THE EARLY DAYS OF IVF

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Fertilizing mammalian eggs in vitro has a history dating back to the early 20th century. Analyses on rodent embryos in short-term culture opened new prospects of research on human embryos in vitro. This phase of research really opened in the 1930s as Pincus and colleagues, Enzmann and Saunders, initially liberated immature rabbit oocytes from their follicles into culture media and discovered how 12 h was needed for their maturation. They also studied human oocytes and drew similar conclusion on timings. This misled later investigators who inseminated the eggs after 12 h in culture and failed to achieve fertilization. Another input into this investigation began in the 1950s, as Edwards completed his PhD on developmental genetics in mice. His studies on oocyte maturation and fertilization in vitro relied on identifying diakinesis and metaphase-2 as major markers of ongoing oocyte maturation. Mouse and other rodent eggs each required ca. 12 h, but primate and human eggs were found to need much longer.

At this time, Edwards also worked with John Paul and Robin Cole in Glasgow and produced the world’s first embryo stem cells, using rabbit embryos from the 2-cell stage to blastocysts. Disaggregated inner mass cells divided endlessly in vitro over 200 or more generations. When blastocysts were cultured intact, trophectoderm forms a thin pavement providing a surface for inner cell mass to differentiate into literally every tissue of the body. Fascinated by the therapeutic prospects of these stem cells, Edwards concentrated on maturing human oocytes in vitro to fertilize them in vitro and obtain human embryos for various purposes. An article on the problem of maturing human oocytes in vitro had already introduced the concept of PGD. Finally, human oocytes were found to require ca. 37 h for full maturation, which implied that insemination should be timed at 35–40 h to achieve fertilization (Edwards, 1965). Applying strict culture conditions based on earlier studies by Whitten, Biggers and Ham, and working largely with his PhD students in Cambridge, human eggs were fertilized in collaboration with Barry Bavister without any obvious need for sperm capacitation in 1969 (Edwards et al., 1969). PGD was finally introduced in rabbits in 1968, working with Richard Gardner who also revealed how single stem cells from mouse inner cell mass injected into recipient blastocysts could colonize all tissues in the resulting chimaeric embryos. Theories on the origin of chromosomal anomalies in mammalian embryos were also formulated at this time.

Data on timing human oocytes in vitro indicated that women would ovulate at 37 h post-HCG. Edwards was now driven by several factors including the discovery of the very high incidence of human infertility, the immense therapeutic prospects of human stem cells, the potential of PGD, and a determination to bring science and medicine and scientific ethics into human conception. Fortuitously reading of Patrick Steptoe’s work on laparoscopy indicated simple access to ovarian follicles to aspirate their oocytes. Initially, the onset of follicle rupture and ovulation in women primed with HMG and HCG was timed at ca. 37 h as forecast, and human oocytes were soon aspirated from their follicles. Ethical opposition to culturing human embryos was intense, and concepts of IVF, PGD and stem cells were rejected desirably; at one stage, Edwards had only three or four supporters in Cambridge. Driven by the clinical imperative, the opposition was rejected as they prepared to culture human embryos in vitro. Astonishingly, all human cleavage stages to blastocysts at day 9 post-fertilization were obtained in the Oldham and District General Hospital, as human embryology in vitro far surpassed results for any other mammalian species. The ethics of human IVF were discussed in Nature in 1971, working with Dave Sharpe, a US lawyer (Edwards and Sharpe, 1971). Edwards canvassed the world’s teratologists about the potential risks of IVF and in vitro culture to children conceived in this manner.

Encouraged by them to continue, and impressed by the lack of anomalies in animal offspring derived from embryos cultured and in many cases operated in vitro, blastocysts were transferred to their infertile mothers treated with HMG and HCG to stimulate several follicles and oocytes to mature. Major endocrine problems emerged, especially a very short luteal phase during stimulated cycles. Overcoming this luteal weakness by the use of the progestagen depot Primiulot ended in total failure at implantation. Only when Ken Bagshawe in London offered to measure HCG in the blood of the Oldham patients around the time of implantation did Edwards and Steptoe discover that several of their patients had short-lived pregnancies, now called biochemical pregnancies,
indicating that transferred embryos had failed to survive in a deficient uterine milieu.

Primolut was abandoned and new approaches to sustaining early pregnancy were designed including clomiphene/HMG, bromocriptine/HMG, oocyte donation, cryopreserving human oocytes and embryos, the first grete intra-Fallopian transfer (GIFT), injecting HCG at midcycle, and finally measuring the LH surge in urine during the natural menstrual cycle. The single maturing oocyte could be aspirated and fertilized in vitro. These efforts resulted in the first IVF child in the world, Louise Brown, born in the UK on July 25, 1978, following the replacement of an 8-cell embryo (Edwards et al., 1980). Space is lacking to cover the subsequent years in Bourn Hall. These years succeeded beyond widest expectations by the conception of 1000 offspring in 8 years, more than one-half of the world’s IVF babies over most of this time. Among new outlooks, male infertility, detailed endocrine analyses, the first paper using molecular Y probes to sex human spermatozoa and embryos, detailed analyses on the incidence of implantation, abortion, births and the normality of IVF children, the ethics of human IVF, and the first international meetings on IVF were all reported from Bourn Hall over this period. Jean Purdy and Patrick Steptoe each died at this critical moment in IVF history.

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. Surprisingly, detailed accounts of early attempts of IVF throughout the world are scarce in the peer reviewed international literature. This has been the incentive for the editor of this journal to invite Dr. Cohen from France to coordinate efforts to bring together pioneers from different continents involved in subsequent IVF development. Taking advantage of the fact that most of these entrepreneurs in clinical science are still active in the field, we believed this to be a unique opportunity to save this information from being lost forever. The aim has been to bring together the stories of three different continents, rather than being complete. The first birth of an IVF child was reported in 1980 in Australia, 1981 in the USA, 1982 in continental Europe. In many other countries around the world (but especially in Europe), first IVF children were subsequently born in 1982 and 1983. The resulting article published in this volume reads like a fascinating novel, and you can still feel the enormous spirit and enthusiasm of these early days. Everyone involved felt that this was potentially something ‘big’ which could change the face of infertility.

Many of the continuing improvements in clinical IVF were initiated in the early 1980s. Illustrative examples include, the development of ovarian stimulation regimens using different compounds during the follicular, midcycle and luteal phase (for historical review see Fauser and Macklon, 2004), the improvement of embryo culture conditions, the development of transvaginal ultrasound (allowing for ovarian response monitoring, the retrieval of oocytes without general anaesthesia and currently also the transfer of embryos into the uterine cavity), the cryopreservation of surplus embryos resulting in additional pregnancy chances, transport IVF (where the IVF laboratory is located at a distance from the clinic), oocyte or embryo donation and improved embryo transfer techniques. In the early 1990s, the important development of ICSI followed, which was pioneered by Devroey and van Steirteghem in Brussels, Belgium. A comprehensive account of this development, allowing the couples suffering from severely compromised male fertility who could not be helped by conventional IVF to conceive, has recently been published in this journal (Devroey and van Steirteghem, 2004). Another breakthrough reported in 1990 was the diagnosis of specific disease mutations in preimplantation embryos after DNA amplification (Handyside et al., 1990).

Despite much initial resistance by the medical community and by society, IVF has now firmly established its place in the clinical management of infertility. Indications for undergoing IVF have expanded from occlusion of the Fallopian tubes, to mild male factor, to unexplained subfertility to severe male factor for ICSI. Many western societies now report that between 1 and 3% of all children born are from IVF (Fauser et al., 2005). No one can contradict the statement that IVF now represents the key treatment of infertility, resulting in a significant contribution to offspring in the Western world. However, we cannot close our eyes for the downside of current IVF practice, chiefly, the high multiple pregnancy rate, cost and complexity of treatment and, therefore, the underexposure to IVF treatment in the nonwestern world.

Dr. Cohen is to be congratulated for bringing together such a group of distinguished colleagues and for producing this fascinating review. We are convinced that the reader will find much valuable information and food for thought.

References