

# [Robert Geoffrey Edwards's Study of Fertilization of Human Oocytes Matured in vitro, 1965 to 1969](#) <sup>[1]</sup>

By: Jiang, Lijing Keywords: [Fertilization](#) <sup>[2]</sup> [Oocytes](#) <sup>[3]</sup>

Robert Geoffrey Edwards, a British developmental biologist at University of Cambridge, began exploring human [in vitro](#) <sup>[4]</sup> [fertilization](#) <sup>[5]</sup> (IVF) as a way to treat [infertility](#) <sup>[6]</sup> in 1960. After successfully overcoming the problem of making mammalian oocytes mature [in vitro](#) <sup>[4]</sup> in 1965, Edwards began to experiment with fertilizing matured eggs [in vitro](#) <sup>[4]</sup>. Collaborating with other researchers, Edwards eventually fertilized a human [egg](#) <sup>[7]</sup> [in vitro](#) <sup>[4]</sup> in 1969. This was a huge step towards establishing human IVF as a [viable](#) <sup>[8]</sup> fertility treatment. During the four years in which Edwards experimented with IVF, he experienced many setbacks. These failures in fertilizing oocytes [in vitro](#) <sup>[4]</sup>, however, contributed to the understanding of how [fertilization](#) <sup>[5]</sup> did or did not happen, which was sometimes different from established dogmas. Edwards also collaborated with gynecologist and surgeon Patrick Christopher Steptoe to study [sperm capacitation](#) <sup>[9]</sup>, which became the overture that heralded a series of successes for the team, culminating in the generation of the first [test-tube baby](#) <sup>[10]</sup> [Louise Joy Brown](#) <sup>[11]</sup> in 1978.

Fertilization in mammals requires both the maturation of oocytes and the capacitation of [spermatozoa](#) <sup>[12]</sup>, a biochemical process that removes the head membranes of [spermatozoa](#) <sup>[12]</sup>, allowing for greater affinity to the ova. In 1965, after succeeded in completing [in vitro](#) <sup>[4]</sup> human [oocyte](#) <sup>[13]</sup> maturation, Edwards designed strategies to capacitate [spermatozoa](#) <sup>[12]</sup>, hoping to allow them to penetrate and fertilize eggs in the laboratory. During a six-week research trip to [Johns Hopkins Hospital](#) <sup>[14]</sup>, in Baltimore, Maryland, in the summer of 1965, Edwards took advantage of the opportunity to experiment on human eggs isolated from pieces of ovaries left after gynecological operations. Through this research, Edwards confirmed that human oocytes spontaneously matured in cultures 37 hours after their removal from ovaries, and he attempted to fertilize these mature eggs by adding treated [spermatozoa](#) <sup>[12]</sup>.

In the 1960s, knowledge about [sperm capacitation](#) <sup>[9]</sup> was limited. It was believed that the only way to capacitate human [sperm](#) <sup>[15]</sup> was to expose it to the chemical and physical environment of the female reproductive tract. In opposition to this, Edwards designed diverse methods to try and induce capacitation outside of the human body. He first removed the seminal plasma that was believed to inhibit capacitation by washing the [spermatozoa](#) <sup>[12]</sup> with cell [culture medium](#) <sup>[16]</sup>, and then incubated them with different chemical and physiological treatments. This did not result in capacitation. In another experiment, Edwards artificially inseminated a [rabbit](#) <sup>[17]</sup> with human [spermatozoa](#) <sup>[12]</sup>, hoping that the [sperm](#) <sup>[15]</sup> would be capacitated in the [rabbit](#) <sup>[17]</sup> female reproductive tracts, only to find that no [sperm](#) <sup>[15]</sup> could be recovered from the [rabbit](#) <sup>[17]</sup> [uterus](#) <sup>[18]</sup> 90 minutes later. After that, Edwards altered this method, incubating human [spermatozoa](#) <sup>[12]</sup> in surgically removed [rabbit](#) <sup>[17]</sup> uteri placed in [culture medium](#) <sup>[16]</sup>. After a one-hour incubation, he flushed the [uterus](#) <sup>[18]</sup> and added the recovered [spermatozoa](#) <sup>[12]</sup> to fourteen cultured human oocytes. Although he found three oocytes with two nuclei, a sign indicating possible [fertilization](#) <sup>[5]</sup>, the nuclei soon faded, showing that these eggs were aberrant and degenerating.

Edwards also tried to capacitate [sperm](#) <sup>[15]</sup> in other experiments at Johns Hopkins. He incubated [spermatozoa](#) <sup>[12]</sup> and oocytes with human cervical mucus, pieces of human endosalpinx (the mucus membrane that lines the fallopian tube), and even moved the sperms and eggs together into the [fallopian tubes](#) <sup>[19]</sup> of rabbits or monkeys, hoping that the [spermatozoa](#) <sup>[12]</sup> would be capacitated. None of these efforts produced desired results. Most of the incubated oocytes were unfertilized; others demonstrated signs that eluded clear interpretation.

In fall of 1965, Edwards returned to Cambridge, where he no longer had access to plentiful human [ovum](#) <sup>[20]</sup> material. During the following year, Edwards put most of his effort into studying sex chromosomes and [Down syndrome](#) <sup>[21]</sup>. A new opportunity to experiment with human eggs arose in 1966, when Edwards was invited to serve as a visiting professor at the [University of North Carolina](#) <sup>[22]</sup> at Chapel Hill and carry out his human IVF project. Edwards accepted the invitation and planned a new way to expose [spermatozoa](#) <sup>[12]</sup> to uterine secretions. Edwards constructed a chamber that was made of cellulose ester membranes that could be placed in a woman's [uterus](#) <sup>[18]</sup>. The pores in the membranes maintained a certain size that prevented leakage of [spermatozoa](#) <sup>[12]</sup>, but allowed for the flow of the female's secretions. Doctors inserted such chambers holding a husband's [sperm](#) <sup>[15]</sup> into volunteers' uteri and let the chambers remain there for 24 hours. The subsequent [in vitro](#) <sup>[4]</sup> [fertilization](#) <sup>[5]</sup> tests nevertheless showed that this approach also failed. Edwards later estimated that inflammatory reactions triggered by the inserted chambers might have interfered with the physiological condition of the [uterus](#) <sup>[18]</sup>, making the [spermatozoa](#) <sup>[12]</sup> less [viable](#) <sup>[8]</sup>. Although Edwards was disappointed by the results, he was relieved that the chamber he designed held the [spermatozoa](#) <sup>[12]</sup> well in the [uterus](#) <sup>[18]</sup>, since he had worried about the integrity of the chamber.

Edwards felt that he was at a scientific impasse. The only way of exposing [spermatozoa](#) <sup>[12]</sup> to the female reproductive tract that he had not yet tried was placing the human [spermatozoa](#) <sup>[12]</sup> in the [fallopian tubes](#) <sup>[19]</sup> and then retrieving them. However, he

could not imagine a way that he could recover [spermatozoa](#)<sup>[12]</sup> from [fallopian tubes](#)<sup>[19]</sup> without causing trauma. In 1967, Edwards happened upon an article describing the new uses of a medical instrument called a laparoscope, which could be used to examine organs and tissues in the abdomen. Biopsies with a laparoscope meant only minor incisions and no long-term hospitalization. The article ignited Edwards's imagination. He reasoned that the laparoscopy technique might help retrieve [spermatozoa](#)<sup>[12]</sup> from [fallopian tubes](#)<sup>[19]</sup> with little pain or harm. He soon phoned the article's author, [Patrick Steptoe](#)<sup>[23]</sup>, a gynecologist working at the Oldham General Hospital, in Oldham, England.

Although Steptoe expressed an interest in using laparoscopy to help Edwards' project, their collaboration did not start until one year later, when they met at a British Fertility Society meeting in London. They soon set up a research laboratory in Oldham so that Edwards could drive to Steptoe's hospital to conduct his research as soon as human ova and retrieved [spermatozoa](#)<sup>[12]</sup> became available. At Oldham, Steptoe encouraged volunteers to have intercourse with their husbands before the scheduled laparoscopy of their [fallopian tubes](#)<sup>[19]</sup>. When the operations were scheduled, Edwards was notified and Steptoe later delivered any recovered [spermatozoa](#)<sup>[12]</sup> from the patients' [fallopian tubes](#)<sup>[19]</sup> to Edwards.

While Edwards and Steptoe were trying hard to fertilize human oocytes *in vitro*<sup>[4]</sup> with [spermatozoa](#)<sup>[12]</sup> retrieved from [fallopian tubes](#)<sup>[19]</sup>, Edwards's PhD student, Barry D. Bavister developed a [culture medium](#)<sup>[16]</sup> that allowed him to accomplish *in vitro*<sup>[4]</sup> [fertilization](#)<sup>[5]</sup> of hamster eggs. Bavister's medium had extra bicarbonate added compared to conventional cell culture media, so that it could enhance the respiration and motility of [spermatozoa](#)<sup>[12]</sup>. Impressed by Bavister's results, Edwards tried the medium with his human *in vitro*<sup>[4]</sup> [fertilization](#)<sup>[5]</sup> studies. Using Bavister's medium, Edwards cultured ova obtained from twelve women for about 40 hours, letting the ova mature *in vitro*<sup>[4]</sup>. Then Edwards inseminated the culture with washed [spermatozoa](#)<sup>[12]</sup>. Thirteen hours after insemination, Edwards found that of the 34 human eggs that matured *in vitro*<sup>[4]</sup>, 18 displayed significant signs of [fertilization](#)<sup>[5]</sup>. Fertilization was noted by [spermatozoa](#)<sup>[12]</sup> found in the [zona pellucida](#)<sup>[24]</sup> or in the perivitelline space, or by demonstrating the existence of pronuclei under the [microscope](#)<sup>[25]</sup>. Edwards, Bavister, and Steptoe published this important work in *Nature* on 15 February 1969.

The 1969 *Nature* paper titled "Early Stages of Fertilization *in vitro*<sup>[4]</sup> of Human Oocytes Matured *in vitro*<sup>[4]</sup>," soon received both positive and negative criticism. While most scientists marveled at the experiment that showed, for the first time, that human eggs could be fertilized *in vitro*<sup>[4]</sup>, the Archbishop of Liverpool, George Beck, denounced the research as morally wrong. Newspapers such as *The Times* also published articles voicing worries about the implications of the human IVF research, suggesting that a "test tube time-bomb" might explode into new forms of [eugenics](#)<sup>[26]</sup>, human [cloning](#)<sup>[27]</sup>, and many other social and ethical catastrophes.

Edwards and Steptoe tried to reply to their critics, but their major focus was on yet another scientific and medical problem that emerged from their success. Although oocytes matured *in vitro*<sup>[4]</sup> could be fertilized, it seemed that the resulting embryos had a tendency to behave abnormally and die during early cleavage. For IVF to be clinically useful, Edwards and Steptoe found it necessary to retrieve mature eggs from women directly, without letting the ova go through maturation *in vitro*<sup>[4]</sup>. As Edwards and Steptoe started to devise the best way to retrieve mature eggs from [humans](#)<sup>[28]</sup> and fertilize them subsequently *in vitro*<sup>[4]</sup>, they began moving from their research phase (in which they often use medical waste for experiments) to testing their strategies in clinical settings with real patients suffering from [infertility](#)<sup>[6]</sup>.

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Robert Geoffrey Edwards, a British developmental biologist at University of Cambridge, began exploring human in vitro fertilization (IVF) as a way to treat infertility in 1960. After successfully overcoming the problem of making mammalian oocytes

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## Subject

[Edwards, R. G. \(Robert Geoffrey\), 1925-](#)<sup>[30]</sup> [Fertilization in Vitro](#)<sup>[31]</sup>

## Topic

[Experiments](#)<sup>[32]</sup> [Reproduction](#)<sup>[33]</sup>

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