoniously. Bob felt passionately that ESHRE should move from reliance on the commercial sector to publishing its three journals in-house. But despite barraging the Executive Committee of ESHRE with a succession of updated proposals, he failed to persuade it to take such a step, which was perhaps too bold for most to contemplate at a time when discussions about open-access journals were already under way. The outcome was that Bob resigned from the editorship of all three journals at rather short notice, giving as the reason the excessive demands that the editorial work was placing on his time. How he had managed so successfully to serve so long as editor for all three journals in conjunction with his many other activities is a further measure of his energy and drive. After his resignation, each of the journals was assigned a separate editor. However, through insisting that his name as founder editor be deleted from all three journals, Bob effectively severed links with the enormously successful society he had co-founded, and several years were to elapse
before his relations with it were largely restored (Brown 2006). In the meantime Bob used his small, extraordinarily efficient and very loyal editorial team to found a new journal, *Reproductive BioMedicine Online*, a bold commitment for a 75-year-old to undertake. With great emphasis on topical editorials, rapid publication and lively debate of contentious issues, this journal soon proved an unequivocal success. What is particularly impressive about Bob’s helmsmanship of this journal during its first decade is the extraordinary breadth and depth of his own editorial and other contributions, which range from genetics and embryology, through reproductive physiology, endocrinology, circadian rhythms and cancer to the many ethical issues raised by the lines of enquiry that he mostly started (Gardner & Johnson 2011).

Bob and Ruth with their five daughters used to make regular visits to the Yorkshire Dales, to which Bob had become very attached since spending a year there during his school days. In their early years in Cambridge the family lived in the Newnham district of the city in a modern house on Gough Way. Later, Duck End Farm in the rural village of Dry Drayton became the home in which Bob and Ruth spent the remainder of their lives. Although Bob had clearly not found agriculture to his taste as an academic subject, he evidently enjoyed it in practice and, especially in retirement, spent a good deal of time on the farm (figure 1). Moreover, he relished being invited to serve as President of the Ribblehead Sheep Show (figure 2). Duck End Farm was an ideal place in which to pursue one of his long-sustained obsessions, namely planting deciduous trees, which he undertook on a sufficiently grand scale to earn him the title of the ‘tree man’. Latterly he also became passionately opposed to shooting and other blood sports and, at least partly in response to witnessing the effects of bovine spongiform encephalopathy (‘mad cow’ disease), adopted a vegetarian diet.
It was a great sadness to his family, and numerous colleagues and friends worldwide, that such an original, energetic, inspiring and engaging individual should have had to endure a progressively debilitating illness throughout the last five years of his life. It was especially hard that it prevented him from going to Stockholm to receive the 2010 Nobel Prize in Physiology or Medicine in person, which would undoubtedly have proved a particularly gratifying antidote to the enduring hostility he had suffered earlier from people who lacked his vision. However, there were three aspects of the award that made it unusual in present times. First, Bob was the sole recipient, although it would presumably have been shared with Patrick Steptoe had he still been alive. Second, news of the award was greeted with essentially universal approval within the scientific community. Third, rather than being given for elegant or clever science that might at some time in the future prove beneficial to mankind, it was for tangible clinical progress, namely the birth of several million babies to couples who would otherwise have remained childless. Altogether, his is an extraordinary legacy!

**Honours and awards**

*Medals and prizes*

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<tr>
<th>Year</th>
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<tr>
<td>1970</td>
<td>Medal of the American Fertility Society</td>
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<td>1971</td>
<td>Darwin Medal, Institute of Biology, UK</td>
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1973 Adair Award, American Gynecological Society
1980 Serono Prize, American Fertility Society
1985 Spanish Fertility Society Gold Medal
1987 Gold Medal, City of Toulouse, France
1988 CBE
1989 Joint winner of the King Faisal International Prize for Medicine
1991 Steptoe Memorial Medal and Prize, British Fertility Society
1994 Berthold-Gedachtnis Medal, German Society of Endocrinology
1996 Pierre Soupart Lecture, Axel Munthe Award, Naples
1998 Gold Medal, University of Sassari, Sardinia
1999 Gold Medal Award of the International Federation of Associations of Anatomists
2000 Bertarelli Foundation Award in Reproductive Healthcare
2002 Distinguished Lifetime Achievement Award, Reproductive Biology Professional Group, American Society for Reproductive Medicine
2003 Award of the Egyptian Ministry of Health
2004 Pioneer in Stem Cell Award, Pittsburgh Development Center
2005 Eardley Holland Gold Medal, Royal College of Obstetrics and Gynaecology, London
2006 30th Joseph Bolivar DeLee Humanitarian Award, Chicago Lying-in Hospital Board of Directors & Department of Obstetrics and Gynecology, University of Chicago
2007 Chevalier dans l’Ordre national de la Légion d’Honneur, Paris
2008 Pride of Britain Award—Lifetime Achievement
2010 Nobel Prize in Physiology or Medicine
2011 Knighthood

Membership of academies, etc.
1983 Honorary Member of the French Society for Infertility
1984 Fellow of the Royal Society
1985 Founder member of the European Society for Human Reproduction and Embryology (ESHRE)
1986 Honorary Member of the Royal College of Physicians
1988–90 President, Ribblehead Sheep Show
Honorary President, British Fertility Society
1990 Honorary Member, Pacific Coast Fertility Society
1992 Honorary Fellow, German Society of Obstetrics and Gynecology
Honorary President, French Gynecological Society
Keys of San Diego City
1993 Honorary Fellow, Royal Society of Medicine
Honorary Fellow, European Society of Human Reproduction and Embryology
1995 Honorary Member, Italian Society of Anatomy
1998 Honorary Member, Association of Clinical Embryologists, UK
Honorary President, Alpha—International Society for Scientists in Reproductive Medicine
Honorary Member, Greek Fertility Society
Honorary Fellow, International Federation of Fertility Societies, San Francisco
1999 Honorary Member, Middle East Fertility Society
Patron, UK National Gamete Donation Trust
2000 Life membership, Indian Society for the Study of Reproduction and Fertility
2001 Honorary Membership, Society for Reproductive Endocrinology and Infertility, American Society for Reproductive Medicine

Doctoral degrees
1983 Hon. DSc, University of Hull
1987 Hon. DSc, University of York
1988 Hon. DSc, Vrije Universiteit Brussel
1992 Hon. DSc, University of Valencia
Hon. DSc, Mons-Hainaut University Belgium
1999 Hon. DSc, Timisoara University, Romania
Hon. DSc, University of Rome, La Sapienza
2000 Hon. DSc, University of Cambridge
2002 Lifetime Honorary Professor, Fourth Military Medical University, Xi’an, China
2004 Hon. DSc, Democritus University of Thrace, Greece
2006 Hon. DM, Karolinska Institutet, Sweden
2007 Hon. DSc, University of Huddersfield, UK

Named lectures
1980 Woodhouse Award and Discourse, Royal Institution, London
1993 Celebratory Lecture at the opening ceremony for the establishment of the Middle East Fertility Society
2002 First Awardee of the Robert Edwards Keynote Lecture, ESHRE, Vienna
2004 Site Lecturer, Genetics and IVF Institute, Fairfax, Virginia
2008 The Physiological Society Annual Review Prize Lecture
Robert Geoffrey Edwards

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REFERENCES TO OTHER AUTHORS


BIBLIOGRAPHY

The following publications are those referred to directly in the text. A full bibliography is available as electronic supplementary material at http://dx.doi.org/10.1098/rsbm.2014.0020 or via http://rsbm.royalsocietypublishing.org.


