ROBERT EDWARDS: NOBEL LAUREATE IN PHYSIOLOGY OR MEDICINE

Nobel Lecture/Nobel Prize Symposium in Honour of
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by

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Today we are here to celebrate the achievements of Robert Edwards. It is however a celebration tinged with sadness. Sadness that Bob himself is not well enough to be here in person, so in preparing this lecture, I have tried to weave into it some of Bob's written and spoken words. Sadness also that neither Patrick Steptoe (1913–1988; Fig. 1) [1] nor Jean Purdy (1946–1985; Fig. 2) [2], two of his key collaborators, are alive to celebrate with him.

TO BEGIN AT THE BEGINNING

Robert Geoffrey Edwards was born on the 27th of September 1925 in the small Yorkshire mill town of Batley. He arrived into a working-class family, the second of three brothers – an older brother, Sammy and a younger, Harry. These brothers Bob describes as competitive, "all determined to win or, if not to win, to go down fighting" [3]. Bob's mother, Margaret, was a machinist in a local mill. She came originally from Manchester, to where the family relocated when Bob was about 5, and where he was educated. In those days, bright working class kids could take a scholarship exam at age 10 or 11 in competition for the few coveted places at a grammar school: the potential pathway out of poverty and even to University. All three brothers passed the exam, but Sammy decided against Grammar School, preferring to leave education as soon as he could to start earning. His mother was furious at this wasted opportunity, and so when her two younger sons passed the exam, there was no question but that they would continue in education. So it was that Bob progressed in 1937 to Manchester Central Boy's High School, which, incidentally, also claims Sir James Chadwick, FRS (1891–1974), another Cambridge professor and Nobel Laureate (in Physics in 1935 for discovery of the neutron [4]), as a former pupil. Bob's summers were spent in the Yorkshire Dales, where their mother took her sons to be closer to their father's place of work. There Bob laboured on the farms and developed an enduring love for the place.

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* At the Nobel Prize Symposium in Honour of Robert G. Edwards, Martin H. Johnson delivered this lecture.

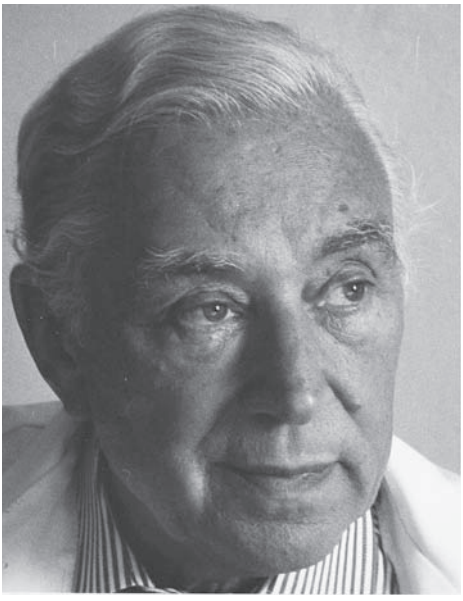

Figure 1. Patrick Steptoe (1913–1988) (courtesy Andrew Steptoe).

Figure 2. Jean Purdy (1946–1985) (courtesy Barbara Rankin).

These early experiences were formative for Bob. He became a life–long egalitarian, for five years a Labour Party councillor [5], willing to listen to and to talk with all and sundry, regardless of class, education, status and background. Second, he developed an enduring love for and curiosity about natural history and especially the reproductive patterns that he observed among the farm's sheep, pigs and cattle in the Dales. Finally, he took great pride in being a 'Yorkshire man' – with traditional attributes of affability and generosity of spirit combined with no-nonsense blunt-speaking. Indeed, following his only meeting with Gregory Pincus (1903–1967) [6] at a conference in Venice in May 1966, at which Bob, the young pretender, clashed with the 'father of the pill' over the timing of egg maturation in humans, Bob paid Pincus the biggest compliment he could imagine, saying "He would have made a fine Yorkshireman!" [7].

Figure 3. Bob on National Service,1940s (courtesy Ruth Edwards).

The aftermath of war was to provide an extended interruption to Bob's education: when he left school in 1943, he was conscripted into the British Army for almost four years. To his surprise as someone who was from a working class family, he was identified as potential officer material and sent on an officer-training course, before being commissioned in 1946 (Fig. 3). However, the alien life-style of the officers' mess was not to his taste and served to reinforce his socialist ideals. The years in the army were broken by 9 months compassionate leave back in the Dales, to which he was released to help out when his farmer friend there became ill. So engaged did he become in farming life that, after discharge from the army in 1948, he returned home to Manchester, from where he applied to read agricultural sciences at the University College of North Wales at Bangor.

Figure 4. John Slee, 1963 (courtesy Ruth Edwards).

Having gained a place and a grant to fund it, the 6 or so months that intervened were occupied in a Government desk job in Salford, Greater Manchester, work experience that reinforced the attractions of agricultural science. So his disappointment in the course offered at Bangor was acute. By that time he was an experienced 23 year old, described by his impressionable 18 year old public-school educated and self-described "unlikely" friend John Slee (Fig. 4), as being "both ambitious and flexible, and unusually confident in his own judgement" [8]. And in Bob's confident judgement, the course on offer was not 'scientific', and he was bored through two tedious years of agricultural descriptions, after which he reported that his teachers were "glad to see the back of him" in Zoology for a year. The Zoology Department offered a course much more to his style and led by the more intellectually challenging Rogers Brambell, FRS (1901–1970) [9]. However, that year was not enough to salvage an honours degree, and in 1951, aged 26 he gained a simple pass. Unbeknown to him at the time, he was not alone in this undistinguished academic embarrassment, as neither "Tibby" Marshall, FRS (1878–1949), the founder of the Reproductive Sciences [10], nor Sir Alan Parkes, FRS (1900–1990), the first Professor of Reproductive Sciences at Cambridge [11], and who was later to recruit Bob there, distinguished themselves as undergraduates. In 1951, however, Bob "was disconsolate. It was a disaster. My grants were spent and I was in debt. Unlike some of the students I had no rich parents… I could not write home, 'Dear Dad, please send me £100 as I did badly in the exams.'" [12].

Characteristically, however, Bob's low spirits did not last long. He learned that John Slee had been accepted on a Diploma course in Animal Genetics

at Edinburgh University under Conrad Waddington, FRS (1905–1975) [13]. Bob applied, and, despite his pass degree and to his amazement, he was accepted. That summer, he worked in various labouring jobs to earn enough to pay his way in Edinburgh [14]. It is tempting to see in these experiences of the youthful Bob Edwards consequences for his later approach to life: he learned that the accepted hierarchies of organisation and ideas were there to be challenged, not simply accepted, and that recovery was possible after what might seem the severest of knock-backs. These were lessons that Bob was to draw on later in his career.

Figure 5. Ruth Fowler in laboratory, Edinburgh, 1950s (courtesy Ruth Edwards).

In Edinburgh, Bob not only started to map out his scientific career, but importantly also met Ruth Fowler (Fig. 5), who was to become his life-long scientific collaborator, and whom he was to marry in 1954, their five daughters following between 1959 and 1964: Caroline, Sarah, Jenny, and twins, Anna and Meg. Bob initially found himself somewhat overwhelmed, even "intimidated" by Ruth's august family background. Her father, Sir Ralph Fowler, FRS (1889–1944) [15], and her maternal grandfather, Lord Ernest Rutherford, FRS (1871–1937) [16], were not only both 'titled', but both also had the most impressive academic credentials imaginable. Ralph Fowler was Plummer Professor of Mathematical Physics in Cambridge from 1932 to 1944, whilst Rutherford was the first Nobel Laureate in Ruth's family, having been awarded the 1908 Nobel Prize in Chemistry 'for his investigations into the disintegration of the elements, and the chemistry of radioactive substances'.

The intellectual spirit of scientific enquiry that Bob experienced in Edinburgh obviously fitted his aptitudes perfectly, for Waddington rewarded his Diploma year with a three year PhD place and funded it with the princely sum of £240.00 per year [17]. Bob's chosen field of research was the developmental biology of the mouse. Bob saw that to understand development involved engaging in an interdisciplinary mix, not just of embryology and reproduction, the conventional view at the time, but also of genetics. Given the scientific and social emphasis on genetics over the last 40 or so years, it is difficult now to realise how advanced a view this was in the 1950s, when genetic knowledge was still rudimentary and largely alien to the established developmental and reproductive biologists of the day, as Bob himself was later to comment [18]. For example, it was in the 1950s that DNA was established as the molecular carrier of genetic information [19–22], that it was first demonstrated that each cell of the body carried a full set of DNA/genes [23–25], and that genes were selectively expressed as mRNA to generate different cell phenotypes [26]. Perhaps of greater importance for Bob at that time, it was only by the late 1950s that cytogenetic studies led to the accepted human karyotype as 46 chromosomes [27–28], that agreement was reached on the Denver system of classification of human chromosomes [29], and that the chromosomal aneuploidies underlying developmental anomalies such as Down, Turner and Klinefelter Syndromes were described [30–32].

Figure 6. Alan Gates at a meeting in Cambridge in the late 1950s (possibly 1957).

Bob worked under his supervisor, Alan Beatty, to generate haploid, triploid and aneuploid mouse embryos and studied their potential for normal development. In order to undertake what were, in effect, early attempts at 'genetic engineering' in mammals, he needed to be able to manipulate the chromosomal composition of eggs, sperm and embryos. Whilst in mice, sperm were abundant, eggs were not, and overcoming this deficit led him to two major discoveries that proved to be of later significance. First, with Ruth, they worked to devise ways of increasing the numbers of synchronised eggs recoverable from adult female mice through a series of papers on the control of ovulation induced by use of exogenous hormones [33]. In doing so, they overturned the conventional wisdom that super-ovulation of adult females was not possible. Second, working with an American post-doc, Alan Gates (Fig. 6), Bob described the remarkable timed sequence of egg chromosomal maturation events that led up to ovulation after injection of the ovulatory hormone (human chorionic gonadotrophin; hCG) [34]. His six years, between 1951 and 1957, in Edinburgh give an early taste of his prodigious energy, resulting in 38 papers. Indeed so productive was this period that the last of the papers resulting from his Edinburgh work did not appear in print until 1963.

It was also in Edinburgh that Bob's interest in ethics was first sparked by the interdisciplinary debates among scientists and theologians that Waddington organised, and, as a result, Bob went on what he describes as a "church crawl", trying the ten of so variants of Christianity on offer in 1950s Edinburgh. He did not emerge from his consumer testing "God-intoxicated" [35], but convinced that man held his own future in his own hands. Bob's humanist ethical sympathies were to be developed further in all his later encounters.

AN AMERICAN DIVERSION

These early 1950s studies in science and ethics were to form the platform on which Bob's later IVF work was to be based, but before that his interests and life took a diversion to the California Institute of Technology for the year 1957–8. Bob describes his year at CalTech as being "a bit of a holiday", but it was a holiday which, with hindsight, had distracting consequences. He went there to work with Albert Tyler (1906–1968) [36], an influential elder statesman of American reproductive science, working on sperm–egg interactions. CalTech was then a hotbed of developmental biology, and Tyler had clustered around him an exciting group of young scientists, which included that year a visit by the English doyen of fertilisation, Lord Victor Rothschild, FRS (1910–1990) [37], who was later to clash scientifically with Edwards over his IVF work [38]. In this clash, needless to say, the younger man triumphed [39], just as he had with Pincus. Tyler was exploring the molecular specificity of egg–sperm interactions and had turned as a model to immunology. Immunology was then at a very exciting phase in its development, with the engaging Sir Peter Medawar, FRS (1915–1987, Nobel Laureate in Physiology

or Medicine, 1960) [40], influentially for Bob, extending his ideas on immunological tolerance to the paradox of the 'fetus as an allograft': a semi-paternal graft nonetheless somehow protected from maternal immune attack inside the mother's uterus. This confluence of reproduction and immunology excited Bob's restless curiosity and hence the choice of Tyler. The subject also offered funding possibilities via the Ford and Rockefeller Foundations and the Population Council, which were increasingly concerned about world population growth and the need for better methods to control fertility. Immuno-contraception then seemed to offer tantalisingly specific possibilities.

So when Bob returned to the UK from CalTech in 1958 at Alan Parkes' invitation to join him at the Medical Research Council (MRC) National Institute for Medical Research (NIMR) at Mill Hill in north London, it was to work on the science of immuno-contraception [5]. This period in the USA initiated a series of 24 papers on the immunology of reproduction between 1960 and 1976. It also prompted Bob's first involvement in founding an international society in 1967 in Varna, Bulgaria when the International Coordinating Committee for the Immunology of Reproduction was created [41]. It was, in retrospect, to prove a distracting diversion from what was to become Bob's main work, albeit one that continued to enthuse Bob for many years, witnessed not least by my own recruitment to enter this field of study with him as a graduate student in 1966. Nonetheless, the period at Mill Hill, between 1958 and 1962, seems to have been a period of increasing intellectual conflict for Bob. Whilst enthusiastically working on the science underlying immuno-contraception, his old interests in eggs, fertilisation and, in particular, the genetics of development were gradually reasserting themselves. His day job was therefore increasingly supplemented by evening and weekend flirtations with egg maturation.

THE CRUCIAL EGG MATURATION STUDIES

Bob claims that the stimulus reawakening his interests in eggs was provided by the then recent consensus about the number of human chromosomes and, more particularly the descriptions in 1959 of the pathologies in man that resulted from chromosomal anomalies [42]. Might these anomalies result from errors in the complex chromosomal dance that he and Alan Gates had observed in maturing mouse eggs? The possible clinical relevance of his work on egg maturation and aneuploidy in the mouse was becoming significant.

So Bob resumed his experimenting with mice, trying to mimic *in vitro* the *in vivo* maturation of eggs. He tried releasing the immature eggs from their ovarian follicles into culture medium containing the ovulatory hormone hCG, to see whether he could simulate their *in vivo* development. Amazingly he found it worked the first time: but it did so whether or not the hormone had been added. It seemed that the eggs were maturing spontaneously when released from their follicles. And the same happened in rats and hamsters.

If this also happened in humans, then the study of the chromosomal dance during human egg maturation was a realistic practical possibility, as was *in vitro* fertilisation and thereby studies on the genetics of early human development. However, Bob's excitement at seeing eggs spontaneously maturing was temporarily blunted by his discovery that Gregory Pincus in the 1930s [43–44] and M.C. Chang (1908–1991) [45–46] in the 1950s had been there before him, using both rabbit and, Pincus claimed, human eggs.

In order to pursue his basic science studies on maturation, he needed a reliable supply of human ovarian eggs. This requirement posed difficulties for a scientist with no medical qualifications, given the elitist attitudes and scientific illiteracy then prevalent amongst most of the UK's gynaecologists. His break-through came initially with Molly Rose, at whose door in the nearby Edgeware General Hospital he arrived after a recommendation from a fellow kindred spirit in John Humphrey, FRS (1915–1997) [47], ten years Bob's senior and the medically qualified Head of Immunology at Mill Hill. Notwithstanding his more privileged social background, Humphrey shared Bob's passion for science, its social application and utility, and his left wing politics – indeed he had been a Marxist until 1940. Bob asked John if he knew anyone who might be helpful, and John suggested Molly Rose and offered to arrange an introduction. So off Bob went, and Molly Rose provided human ovarian biopsy samples intermittently for the next ten years.

Between 1960 and 1962, Bob tried to repeat and extend Pincus' observations, using not only human but also dog, monkey and baboon eggs, but with such limited success compared with smaller rodents that in a 1962 *Nature* paper [48], he carefully interprets the few maturing human and baboon eggs that he observed as artefacts. But by this time, Bob's quest for human eggs, and his dreams of IVF and studying early aneuploidies in human embryos, had reached hostile ears, most notably those of the then Director of the Institute, Sir Charles Harington, FRS (1897–1972), who banned any work on human IVF at NIMR [49]. Alan Parkes was no longer able to defend Bob, having left in 1961 to take up his chair in Cambridge and, although he had asked Bob to join him, there was no post until 1963. By the time Bob left Mill Hill in 1962 for a year in Glasgow, he had encountered just a taste of the opposition to come.

THE MOVE TO CAMBRIDGE

Bob had been invited to Glasgow University's Biochemistry Department by John Paul, then the acknowledged master of tissue culture in the UK, who had heard of Bob's attempts to generate stem cells from rabbit embryos [18]. The invitation was to result in a paper [50] remarkable for its prescience – the *first of eight landmark papers* (Table 1) that I identify in this contribution. It describes the production of embryonic stem cells from rabbit embryos – capable of proliferating through over 100 generations and of differentiating into various cell types. This report was published some 18 years before Evans and Kaufman described the derivation of ES cells from mouse embryos [51].

That this work has largely been ignored by those in the stem cell field is probably mainly attributable to its being too far ahead of its time. Thus, reliable molecular markers for different types of cells were not available then, nor were appropriate techniques with which to critically test the developmental potential of the cultured cells.

Table 1. The eight landmark papers

1. Cole R.J., *Edwards R.G.,* Paul J. (1965) Cytodifferentiation in cell colonies and cell strains derived from cleaving ova and blastocysts of the rabbit. *Exp. Cell Res.* 37: 501–4.
2. *Edwards R.G.* (1965) Maturation in vitro of human ovarian oocytes. *Lancet* 286: 926–9.
3. Gardner R.L., *Edwards R.G.* (1968) Control of the sex ratio at full term in the rabbit by transferring sexed blastocysts. *Nature* 218: 346–9.
4. *Edwards R.G.,* Bavister B.D., Steptoe P.C. (1969) Early stages of fertilization in vitro of human oocytes matured in vitro. *Nature* 221: 632–5.
5. Steptoe P.C., *Edwards R.G.* (1970) Laparoscopic recovery of preovulatory human oocytes after priming of ovaries with gonadotrophins. *Lancet* 295: 683–9.
6. Steptoe P.C., *Edwards R.G.,* Purdy JM. (1971) Human blastocysts grown in culture. *Nature* 229: 132–3.
7. *Edwards R.G.,* Sharpe DJ. (1971) Social values and research in human embryology. *Nature* 231: 87–91.
8. Steptoe P.C., *Edwards R.G.* (1978) Birth after the reimplantation of a human embryo. *Lancet* 312: 366.

Bob arrived in Cambridge from Glasgow in 1963. He describes how he immediately reacted against the then extant "misogynist public-school traditions; the exclusivity…; the privileges given to the already privileged". But he set against that the "sheer beauty of the place… the concern with the truth and high seriousness… the ambience of scientific excellence… I was surrounded by so many talented young men and women." [52] He continued to pursue both the immunology of reproduction and egg maturation, working furiously on the latter to collect pig, cow, sheep, the odd monkey and some human eggs. Eventually, he was able to show that eggs of all these species would indeed mature *in vitro*, but that the eggs of larger animals simply needed longer than those of smaller ones, human eggs taking some 36 hours rather than the 12 or less hours erroneously reported by Pincus [44]. These cytogenetic studies were reported in two seminal papers in 1965 [53–54], both of which are primarily concerned with understanding the kinetics of the meiotic chromosomal events. As the *second landmark paper*, I have selected the one in *The Lancet*, in which Bob's breath-taking clarity of vision is evident as he sets out a programme of research that predicted the events of the next 20 years and beyond (Table 2). You will notice the heavy focus on the early

study and detection of genetic disease compared with the slight emphasis on infertility alleviation, unsurprising given Bob's research interests. Indeed, within three years he had, with my fellow graduate student Richard Gardner, provided proof of principle for preimplantation genetic diagnosis (PGD), in a paper on rabbit embryo sexing published in 1968 [55] and my *third landmark paper*. Later, in the 1980s, Bob was to play a key role in promoting the development of PGD clinically [56], and PGD was to prove a powerful political tool in convincing the UK Parliament to permit research on human embryos. And then by 1969 he had reported the first step towards PGD in humans by describing IVF [57] – a *fourth landmark paper* in as many years.

Table 2. Key points in the programme of research laid out in the Discussion to Edwards' 1965 *Lancet* paper (*landmark paper 2*) [54].

1. Studies on non-disjunction of meiotic chromosomes as a cause of aneuploidy in humans.
2. Studies on the effect of maternal age on non-disjunction in relation to the origins of trisomy 21.
3. Use of human eggs in IVF.
4. Culture of fertilised human eggs in vitro.
5. Use of priming hormones to increase the number of eggs per woman available for study/use.
6. Study of early IVF embryos for evidence of (ab)normality – especially aneuploidies arising prior to or at fertilisation.
7. Control of some of the genetic diseases in man.
8. Control of sex-linked disorders by sex detection at blastocyst stage and transfer of only female embryos.
9. Para-cervical transfer of IVF embryos into the uterus.
10. Use of IVF embryos to circumvent blocked tubes.
11. Avoidance of a multiple pregnancy (as observed after hormonal priming and *in vivo* insemination) by transfer of a single IVF embryo.

THE PROBLEM OF FERTILISATION RESOLVED

Underlying both the 1965 and 1969 papers are two scientific struggles: the first being simply but critically the continuing difficulty in obtaining a regular supply of ovarian tissue. Local Cambridge sources proved unreliable, and Molly Rose was now 2–3 hours' drive away in north-west London, so during the summer of 1965, Bob turned to the USA for help and initiated his now famous contacts with Howard and Georgeanna Jones [58], then at the Johns Hopkins Medical School in Baltimore. This supply of American eggs allowed Bob to confirm the maturation timings published in 1965 [54]. However, it was the second struggle that was by then occupying most of his attention, namely that in order to fertilise these *in vitro* matured eggs, he had to 'capacitate' the sperm. 'Capacitation' is a final maturation process, which sperm will usually undergo physiologically in the uterus, and that is essential for the acquisition of fertilising competence. Failing to achieve this convincingly

at Johns Hopkins, he made a second transatlantic summer journey in 1966 to visit Luther Talbot and his colleagues at Chapel Hill. Bob applied his usual ingenuity to try a variety of ways to overcome the problem of sperm capacitation, but no reliable evidence for success was forthcoming [59, 60]. Then in 1968 both struggles began to resolve.

Figure 7. Bob with Bunny Austin, 1960s (courtesy Ruth Edwards).

Resolving the problem of sperm capacitation was the initial attraction to Bob of Patrick Steptoe's laparoscopic technique, Bob seeing it as a way of recovering capacitated sperm from the oviduct [61]. However, the actual solution to this problem lay nearer home. Parkes had retired as Professor in 1967, to be replaced by Colin 'Bunny' Austin (1914–2004) [62] (Fig. 7). In the early 1950s, Bunny, and independently M.C. Chang [45], had discovered the requirement for sperm capacitation [63–64], and so Bunny set his graduate student, Barry Bavister (1943–), to work to try and resolve how to reliably capacitate hamster sperm *in vitro*. Bavister demonstrated a key role for pH in a short paper published in 1969 that showed how higher rates of fertilisation could be obtained by simply increasing the alkalinity of the medium [65]. Bob seized on this observation and co-opted Barry to his project of capacitating human sperm. That proved to do the trick, leading to the 1969 paper [57].

The problem of the intermittent egg supply in the UK was also resolving. Bob continued to rely on surgeons to provide him with ovarian biopsies from which to mature eggs *in vitro*, indeed four are thanked in the 1969 *Nature* paper. According to Bob [66], Molly Rose provided the first group of eggs to be fertilised, and although invited to be a co-author, declined for reasons unknown. Also thanked are Norman Morris [67], Janet Bottomley and Sanford Markham, and although it is not known whether they provided any of the ovarian eggs for *in vitro* maturation described in the paper, Patrick clearly did so [66], and at last provided for Bob a potentially more stable clinical partnership.

The 1969 *Nature* paper describing IVF in humans [57] makes modest claims, only two of 56 eggs reaching the two-pronuclear stage. But, like Bob's

other papers, it is a model of clarity, describing well-controlled experiments, cautiously interpreted. This paper convinced where previous claims [68–73] had failed, precisely because the skilled hands and creative intellect that lay behind it are so evident from its text. With its publication, announced to the media on St Valentine's Day [74], all hell was let loose.

THE BATTLES BEGIN

So 1969 seemed to Bob to be a good year. Not only did IVF succeed at long last, and his partnership with Patrick seemed set to flourish, but also so impressed were the Ford Foundation with Bob's work that they paid for him to be awarded a Ford Foundation Readership (a half way step to a professorship) in the University. Elated by his promotion and their achievement, Bob and Patrick pressed on, the latter's laparoscopic skills coming to the fore, first in 1970 with the collection of *in vivo* matured eggs from follicles after mild hormonal stimulation [75], and then achieving regular fertilisation of these eggs and their early development through cleavage to the blastocyst stage [76] – my *fifth and sixth landmark papers*. So well was the work going that in February 1971 they confidently applied to the UK Medical Research Council for funding to bring Patrick to Cambridge from Oldham General Hospital in Greater Manchester, where Patrick worked [77].

However, any illusions that Bob may have had that their achievements would prove a turning point in his fortunes were soon shattered, and just 2 months later on April Fool's Day 1971 the MRC decided to reject the grant application [77]. The practical consequences of this rejection were profound – both psychologically and physically – not least that for the next 7 years, Bob shuttled on the 12 hour round trip between Cambridge and Oldham, leaving Ruth and his five daughters in Cambridge.

The professional attacks on Bob and his work took a number of forms [77], and one must try to make a mental time trip back to the 1960s/70s to understand their basis. Despite the nature of the political and religious battles to come, his scientific and medical colleagues did not focus on the special status of the human embryo as an ethical issue. However, ethical issues were raised professionally, but took quite a different form. Thus, it is difficult now to comprehend the complete absence of infertility from the consciousness of most gynaecologists in the UK at the time, to which Patrick Steptoe was a remarkable exception [78]. Indeed, Bob's strong commitment to treating infertility came to the fore only after he teamed up with Patrick, his previous priority being the study and prevention of genetic and chromosomal disorders. In the several reports from the Royal College of Obstetricians and Gynaecologists and the MRC during the 1960s examining the areas of gynaecological ignorance that needed academic attention, infertility simply did not feature [77]. Overpopulation and family planning were seen as dominant concerns and the infertile were ignored as at best a tiny and irrelevant minority and at worst as a positive contribution to population control. This was a values system that Bob simply could not accept,

and the many encouraging letters Bob was to receive from infertile couples provided a major stimulus to his continued work later, despite so much professional and press antagonism and so many set-backs. For his medico-scientific colleagues, however, the fact that infertility was not seen as a clinical issue, meant that any research designed to alleviate it was not viewed as experimental treatment, but as using humans for experiments. Given the sensitivity to Nazi 'medical experiments', and the public reaction and disquiet surrounding the recent publication of '*The Human Guinea-pig*' [79], this distinction was critical. The MRC, in rejecting the grant application, took the position that what was being proposed was human experimentation, and so were very cautious, emphasising risks rather than benefits, of which they saw few if any [77].

Bob and Patrick were also attacked for their willingness to talk with the media. It is even more difficult nowadays, when the public communication of science is so embedded institutionally, to understand how damaging to them this was. The massive press interest of the late 1960s was unabated in the ensuing years, and so Bob was faced with a choice: either he could keep his head down and allow press fantasies and speculations to go unanswered and unchallenged, or he could engage, educate and debate. For Bob this was no choice, regardless of the consequences for him professionally. His egalitarian spirit demanded that he trust to common people's common sense. His radical political views demanded that he fought the corner of the infertile, the underdog with no voice. The Yorkshireman in him relished engagement in the debate and argument. In the *seventh landmark paper* selected, published in *Nature* in 1971 with Dave Sharpe [80], he acknowledges the risk to his own interests of so doing. Risky it clearly was, one of the scientific referees on their MRC grant application starting his referee's report declaring his strong distaste for all the media exposure [77]. Bob was a pioneer in the public communication of science, and paid a heavy price for being so.

The Edwards and Sharpe paper [80] is a *tour de force* in its survey of the scientific benefits and risks of the science of IVF, in the legal and ethical issues raised by IVF, and in the pros and cons of the various regulatory responses to them. It sets out the issues succinctly and anticipates social responses that were some 13–19 years into the future. In subsequent years, Bob built on his strong commitment to social justice based on a social ethic, as he engaged at every opportunity with ethicists, lawyers and theologians, arguing, playing 'devil's advocate' (literally, in the eyes of some), and engaging in what we would now call practical ethics, as he hammered out his position and felt able to fully justify his instincts intellectually.

Figure 8. Louise Brown holding the 1000th Bourn Hall baby, 1987 (courtesy Bourn Hall Clinic).

But all this was to little avail. Indeed, Bob was continually frustrated at the unwillingness of most of the establishment to engage seriously in ethical debates in advance of the final validation of IVF that was to come in 1978 with the birth of Louise Brown (Fig. 8), and my *eighth and final landmark* paper [81]. Only then did most UK social hierarchies, such as the MRC, the British Medical Association, the Royal Society and Government move gradually from their almost visceral reactions against IVF and its possibilities to serious engagement with the issues [56]. Then, to their credit, both the MRC and the Thatcher Government of the time came on board, but it was not until 1989, 24 years after Bob's 1965 landmark paper in the *Lancet*, that the UK Parliament finally gave its stamp of approval to his visionary work, and then only after a fierce battle lasting some 11 years [82]. Eleven years since the eighth and final landmark paper was published announcing the birth of Louise Brown. And of course, it has taken 45 years since that 1965 paper for us to be celebrating the award of the Nobel Prize to this remarkable man.

Figure 9. Bob, Jean and Patrick at Bourn Hall, 1981 (courtesy Bourn Hall Clinic).

CONCLUSION

The eight landmark papers I have selected (Table 1) present us with a man of vision and foresight, imagination and intellectual rigour, and extraordinary energy and drive: witness his prodigious output of papers between 1954–2008 [83]. A man who could inspire colleagues to tread with him on a difficult scientific path besieged by public and professional animosity, of whom two in particular, Patrick and Jean, we miss today (Fig. 9). And these papers do not even begin to touch Bob's other academic and personal qualities, so evident in the way he has founded and generously nurtured journals and international societies [84, 85], transforming the intellectual landscape not just of gynaecology, but also of ethics and social anthropology. Truly the 'father of Assisted Reproductive Technology' in its widest interdisciplinary sense: the only sense in which Bob knows it. For Bob, it is truly the Nobel Prize for Physiology AND Medicine: there can be no OR about it.

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