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THIRTY YEARS OF IVF

Thirty years of IVF: The legacy of Patrick Steptoe and Robert Edwards

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Abstract
In this article, the author presents a review of the early collaboration between Patrick Steptoe and Robert Edwards, gynecologist and scientist, which ultimately led to the birth of Louise Brown in 1978, the first baby to be born as a result of *in-vitro* fertilisation. Following this momentous event, the author shows how Steptoe and Edwards continued to influence further developments in the treatment of infertile couples, both in the United Kingdom and Worldwide.

Keywords: *In-vitro fertilisation (IVF), IVF treatment*

> 'To understand science it is necessary to know its history'
>
> *Auguste Compte, 1798–1857*

> 'A thorough comprehension of the history of IVF will improve the depth of appreciation of challenges we are facing today, hopefully resulting in improved outcomes of future treatments'.
>
> *Editorial. Human Reproduction, 2005*

> 'This is not the beginning of the end, but only the end of the beginning'
>
> *Patrick C Steptoe, Quote from the Press Conference following the birth of Louise Brown, 25 July 1978*

The very close working relationships between physicians, scientists, nurses, counsellors, administrators and ethicists that exist in Assisted Reproductive Technology (ART) programmes is almost unique in the field of medicine and science. The embodiment of this collaborative effort can be discovered in the close working relationship which existed between the 'founding fathers' of ART – Patrick Steptoe and Robert Edwards. The coming together of Steptoe and Edwards in 1968 and their subsequent work together, assisted by Jean Purdy, their nursing and laboratory colleague, finally culminated in the birth of Louise Brown, the world's first 'Test-tube baby', in July 1978.

In 2008, we celebrated the 30th anniversary of this momentous event and we also marked the 20th anniversary of the death of Patrick Steptoe. In this article, the early history of *in vitro* fertilisation (IVF) is reviewed from the perspective of Patrick Steptoe and Robert Edwards, who together 'created' Louise Brown. An understanding and knowledge of the early history of IVF is important to our understanding of the practice of IVF today. Although others had been involved in the early development of animal, and later human IVF, it was through the determination and dedication of Steptoe and Edwards, together with Jean Purdy, that they achieved the first birth. This was some 2 years before workers in Australia, and later still in the United States, achieved their first births. The story of the Steptoe and Edwards' collaboration, their early years of disappointment and failure, culminating in their eventual success with the birth of Louise Brown is a fascinating story (Edwards & Steptoe, 1980). Their influence on today's practice of assisted reproductive technology (ART), and even on our future practice, is still relevant.

Patrick Christopher Steptoe was born on 9 June 1913, the seventh of a family of 10 children. He came from a musical family, studied music as a child and nearly took it up as a career; however, he chose

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medicine and qualified as a doctor from St George's Hospital, University of London, in 1939. At the outbreak of the Second World War, he joined the Royal Navy Volunteer Reserve as a Surgeon. While serving in the Mediterranean, his ship was sunk and he became a prisoner of war in Italy. It is said that, because of his unique position as a Medical Officer, he was able to help fellow prisoners to escape; however, he was found out and put into solitary confinement. He was released in 1943. On returning to the United Kingdom he specialised in obstetrics and gynecology, with a special interest in infertility, and in 1951 became a Consultant at Oldham General Hospital, in the North of England. There, he had a large National Health Service (NHS) practice and it was there that he pursued and developed his interest in laparoscopy, which he had studied under both Frangenheim and Palmer in Europe. He further developed the technique, and finally published his seminal textbook 'Laparoscopy in Gynecology' in 1967 (Steptoe, 1967). During the early years of laparoscopy in the United Kingdom, this was the 'bible' from which all young gynecologists, including the Author of this article, learned the technique of laparoscopy. It was because of his ability to visualise the female pelvic organs during laparoscopy that he wrote his first major paper – 'Laparoscopy and ovulation', published in The Lancet in 1968 (Steptoe, 1968). He also discovered that it was possible to aspirate oocytes from follicles under direct vision using a laparoscope, the experience of which he later published in 1970 (Steptoe & Edwards, 1970).

Robert ('Bob') Geoffrey Edwards was born in 1925 and educated at Manchester Central High School. After doing his National Service in the Army, serving in Palestine, Syria, Jordan and Iraq, he went to the University of Wales at Bangor in 1948. There, he gained his BSc degree, and then moved on to The Institute of Animal Genetics at Edinburgh University in 1951, where he worked on mouse oocytes and embryos, gaining his PhD in 1955. While he was there he met and later married another young scientist, Ruth Fowler, with whom he published several papers. From Edinburgh he went to California for a year and then, in 1958, moved on to The National Institute of Medical Research, London, where his interests changed from animal to biomedical research. It was during this time that he became interested in human oocyte development and the possibility of achieving *in vitro* fertilisation of human gametes. At the Institute he did some of the very earliest work on *in vitro* maturation of human oocytes from small slices of human ovaries, provided by a gynecologist in London (Edwards, 1965). He also at this time further pursued his interest in embryonic stem cells derived from mammalian embryos, which he further developed during a year spent at Glasgow University (Cole et al., 1965). However, Edwards then moved to The University of Cambridge in 1963 to join two of the 'greats' in animal reproductive physiology; Professors Alan Parkes and 'Bunny' Austin, where he continued to work on immunology and oocyte maturation. In 1965, Edwards spent some time in the Unites States at The Johns Hopkins University, where he collaborated with two other 'greats' in the field of human ART: Drs. Howard and Georgeanna Jones. He again worked on human oocytes (Edwards et al., 1966), and forged a lifetime friendship with the Joneses.

On returning to Cambridge, Edwards continued to have difficulty in finding human oocytes, not only for his research, but also to pursue his research on the treatment of human infertility. At that time he became aware of the work of Patrick Steptoe, who, by use of the laparoscope, was able to view a woman's ovaries and who had developed a technique to aspirate oocytes from ovarian follicles. Edwards therefore contacted Steptoe in 1968 and expressed his interest in working together. They subsequently met at the Royal Society of Medicine in London, where Patrick Steptoe was giving a lecture on laparoscopy, during which he showed the first laparoscopic photographs of ovaries in the female pelvis. This early pioneering work on laparoscopy caused much criticism and even hostility among Steptoe's peers, who branded it as an unsafe procedure which would never 'catch on'! Edwards approached Steptoe at the end of this meeting, introduced himself and suggested that they should collaborate; a suggestion which was readily accepted by Steptoe.

From 1968 until 1978, Steptoe and Edwards' early pioneering work on human *in vitro* fertilisation was done in Dr Kershaw's Cottage Hospital at Royton, near Oldham. They very soon started to produce important papers on early human IVF, including: 'Identification of the mid-piece and tail of the spermatozoon during fertilisation of human eggs *in vitro*' (Bavister et al., 1969), and 'Laparoscopic recovery of pre-ovulatory human oocytes after priming of ovaries with gonadotrophins' (Steptoe & Edwards, 1970). They also carried out the first treatment cycles of oocyte recovery with tubal insemination (ORTI) which was much later developed by others, becoming known as gamete intrafallopian transfer (GIFT). Other important papers included: 'Control of human ovulation, fertilisation and implantation' (Edwards & Steptoe, 1974) and 'Induction of follicular growth, ovulation and luteinisation of the human ovary' (Edwards & Steptoe, 1975). All of these papers and others were produced during a time of intense activity in

Oldham, with Edwards and Jean Purdy travelling hundreds of miles from Cambridge to Oldham on a regular basis.

During these early years there was much controversy and criticism of their work, especially when they started their first human embryo transfers in 1972 (Edwards & Steptoe, 1980). Difficult years followed, in which none of their first 40 patients became pregnant until, in 1976 they did achieve their first IVF pregnancy. There was huge disappointment, however, when it was discovered that this was an ectopic pregnancy (Steptoe & Edwards, 1976). It is of interest to note that this pregnancy was achieved through a single blastocyst transfer! Finally, Mrs Leslie Brown was referred to Steptoe for infertility treatment in 1976 and, after a total of 102 failed embryo transfers, including the one ectopic pregnancy, Leslie Brown became pregnant. This was achieved in a natural cycle IVF with one oocyte collected, fertilised and transferred as an 8-cell embryo. Mrs Brown suffered a difficult pregnancy, but Louise Brown was finally delivered by caesarean section on Tuesday 25 July 1978. Much to the relief of everyone, she was a normal, fit and healthy baby. (Figure 1). This momentous achievement was announced with a simple publication in a letter to The Lancet (Steptoe & Edwards, 1978), but was reported throughout the World with major headlines (Figure 2). The arrival of Louise was heralded as 'The Baby of the Century'. Indeed, the achievement of this birth has been equated in importance with other major World 'firsts' in medicine, such as the discovery of vaccination and penicillin.

Steptoe and Edwards experienced euphoria at that time, but also suffered from criticism from a number of quarters. The Vatican said that this was: 'An event which can have very grave consequences for humanity' and Dr. James Watson, of the DNA helix discovery, is quoted as saying: 'This was dabbling with infanticide'. The Archbishop of Liverpool, and others, said that it was 'morally wrong'. Despite all this criticism, when Steptoe and Edwards presented the results of their work later in 1978 at the Royal College of Obstetricians and Gynecologists in London, they received a standing ovation; something which had never occurred before in the whole history of the College. At the American Fertility Society meeting in 1978, they also received a standing ovation at the end of their presentation.

On 4 January 1979, they achieved the birth of their second baby, Alastair Macdonald, who was the world's first boy conceived by IVF. During the 2 years that followed these momentous events, no institution in the United Kingdom would provide any support or funding for Steptoe and Edwards to continue their clinical or research work. The National Health Service, Universities and the

Figure 1. Patrick Steptoe, Jean Purdy and Robert Edwards at the birth of Louise Brown on 25 July 1978.

Figure 2. International press response to the birth of Louise Brown on 25 July 1978.

Medical Research Council were all unwilling provide any funding to help them to set up a clinic, and so they were forced to do so privately. This they did in Bourn, a village near to Cambridge, in a beautiful old Jacobean manor house called Bourn Hall, where they founded the world's first IVF treatment and research centre – Bourn Hall Clinic.

Elsewhere, meanwhile, work on human *in vitro* fertilisation was progressing and, in Melbourne, Australia, the world's fourth IVF baby, Candice Reed, conceived through the work of the team of Professor Carl Wood and Dr Alan Trounson, was born in June 1980 (Lopata et al., 1980). The first IVF baby to be born in the United States was conceived in Bourn Hall, but the first baby conceived by IVF through the work of the pioneers Doctors Howard and Georgeanna Jones in America, Elizabeth Carr, was born on 28 December 1981 (Jones et al., 1982).

Bourn Hall Clinic opened its doors in September 1980. Steptoe and Edwards and their Team continued their research, achieving a number of key publications including: 'Current status of *in vitro*

fertilisation and implantation of human embryos' (Edwards & Steptoe, 1983), in which they reported the results of their first 1,200 IVF cycles, and noted an increase in clinical pregnancy rates from 16.5% initially, to 30% by 1983. In 1982, the world's first IVF conference was held at Bourn Hall, with many of the early pioneers of human IVF from around the world attending. A total of 30 clinicians and scientists took part in this very relaxed and informal exchange of information on the clinical and scientific aspects human IVF. By 1986, it was estimated that 2,000 babies had been born world wide, 1,000 of these from Bourn Hall, and the team there published their observations on their first 500 births in Human Reproduction in 1986 (Steptoe et al., 1986).

Patrick Steptoe was one of the 'founding fathers' of the British fertility Society in 1974, served as the Society's Chairman from 1974 to 1986, and President from 1986 until his death in 1988. He also served as Chairman of the International Federation of Fertility Societies from 1977 to 1980, and he was elected as the first English Vice-President of the American Fertility Society in 1986.

Patrick Steptoe and Robert Edwards were given a number of awards and honours by the medical and scientific communities (Figures 3 and 4) and were both awarded the honour of CBE in the New Years Honours List of 1988. Of particular pride to Patrick Steptoe was his election to a Fellowship of the Royal Society in 1988, an honour that has been afforded to very few clinicians in the past. It was unfortunate that, at the height of his achievements and fame, Patrick Steptoe fell ill with prostate cancer and finally died on 21 March 1988. Robert Edwards continued to work as Scientific Director at Bourn Hall and as Editor of the newly formed journal 'Human Reproduction', which he co-founded, until 1994, when he left to start up a new journal – 'Reproductive BioMedicine Online'.

During the past 30 years of IVF, there have been a number of major advances in the practice of IVF and the other ARTs. Treatment is now available almost worldwide and many countries have introduced regulation of ART. It is estimated that more than 4 million babies have been born worldwide as a result of the ARTs. The whole process of IVF treatment – cycle monitoring, follicular stimulation, oocyte recovery and embryo transfer – has been greatly simplified, with oocyte recovery now universally carried out using the vaginal ultrasound technique, rather than the laparoscopic approach practiced by Steptoe 30 years ago. This Author well remembers, while being taught laparoscopic oocyte recovery by Steptoe some 25 years ago, his expressing the firm opinion that ultrasound oocyte recovery would never replace the direct vision laparoscopic approach!

Figure 3. Robert Edwards and Patrick Steptoe receive Honorary Degrees at Hull University 1983.

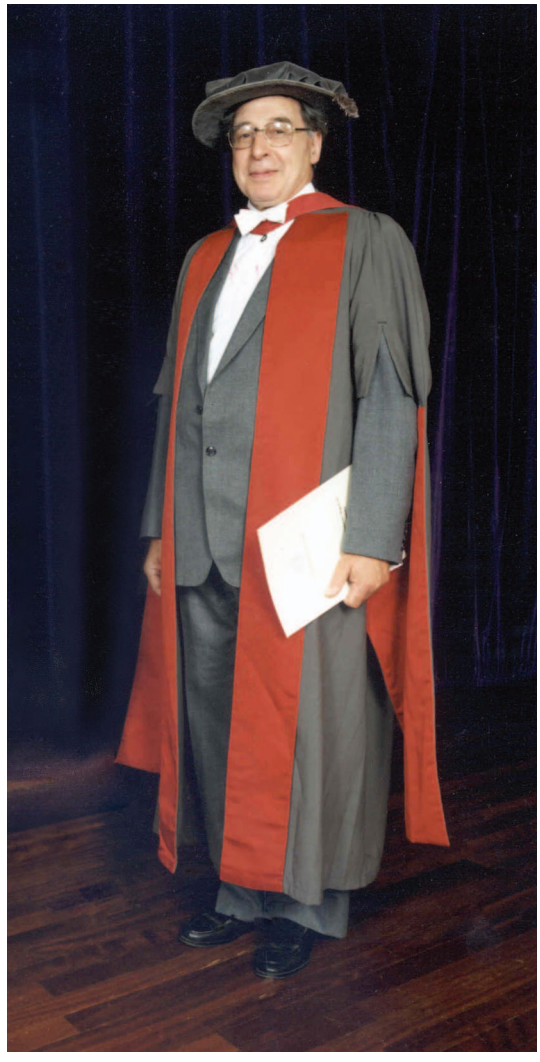

Figure 4. Robert Edwards on the occasion of the conferment of an Honorary Doctorate of the University of York in 1987.

Success rates of IVF/ART have gradually increased, overall by about 1% point per year over the last 30 years, brought about by advances and

improvements in laboratory and clinical practices. Since the early 1980s, we are have been able successfully to cryopreserve surplus IVF embryos; while more recently, oocyte freezing increasingly is being practised.

There have been many changes in superovulation protocols over the years, since the earliest times of natural cycles, which had resulted in the birth of Louise Brown. This was followed by the use of clomiphene with or without urinary gonadotrophins, as pioneered by Drs. Howard and Georgeanna Jones (Jones et al., 1982). The use of gonadotrophin releasing hormone agonists (GnRH-a), originally developed by Professor Ian Craft's team in London to prevent premature luteinising hormone (LH) surges, was introduced in the mid-1980s (Porter et al., 1984). There followed the development of highly purified, and then recombinant, gonadotrophins in the early 1990s, and more recently, use of the GnRH-antagonists are increasingly being used in stimulation cycles.

In the early years of clinical and scientific IVF research, a large number of ethical concerns were identified and addressed. Interestingly, Robert Edwards and David Sharpe wrote about these issues as early as 1971 in a key paper titled: 'Social values and research in human embryology' (Edwards and Sharpe, 1971), in which they emphasised the absolute need for research on human reproduction to be conducted under the strictest ethical guidelines. Bourn Hall Clinic established the world's first Ethics Committee for ART to assist the Clinic Staff to deal with some of the difficult ethical dilemmas that arose in their daily practices.

In 1982, the United Kingdom Government commissioned a working group, which subsequently reported in 1984 (Warnock et al., 1984). In this report, it was recommended that regulatory and licensing procedures be put in place for

- All treatment involving the creation of human embryos outside the body;
- All treatment involving donated gametes;
- All storage of human gametes and embryos;
- All research on human embryos.

After 6 years of Voluntary and later Interim Licensing Authority oversight, an Act of Parliament was passed, known as 'The Human Fertilisation and Embryology Act 1990', which made the United Kingdom the first country to impose strict regulation of the practice of ART.

Over the years, a large number of ethical issues have been addressed, often by radically different approaches in different countries. The ability to select the sex of a child by sperm sorting was one of the early issues that was addressed in the UK and, following appropriate discussion and debate, is allowed for the prevention of inherited sex-linked conditions, but not for social reasons. Other countries do allow sex selection for social reasons as well. Other contentious issues, such as: surrogacy, gamete and embryo donation, embryo research, pre-implantation genetic diagnosis and screening and cloning, have all been dealt with by countries in different ways. It is improbable that international uniformity of opinion, let alone European uniformity, will ever be achieved.

As the age of women starting their families has increased during the last 20 years, so has the age of women seeking help by ART, and the number of women over the age of 40 seeking treatment has risen greatly. Reports of women over the age of 50 having babies following ART and even over 60 have been recorded, for all of whom donor oocytes have been used. Single women are now able to have children using donor sperm and it is common for couples in same sex relationships to be helped to have children as well. Surrogacy has now become an accepted practice in a number of countries and has been successful in helping women with congenital or acquired absence of the uterus, recurrent miscarriage or repeated IVF failure to have their own genetic children with the help of a host surrogate.

Because of the imposition of severely restrictive regulation in some countries and relatively liberal regulation in others, more and more couples are now practising what has been termed 'reproductive tourism'. This is especially the case for women requiring egg donation, surrogacy or sex selection procedures. It is hoped that the introduction of pre-implantation genetic diagnosis (PGD) and aneuploidy screening (AS) will help to prevent the birth of children with severe genetic abnormalities and possibly to improve the chance of older women in particular, to achieve pregnancies, without the increase in the incidence of abnormal children that is expected with women of advanced age.

Accusations are now being made that human reproductive technology is advancing too far and too fast, and that 'designer babies' will become common. Cloning also frequently appears as an issue in the media and success with animal cloning has shown that human cloning will soon be possible. This causes a great deal of concern to most workers in the field and to the general public. It is to be hoped that much more extensive research will be carried out before any attempts are made to clone humans, if good reasons to do so are ever put forward. Many countries have legislated to prevent cloning for reproductive purposes, but some, including the UK, have allowed cloning research to continue for future therapeutic purposes.

The increased incidence of multiple pregnancies following ART has been a major complication and

concern of ART practitioners for many years, with some 50% of all IVF births now being part of multiple births. Twin and high order multiple births are now considered to be a complication of IVF/ART and efforts are being made in many countries to reduce the incidence. There is a strong move to pursuing single embryo transfer in selected patients, and it has been shown that if 70% or more of women have single embryo transfer, the incidence of multiple pregnancies can be reduced to less than 10%.

One of the fundamental questions in ART today is: Why are we (ART practitioners) not better at what we do? The fact remains that 50–70% or more of all couples fail at each attempt at IVF/ART. Research on the factors affecting implantation of embryos is badly needed and methods of studying embryo culture media, the embryos themselves and the endometrium, by examining the genomic, proteomic and metabolomic profiles of these will, hopefully, in the future lead to much higher implantation and success rates.

Finally, the social implications of infertility throughout the world should not be underestimated. The effects on couples both in developed and developing countries are profound. The emotions experienced by infertile women, in particular, can be devastating. If the estimated 15% of couples wishing to conceive are unable to do so, the size of the problem globally becomes massive. The effect of women, mainly in the developed countries, waiting until later and later in their lives to start their families has had profound implications. Increasingly they are being forced to decide between having a family or a career, or struggling to achieve both at the same time. The consequent stresses this social change places on women, their families and society should not be underestimated.

Both Patrick Steptoe and Robert Edwards were very much aware of the personal and social consequences of infertility and were both passionately committed to helping infertile couples by developing the science of IVF to circumvent the problem, in the knowledge that, in most cases, the infertility itself was not curable.

This passion to help the infertile can be found in many of Patrick Steptoe's 'pre-Edwards' papers, and it is exemplified by his sheer dogged determination to pursue his ambitions for infertile couples, in spite of the hostility of the 'establishment' and having to perform his pioneering laparoscopic work within the context of a very busy NHS gynecological and obstetric practise. Following the birth of Louise Brown in 1978, Steptoe was quoted as saying: 'I am not a wizard or a Frankenstein. All I want to do is to help women whose child-producing mechanisms are slightly faulty' (Time Magazine, 1978).

Similarly, when one reviews some of the early papers of 'Bob' Edwards, one can fully appreciate the real passion he felt then, as he does still, to help infertile couples to have children. It is perhaps even more interesting, however, to see how he displayed such an amazing, almost uncanny, ability to forecast the future clinical and scientific directions along which the field of human assisted reproduction would progress. Many of the advances that we take as recent developments in the field of ART, Edwards himself researched and/or predicted. In 1958, he developed the first embryonic stem cells from rabbit embryos (Cole et al., 1965), and forecast the potential therapeutic use of stem cells developed from human embryos. Many other of his forecasts are now in everyday use, for example: in 1965 he was able to mature human oocytes *in vitro*, which could be developed for stem cell research. He also predicted pre-implantation genetic diagnosis of embryos, sex selection, nuclear transfer, human cloning, blastocyst culture and transfer, IVF surrogacy, gamete intrafallopian transfer, the importance of avoiding multiple pregnancies and the cryopreservation of human oocytes and embryos (Edwards, 2009).

Looking to the future, it is likely that improved implantation rates will be achieved and single embryo transfer, probably at the blastocyst stage, will become the norm for the majority of patients. Embryo selection using techniques such as pre-implantation genetic diagnosis and aneuploidy screening will increasingly be used, and factors affecting implantation, determined by genomic and proteomic techniques, increasingly will be employed to improve results of treatment. Cryopreservation of oocytes and ovarian tissue will become common, alongside *in vitro* maturation of primordial and immature oocytes; all of which were forecast by Edwards.

In 2008, the year in which we celebrated the 30th anniversary of the birth of the worlds first 'test tube baby', we should pay tribute to all the early pioneers of IVF world-wide, but, in particular to Patrick Steptoe and Robert Edwards, whose remarkable achievements this paper has, albeit all too briefly, attempted to highlight. We, their scientific and clinical colleagues and friends, acknowledge the truly remarkable contribution that Patrick and Bob have made in their chosen field of IVF/ART, for which we all salute you. What greater testament could there be to a lifetime of dedicated work than to have been responsible in very large measure for the births of an estimated four million children!

'Pygmaeos gigantum homeris impositos, pleusquam ipsos gigantes videri'

(Dwarves on the shoulders of giants see further than the giants themselves).

Quote: Stella Didacus (1524–1578)

'There cannot be the slightest doubt that it was he who had the notion that *in vitro* fertilization in the human was possible in spite of previous failures. Perhaps the greatest lesson was the demonstration of the power of intimate collaboration of basic and clinical science for the betterment of the human condition'.

Quote from: 'In the beginning there was Bob'
Howard W. Jones, Jr
Human Reproduction 1991

'What does it mean to live a good and worthwhile life? One of the simplest ways of thinking about a good life is whether a person leaves the world a better place than they found it. I think in this respect, Patrick led a very good life, helping in his own way to make the world a better place'.

Quote: Prof. Andrew Steptoe
Bourn Hall Founders' Day
July 2008

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