

Why the Medical Research Council refused Robert Edwards and Patrick Steptoe support for research on human conception in 1971

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BACKGROUND: In 1971, Cambridge physiologist Robert Edwards and Oldham gynaecologist Patrick Steptoe applied to the UK Medical Research Council (MRC) for long-term support for a programme of scientific and clinical 'Studies on Human Reproduction'. The MRC, then the major British funder of medical research, declined support on ethical grounds and maintained this policy throughout the 1970s. The work continued with private money, leading to the birth of Louise Brown in 1978 and transforming research in obstetrics, gynaecology and human embryology.

METHODS: The MRC decision has been criticized, but the processes by which it was reached have yet to be explored. Here, we present an archive-based analysis of the MRC decision.

RESULTS: We find evidence of initial support for Edwards and Steptoe, including from within the MRC, which invited the applicants to join its new directly funded Clinical Research Centre at Northwick Park Hospital. They declined the offer, preferring long-term grant support at the University of Cambridge, and so exposed the project to competitive funding mode. Referees and the Clinical Research Board saw the institutional set-up in Cambridge as problematic with respect to clinical facilities and patient management; gave infertility a low priority compared with population control; assessed interventions as purely experimental rather than potential treatments, and so set the bar for safety high; feared fatal abnormalities and so wanted primate experiments first; and were antagonized by the applicants' high media profile. The rejection set MRC policy on IVF for 8 years, until, after the birth of just two healthy babies, the Council rapidly converted to enthusiastic support.

CONCLUSIONS: This analysis enriches our view of a crucial decision, highlights institutional opportunities and constraints and provides insight into the then dominant attitudes of reproductive scientists and clinicians towards human conception research.

Key words: Robert Edwards / funding / history / human conception / IVF / Medical Research Council / Patrick Steptoe

Introduction

The first human birth after *in vitro* fertilization (IVF) represents a landmark in the history of the reproductive sciences (Steptoe and Edwards, 1978; Pfeffer, 1993; Marsh and Ronner, 1996; Strauss, 2001; Henig, 2004; Hopwood, 2009). Cambridge physiologist Robert Edwards and Oldham gynaecologist Patrick Steptoe led the team that in 1978 finally confirmed the effectiveness of the IVF method they had described in 1969 (Edwards *et al.*, 1969). They did so without state support. In February 1971 they had sought

funding for a long-term programme of research on human conception from the Medical Research Council (MRC), then, with 27% of the civil science budget, the major funder of biomedical research in the UK (Landsborough Thomson, 1973, p. 204; Austoker and Bryder, 1989). The application was declined, but the work continued nonetheless, largely with private money. The birth of Louise Brown vindicated Edwards and put pressure on the MRC to justify and reverse a decision that now looked wrong; it quickly became a major supporter of IVF research. In hindsight, this change of policy may seem obvious, and the original rejection the act of a medical establishment that failed

to back a maverick pioneer. In some ways it was. Yet it is the 1978 decision that was made on surprisingly thin evidence, whereas that of 1971 was the outcome of complex negotiations, extensive deliberation and due process. Both decisions, we suggest, become understandable when viewed in context and in their own time.

The rejection of Edwards' and Steptoe's application has been much criticized (Edwards, 1974, 1983, pp. 56–57, 1996b, p. 445, 2001), but how it was reached has been a matter for conjecture. The MRC's stated reason was ethical; it wanted primate studies first and expressed reservations about the 'purely experimental' use of laparoscopy. Edwards ascribed particular significance to a claim by MC Chang of the Worcester Foundation that IVF rats were born with small eyes (Edwards and Steptoe, 1980, p. 107), and mentioned the 'belief that infertility should not be treated because the world was overpopulated' (Edwards, 1983, pp. 56–57). Professional animosity towards Steptoe is often cited (Edwards, 1996a, b; Philipp, 1996; Reiss, 1996). On the basis of unreferenced documents and conversations with participants, Gunning and English (1993, p. 6) indicated issues that we agree did exercise board members and referees. They had focused on patient safety and offspring normality, and were concerned about 'the proposed facilities and arrangements for patient care'. The 'establishment' wanted contraception, not new infertility treatments. The decision-making process, however, and its disciplinary, institutional and wider politics, remains unexplored. More generally, although Edwards, his colleagues, journalists and academics have reviewed important aspects of the research that led to the birth of Louise Brown (Edwards and Steptoe, 1980; Edwards and Purdy, 1982; Edwards, 1986, 2001, 2005a, b; Challoner, 1999; Bavister, 2004a; Henig, 2004), this reproductive revolution has yet to receive sustained historical attention.

Here, we use various archives to reinvestigate the MRC decision, emphasizing its institutional contexts and the concerns of the community of reproductive biologists and clinicians. We find that, since 1969, the Council had sought to develop a more active research culture in obstetrics and gynaecology, especially by funding schemes that brought together clinical and non-clinical scientists, and we confirm that within these plans infertility was accorded a low priority. The Edwards and Steptoe application, although seen in some ways as problematic from the start, was nevertheless received with sufficient enthusiasm that staff considered housing the work in an MRC institute. Edwards' rejection of this option meant trying to establish clinical facilities in Cambridge at a difficult time, and exposed the application to critical referees. By considering their arguments, we provide insight into the then dominantly sceptical attitudes of reproductive scientists and clinicians towards human conception research—attitudes that would change dramatically after 1978.

Sources

Our archival evidence is mainly from the MRC records at the National Archives (NA), with supporting documents from the Royal College of Obstetricians and Gynaecologists (RCOG), Addenbrooke's Hospital (AHGR), Cambridgeshire County Council (KAR) and Cambridge University Library (CUL). In addition, Ruth Edwards gave us access to Robert Edwards' private papers (RGE).

MRC materials are stored under the 'FD' series in 24 divisions, further divided into sub-series of folders, each containing up to

several hundred unnumbered items. We identify archival sources in footnotes with short descriptions and dates followed by division/sub-series (e.g. Smith to Jones, 1 June 1970: NA FD 10/459), and use similar notations for other archives.

Extended interviews with several key players including Robert Edwards, James Gowans, Anne McLaren and Roger Short provided background knowledge for our archival research, and we clarified issues arising from it in interviews in 2009 with Graham Cannon, Malcolm Godfrey, Barbara Rashbass, Ralph Robinson and Duncan Thomas. Edited transcripts of these five interviews can be viewed as Supplementary Materials 3–7 and are referred to in footnotes. Correspondence with Michael Bright (retired consultant obstetrician) is referenced as personal communication. The interview protocols received ethical approval from the Human Biology Research Ethics Committee of the University of Cambridge and were certified as compliant with the ethical guidelines of the London School of Economics.

Adjusted 2008 prices were calculated using www.measuringworth.com. For biographical details of key people mentioned in the text, and membership of key committees and boards see Supplementary Materials 1 and 2.

Reproductive science in the UK around 1970

After World War II the state became the major supporter of biomedical science. The reproductive sciences, straddling agriculture, medicine and academic biology, had struggled for legitimacy in the early twentieth century, and approached human reproduction hesitantly and selectively, but by the late 1960s were increasingly established (Pfeffer, 1993; Oudshoorn, 1994; Marsh and Ronner, 1996; Clarke, 1998; Wilmot, 2007).

Concern about world overpopulation was reaching a peak and dominated UK and global policies on reproduction (Ehrlich, 1968; Pfeffer, 1993; Clarke, 1998, pp. 202–203; Connelly, 2008). UK laws regulating abortion and birth control advice were relaxed and the oral contraceptive pill was taken on a large scale (Reed, 1984, p. 311; Marks, 2001). Population-control interests also funded much reproductive research. In the USA, federal funding for contraceptive development increased over 6-fold between 1965 and 1969, and private philanthropic funding went up 30 times (Marks, 2001, p. 29). Major private players were the Ford and Rockefeller Foundations, the Population Council and the International Planned Parenthood Federation (Clarke, 1998, pp. 207–230; Connelly, 2008, pp. 195–236). The United Nations Fund for Population Activities was established in 1968, and led in 1972 to the influential Human Reproduction Programme of the World Health Organization, with its focus on population control (Connelly, 2008, pp. 232ff).¹ Between 1965 and 1972, worldwide support for contraceptive research had risen from \$31 to \$110 million (Marks, 2001, p. 31; Connelly, 2008, p. 233).

State funding of reproductive studies in the UK in 1970 was largely divided between the Agricultural Research Council (ARC; Wilmot, 2007) and the MRC (Landsborough Thomson, 1973, 1975; Austoker and Bryder, 1989), which tended to be interested respectively in farm

¹Malcolm Godfrey, 2009, Supplementary Material 3, pp. 21–22.

animals and humans, although both supported research on laboratory species. In November 1969, an internal MRC review listed a portfolio of reproductive project grants with nine in clinical pathology, 24 in clinical physiology and 17 in basic science.² Scientific priorities drove and followed funding, as medicine and agriculture offered opposite problems for reproductive science. For example, in the fifth volume of a major teaching text on *Artificial Control of Reproduction*, 85 of 152 pages were devoted to limiting human fertility (Austin and Short, 1972). In striking contrast, 31 of the remaining 67 pages were about how to increase animal reproductive rates in order to feed the burgeoning mouths—a Green Revolution solution to ‘medically induced’ overpopulation. In the UK, academic obstetrics and gynaecology tended to give infertility treatment and research a low priority, in part perhaps because, within the National Health Service, it could compete less effectively for resources than areas that were then more high-tech. In contrast, clinicians in the USA, with private practice flourishing, worked to raise the scientific status of infertility and organized the American Society for the Study of Sterility in 1944 (McLane, 1959; Pfeffer, 1993, pp. 110–141; Duka and DeCherney, 1994; Marsh and Ronner, 1996).

Although practitioners’ histories typically trace IVF and embryo transfer back into the nineteenth century (Biggers, 1984), it was made a recognizable line of research work only in the mid-1930s by the American physiologist Gregory Pincus (Schreiber, 2007). Inspired by Pincus, staff under John Hammond at the ARC-funded Animal Research Station in Cambridge would aim to do for female stock what artificial insemination already promised for the male (Polge, 2007), while at his leading fertility clinic, Boston gynaecologist John Rock experimented with ‘conception in a watch glass’ (Anon, 1937; Marsh and Ronner, 2008, p. 91). He and his technician Miriam Menkin claimed human IVF in 1944 (Rock and Menkin, 1944), but did not pursue the work, and criteria became more stringent in the 1950s (Thibault, 1969). Thus, by the late 1960s, convincing results of IVF leading to a live birth had been reported only for rabbit, hamster and mouse (Chang, 1959, 1968; Yanagimachi and Chang, 1963; Whittingham, 1968), with guinea-pig (Yanagimachi, 1972) following soon thereafter. The uterine transfer of flushed *in vivo* fertilized and cultured embryos had been more successful, and by 1969 had been achieved in rabbit, goat, sheep, ferret, rat, mouse, cow and pig (Betteridge, 1981; Hammer, 1998; Alexandre, 2001). These achievements opened up the early mammalian embryo to experimental manipulation, an opportunity seized most strikingly by Andrzej Tarkowski and Beatrice Mintz during the 1960s (Graham, 2000; Johnson, 2009). Human chimaeras, genetic selection and modification, and even cloning, were all contemplated. In the general press and popular literature, human IVF presaged a near-future brave new world, a science-fiction vision that Cambridge scientists had done much to promote (Squier, 1994; Henig, 2004).

Robert Edwards made his mark during this exciting period (Edwards and Steptoe, 1980; Austin, 1991). He was born in 1925 into a working-class family in Batley, Yorkshire, and, after demobilization from the army, had studied agriculture and zoology as a mature undergraduate at the University College of North Wales (Bangor, 1949–1951) and then undertaken doctoral and post-doctoral training in developmental genetics at the Institute of Animal Genetics in Edinburgh (1952–

1957). After a year at the California Institute of Technology, he joined the staff of the MRC’s National Institute for Medical Research (NIMR) at Mill Hill (1958–1962), and then spent a year in the Department of Biochemistry in Glasgow. In 1963, aged 38, he was recruited to the University of Cambridge by Alan Parkes, the first Mary Marshall and Arthur Walton Professor of the Physiology of Reproduction, with whom he had worked at the NIMR. Edwards joined the Physiology Department’s Marshall Laboratory as a Ford Foundation Fellow and became Ford Foundation Reader in 1969. His remit was to work on methods of fertility control, which he interpreted, with Foundation approval, as including infertility alleviation (Parkes, 1985, p. 80).

By the time Edwards moved to Cambridge, his research reflected his broad interdisciplinary background and varied interests. Over 40 published studies covered sperm and egg maturation, the genetics of gamete and early embryo biology, and immunological aspects of reproduction. But his increasing excursions into human egg studies attracted most attention within and beyond reproductive science. This research investigated the timing and conditions required to mature animal and human oocytes and then to fertilize the eggs *in vitro* (Edwards, 1965a, b, 1966; Henderson and Edwards, 1968), and depended on partnerships with clinicians to provide human ovarian material (Clarke, 1987). Having worked with several partners during the 1960s (notably Molly Rose at Edgware General Hospital, Victor Lewis at Hammersmith Hospital, Ian Donald in Glasgow and Howard Jones in Baltimore: Edwards, 1996b, 2001), Edwards met Patrick Steptoe at a meeting at the Royal Society of Medicine in 1968 after reading one of his papers (Steptoe, 1968) earlier that year and phoning him to explore the possibility of collaboration (Edwards, 1996a, b).

Steptoe (1913–1988), who was 12 years older than Edwards, had trained in London at King’s College and St George’s Hospital Medical School, London. He was senior consultant in obstetrics and gynaecology at Oldham District and General Hospital near Manchester, where he had worked since 1951. He had a longstanding interest in infertility, and pioneered the introduction into the UK of laparoscopic gynaecological investigation—now central to endoscopic, or ‘keyhole’, surgery—developing its safe use and exploring its application for intra-abdominal investigations and for surgical procedures, such as tubal sterilization (Steptoe, 1967). Now regarded, with Raoul Palmer of France and Hans Frangenheim of Germany, as one of the three founding fathers of laparoscopy (Keith, 2007), his senior colleagues in the UK at first greeted the technique with a ‘lukewarm response’ and even ‘mirth and derision’ (Edwards, 1989, 1996b; Reiss, 1996). The first fruit of the Edwards and Steptoe partnership matured rapidly in the 1969 *Nature* paper with Barry Bavister, a Cambridge PhD student. This landmark article described the successful formation of seven human pronuclear-stage zygotes among 34 laparoscopically recovered and *in vitro* matured eggs inseminated *in vitro* (Edwards *et al.*, 1969). It caused a sensation.

Claims to success with either animal or human IVF had long excited media attention (Marsh and Ronner, 2008, p. 109), as had Edwards’ earlier egg maturation work (Byrne, 1965; Gould, 1966; Leach, 1966). This interest was further stimulated when, with his graduate student Richard Gardner, he demonstrated that he could determine reliably the sex of rabbit embryos by a method that allowed them to develop to term *in utero* (Edwards and Gardner, 1967; Gardner and Edwards, 1968). They explicitly identified the implications for human sex selection (Anon, 1968; Edwards and Gardner, 1968).

²NA FD 7/912.

Against this background, the 1969 *Nature* paper with Bavister and Steptoe took the excitement to fever pitch. Although the authors explained the limitations and problems of moving IVF from laboratory to clinic, they also suggested routes by which these might be managed or overcome. *Nature* editor John Maddox, a consistent Edwards promoter (Maddox, 1968), had in 1967 launched a collaboration between his journal and *The Times* of London, and used it to publicize the new work. An article announcing the 'Move towards test-tube babies' featured in *The Times* the day before the *Nature* paper was published (St Valentine's day), and was syndicated round the world. Headlines including 'This human time bomb' and 'Next: chance to choose baby's sex' (*Daily Mail*), 'Life outside the body' (*Daily Express*) and 'Test tube baby factory' (*Sunday Mirror*) firmly, and controversially, placed Edwards and Steptoe in the public eye.

Organizational innovations

On the basis of this extended period of research, its culmination in the 1969 paper, and their subsequent success in developing human embryos *in vitro* (Edwards et al., 1970; Steptoe et al., 1971), Edwards and Steptoe had decided by mid-1970 to approach the MRC for long-term support. They wished, above all, to bring Steptoe to Cambridge so that Edwards and his nurse-assistant Jean Purdy would not have to travel to and from Oldham (Edwards and Steptoe, 1980, pp. 97–98, 1985, p. viii). Edwards was relatively inexperienced at MRC grant applications, having been a directly funded MRC employee and then supported by the Ford Foundation at Cambridge. However, their approach to the MRC coincided with strategic and organizational developments that might have been expected to create a receptive climate.

Strategically, the MRC had begun to respond to a widely perceived research deficit in obstetrics and gynaecology, first identified in the 1967 RCOG Macafee Report (1967) on 'training for the speciality and matters related thereto'.³ The MRC produced its own in-house report along much the same lines in July 1969.⁴ Driven largely by the principal medical officer Malcolm Godfrey,⁵ this report identified several areas ripe for research, including fertility control, hormonal control of the female tract, toxæmia, and the normal physiology of pregnancy, neonate and fetus. Infertility was not specifically mentioned.

The MRC report explored a range of initiatives for promoting quality research, of which two are pertinent. The first was a proposal to establish one or more multi-disciplinary units of reproductive physiology linked to university departments of obstetrics and gynaecology. The aim was to bring first-rate scientists and clinicians together. The second was a strong commitment to reproduction forming a major component of the MRC's Clinical Research Centre (CRC) at Northwick Park Hospital at Harrow, which had opened on 8 September 1970 under the directorship of Graham Bull. Over 10 years in planning and four in construction, the CRC provided an integrated site for the study and treatment of patients. It combined a 630-bed district general hospital with new research laboratories for 134 research positions (BMJ, 1969, 1970; Landsborough Thomson, 1975, pp. 31–33;

³RCOG GB 1538 M1.

⁴Research in Obstetrics and Gynaecology: Report to the Secretary of the Council by Section A1, General Clinical Medicine: NA FD 7/912.

⁵Godfrey, 2009, Supplementary Material 3, pp. 3–8.

Booth, 1986; SCST, 2005). A Division of Developmental/Reproductive Biology, intended to cover obstetrics, gynaecology, fertility and pregnancy, and comprising a multi-disciplinary team of seven to eight workers—'possibly two obstetrician/gynaecologists, one or more paediatricians, and one or more general biologists'—was due to open in 1971.⁶ However, Bull had difficulty recruiting research leaders in reproductive biology. By 1 July 1970, he had 'investigated' 25 people and sought memoranda from seven, of whom four had declined, two proved 'unsuitable' and only one was 'fairly promising'.⁷

Council accepted the in-house report, and set up a Sub-Committee on Obstetrics and Gynaecology (SCOG) to implement the proposals.⁸ From the first meeting that July until its disbanding in October 1971, the SCOG influentially shaped MRC policy. On 29 October 1970, the chair, Stanley Peart, a renal physiologist and the Professor of Medicine at St Mary's Hospital Medical School London, invited UK clinical school deans to bid for MRC units in reproductive physiology.⁹

The invitation arrived in Cambridge at a time of flux. In 1969 the university, which had previously provided no clinical teaching, had formally started planning a clinical school for students who had hitherto mostly completed their training in London (Rook et al., 1991, pp. 405–419; Weatherall, 2000). The consultant physician Theodore Chalmers was seconded for the calendar year 1970 to set up the organization,¹⁰ and became part-time clinical dean in 1973 and full time in 1974. His preparations included arranging for appointments to university clinical teaching posts, including the professorship in a new Department of Obstetrics and Gynaecology (Rook et al., 1991).¹¹ However, neither the position nor the department existed when Peart's letter arrived.¹²

Thus, as the MRC attempted to remedy a widely perceived academic research deficit in obstetrics and gynaecology, situations such as those at the CRC and Cambridge presented opportunities for the proven medico-scientific partnership of Steptoe and Edwards, but raised questions about protocols, priorities and procedures.

Preliminary negotiations and initial concerns

The earliest evidence of Edwards' approach to the MRC is a letter of 17 August 1970 to the chief executive officer, John Gray, asking whether his and Steptoe's programme of scientific and clinical research on human development *in vitro* might qualify for support. Notably, in light of subsequent events, Edwards expressed particular concern about the 'considerable' cost of clinical and other facilities. The senior medical officer, Sheila Howarth, responded, and thereafter she, or initially her deputy, Duncan Thomas, is recorded as mediating all contact between Edwards and the MRC. A former cardiologist, Howarth had been with the Council for 6 years, and remained there—later as principal medical officer—until her retirement in

⁶NA FD 13/157, 13/171 and 7/912.

⁷Minutes of first SCOG meeting, 1 July 1970: NA FD 7/912.

⁸Minute 37, 25 February 1970: NA FD 13/158 and 7/912; see Supplementary Material 2(A) for membership.

⁹Letter: NA FD 7/1637.

¹⁰UCHMC minute 211, 7 December 1970: AHGR 4/2/7/7.

¹¹Sheila Howarth, note of telephone conversation with Chalmers, 4 December 1970: NA FD 10/161.

¹²Howarth memo, 4 December 1970: NA FD 7/1637.

1980. Thomas was newly appointed after a period of successful haematological research in the USA, and would leave the MRC the following summer.¹³

Edwards visited MRC head office on 24 August, when he summarized for Thomas the progress of their work and plans, and estimated a budget of £150 000 for set-up and £20 000 annual running costs. Howarth, who seems to have joined the meeting later,¹⁴ 'enquired whether the DHSS [Department of Health and Social Security] had been kept fully briefed on the work in Oldham. Dr Edwards thought that Mr Steptoe had informed the DHSS about his work, but he did not seem very sure about this'.¹⁵ Howarth pointed out the need to work closely with the DHSS and cited surgeon Roy Calne's arrangements for transplants at Douglas House in Cambridge as a model (Calne, 2008).

On 23 September 1970 Edwards submitted an 11-page outline proposal in his name alone, but explaining that the full application would be joint.¹⁶ The several archival records of the costings are difficult to sequence over the period 23 September to 21 October 1970, but an initial total estimate of £47 500 capital and £54 250 annual running costs (excluding Steptoe's salary) seems later to be reduced and resolved into MRC (£10 465 and £4005) and DHSS (£16 000 and £48 500) components, respectively. Later documents suggest salary costs for Steptoe of £4675 p.a., which adds in a further £23 375. Over a 5-year grant this would give a total of £312 365 (MRC ~£53 865 and DHSS £258 500, assuming the MRC bore the research component of Steptoe's salary), equivalent to about £3.3 million at 2008 prices.

Thomas and Howarth expressed early reservations about a proposal of 'unusual complexity'. 'Dr Edwards is obviously "thinking big!" ... a quarter of a million pounds for his first year of operation ... at a time of impending financial stringency, support of this magnitude seems highly unlikely'.¹⁷ This inflated figure was probably based on an internal MRC estimate of £160 000 capital and £74 000 annual running cost, because Edwards' own costings were seen as unrealistic.¹⁸ The officers questioned the viability of the whole scheme: 'Dr Edwards is not medically qualified, yet virtually all of what he is requesting relates to providing clinical facilities for patients. I would have thought that a unit of this size, without the active involvement of somebody who is already part of the current Cambridge clinical scene, would run into all sorts of problems'. Was the area 'really ready for a full scale clinical development as a priority area? It is certainly not "population control"', which had been identified as high priority.¹⁹ The proposal 'bristles with difficulties practical, ethical and financial'.²⁰

Howarth's superior, Godfrey, responded more positively to her: 'This might be very important and deserves enormous effort to get it on the right lines—which it certainly isn't at present, exactly what Dr Edwards is going to do and how he will do it and what he needs

not being crystal clear'.²¹ Godfrey accepted Howarth's suggestion that, before further discussions with Edwards and Steptoe, she should sound out the DHSS and seek independent expert advice. Thomas solicited opinions from the reproductive neuroendocrinologist Geoffrey Harris (Anatomy, Oxford) and from Alec Turnbull (Obstetrics and Gynaecology, Cardiff), an expert on the physiology of late pregnancy and parturition and a member of both the SCOG and the MRC's Clinical Research Board. Parkes and the reproductive physiologist and endocrinologist at the Cambridge Veterinary School, Roger Short, were reserves, but not used.²² Bull (CRC, Northwick Park) is recorded as having already been sent a copy.²³ The two referees were invited to give 'a preliminary assessment of the proposals, their scientific merits, their feasibility and what they might require in the way of support [, plus] an assessment of Dr Edwards himself ... especially in relation to his capacity to direct such a large multidisciplinary programme'.²⁴

The referees had responded by 30 November. Harris assessed Edwards as 'a man of very original ideas and much drive' but wondered whether he needed 'a continuous brake' in order not to take on too much.²⁵ Turnbull reported: 'the worst I have heard of Edwards is that any reproductive biologist could have done the same if he had had access to the material Steptoe has provided'.²⁶ Both welcomed the more scientific part of the outline, but expressed concerns about the very broad clinico-scientific scope (Harris) and Edwards' capacity to manage the clinical work in Cambridge (Turnbull). Turnbull also doubted the quality of Ivor Mills of the Department of Investigative Medicine, one of Edwards' proposed clinical colleagues, and expressed concern about patient safety in the proposed clinical unit. He mentioned that Steptoe had recently not been appointed to a consultant's post in Cambridge because 'he is now 56 or 57, I think, and it was decided to appoint a younger man'. (Ralph Robinson was appointed on 1 January 1969.)²⁷

Both referees disapproved of Edwards' 'tendency to seek publicity in the press, television and so on' (Turnbull). Harris 'hesitate[d] to raise any ethical considerations ... (since ethical views change so rapidly these days). However, under the present climate I feel the "test-tube baby" atmosphere, which has been propagated in the last year or so, could lead to difficulties in the mind of the general public'. Turnbull raised, but immediately qualified, an ethical issue:

There might be worries about the normality of the children which were born if successes were ever achieved. On the other hand, I think these theoretical considerations might tend to be outweighed by the tremendous pressure which would be created by infertile women themselves, even if slight success could be achieved. When the first reports of this possible method of treating infertility appeared in the press, I had letters from a large number of women in Wales asking if there was any possibility if they could have 'test tube' babies. There is a relatively small number of women ... who would be desperately anxious to conceive ...

¹³Thomas, 2009, Supplementary Material 4, pp. 2–4.

¹⁴Thomas, 2009, Supplementary Material 4, pp. 6–8; Edwards to Howarth, 30 August 1970: RGE.

¹⁵Thomas' record of meeting, 26 August 1970: NA FD 10/161.

¹⁶The proposal does not differ substantially from the final application, which is described below.

¹⁷Thomas on Edwards' visit, 24 August 1970: NA FD 10/161.

¹⁸Howarth to Godfrey, 28 October 1970. NA FD 10/161.

¹⁹Thomas to Howarth, 23 September 1970: NA FD 10/161.

²⁰Howarth to Godfrey, 28 October 1970: NA FD 10/161.

²¹Godfrey to Howarth, 29 October 1970: NA FD 10/161.

²²Howarth to Thomas, 29 October 1970: NA FD 10/161.

²³Receipt acknowledged 1 November 1970: NA FD 10/161.

²⁴Howarth to Thomas, 29 October 1970: NA FD 10/161.

²⁵Harris to Thomas, 13 November 1970: NA FD 10/161.

²⁶Turnbull to Thomas, 27 November 1970: NA FD 10/161.

²⁷Edwards, reference for Steptoe, 14 May 1969: RGE.

This is the only statement we have found in the MRC responses on possible benefits to the infertile, and even here these are qualified as a minority interest.

These preliminary reports were positive about Edwards as a scientist, but raised concerns about his proposed foray into the clinic, while making its promise for the infertile clear. Geoffrey Dawes, the fetal physiologist and director of the Nuffield Institute for Medical Research in Oxford, was also reported as thinking well of Edwards' science.²⁸ Godfrey argued that the Council would have to decide 'whether or not they would be prepared to face' the potential ethical problems, while noting that 'Professor Turnbull clearly feels they [the risks] should be accepted'. Godfrey concluded after discussion with Howarth that, since opinions were 'so favourable', three avenues of enquiry should be pursued. (i) '[I]t would be right to discuss the preparation of more realistic proposals with him [Edwards]', but Howarth recorded that, while she would 'attempt to persuade him to reduce the size of his application. I myself think that he will be unwilling to do this'. (ii) She should explore informally with the University of Cambridge whether or not the MRC's recent call from Peart for clinical school bids for a reproductive physiology unit might provide a way to accommodate Edwards' proposal there (Turnbull had also suggested this). (iii) Bull should approach Edwards about locating the project at Northwick Park.²⁹

CRC and unit options fail

Bull welcomed the possibility of resolving his recruitment difficulties by locating Edwards' entire programme, including Steptoe, at the CRC, where provision had been made for 120 maternity beds, 20 for research.³⁰ He immediately invited Edwards to visit to discuss the possibility of transferring the work there.³¹ However, Bull reported on 18 December that Edwards had visited Northwick Park and that, although 'most appreciative of the facilities available [there] which he thought were just right', he felt 'that at the CRC he would suffer from a lack of freedom, especially ethical freedom, which he could enjoy as an independent Reader in Cambridge', where the quality of students was so high (Edwards, 2005a, b, p. 302). Although Edwards wished to revisit the CRC option were his MRC application unsuccessful, Bull was in too much of a hurry to fill posts.³² Bull was over-optimistic: this appointment had still not been made by November 1972.³³ But Edwards had effectively closed this avenue of enquiry.

Exploring an MRC reproductive physiology unit at Cambridge depended on negotiating the considerable internal tensions involved in setting up a clinical school that would satisfy the often conflicting demands of a research-oriented university and the service-led NHS via the DHSS and local hospital boards—not infrequently problematic for the MRC at that time (Booth, 1986; Reynolds and Tansey, 2000, pp. 20–25; Stewart, 2008; Valier and Timmermann, 2008).³⁴ Much of the university viewed the proposed clinical school with suspicion

and it was finally approved against considerable opposition by 446 to 225 votes in November 1970.³⁵ Although Edwards' draft application, with its potential to combine clinical gynaecology and basic science, was in principle both attractive and timely for the MRC, it challenged existing institutional arrangements and funding models, as well as professional attitudes then prevailing in the UK.³⁶ This was especially so for Cambridge, with no academic department of obstetrics and gynaecology, and beds split between two locations, both earmarked for closure when a new hospital was completed: those for obstetrics in a former workhouse in Mill Road and for gynaecology, many of them only recently freed up by orthopaedics, on the somewhat dilapidated Old Addenbrooke's Hospital site 3/4 mile away in Trumpington Street. There were long waiting lists and only three overstretched consultants: Oswald [Ozzie] Lloyd, Janet Bottomley and Ralph Robinson, who was the most junior (only 34 and in post for a few months) but responsible for working with Chalmers to set up the academic department and recruit a professor.³⁷

It was against this unpromising clinical background that Howarth was to inform Edwards about Peart's October call to medical schools for bids for a unit of reproductive physiology, but before she could do so, he learnt about it indirectly, via C.R. 'Bunny' Austin, who had received a copy from Chalmers. Austin was Charles Darwin Professor of Animal Embryology and now head of the Marshall Laboratory where Edwards worked. Thus, on 5 December, 3 days after Godfrey and Howarth had agreed the three options to be explored, Edwards wrote to Howarth expressing enthusiasm about the call and identifying their proposal as 'a good fit', in tones that indicate he was encouraged by the meshing of their work with MRC strategic policy.³⁸ Of this letter, Howarth recorded that he made 'a bid of his own for the Unit'.³⁹ She had already raised with Chalmers by telephone the previous day the possibility of the application from Edwards and Steptoe forming the Cambridge bid and would follow this up.⁴⁰

Chalmers had responded negatively that it was 'the view of the clinicians that any clinical appointment for Mr Steptoe would not meet the needs of the University for an academic obstetric teacher within the new medical school'. The university had its sights on recruiting a new clinician as professor (David Baird from Edinburgh and Melville Kerr from McMaster University in Canada were mentioned) as well as retaining Short, who was threatening to leave for Edinburgh, and was even contemplated briefly by Chalmers as professor himself, despite being a vet.⁴¹ Chalmers also expressed concern that there was no accommodation for Steptoe—a problem for any incoming professor—and indeed the teaching base for obstetrics and gynaecology for the eventual appointee, Charles Douglas, occupied a portacabin from 1976 to 1983.⁴² Chalmers had emphasized throughout that

²⁸Thomas to Howarth, and via her, to Godfrey, 30 November and 1 December 1970: NA FD 10/161.

²⁹Howarth to Godfrey, 1 December and reply 2 December 1970: NA FD 10/161.

³⁰SCOG minutes, 1 July 1970: NA FD 7/912.

³¹Bull to Edwards, 2 and 12 December 1970: RGE.

³²Howarth note, 18 December 1970, on conversation with Bull: NA FD 10/161.

³³Stocktaking review of research policy, November 1972, Section BI Population Control, p. 3: NA FD 13/185.

³⁴Godfrey, 2009, Supplementary Material 3, pp. 18–20.

³⁵Minute 69, 26 November 1970 meeting, UCH Board of Governors: AHGR 3/2/1/14; *Cambridge University Reporter*, 18 November 1970, p. 235.

³⁶Thomas, 2009, Supplementary Material 4, p. 10.

³⁷Robinson, 2009, Supplementary Material 5, p. 6; Cannon, 2009, Supplementary Material 6, p. 8.

³⁸5 December 1970: NA FD 10/161; letter copied to Mills and Matthews on 7 December 1970: RGE.

³⁹Howarth to Owen, 7 December 1970: NA FD 10/161.

⁴⁰Memos of conversations dated 4, 15 and 18 December 1970: NA FD 10/161.

⁴¹Robinson, 2009, Supplementary Material 5, p. 17.

⁴²Robinson, 2009, Supplementary Material 5, p. 18.

Edwards' plans, although having 'University support in principle, should be treated as a separate exercise' from a possible MRC unit.⁴³

The Cambridge bid confirmed this intention,⁴⁴ but itself failed. The application was seen by MRC office staff as premature, because, despite all the other advantages of Cambridge, obstetrics and gynaecology were weak and there was no functional clinical school.⁴⁵ The bid did not make the short list.⁴⁶ The ambivalence and fragility of the clinical school effectively closed the second of Godfrey's three options, leaving only the third: to pursue long-term grant support.

Edwards favoured this option, but it had two major disadvantages. First, it shifted the application from strategically planned and directly funded to competitive indirect funding mode at the Council's Clinical Research Board (CRB), established in 1953 to stimulate specifically clinical research (Landsborough Thomson, 1975, p. 26; Booth, 1986, p. 443; Reynolds and Tansey, 2000). Second, it put the onus on the applicants themselves to make suitable clinical arrangements, including addressing the clinical management and ethical questions raised by the preliminary referees—a challenging task in Cambridge, as the MRC had already concluded. For these reasons, Howarth had expressed major reservations: 'The CRC could provide most of what Dr Edwards wants, whereas in Cambridge the position would be very sticky indeed. If Dr Edwards decides that he does not want to go to Northwick Park, then we shall have to see him again and try to persuade him to trim his application to a more acceptable magnitude; and we shall have to explore further the possibility of others providing for his clinical needs in Cambridge, which I fear will be a lengthy business'.⁴⁷ Edwards, in contrast, interpreted both the CRC offer and the fit of his proposal with the strategic plan as encouraging.

The Department of Health and Social Security and the local hospitals

The DHSS shared the emerging concern among some at the MRC about the clinical and ethical management of the project, which built a potent sceptical combination.⁴⁸ Godfrey had agreed with Richard Cohen, the deputy chief medical officer at the DHSS on secondment from the MRC, to consult on any application at an early stage.⁴⁹ 'The whole application', Howarth argued, 'is clouded by unresolved ethical issues of a formidable nature, and a preliminary sounding of Cohen by Dr Godfrey suggests that there might well be problems as far as DHSS is concerned'. Howarth herself had spoken to Cohen, 'who considers that the issues are so serious that on receipt of the application he and [the chief medical officer at the DHSS] George Godber would wish to discuss them with [the secretary of state] Sir Keith Joseph'.⁵⁰

The prospect of needing high-level political clearance fed Howarth's own reservations about a 'mammoth', 'ambitious and expensive application' in which she saw Steptoe as Edwards' 'tame gynaecologist'.⁵¹ Herself experienced in cardiological research, she judged Edwards 'a babe in arms as far as patient care is concerned' and feared 'considerable trouble'.⁵² She reiterated to Edwards the advice she had given at their initial meeting that the MRC could fund only the scientific aspects of the work and that clinical facilities would need a parallel bid to the DHSS, and that therefore the scientific and clinical arms of the proposal should be identified and costed separately.⁵³ She also said that if the MRC approved the scientific part, the Council would then consult with the DHSS about additional funding for the clinical beds, posts and other NHS services. She told him that if he 'wished to experiment on patients then DHSS would have to consider the ethical issues involved on which they might well seek Council's advice'. Notwithstanding Turnbull's view, it seems clear that Howarth saw the proposed activities as 'experimental research', not 'experimental treatment'. She suggested to Edwards that he 'spell out precisely what he proposes to do with the blastocysts, and how he proposes to check whether the embryos are normal'.⁵⁴

At the local NHS level, the United Cambridge Hospitals (UCH) Board responded altogether more positively. Edwards had initiated discussions with the secretary W. Graham Cannon earlier that summer, enquiring about its ability and willingness to accommodate an MRC-funded programme.⁵⁵ The Medical Committee agreed on 5 October 1970 to support the project provided non-NHS funds bore all research costs.⁵⁶ The committee made up jointly of members of the UCH Board, together with members from the East Anglian Regional Hospital Board, subsequently gave permission for the work. This decision may have been based on erroneous information provided by Mills, one of Edwards' named collaborators and an influential committee member,⁵⁷ who is minuted as saying 'financial support had already been granted' by the MRC.⁵⁸

However, the pressure on NHS beds in Cambridge, and an acknowledged need for additional consultant cover at Newmarket General Hospital,⁵⁹ led the Medical Committee to explore the possibility of relieving the local understaffing through a part-time NHS post for Steptoe.⁶⁰ Accordingly, Steptoe was interviewed for, and most likely offered, a part-time consultant appointment on 15 January 1971; this was still under discussion in early March, presumably pending the MRC decision.⁶¹ Indeed, a temporary clinical assistant was authorized at Newmarket from 1 April 1971: 'It was hoped to provide within the next twelve months a permanent solution to the present situation',⁶² although in fact Michael Bright was not appointed

⁴³Memos of conversations dated 4, 15 and 18 December 1970: NA FD 10/161.

⁴⁴CSPC 102, 8 January 1971: CUL GB box 111.

⁴⁵Summary of unit bids [January 1971?]: NA FD 7/1637.

⁴⁶Rejection, 5 February 1971: CUL GB box 111.

⁴⁷Howarth to Thomas, 15 December: NA FD 10/161.

⁴⁸Godfrey, 2009, Supplementary Material 3, pp. 21–22.

⁴⁹Godfrey, notes of conversation, 2 and 11 December 1970, 11 February 1971, 8 and 24 March 1971: NA FD 10/161.

⁵⁰Howarth to the MRC's second secretary, S. Griff Owen, 7 December 1970: NA FD 10/161.

⁵¹Howarth to Godfrey, 1 December and to Owen, 7 December 1970: NA FD 10/161.

⁵²Howarth to Thomas, 14 January 1971: NA FD 10/161.

⁵³Thomas, 26 August 1970: NA FD 10/161.

⁵⁴Thomas, notes of meeting, 22 January 1971: NA FD 10/161.

⁵⁵Cannon and Edwards letters, 3, 8, 9 and 14 July 1970: RGE.

⁵⁶Medical Committee, minute 156: AHGR 4/2/7/7; Cannon to Edwards, copied to Howarth, 12 October 1970: NA FD 10/161.

⁵⁷Robinson, 2009, Supplementary Material 5, p. 12.

⁵⁸Meeting of 4 November 1970, minute 5e: AHGR 3/2/1/14.

⁵⁹Robinson, 2009, Supplementary Material 5, pp. 15–16.

⁶⁰EARHB minute 158, 18 November 1970: KAR 83/42/UNCAT/24.

⁶¹Howarth memos, 14 January and 16 March 1971: NA FD 10/161; JCCR minute 2(g), 4 March: AHGR 3/2/1/14.

⁶²EARHB minute 250(b), 17 March 1971: KAR 83/42/UNCAT/24.

until 1 May 1974.⁶³ Thus, the hospital boards saw an opportunity to meet a local NHS need by supporting Steptoe's research in Newmarket.

The East Anglian Regional Hospital Board later agreed to Edwards' suggestion in early January that a nearer alternative to Newmarket for the clinical research component would be to adapt a large vacant house, 48 Bateman Street, Cambridge, previously leased by Trinity Hall to the Ely Diocesan Association for Social Work as a home for unmarried mothers (Dimock, 1963).⁶⁴ The deputy secretary of the Cambridge Board, Cannon, reassured Howarth that they would be happy with this arrangement, subject again to full coverage of costs.⁶⁵ It was agreed that Steptoe's time would be split between NHS practice in Newmarket and clinical research in Cambridge.

Thus, in contrast to the reservations expressed by the DHSS and the university clinical school, the local hospital boards and their officers strongly supported the proposed research, albeit perhaps opportunistically, since Cannon claims that their policy was to accept any team capable of raising its own funds.⁶⁶

The definitive application

Encouraged by the MRC's earlier invitation to locate the project at Northwick Park, as well as local support, Edwards and Steptoe submitted their application for 'Studies on Human Reproduction' on 10 February 1971.⁶⁷ It was immediately copied to Cohen at the DHSS.⁶⁸ Despite Howarth's advice to scale down the bid, the full application remained as wide-ranging, and was only marginally less costly to the MRC (£50 000 compared with £53 865).

The proposal began with reasons for studying humans: 'The basic research [in human volunteers] is helping our understanding of various aspects of human reproduction. Clinical application of the findings could lead to the alleviation of infertility in some cases, and might eventually provide the means for averting the birth of children with certain inherited disorders. We feel that close collaboration already achieved between scientific and clinical groups must be strengthened to promote these and other studies'. Thus, interdisciplinary research that matched the MRC strategy was set out, but in two areas that did not feature among those the Council considered important.

A single-page 'Objectives' section added contraception as a projected outcome, and went on to specify the main topics: the underlying endocrinology and cell biology of the menstrual cycle; the anatomical and endocrinological responsiveness of the ovary to gonadotrophins; the control of ovarian oocyte maturation, particularly in the context of their metabolism and the generation of chromosomal anomalies such as Down's Syndrome; the biochemistry of ovulation; sperm capacitation; fertilization and conditions for cleavage to blastocysts; sex diagnosis in the early embryo; uterine and endocrine factors involved in implantation; and factors affecting embryo transfer. Each topic involved basic research, and was practically relevant for human IVF and embryo transfer.

⁶³Bright, pers. comm., by email, 20 September 2009.

⁶⁴Howarth, notes of phone conversation with Edwards, 14 January 1971; Thomas, notes of meeting with Edwards at MRC, 20 January 1971: NA FD 10/161.

⁶⁵Cannon to Howarth, 24 March 1971: NA FD 10/161.

⁶⁶Cannon, 2009, Supplementary Material 6, p. 19.

⁶⁷NA FD 10/161.

⁶⁸Howarth to Cohen, 12 February 1971: NA FD 10/161.

Six pages then reviewed how Edwards' and Steptoe's own work and that of others had led to these objectives, which were further expanded to include the immunology of reproductive tissues in the context of both fertility control and infertility alleviation (antisperm antibodies, ovarian immune damage and the fetus as a potential target of maternal immune attack). Six appendices over 12 pages fleshed out this background and the experimental approaches to be developed. Appendix 1 set out Steptoe's claim to be 'largely responsible for the introduction and development of endoscopic methods of diagnosis and treatment of gynaecological disorders'. Overall, the proposal is typical of its time in that it relies on coupling objectives with evidence of a track-record of achievement. Significantly, it did not make a strong case for the study of infertility or justify its 'experimental treatment', and therefore did not address the ethical management of patients.

The proposal concluded by laying out the advantages of an integrated programme of study in Cambridge over the division between Cambridge (science) and Oldham (clinic), which was described as 'involving much waste of time, dispersal of effort, and neglect of opportunities'. Named local scientific collaborators included Austin, Robin Coombs (Immunology Division, Department of Pathology) and Mills. Support from Sir Bryan Matthews (Head of Physiology) and Chalmers was recorded.

Internal MRC notes refer to 'great difficulties in getting a final application The application is for five years in the first instance, but we know that Dr Edwards would really like support on a Unit basis (as in the Cambridge "bid" in response to Peart's call).⁶⁹ Units were also subject to quinquennial review, but with greater expectation of renewal. Memos also query the legitimacy or accuracy of costings, but for the Clinical Research Board the executive finally estimated the 5-year cost to the MRC as £50 000. The DHSS-attributable budget was estimated much higher at £16 000 capital and £48 050 annual recurrent costs (£256 000 over 5 years).⁷⁰

The referees' reports

Ambitious interdisciplinary objectives demanded diverse referees. Howarth selected them after suggestions from Thomas. As clinicians, he had proposed Turnbull, Denys Fairweather (University College Hospital, London), Peter Huntingford (St Mary's Hospital, London) and Sir Norman Jeffcoate (Liverpool, Obstetrics and Gynaecology). As President of the RCOG, Jeffcoate was an obvious heavyweight, but sceptical about the value of infertility treatment, and so perhaps unlikely to be sympathetic (Jeffcoate, 1954; 1962, p. 682; Pfeffer, 1993, p. 134). As biologists, Thomas named Short, Harris, Dawes, Peter Heald (Biochemistry, Strathclyde) and Anthony Allison (NIMR, London), and for genetics Cedric Carter (director of the MRC Clinical Genetics Unit at the Institute of Child Health, London) and Conrad Waddington, Edwards' professor as a PhD student and director of the Institute of Animal Genetics in Edinburgh.

Howarth chose Jeffcoate, Short and Harris, and asked Thomas also to consult H. John Evans (director of the MRC Clinical and Population Cytogenetics Unit in Edinburgh) on the chromosomal studies, Tony Glenister (Anatomy, Charing Cross Hospital Medical School,

⁶⁹Howarth to Godfrey, 1 March 1971: NA FD 10/161.

⁷⁰Summary for Board, 1 April 1971: NA FD 10/161.

London) on embryo culture work, and Stanley Clayton (Obstetrics and Gynaecology, King's College, London) on clinical issues. Turnbull no longer featured as a referee. Howarth does not seem to have picked up a query by Thomas as to whether or not a legal opinion was needed. All six referees were to be asked about Edwards' standing and the scientific merit of the project. Although we have found no request letter, it is clear that, alerted by the reports on the preliminary application and discussions with the DHSS, the MRC specifically invited referees to highlight ethical difficulties.⁷¹

The referees reported between 15 and 26 March.⁷² Evans did so through a phone report summarized by Howarth, and Harris briefly supplemented his earlier comments on the draft application. The reports developed themes that the MRC officers and the initial referees had already aired, showing consensus about the quality of the applicants, management and ethical issues, and media exposure. The full application had not overcome the initial concerns.

First, Edwards and his science were generally held in high regard. Glenister, who gave the most thorough and detailed assessment of the experimental proposals, was 'confident that he will produce valid scientific data'. Clayton, Short and Jeffcoate concurred: 'the scientific work now in progress at Cambridge is excellent' (Clayton), and 'Edwards is a man of undoubted ability. He has tremendous energy and enthusiasm and Council could be assured of a return for any financial investment' (Short). Interestingly, none of the referees expressed any scepticism about the claims to IVF made by Edwards *et al.* (1969), despite doubts expressed in the literature of the time (Rothschild, 1969; Mastroianni and Noriega, 1970; Brackett *et al.*, 1971).

Comments on the scientific specifics were more mixed. Evans reported that from a genetic perspective the proposal was only patchily good and 'not detailed enough'. He singled out for adverse comment the research that would enable sexing of preimplantation embryos to avoid inherited sex-linked disorders, claiming that 'in vitro fertilising and sexing followed by implanting would be a complicated and unnecessary method for attempting to avoid birth of children with inherited sex-linked disorders', and that it offered no advantage over existing methods of amniocentesis, Y-fluorescent staining and termination, which had been legalized in 1967. Short concurred that preimplantation diagnosis is 'surely fanciful', and also preferred amniocentesis and termination. Both Short and, earlier, Turnbull criticized the studies on the endocrine control of ovulation as 'unoriginal'. Most of the basic research gained general approval, but with criticism of lack of detail about methods, and concern that 'the projects... appear to me... too extensive' (Harris). 'The proposed transfer of artificially conceived embryos to the uterus of infertile women raises a number of embryological and technical points which do not appear to have been considered sufficiently, at any rate in the application' (Glenister). Short was 'not sufficiently convinced of the scientific merit of all the projects in this application to feel that it justifies the full measure of financial support that is requested'.

Steptoe's role was seen as still more problematic. Jeffcoate interpreted the whole application as funding only his clinical research:

'Mr Edwards himself is not asking for any grant and apparently has all he requires for his side of the work'. Jeffcoate acknowledged Steptoe's expertise and international reputation in developing laparoscopy, which even by 1972 was practiced at only limited gynaecological centres in the UK and then almost exclusively for tubal sterilization (Pop Report, 1973, p. C4).⁷³ Jeffcoate describes him as 'almost obsessed with the procedure', and 'exaggerat[ing] its importance'. 'Knowing how obsessive is Mr. Steptoe's approach I think he would find it difficult to keep the reins on himself and remain critical and detached; the same too applies to Mr. Edwards'. Expressing scepticism about Steptoe's accomplishments, Jeffcoate alleged that the technique is 'easily learned and carried out by any competent gynaecologist', but also risky: 'no matter how expert the surgeon, laparoscopy is not without risks and, in this country in recent years, women have died as the result and have suffered serious injuries leading to medico-legal problems'. Jeffcoate did not claim that any of these problems were associated with Steptoe himself, but did share Turnbull's concerns that he would lack the support of colleagues, claiming that he had 'learned in confidence that none of the senior local gynaecologists have been consulted [about a local attachment for Steptoe] and, if they were, they would not be agreeable'. At interview, retired local gynaecologist Michael Bright said: 'I do know that Patrick would have received a warm welcome in Newmarket, but I am not sure how well he would have been received in Cambridge'.⁷⁴ Clayton similarly praised Edwards' work, but had 'some reservations about... the part to be played by Mr Steptoe'. 'I have stated publicly my high regard for the part Mr Steptoe has played in the introduction of laparoscopy into gynaecological practice', but 'it is now... not something esoteric which only one man can do'.

The imbalance in the estimations of Edwards and Steptoe fed a critical focus on patient care and clinical management. Thus Jeffcoate disparaged the proposal 'to take over and equip with a bare minimum what I am told is an old and inconvenient house formerly used to accommodate unmarried pregnant girls. There it was not possible to provide even for normal confinements and the arrangements were quite primitive. Mr Steptoe's contribution... requires... a complete gynaecological department... if it is to be safe and productive'. 'Laparoscopy should only be carried out in a fully equipped hospital and with full operating room facilities'. Clayton was troubled about extravagant and vague plans for patients. These concerns over the clinical arrangements, and doubts about Steptoe's objectivity, fuelled ethical worries.

Most referees accepted the invitation to raise ethical concerns, especially about the risk to the health of the patients from whom oocytes were to be recovered and into some of whom the resulting embryos were later to be placed. Any novel treatment confronts the issue of risk and safety. The problem for Edwards and Steptoe was that the MRC and its referees either did not recognize infertility as a serious health condition or did not consider them close to treating it. Nor had Edwards made the case. So the treatment component of the proposal was not registered by referees as relevant, and the women are generally described as though 'purely' research subjects. 'In my view it is also unethical to subject women, even volunteers, to laparoscopy for purely experimental purposes such as to obtain

⁷¹Thomas to Howarth, 22 February 1971 and Howarth to Thomas, 2 March 1971: NA FD 10/161.

⁷²Referees reports: NA FD 10/161.

⁷³Robinson, 2009, Supplementary Material 5, p. 22.

⁷⁴Bright, pers. comm., by email, 20 September 2009.

follicular fluid and granulosa cells. These procedures are not without hazard and, unless clearly in the interests of the women concerned, cannot be justified' (Jeffcoate). Clayton envisaged 'ethical difficulties' with ovulation induction and laparoscopy performed for 'purposes of research alone'. 'The proposals are not entirely clear, but imply that some laparoscopic examinations would be purely for research'. Short put it in a nutshell: 'From the ethical viewpoint, it is one thing to subject a woman to a course of gonadotrophin therapy and a laparoscopy in order to treat her infertility. But is it justifiable to carry out these procedures solely for the purposes of obtaining ova for *in vitro* experiments, which in themselves offer no immediate benefit to the patient?' He considered embryo transfer 'highly questionable' ethically, and judged that 'it would be wrong to place a major emphasis on techniques for augmenting fertility in infertile patients when we desperately need methods for limiting fertility in the normal population'. Only Turnbull's comments on the preliminary application had considered that there might be a therapeutic justification—and he was no longer a referee.

In marked contrast to the ethical debate in the 1980s, which came to focus on the moral status of the embryo (Gunning and English, 1993, p. 6; Warnock, 1984; Mulkay, 1997; Johnson, 2006), only Glenister addressed this point: 'I would question the ethics of initiating and maintaining an incipient human life for experimental and scientific purposes. Not only can the consent of the subject of the experiment [he means the embryo] not be obtained (the question that already occurs when dealing with children), but in this instance, the individual being experimented on does not stand to benefit from the experiment. Thus, as far as the artificially produced conceptus is concerned the procedures are at the level of animal experimentation'. However, other referees were concerned that those embryos to be placed *in utero* might be abnormal.

Fears about teratological risk led four—Clayton, Glenister, Short and Harris—to recommend 'a great deal of animal work, and that in primates' first (Clayton). Glenister made the point that the only criterion of 'normality of fertilization and resulting conceptus is the eventual birth, after transfer, of a normal baby. This... has so far been achieved only in a very small number of animal species. I have little doubt that the necessary technology to achieve this result in man will be evolved in due course, but the question arises whether similar experimental work with primates would not only be more justifiable, but scientifically more rewarding at the present time. Controlled experiments could be carried out in such numbers and planned in such a way as could not be justified with human patients. The fact that such projects would be more expensive hardly detracts from the advisability of undertaking such work'. Short commended the studies of IVF with human eggs but added: 'it would seem advisable to proceed with caution, and go back to primates to investigate the fate of transferred primate embryos fertilized *in vitro* before one can extend the technique to women'. He ends succinctly by advocating 'a primate colony in Cambridge rather than a human colony in Newmarket'. Primates were also seen as a way of avoiding experimental laparoscopy. For Clayton, 'work on monkeys might be no more expensive and more rewarding'. It is clear today that such a route would have been costly and unproductive (Bavister, 2004b; Hewitson, 2004), but the value of primate testing was actively debated in the early 1970s (Diczfalusy and Standley, 1972; Edwards, 1974; Short, 1975). Even Edwards (1972) admitted that although 'human data

are now far more extensive, there are various clinical opportunities which could be developed more quickly if substantial studies on the non-human primates were available'. Among Edwards' referees in 1971, use of primates offered the preferred route over use of human beings, not a parallel path.

Amplifying these ethical concerns was the strong public interest. Several referees expressed very strong distaste for the publicity-seeking of which they accused Edwards and Steptoe. Indeed, Short began his report by declaring his disapproval: 'Dr Edwards feels the need to publicise his work on radio and television, and in the press, so that he can change public attitudes. I do not feel that an ill-informed general public is capable of evaluating the work and seeing it in its proper perspective. This publicity has antagonised a large number of Dr. Edwards' scientific colleagues, of whom I am one'. Jeffcoate: 'Indeed, both Mr Steptoe and Mr Edwards are, with the best of intentions, becoming over enthusiastic so that some of their work has attracted much publicity and also adverse criticism from the standpoint of medical ethics'. It may seem strange in these days of public engagement grants, but in 1971 medical professionals were still strongly discouraged from 'self-promotion', including talking to the media (Loughlin, 2005; Nathoo, 2008, pp. 33–56). Even today, many scientists who engage in public discussion are concerned about being seen as scientific spin-doctors or even 'media tarts' (Burchill et al., 2009).

Press interest had been an inevitable feature of their work, but Edwards, and to a lesser extent Steptoe, took a principled decision to engage and educate the public on this controversial topic (e.g. Anon, 1965; Edwards and Gardner, 1968; Edwards and Steptoe, 1980, pp. 101–102; Edwards, 1989, 2005a, b). Edwards saw progress in this field as dependent on activism for social reform of the kind that had recently liberalized laws on abortion and homosexuality, but recognized the risk: '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'. He considered this necessary to prepare society to 'keep pace' with 'the transition of scientific discovery into technological achievement' (Edwards and Sharpe, 1971). Taking this stand, which was widely adopted by others in the 1980s (Mulkay, 1997; Braude, 2009), harmed his case with the MRC. By competing for funding, but not anticipating or adequately countering criticisms and doubts to which the MRC was already alerted, Edwards was treading a risky path.

The decision and the immediate aftermath

The Clinical Research Board⁷⁵ considered the application on 1 April 1971 and was asked to assess: (i) scientific merits, (ii) ethical aspects and (iii) the scale and period of the requested support. A three-page in-house summary was available,⁷⁶ as would have been the application itself and—probably but not necessarily⁷⁷—the reports of the six definitive referees. No written submission from the DHSS has been found, but George Godber, who is reported as finding matters reproductive 'not pukkah doctoring' (Sheard and

⁷⁵CRB membership: Supplementary Material 2, Table 2B.

⁷⁶Summary for board; NA FD 10/161.

⁷⁷Godfrey, 2009, Supplementary Material 3, p. 14.

Donaldson, 2006, p. 118), and John H.F. Brotherston, chief medical officer in the Scottish Home and Health Department, were present. Godber was ready to consult Keith Joseph in the event of a positive decision.⁷⁸ Gray, Owen and Godfrey were there too, and Howarth, although not listed by name, would have presented the administrative summary.⁷⁹ The Board members with the most relevant expertise were Peart, chair of the SCOG and Turnbull, who presumably presented the scientific case to the Board.⁸⁰ Whether he repeated the case for IVF and embryo transfer as therapeutic is unknown, but possibly not, since the other referees had placed him in a minority of one.⁸¹

Given the referees' reports, the decision hardly comes as a surprise: 'The Board accepted that Dr Edwards was an investigator of high scientific standing, energy and originality. Board members and referees, however, all had serious doubts about the ethical aspects of the proposed investigations, especially those relating to the implantation in women of oocytes fertilized *in vitro*, which was considered premature in view of the lack of preliminary studies on primates and the present deficiency of detailed knowledge of the possible hazards involved. Reservations were also expressed about the procedure of laparoscopy for purely experimental purposes, and about the proposed facilities and arrangements for patient care. *Recommendations*: (i) The application should be declined on ethical grounds and the reason should be conveyed to Dr Edwards and Mr Steptoe. (ii) It should be suggested, without commitment, to Dr Edwards that he might formulate an application to the Council for support of a similar programme of work on primates'.⁸²

That meeting considered five other applications for long-term support: from C.T. Dollery (clinical pharmacology), C.E. Dent and C.G. Clark (pathological crystals in man), I.M. Marks (brief psychological treatments and their mechanisms of action), J.N. Walton (studies of neuromuscular disease in man and animals) and D.F. Roberts (quantitative inheritance and human disease). The total allocation for long-term awards is recorded as '£261 000 and for project grants £140 000 for recurrent and £11 000 for non-recurrent awards'. Three long-term bids were approved: Dollery, part-funded at £64 000; Dent and Clark, £49 000; and Walton, £98 000. An additional long-term award to J.G. Edwards of £57 000 for research on alcoholism features only in the minutes of Council, which met on 22 April.⁸³ Thus Edwards and Steptoe's bid at £50 000 was within the range of those funded, although expensive for the DHSS.

Howarth relayed the decision to Edwards on 28 April in a short letter, which he found 'devastating' (Edwards and Steptoe, 1980, p. 108). He rang Howarth on 6 May, asking to come and put his case to Council, and for a more detailed statement of reasons for non-funding plus a summary of criticisms in enough detail to formulate a primate programme that might meet concerns. Edwards related how Pincus had answered point-by-point specific objections from a funding body, which, it was claimed, had also wanted primate studies for testing of the oral contraceptive pill. (We have found no

record to support this claim.) 'Dr Edwards would like to adopt the same course in regard to the Council', Howarth recorded, 'but I had to say again firmly that this was not possible'. She then noted that 'Dr Edwards did a smart sidestep'; he 'changed course and asked whether the Council realised how difficult it would be to do primate work in this country'. 'Finally, Dr Edwards climbed down and said that he would make further enquiries about where primate work would be done and would like to discuss this with me on the telephone again tomorrow'.⁸⁴ No record has been found that they communicated again.

During this exchange, Edwards expressed concern that the confidentiality of the MRC decision be rigorously maintained so that the negative outcome did not prejudice applications elsewhere. Howarth 'told him that Council leaned over backwards in trying not to influence decisions by other bodies, but I reminded him that as clinical facilities were required other funding sources would no doubt also wish to be assured that lines had been cleared with the Health Departments'. Contrary to this assurance, Peter Condliffe of the National Institutes of Health (NIH) was told: 'in confidence the result of the consideration by CRB and Council of Dr RG Edwards' recent application for long-term support... I thought it possible that he might make an approach to NIH and that the Council's reasons for turning down the application in the form in which it had been submitted ought to be known to NIH'.⁸⁵

Howarth also wrote in July to both Cambridge and East Anglian Hospitals' Boards: 'We heard informally that the East Anglian Regional Hospital Board had been asked to provide facilities for Dr Steptoe at Newmarket, the work to be carried out under the auspices of the Board of Governors of the United Cambridge Hospitals. Apparently the DHSS was kept in the picture about this and felt that it was important for the RHB to know about the ethical objections in view of the complex situation'.⁸⁶ This letter was in reaction to an earlier one from the board to Steptoe, copied to Howarth, saying they were sorry that the bid to the MRC had failed.⁸⁷ They were still hoping funding would be obtained and were proceeding with plans at Newmarket for 12 new beds and an additional operating theatre in a prefabricated unit plus a lift to the first floor where more beds would bring the number to the 30 required for RCOG recognition. They may then have been unaware of the reasons for non-funding, believing that this was 'probably because of the high estimated cost'.⁸⁸ Notwithstanding, on 29 September 1971, Mills is reported to have told Howarth that the East Anglian Board 'would like to appoint Mr Steptoe as a practising gynaecologist to Newmarket, [but] they were unprepared to contemplate providing clinical facilities for the... experimental programme since Dr Edwards had told him that the [Medical Research] Council had declined the proposals on ethical grounds'. Yet United Cambridge Hospitals had not rejected the work. Indeed the Bishop of Ely, as a member of the committee, is quoted as saying he 'had been unable to see where the difficulties lay'.⁸⁹

⁷⁸Note of phone conversation between Cohen and unidentified MRC employee, 24 March 1971: NA FD 10/161.

⁷⁹Godfrey, 2009, Supplementary Material 3, p. 14; Thomas, 2009, Supplementary Material 4, p. 20.

⁸⁰Thomas, 2009, Supplementary Material 4, pp. 7, 18, 20; Godfrey, 2009, Supplementary Material 3, p. 14.

⁸¹Godfrey, 2009, Supplementary Material 3, p. 16.

⁸²Minute 34: NA FD 15/115.

⁸³Minute 72: NA FD 13/171.

⁸⁴Howarth, note of telephone conversation, 6 May 1971: NA FD 10/161.

⁸⁵Note, 15 June 1971: NA FD 10/161.

⁸⁶Barbara Rashbass, MRC, to Elizabeth Cloak, DHSS, 6 April 1978: NA FD10/161.

⁸⁷25 May 1971: NA FD 10/161.

⁸⁸CCR 2 June 1971, minute 2(d): AHGR 3/2/1/14.

⁸⁹Howarth memo, 29 September 1971: NA FD 10/161.

Oldham Area Health Authority, while withdrawing NHS support, continued to provide some basic facilities. Ford Foundation support for ‘experiments on re-implantation’ also fell away, again for ethical reasons, and in spite of Edwards’ step-by-step account of the ethical procedure he and Steptoe followed when agreeing to treat patients experimentally.⁹⁰ The work was thus left dependent on funding from private individual donors—recruited paradoxically by the very publicity that had so antagonized the referees for state funding (Wright, 1970; Stevenson, 1973; Edwards and Steptoe, 1980, pp. 109–110; Edwards, 1983, p. 57; Edwards, 1989, pp. 10–11; Edwards, 2005a, p. 303).

Edwards’ and Steptoe’s formal letter to ‘The Chairman and members of the Medical Research Council’ expressed surprise at the decision, ‘since we were actually invited to join the MRC Clinical Research Centre at Harrow to direct a Division in pursuit of these very studies’. They offered, as promised, a robust point-by-point refutation of the reasons given for rejection. Although admitting that embryo transfer is not risk-free, Edwards and Steptoe challenged the view that it would be too risky in humans, claiming that animal studies did not show any detectable anomalies in the fetuses, and that methods for detecting anomalies *in utero* existed. Like Turnbull, they claimed ethical justification on humanitarian grounds for attempting embryo transfer to alleviate infertility, adding that ‘the comments on the use of laparoscopy for “purely experimental” purposes are unfortunate’. Reports of its dangers were irresponsible, they wrote: most hazards came from diathermy using high-frequency currents to produce heat. Steptoe did not employ this approach and in more than 3000 cases had had no mortality and only occasional minor complications. In response to the demand for primate work, they pointed out that there was no general agreement among scientists and doctors on the value of primates as human models, nor on which primate model to use. Little was known, they countered, about early pregnancy in primates compared with humans, and primate size and anatomy made both laparoscopic oocyte recovery and trans-cervical embryo transfer impossible. Throughout medical history work on primates had rarely preceded human trials.⁹¹

Howarth drafted the MRC’s response: ‘In view of the unanimous view of CRB members and referees that the particular item on which they lay most stress—namely the implantation of oocytes fertilised *in vitro* into women—is premature, I can see no case for reconsideration’.⁹² Replying to Edwards, Gray emphasized the integrity and thoroughness of the MRC’s decision. The ‘advice of a wide spectrum of expert referees was also available and they showed unanimity in their opinion that your proposed work on implantation in women of oocytes fertilised *in vitro* was premature’. He stressed that the MRC did not routinely give detailed reasons for decisions, reminding Edwards that in this case it had already done more than usual in explaining the specific ethical issues that arose. Gray concluded by noting that Council would not reconsider declined applications ‘unless it can be shown either that there are certain vital new facts which might have caused them to arrive at a different decision had they known of them when the application was considered; or that there have since been changes in circumstances which might cause

them to alter that decision. I can find evidence of neither of these circumstances in your letter’.⁹³

Notwithstanding this rejection, the MRC subsequently awarded Edwards two project grants: one in 1975 on ‘the growth and differentiation of graafian follicles in the ovary (rodents)’, although a request ‘to extend the study to human follicles was declined’, and a second in 1976 to ‘Dr Edwards and [Azim] Surani for work on the cellular and molecular aspects of blastocyst–uterine interactions at implantation (rodents)’.⁹⁴

Changing MRC policy

Having reached a unanimous decision, justified it, and discouraged further local hospital or international financial support, the MRC was concerned that negative media stories might arise from Edwards’ and Steptoe’s continued research and from their campaigning so disapproved of by referees. Howarth warned Gray via Godfrey: ‘I think we should perhaps prepare ourselves for a little publicity, since Dr Edwards has always been very forthcoming about his results through popular media’.⁹⁵ She later asked: ‘what line we were to take if the newsworthy Dr. Edwards was mentioned at the forthcoming press conference. It is conceivable that the result of the application to Council may be known and I think we ought to prepare our line in advance. May we discuss please?’⁹⁶ We have yet to find evidence of immediate press fallout (but see Edwards and Steptoe, 1980, p. 109), although the subject did break again in October that year around a meeting in Washington, DC, at which Nobel laureate James Watson of Harvard and others attacked Edwards. British embryologist Anne McLaren stated: ‘I fear Dr Edwards will go too far, too fast. I am worried by the possibility that the desire to be first in the field will bias the judgment of those in a position to carry out egg transfer. . . . However, babies produced in a test-tube . . . will be routine procedure within twenty years’ (Edwards and Steptoe, 1980, pp. 112–116; see also Kass and Glass, 1971; Watson in Anon, 1971a; Perutz in Anon, 1971b, c). Thereafter press comments became an intermittent MRC concern.

For example, at a press conference on 23 July 1974 by Gray, together with Bull and Council member Alan Dornhorst, to launch the MRC Annual Report, Gray said of human IVF work: ‘The Council would not fund research in the field unless they were provided with satisfactory evidence that there would be no increased risk of abnormal offspring’.⁹⁷ This statement did not relate to the annual report, which does not mention IVF, but probably to press reports arising from the BMA annual meeting in Hull about the controversial and never subsequently substantiated claim by Douglas C.A. Bevis of Leeds University that: ‘Three babies have been born after fertilization of a human egg in the laboratory’ (Anon, 1974a, b, c; Roper, 1974). The day after the press conference, Gray recorded that Sir Douglas Black, chief scientist at the DHSS, shared his view. Gray’s statement remained the MRC’s sole public utterance on IVF in humans and the closest it came to a formal policy until 1978.⁹⁸

The MRC also assembled relevant evidence to support its stance. This includes a report of an NIH meeting on gene therapy, at which

⁹³Gray to Edwards, 23 June 1971: NA FD 10/161.

⁹⁴S. Ramaswamy, summary of Council policy on IVF, 28 July 1978: NA FD 10/161.

⁹⁵Howarth to Gray via Godfrey, 21 June 1971: NA FD 6/161.

⁹⁶Memo, 8 July 1971, annotated by Godfrey on 9 July: NA FD 10/120.

⁹⁷Ramaswamy summary, 28 July 1978: NA FD 10/161; Roper (1974).

⁹⁸Note by Gray, 24 July 1974: NA FD 10/161; Gunning and English (1993, p. 10).

⁹⁰Letters between Edwards and R.T. Mahoney, 12 and 26 May 1972, 8 January 1973: RGE.

⁹¹Edwards and Steptoe to MRC, 11 June 1971: NA FD 10/161; see also Edwards (1974).

⁹²Howarth to Gray via Godfrey, 21 June 1971: NA FD 10/161.

a prominent American mammalian developmental biologist is reported to have said that in her opinion the blastocysts grown *in vitro* were definitely abnormal and if implanted into a human uterus would almost certainly develop into monsters. Condliffe of the NIH wrote that, although 'not everyone' at the 'stormy' meeting agreed, he accepted this.⁹⁹ They also discussed 'the need to air some of the problems—ethical and otherwise raised by this type of work—[sic] amongst responsible people in the scientific community before public attack was made on organisations supporting such work'. Presumably it was not the NIH or the MRC that risked attack, but perhaps the Ford Foundation, who still paid Edwards' salary. It did later pull out of funding the human embryo implantation research due, Edwards claimed, to the 'ethical controversy surrounding in-vitro fertilization in the USA' (Edwards, 1989, p. 10).

The first evidence of policy doubts within the MRC appears in January 1975 (Gunning and English, 1993, p. 10). The Cell Board, which had replaced the CRB in the early 1970s with a remit that combined basic and clinical research (Booth, 1986, p. 446), set up a small advisory group. It was to report on all aspects of research on *in vitro* methods of human fertilization, with Edwards' erstwhile critical referee, Short, now in Edinburgh, as its chair. The other members were Walter Bodmer, the Oxford geneticist, Ian Cooke, the Sheffield fertility physician, and McLaren. Bodmer had chaired a British Association (BA) Working Party (1972–1973) to study 'the scientific, social, ethical and legal implications of recent advances in genetics and biology' (Jones and Bodmer, 1974, p. v). It had met eight times, its regular members including McLaren, Austin, Maddox, Shirley Williams MP, David Owen MP, Gordon Dunstan, theologian and Edwards himself. Given the broadly like-minded, leftish and at least potentially sympathetic membership of the BA working party, perhaps Edwards' ethical and scientific arguments there won over Bodmer and softened McLaren's concerns, and thereby facilitated the more liberal policy proposal that Short's committee of four produced. Thus, the draft report submitted to the Cell Board that November recommended that:

- (i) There should be no objection to obtaining ova from women for research purposes, provided that there are defined medical reasons for opening the abdomen, and provided that the woman gives her consent.
- (ii) There should be no objection to the process of IVF of human ova obtained in this way.
- (iii) There should be no legal or ethical objections to the transfer of *in vitro* fertilized ova to the uterus. Embryo transfer should only be carried out in patients who have been carefully selected beforehand, and any pregnancy resulting from such a procedure should be carefully monitored by ultrasound, amniocentesis and serial hormone assays.
- (iv) The anonymity of any offspring resulting from embryo transfer should be strictly preserved.
- (v) Improved techniques of tubal surgery are likely to be of much more immediate and lasting benefit, and more cost-effective, for the treatment of tubal occlusion than IVF and embryo transfer.¹⁰⁰

This report, especially points (i) and (iii), would have represented a substantial shift in policy for the MRC, challenging the previous ethical grounds for rejecting Edwards' and Steptoe's application. The chair, Short, may also not have been fully committed to its conclusions (Short, 1975). Perhaps for these reasons, the Cell Board decided that

it could not endorse it without detailed supporting evidence, and that no active initiative was required at that time. Council policy therefore remained as enunciated by Gray the previous year.

By mid-1978, with massive international publicity for Louise Brown's imminent birth, unease intensified within the DHSS, now under a Labour Secretary of State David Ennals, and within the MRC, under a new Secretary James Gowans. Barbara Rashbass, MRC senior medical officer, wrote to McLaren on 24 May 1978 to ask if Council policy on human IVF and embryo transfer was 'ripe for review'. McLaren reiterated the 1975 report's conclusions, but saw, somewhat ambivalently, no urgency for a review of policy other than to fund research on IVF, but not embryo transfer.¹⁰¹

After the birth on 25 July, the pressure increased. A *Times* report credited '[t]he personalities of Mr Patrick Steptoe and Dr Robert Edwards' for the 'way they perfected the method of in vitro fertilization against enormous odds. In all probability most other people would have found them insurmountable'. The paper commented that 'their fields of study do not figure on the Medical Research Council's and the Department of Health and Social Security's priority lists for the allocation of their overstretched resources' (Anon, 1978). The same day, the DHSS informed Howarth that the Government would expect some explanation of MRC policy: 'The Secretary [Ennals] would be grateful if he could have a briefing note about why we did not support Edwards/Steptoe... He feels vulnerable from a public relations point of view'. Howarth provided a history on 28 July.¹⁰²

Brown's birth had changed everything. An initiative from the 4 October 1978 Cell Board came to the 26 October meeting of Council, which set up a small working group to review policy on human IVF.¹⁰³ Given the proof of principle provided by two healthy births, one 11-week ectopic pregnancy, two chemical pregnancies (positive for pregnancy hormones, but no evidence of a sustained implant), one premature loss of a normal fetus at 21 weeks, and one miscarried triploid fetus (Edwards and Steptoe, 1980, pp. 128, 131, 133 and 183), the MRC reconstructed IVF as an experimental treatment and no longer as purely a research procedure.¹⁰⁴ It decided: (i) to endorse 'scientifically sound research involving both human and non-human gametes, where there is no intention to transfer the embryo to the uterus... and if the aim of the research is clearly defined and ethically acceptable'; (ii) 'that consent... should be obtained... from the donor of both ovum and sperm'; and (iii) that 'human IVF with subsequent embryo transfer should now be regarded as a therapeutic procedure covered by normal doctor/patient ethics'. Council's role 'should be to maximise opportunities to make the procedure safer and more successful while coincidentally increasing knowledge of human reproduction'. The change of policy was announced in the 1978/1979 Annual Report. It not only provided for all that Edwards and Steptoe had previously been denied, but also sanctioned the production of human:animal hybrids for research purposes,¹⁰⁵ possibly because Short wanted to use the hamster egg test to assess human sperm fertility. With this decision, the MRC

¹⁰¹ McLaren to Rashbass, 3 July 1978: NA FD 13/242.

¹⁰² Ramaswamy summary, 28 July 1978: NA FD 10/161.

¹⁰³ Minute 144: NA FD 13/243; Gunning and English (1993, pp. 15–17); Membership: Table 2C, Supplementary Material 2.

¹⁰⁴ Council minute, June 1979: NA FD 10/1229.

¹⁰⁵ Ramaswamy summary, 28 July 1978: NA FD 10/161.

⁹⁹ Note, 15 June 1971: NA, FD 10/161.

¹⁰⁰ Report of a Working Group on *In Vitro* Fertilization and Embryo Transfer, 1975: NA FD 10/161.

became a strong and major supporter of research on human IVF and human embryos (Gunning and English, 1993).

Discussion

This study provides the first detailed analysis of the role of the MRC in a landmark event in the history of reproduction. It builds on Gunning and English (1993) to show why UK research on human IVF was refused state funding between 1971 and 1978, and in the process recovers scientific and clinical attitudes to human conception research. We show that the failure of Edwards' and Steptoe's application for long-term support was not simply due to widespread establishment hostility to IVF. It failed, we argue, for more complex reasons. In particular, the referees and the Clinical Research Board saw the institutional set-up in Cambridge as problematic with respect to clinical facilities and patient management; gave infertility a low priority, especially compared with population control; assessed interventions as purely experimental rather than as potentially therapeutic, and so set the bar for safety high; feared fetal abnormalities and so wanted primate experiments first; and were antagonized by the applicants' high media profile. Yet we also find that Edwards' initial request did not meet with universal opposition. Had he accepted different institutional arrangements, the outcome might have been very different. The referees agreed that he was working to high standards of performance and achievement. The principal medical officer showed cautious enthusiasm for the project as fitting within the MRC's strategic plan for reproductive physiology. Turnbull clearly recognized its possibilities and judged the risks worth considering. Bull, director of the new Clinical Research Centre at Northwick Park, saw Edwards and Steptoe as potentially solving a recruitment problem.

Edwards' rejection of Bull's offer was decisive because it greatly raised the administrative hurdle the application had to clear. Paradoxically, but crucially, Edwards saw it differently. The invitation led him to believe that the MRC viewed the whole proposal favourably, an assumption reinforced when he learnt of Peart's call for unit bids as part of the strategic plan for reproductive sciences. Lacking MRC committee experience, he may not have fully appreciated the difference between the vagaries of indirect competitive-mode funding and block-grant direct support at the CRC or in an MRC unit. Seizing the opportunity presented by the CRC offer, and arguing his case internally, might have better suited his style than preparing an application that would satisfy anonymous referees.

Deciding to stay in Cambridge meant that Edwards had to arrange clinical services. This requirement proved a major weakness given ambivalent local professional attitudes to Steptoe and structural challenges. The hospital boards were willing to make space for the work, and basing Steptoe in Newmarket would even have filled a clinical service gap. But, in the University of Cambridge, obstetrics and gynaecology were so inactive in research that it could mount no serious bid for a reproductive physiology unit. The university was more interested in trying to retain Short, who was known to be influential within the MRC.¹⁰⁶ He must have seemed the obvious leader of a unit application, which would hardly have been more successful if based around Edwards and Steptoe. Their controversial proposal may have seemed unhelpful to a vulnerable clinical school.

Having opted for Cambridge, and then been denied consideration for a unit, Edwards was left exposed. Relatively inexperienced in MRC grantsmanship, he was enthusiastic about the clinical facilities that were the major cost, but Steptoe had yet to establish an East Anglian base, and Edwards himself had no medical standing in an age when the hierarchy favoured those with medical qualifications.¹⁰⁷ Edwards thus had little chance of convincing a clinical board, especially given the reservations of the DHSS. The focus on patient management was so sharp because research on infertility had such a low priority among the leaders of British obstetrics and gynaecology (Pfeffer, 1993, pp. 136–139). Turnbull was the sole champion of infertility treatment among the preliminary referees, but his role thereafter is uncertain. Was his reference not mentioned again because he was on the CRB, and did he put that case there? In general, infertility did not feature in the RCOG and MRC reports, which assumed that effective population control and improved pregnancy outcomes were the main tasks for scientific medicine. This approach fed, and was fed by government policy.¹⁰⁸ Research on IVF was reckoned likely, if anything, to make the population problem worse.

These priorities weighed heavily with MRC staff and referees, and Edwards and Steptoe did little to challenge them and so legitimate therapeutic research on infertility (Clarke, 1998, pp. 52–54). Their patients were thus seen in the MRC papers as pure research subjects until 1979, giving them a different status from patients undergoing experimental treatments (Lansborough Thomson, 1975, p. 29). This distinction had been set out by the MRC in 1964:

A distinction may legitimately be drawn between procedures undertaken as part of patient-care which are intended to contribute to the benefit of the individual patient, by treatment, prevention, or assessment, and those procedures which are undertaken either on patients or on healthy subjects solely for the purpose of contributing to medical knowledge and are not themselves designed to benefit the particular individual on whom they are performed. The former fall within the ambit of patient-care and are governed by the ordinary rules of professional conduct in medicine. (MRC, 1964, p. 178).

Even if the work had been regarded as experimental treatment, it might have foundered, given contemporary concerns about adverse outcomes from reproductive interventions. Thus, thalidomide-induced birth defects and thrombotic side-effects of the pill had achieved public notoriety in the 1960s (Lenz, 1961; Marks, 2001, pp. 138–157). Referees did not mention these cases, but may have been influenced by them, especially given that the prosecution in West Germany of the pharmaceutical company producing thalidomide had only ended the previous December (Daemmrich, 2002). There is no evidence that referees considered whether or not patient consent procedures could render the work ethical or undertook a risk/benefit analysis by estimating the likelihood of malformations or morbidities in relation to live births. Paradoxically, Edwards had probably applied more ethical knowledge, thought and practical experience to these matters than most of his critics (Edwards and Sharpe, 1971), but this was not apparent in his submission.

Since the MRC officers, the DHSS and the initial referees highlighted many of the key concerns early on, a stronger working relationship

¹⁰⁷Thomas, 2009, Supplementary Material 4, p. 10.

¹⁰⁸In a speech to the Family Planning Association national conference on 20 July 1970, Keith Joseph reported a trebling of expenditure on family planning provision; note on file, 22 July 1970: NA FD 10/120.

¹⁰⁶Godfrey, 2009, Supplementary Material 3, pp. 3–4.

with MRC staff might have helped, but Edwards and Howarth, his key MRC contact, do not appear to have worked well together. Both were from Yorkshire, but in other respects they differed. She was medically qualified, and from 1943 to 1955 had helped pioneer cardiac catheterization (Owen, 2000). Our MRC interviewees suggest that she had a strong personality,¹⁰⁹ and met in Edwards another strong character, who was also clearly and energetically unconventional, requesting large sums with a freewheeling style that fitted poorly with expectations at the MRC.¹¹⁰ Neither Steptoe nor Edwards were seen at the MRC as being part of the 'establishment'.¹¹¹ Steptoe came from a minor northern hospital, while Edwards, although from Cambridge, was neither medically qualified nor yet a professor.¹¹² Howarth and Thomas expressed shock at Edwards' apparent naïveté about the management of patients. Howarth's own reservations, not least in the sceptical phrases that spice her memos, were reinforced by, and may have encouraged, negative reactions in others. But there is no evidence that, for example, she skewed the selection of referees or solicited negative comments. Jeffcoate was an obvious choice and the initial referees had themselves highlighted ethical issues. Godfrey has pointed out that, at that time, Howarth 'would have primarily been concerned with "direct" MRC support [such as] units [and] external scientific staff', so when Edwards declined or was denied these routes and went for indirect competitive support, she may have been on less familiar ground.¹¹³ She did point out key weaknesses, but Edwards' misplaced optimism was punctured only when he received the rejection.

The decision not to fund had major consequences for Edwards and Steptoe (Edwards, 1983, pp. 56–57) and fixed the MRC stance on human IVF for 8 years. A strategic approach to medical-scientific collaboration in obstetrics and gynaecology had been forged by committees and reports in the later 1960s. In contrast, MRC 'policy' on IVF was arrived at far less coherently through referees, a funding committee and a press conference. Although, for reasons that have yet to be explained, the Council started to review its stance in 1975, only success in achieving two healthy live births from seven IVF pregnancies brought a decisive, if evidence-light, change.

This article has focused on Edwards' and Steptoe's failed application, because of the transformative impact of their research programme. Their work helped shift the reproductive sciences from aiming to prevent human reproduction to seeking to manipulate it, including to promote fertility. That the MRC did not foresee this potential for transformation has parallels in the larger history of the reproductive sciences. Although states have assumed major roles in reproductive policy-making in the twentieth century, state agencies have found it difficult to sponsor certain kinds of reproductive innovation in what has been perceived as a 'controversial' field (Clarke, 1990).¹¹⁴ Another example is the pill, which was made possible by the population control lobby and private funding, whilst subsequently international agencies have played a significant role. Edwards and Steptoe similarly came to rely largely on a private

donor for the work leading to Louise Brown's birth. The MRC supported IVF and embryo research only from the 1980s, although curiously not research follow-up of IVF pregnancies. Health professionals, politicians and the general public still view innovative technologies ambivalently, especially those associated with reproduction (Beck, 1992, pp. 206–211). In tension with the promise of new treatments and cures, such as PGD, human embryonic stem cell derivation, and cloning by somatic cell nuclear transfer, there exists a precautionary awareness of the risks their development may entail (Kerr and Franklin, 2006).

The opposition that reproductive scientists have faced has tended to be condensed into almost mythical moments of rejection. Edwards' and Steptoe's turning down by the MRC might be compared with Pincus' failure to obtain tenure at Harvard in the 1930s, which also turns out to have involved more and different factors from those highlighted in the standard account (Schreiber, 2007, pp. 129–144). These oft-recalled events have served important legitimating functions, for example, in pitting courageous mavericks against conservative establishments. They contain important elements of truth: Edwards and Steptoe were outsiders and did pioneer—against prevailing wisdom—new ideas, therapies, values, public discourses and ethical thinking. But the standard histories also risk promoting an unduly simple view of how such decisions work. Richer accounts may be better guides to action, in the present as well as the past.

Supplementary data

Supplementary data are available at <http://humrep.oxfordjournals.org/>.

Authors' roles

M.H.J. undertook interviews, transcript checking, archival research, and secondary literature research, and prepared and revised manuscript drafts; S.B.F. undertook interviews, transcript checking, archival research and secondary literature research, and commented on manuscript drafts; M.C. undertook archival searching; N.H. researched secondary literature, checked interpretation and, where appropriate, transcription of archival and primary printed material, and helped prepare and revise the manuscript.

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¹⁰⁹Godfrey, 2009, Supplementary Material 3, pp. 23–24; Thomas, 2009, Supplementary Material 4, p. 4.

¹¹⁰Thomas, 2009, Supplementary Material 4, pp. 5, 7–8, 24–25.

¹¹¹Thomas, 2009, Supplementary Material 4, pp. 14–15.

¹¹²Thomas, 2009, Supplementary Material 4, pp. 24–25.

¹¹³Godfrey, 2009, Supplementary Material 3, p. 12.

¹¹⁴Rashbass, 2009, Supplementary Material 7, pp. 8–9.

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