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EDITORIAL

In Vitro Fertilization: Success, Controversy and Tragedy

Reproduction is essential for survival of all biological species. The processes of fertilization, embryonic growth, differentiation and development are amongst the most dramatic phenomena in nature. They are also so common that they are hardly noticed. The fusion of a sperm cell with an egg can set off an amazing chain of events, that can lead to the birth of a wonderfully formed baby. The remarkable ease with which reproductive functions are fulfilled in nature and the widespread familiarity with the processes of conception and birth have obscured the importance of the field of reproductive biology. The award of the Nobel Prize in Physiology or Medicine to R. G. Edwards, has turned the spotlight, albeit briefly, onto a field that appeared to have faded from centrestage, a long time ago. Ever since the famous and ominous prophecies of Malthus, in the 19th century, contraception research has dominated the field. Indeed, when Edwards began his work on fertilization under laboratory conditions, in test tubes or more appropriately petri dishes (*in vitro* in the parlance of the field), there was little to suggest that human life might indeed be conceived in prosaic, laboratory conditions by sperm–egg fusion. In a paper published 45 years ago, Edwards noted that 'the investigation of early development in many mammalian species is restricted by the difficulty of obtaining sufficient numbers of oocytes and embryos at particular stages of development'. In introducing a technique to facilitate *in vitro* maturation of 'mouse, sheep, cow, pig, rhesus monkey and human ovarian oocytes', he looked ahead: 'With this technique it should eventually be possible to study pre-ovulatory development and perhaps fertilization and pre-implantation development in various species including man' (Edwards, R. G., *Nature*, 1965, **208**, 349). The same year in reporting 'maturation *in vitro* of human ovarian oocytes' he pointed out, that 'perhaps the greatest challenges of the present work lie, however, in the prospect of obtaining fertilized human eggs'. The concluding sentences of this report look into the future: 'Nevertheless, the plentiful supply of oocytes from one ovary could ultimately allow us to grow human embryos *in vitro*, and even control the genetic disorders of man' (Edwards, R. G., *Lancet*, 1965, 926–929). Four years later, in reporting on the 'early stages of fertilization *in vitro* of human oocytes matured *in vitro*'. Edwards *et al.* clearly outline a clinical use of human embryos: 'Fertilized human eggs could be useful in treating some forms of infertility, and many infertile patients will probably be older women' (Edwards, R. G., Bavister, B. D. and Steptoe, P. C., *Nature*, 1969, **221**, 632). In August 1978 a very brief note entitled 'Birth after the reimplantation of a human embryo' appeared in *Lancet*. The text was technical, matter of fact and barely more than half a column. The procedure for producing the world's first 'test-tube baby' was summarized in one sentence: 'Pregnancy was established after laparoscopic recovery of an oocyte on 10 November 1977, *in vitro* fertilization and normal cleavage in culture media, and the reimplantation of the 8-cell embryo into the uterus 2½ days later'. The much celebrated baby 'was safely delivered by caesarean section on 25 July 1978' as 'a normal healthy infant girl weighing 2700 g' (Steptoe, P. C. and Edwards, R. G., *Lancet*, 1978, 366). Reading the stark, economical prose of the Steptoe–Edwards note, over three decades and four million babies later, one cannot help wondering how many lives have been touched by this scientific advance.

When the Nobel Prize was announced, Patrick Steptoe (1913–1988) had already passed on over two decades earlier. As the gynaecologist and surgeon, Steptoe was a key contributor to the success of the *in vitro* fertilization (IVF) procedure. Obtaining human eggs would have proved a major obstacle if Steptoe had not pioneered the use of laparoscopy, a technique invented by Raoul Palmer in France and Hans Frangenheim in Germany in the 1950s. Highlighting Steptoe's work, a decade after his death, Grzegorz Litynski relates an anecdote on laparoscopic sterilization: 'I can't do it (sterilization) often enough in France as it's a Catholic country', confided Raoul Palmer to Steptoe in private conversation. 'And Hans Frangenheim also has difficulties because he's working in a Catholic region of Germany. But you Patrick, live in England, and you could work unimpeded' (*JSLS: Journal of the Society of Laparoendoscopic Surgeons*, 1958, **2**, 99). In 1967 Steptoe published the first textbook, *Laparoscopy in Gynaecology* which was to influence medical practice. In Litynski's words: 'When laparoscopic sterilization was introduced a few years later on a large scale in the United States, Steptoe's book became a standard text. In a sense, his work served as a bridge between the European scientists and the expanding market in North America' (p. 100). Soon after, the Steptoe–

Edwards collaboration began in 1968, leading a year later to the first demonstration of fertilization of human oocytes *in vitro* in 1969. The birth of the first 'test-tube baby' was to happen nine years later. During this period Steptoe and Edwards were resolute in their effort to achieve 'human birth after *in vitro* fertilization' despite the absence of funding from public sources. The historical account, 'Why the Medical Research Council refused Robert Edwards and Patrick Steptoe support for research on human conception in 1971', must be read by all those who are interested in the processes of decision making, when uncharted territories are explored and when troubling ethical concerns surface in public debate (Johnson, M. H. *et al.*, *Human Reproduction*, 2010, **25**, 2157). The authors adopt a tempered view in their retrospective. They note that many accounts of the controversies of the 1970s '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'.

Discussions of ethical issues were always central to any consideration of *in vitro* fertilization in the 1970s. There were also major criticisms about the use of laparoscopic techniques. In 1989, Edwards described the trials of the 1970s in a memorial tribute to Steptoe. His essay entitled 'Tribute to Patrick Steptoe: beginnings of laparoscopy' is probably one of the most readable accounts of the road travelled to produce the first 'test-tube baby'. Theirs appears to have been a perfect collaboration, cemented by shared goals, complementary skills, total committment and similar views on the difficult ethical questions raised by their work. Edwards describes Steptoe: 'He never was a man to publish vast numbers of papers, and I soon learned how I would have to pick up my pen and write our joint articles throughout our time together!'. In his moving tribute Edwards asks: 'Who else I wonder, would have helped to conceive Louise Brown in the circumstances existing in Oldham in the 1970s?' (*Human Reproduction*, 1989, **4** (Suppl.), 1–9). Edwards willingly engaged in public discussion on ethical issues raised by the move towards *in vitro* fertilization. In an article published in 1971, Edwards and D. J. Sharpe, a lawyer, discuss 'social values and research in human embryology' (*Nature*, 1971, **231**, 87). Reading this article, nearly four decades after its publication, I could not but marvel at its direct relevance to many issues that we confront in areas where scientific advances 'catch unprepared a society that lacks either ready made attitudes or the institutional means of forming new ones'.

In vitro fertilization and 'test-tube babies' are no longer subjects that attract debate. In being reminded by the Nobel award of another time and another age, I cannot but return to the tragic story of the circumstances that surrounded the birth of India's first 'test-tube baby' on 3 October 1978, a few months after the success at Oldham. The procedure used by Subhas Mukherjee (1931–1981) and his collaborators used protocols distinct from those employed by Edwards and Steptoe. Mukherjee's report of his successful use of '*in vitro* fertilized frozen-thawed human embryo' to achieve successful implantation and uneventful pregnancy did not bring him any accolades. Instead, his experiment invited the unwelcome attention of an inquiry committee appointed by the Government of West Bengal. His subsequent harassment by bureaucratic agencies and his transfer to an institute of ophthalmology, a subject far from his area of specialization led to his suicide in July 1981. The story of Subhas Mukherjee has been kept alive in Kolkata by his colleagues and admirers, but it is not a story that is widely known. In 1997, T. C. Anand Kumar, published in this journal, a remarkable account of the 'architect of India's first test-tube baby' (*Current Science*, 1997, **72**, 526). Anand Kumar (1936–2010) who was widely credited with being responsible for the birth of India's first test-tube baby in 1986, took the unusual step of studying Mukherjee's notes and papers to reach the conclusion that this achievement must be recognized, albeit posthumously. Anand Kumar died a few months ago and an obituary notes that 'such generosity and honesty is a rare attribute' (Mehta, R. H., *Current Science*, 2010, **98**, 569). The critical step was 'the successful cryopreservation of an 8-cell embryo, storing it for 53 days, thawing and replacing it into the mother's womb, resulting in a successful and live birth as early as 1978 – a full five years before anyone else had done so'. He published his work 'in an obscure journal' (Mukherjee, Subash, Mukherjee, Sujit and Bhattacharya, S. K., *Indian Journal of Cryogenics*, 1978, **3**, 80). As Anand Kumar notes, quoting a WHO report: 'Embryo cryopreservation has now become a routine adjunct to IVF procedures and various methods of freezing are employed'.

Mukherjee did his work under difficult conditions in an unresponsive and indifferent environment, which turned hostile when he reported success. His work was done when contraception research was strongly supported. 'Family planning' was a popular slogan; 'family welfare' was to be invented after the forced sterilization excesses of the Emergency years (1975–1977). Mukherjee's work was carried out in the backdrop of those difficult years. Ironically, the apparent freedom from an oppressive government that followed the lifting of the Emergency, had little or no effect on the heavy hand of officialdom, that eventually drove Mukherjee to take his own life. This year's Nobel award in medicine is a tribute to resolute experimenters who have achieved difficult goals in the face of great public opposition. The story of *in vitro* fertilization is one of great drama, controversy and sadly, tragedy.

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