First in vitro fertilization baby—this is how it happened

Simon Fishel, Ph.D., F.R.S.B.

CARE Fertility Group, London, United Kingdom

On July 25, 1978, the first human was born following extracorporeal fertilization, an event that opened up a new medical science: expanding our knowledge of and developing novel treatments for infertility, radically changing the opportunities for families with inherited monogenic disorders, generating the new discipline of clinical embryology, and paving the way for studies into stem cell biology. In vitro fertilization (IVF), as it became known in its simplest form, went even further: it engaged the myriad of minds in human society. Not only were books written on the moral status of the human embryo, the ethics of IVF practice, and exercising governments on appropriate—which turned out to be disparate—regulation, it redefined family life! The prediction I made in 1985 that one day we may see five "parents" for one child became a reality quicker than we could have imagined at the time. The new medical science marched inexorably on in almost all countries of the world—a universal human plight at last had an opportunity for remedy: more than 10 million couples seeking a resolution to their infertility became parents, men who had no option to have their own genetic child became genetic fathers, and ever-increasing monogenic conditions were not being passed on to the next generation. The future may well bring to bear the opportunity for in vitro–developed viable gametes to generate successful pregnancies, and other "futuristic" opportunities for IVF science. But its story began over a century ago with seeking an understanding on how an egg matures and how to achieve successful fertilization—a fundamental scientific inquiry. It took one man to go beyond that scientific endeavor, to take head on a society unprepared and unwilling to accept human fertilization in vitro and unempathetic to the plight of the infertile; one man to see what prospects lay ahead for humanity should IVF become a reality, and for that man to battle every step of the way for nearly 2 decades to achieve that dream. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)

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EX OVO OMNIA

Pincus and Enzmann in 1935 (1), were, as far as I am aware, original in asking whether the first oocyte maturation division is an essential prelude to fertilization; although 30 years earlier Heape (2) observed the presence of polar bodies 9 hours after copulation in rabbits (rabbits only ovulate after copulation). Heape was, according to Pincus and Enzmann, only "partially correct"! Pincus and Enzmann assessed oocyte maturation in the rabbit in detail and accurately concluded on the process of maturation of rabbit oocytes, and especially that the oocyte contained a nucleus before copulation and that 2 hours later the initiation of diakinesis occurred, at another 2 hours the polar spindle is formed with dissolution of the nuclear membrane, and by 8 hours after copulation the first polar body was formed. It was another hour for the second spindle to be formed, and ovulation occurred between 9.5 and 10.5 hours after copulation; but this remained intact with only the single polar body until fertilization took place. These catalogued events of over 80 years ago will resonate with mammalian embryologists today. Although their report was entitled "mammalian," it was by far from certain that the timing was representative of all mammalian species. However, this important paper was not only the first to assess accurately the process of oocyte maturation in a mammal; the authors also correctly concluded that removal of the oocyte from its mature follicle can bring about maturation to the state where such oocytes can be normally fertilized. What they inaccurately assessed was that the period for human oocyte maturation was 12 hours.

Little interest was shown in human oocytes until 1944 and 1948 with the publications of Rock and Menkin (3, 4) and in 1955 with Shettles (5) ostensibly recording fertilization and the subsequent development of human embryos, although Edwards always maintained this work was "almost certainly erroneous" due to no clear evidence of oocyte maturation and the events associated with what we understand about fertilization and early cleavage. Without a record of such events Edwards stated that there was always the risk it was parthenogenetic activation and cleavage. (Although this criticism is tenuous too, because today

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Reprint requests: Simon Fishel, Ph.D., F.R.S.B., CARE Fertility Group, Park Lorne, 111 Park Road, London NW8 7JL, United Kingdom (E-mail: simon.fishel@carefertility.com).

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we know that only metaphase-2 oocytes will readily become parthenogenetically activated or fertilize with subsequent cleavage. Indeed, successful fertilization may occur over a wide timeframe. Trounson et al. [6] believed that a delay of 5–6.5 hours before insemination was required for maximizing the incidence of fertilization and pregnancy, which we now know is erroneous—successful fertilization may occur immediately after ovulation or much later without compromising results [7].) It remained for another 10 years following the Shettles paper for the inquiry of Edwards finally to elucidate and document precisely the detailed events of human oocyte maturation following release from the follicle: germinal vesicle breakdown up to 24 hours; diakinesis duration, 25–28 hours; metaphase-1, 36–43 hours; and metaphase-2 and polar body release, 36–43 hours (8). That the elucidation of oocyte maturation of human eggs took so long portrays in part the beginnings of the enormous hurdles Edwards had to overcome finally to achieve his dream.

THE SPIRIT OF DISCOVERY

Robert (Bob) Geoffrey Edwards, born in 1925 in Yorkshire, initially studied agriculture at the University of Bangor, North Wales, from 1948 to 1951 but, disenchanted, eventually switched to zoology. He then pursued a genetics course at Edinburgh University in Professor Waddington's department. Edwards left Edinburgh for a year at the California Institute of Technology having now an interest in immunology and attracted by the views of Professor Albert Tyler, who likened the "interaction between sperm and oocytes to the reaction between antigen and antibody." He returned to England in 1958 on a 5-year contract to work with Professor Alan Parkes intending to work on immunology and contraception at the National Institute for Medical Research at Mill Hill, where he also met the eminent Australian veterinary scientist and reproductive physiologist Colin "Bunny" Austin, who was a specialist on mammalian fertilization, and codiscovered "capacitation" in 1951. At this time Edwards oscillated between work on immunology of reproduction and a growing interest in embryology, particularly new work being published on human chromosomes and the recent evidence that the common compliment for humans was 46. It was in 1960 that Bob Edwards began his passion and quest for understanding the ripening of human oocytes, their fertilization, and the prospect of replacing an embryo into the woman. He first had to step back to mice to repeat the published work of others to map oocyte maturation in vitro. Previously, as mentioned above, Pincus had worked with human oocytes recovered from extracted ovaries. What was astonishing was that Pincus being first to elucidate this in rabbit and (although with flawed timing) man; nothing further had been published in the intervening 25 years!

During Edwards 5-year tenure at Mill Hill he spent time trying to persuade gynecologists to provide him with human ovarian tissue. It was Dr. Molly Rose working at the Edgware General Hospital that became his first significant collaborator in this. But all that happened in these early studies was that Edwards could not repeat Pincus's work on human oocytes. This gave Bob cause to pause and time for thought. While at the institute he obtained rhesus monkey ovarian tissue to see whether Pincus had just got the timing wrong—on the premise that primate oocyte maturation had a very different program to the one reported for rabbit. His first and apparently only attempt with a few rhesus oocytes demonstrated no germinal vesicle breakdown by 15 hours, but potentially it was happening at 18 hours—this he observed on the one remaining oocyte he studied! Molly Rose obtained some more human ovarian tissue for Bob, and from the few observations on the rhesus oocytes he decided to leave these new human oocytes much longer. The first evidence of the timing of human oocyte maturation occurred at that time—but regrettably with no record of the discovery (and that's another story!).

In 1963 Edwards moved to the Physiology Laboratory, Cambridge, rejoining Alan Parkes who in 1961 was the newly appointed Marshall professor. Bob had to make new contacts with gynecologists at the Cambridge Addenbrookes hospital to continue his work on human oocytes, but the tissue was slow in coming, and he reverted to working more on bovine, sheep, and occasionally monkey (which Bob included in his paper in *Nature* on October 23, 1965 [9]). Eventually, in 1965 Edwards had three ripening human oocytes and used his sperm in an attempt to fertilize them. At the time the conventional wisdom was that sperm need to "capacitate" in the reproductive tract before fertilization could take place. Edwards never achieved fertilization, only "one spermatozoon passed through the outer membrane of an oocyte." Perhaps conventional wisdom was right? (eventually, we knew it wasn't!).

Needing more inspiration Bob (at the advice of his wife Ruth) contacted Vicktor McKusick, a geneticist working on inherited disorders at Johns Hopkins, who suggested that Edwards takes a few weeks to work with the husband and wife gynecologist team Professors Georgeanna and Howard Jones at the Johns Hopkins hospital. Edwards secured a grant from the Ford Foundation and in July 1965 headed to the United States for 6 weeks. Obtaining ovarian tissue from the Joneses, Bob had enough human oocytes to confirm that maturation was 36 hours. However, fertilization of the oocytes still eluded Bob, even after collecting sperm from the cervix of several of Howard Jones' patients after sexual intercourse.

Although the data from that trip, eventually published in the *Lancet* in 1965 (8), seem indispensable to those of us in reproductive biology, the *Lancet*'s response to Edwards was that they "could not see the point of the work"!

IN SEARCH OF HUMAN FERTILIZATION IN VITRO

A further 2 years on, toward the end of 1967, and as yet unable to achieve fertilization of matured eggs, Edwards learned of laparoscopy and how this may make it easier to get the material he needed. He contacted Patrick Steptoe, who during the early 1960s was pioneering laparoscopy in the United Kingdom, having learned from the father of gynecological laparoscopy, the Parisian Raoul Palmer. During that time John Webster had joined Steptoe, in 1963—a pivotal appointment for what lay ahead! The progress of Palmer's work was made possible by the development of instrumentation by Hans Frangenheim of Koln, particularly an improved