Robert Geoffrey Edwards's Study of in vitro Mammalian Oocyte Maturation, 1960 to 1965 [1]

By: Jiang, Lijing Keywords: human oocyte maturation [2]

In a series of experiments between 1960 and 1965, Robert Geoffrey Edwards discovered how to make mammalian egg [4] cells, or oocytes, mature outside of a female's body. Edwards, working at several research institutions in the UK during this period, studied *in vitro* [3] fertilization [5] (IVF) methods. He measured the conditions and timings for *in vitro* [3] (out of the body) maturation of oocytes from diverse mammals including mice, rats, hamsters, pigs, cows, sheep [6], and rhesus monkeys, as well as humans [7]. By 1965, he manipulated the maturation of mammalian oocytes *in vitro* [3], and discovered that the maturation process took about the same amount of time as maturation in the body, called *in vivo* [8]. The timing of human oocyte [9] maturation *in vivo* [8], extrapolated from Edwards's *in vitro* [3] study, helped researchers calculate the timing for surgical removal of human eggs for IVF.

In the early 1960s, Edwards began to investigate the potential of using reproductive technology [10] for fertility treatment in humans [7]. At that time he studied mouse [11] reproduction at the National Institute for Medical Research in Mill Hill, London. Edwards learned that several of his friends suffered from infertility [12] issues and that a proportion of the human population could not generate offspring because of physiological reproductive problems. In 1951, Min Chueh Chang at the Worcester Foundation of Experimental Biology in Shrewsbury, Massachusetts, fertilized *in vitro* [3] rabbit [13] eggs, the first such process for any mammalian egg [4]. Edwards began to see IVF as a method that could assist people with some fertility problems, and he began to study IVF technology.

As a first step, he designed experiments to study whether mammalian oocytes could mature *in vitro* [3]. Fertilization in mammals requires proper conditions for both the eggs and sperm [14]. In most mammals, the primary oocytes contained in the ovarian follicles are maintained in an early meiotic stage. For fertilization [5] to occur, these primary oocytes have to mature.

In the bodies of most mammals, the maturation process of oocytes can be activated by secretion or injection of luteinizing hormone [15], and sometimes with the aid of follicle-stimulating hormone [16]. Edwards induced maturation of mouse [11] eggs *in vitro* [3] by adding these hormones [17] to the eggs *in vitro* [3]. Mouse oocytes mature *in vivo* [8] after a surge of luteinizing hormone [15] and take about twelve hours to mature. After removing oocytes from mouse [11] ovarian follicles and culturing them in glassware and nutrients, Edwards supplemented the cultures with follicle-stimulating hormone [16], and with human chorionic gonadotrophin [18], a luteinizing hormone [15]. He also set up controls in which no hormones [17] were added.

Edwards' results showed that both the oocytes in cultures supplemented with hormones [17] and the control oocytes spontaneously matured after twelve hours of incubation. Edwards looked at the oocytes under a microscope [19], and he observed signs of oocyte [9] maturation in the nucleuses, finding that the eggs had entered a meiotic stage corresponding to a mature egg [4].

As Edwards began to write about the maturation of mouse [11] oocytes for publication, he encountered papers written by Gregory Goodwin Pincus [20], at Harvard University [21] in Cambridge, Massachusetts, published in the 1930s about *in vitro* [3] maturation of rabbit [13] and human oocytes. Pincus's data showed that both human and rabbit [13] oocytes mature *in vitro* [3] in twelve hours. Based on this result, and on his own data, Edwards speculated that oocytes of all mammals would spontaneously mature *in vitro* [3] in about twelve hours after being liberated from follicles. Edwards soon extended his work to eggs of rabbits, baboons, monkeys, and dogs. With the help of Molly Rose, a gynecologist working at Edgware General Hospital in Middlesex, UK, Edwards acquired pieces of human ovaries and started experimenting with them.

Edwards's source of human eggs was from pieces of ovaries removed from surgeries, and he had to induce maturation of eggs *in vitro* [3] prior to trying to fertilize them. Edwards planned to mimic the *in vivo* [8] maturation environment by adding follicle-stimulating hormone [16] and luteinizing hormone [15] into a sterile dish in which he had placed primary oocytes, hoping to stimulate maturation *in vitro* [3].

From 1960 to 1962, Edwards's attempts to follow Pincus's procedures were of no avail. The experiments on human oocyte [9] *in vitro* [3] maturation did not progress as Edwards said he had expected. Later research showed that parts of Pincus's data were incorrect. Human primary oocytes start to mature after twenty-five hours of culturing, not twelve hours. The hypothetical 12-hour rule of *in vitro* [3] oocyte [9] maturation that Edwards had formulated thus limited the length of time he initially considered as reasonable to leave the eggs in cultures, which was twenty-four hours. Furthermore, human ovary [22] samples were so scarce that Edwards could only procure eight to ten human oocytes per year, a rate that reduced his chances for identifying the correct timing of maturation.

In early 1963 Edwards kept two human eggs in cultures for more than twenty-four hours. For the first time, he observed the germinal vesicles in human oocytes disappear, indicating that human oocytes start to mature at twenty-five hours after adding the luteinizing hormone [15]. Human oocytes take about thirty-seven hours total to mature *in vitro* [3] to a state ready for fertilization [5].

Edwards noted other applications that human IVF might bring about besides fertility treatment. For example, scientists had established that individuals with Down syndrome [23] have three sets of chromosome 21. Edwards argued that if researchers observed abnormal development in human oocytes *in vitro* [3], then they could better investigate chromosome disorders such as Down syndrome [23].

In 1962, Edwards went to Glasgow University in Glasgow, Scotland, to study how rabbit [13] embryonic cells turned into more specific kinds of cells. He worked with developmental biologists John Paul and Robin Cole. The group grew cells, such as blood, nerve, and connective tissue cells, from rabbit [13] blastocysts in cultures. Those cells were later called embryonic stem cells [24]. Edwards noted the prospects of grafting [25] similar human cells generated from IVF to treat degenerative diseases. Convinced of the value of IVF work, Edwards moved to University of Cambridge in Cambridge, England, in 1963 and continued his work there.

At Cambridge, Edwards continued to study human oocytes *in vitro* [3]. After studying the timings of oocyte [9] maturation from a variety of mammalian species, Edwards noted that the time needed for oocyte [9] maturation *in vitro* [3] in each species is the same as the time needed for maturation and ovulation [26] *in vivo* [8]. Oocytes mature and ovulate in mammals' bodies after the luteinizing hormone [15] surge, which stimulates ovulation [26]. For mice, it takes oocytes about twelve hours to mature both *in vitro* [3] and *in vivo* [8] after the hormone [16] surge. For sheep [6], oocytes mature in about forty hours. Edwards predicted that human ovulation [26] would occur about thirty-seven hours after the luteinizing hormone [15] surge, the span of time that Edwards observed oocytes matured *in vitro* [3].

Edwards still faced the relative unavailability of human ovaries in Cambridge and experimented with only four oocytes during his first year there. Edwards then wrote to Victor McKusick, a doctor working at the Johns Hopkins Hospital [27] in Baltimore, Maryland, asking for help in providing ovary [22] materials. He noted that physicians at Johns Hopkins conducted Stein-Leventhal operations, in which wedges of ovaries were removed. In his reply letter, McKusick invited Edwards to visit Johns Hopkins to pursue his research as well as to meet other interested gynecologists in Baltimore.

Edwards accepted the invitation and arrived in Baltimore in July 1965. During the six weeks that he stayed at Johns Hopkins, Edwards tested the timings of *in vitro* [3] maturation in forty-eight human oocytes. Forty-six of the oocytes fully matured in thirty-six hours, confirming his Cambridge results. At Johns Hopkins, Edwards also met Howard Jones [28] and Georgeanna Jones, two gynecologists who later become experts in human IVF and contributed to the generation of the first test-tube baby [29] in the US, Elizabeth Carr, delivered in 1981.

Edwards summarized his research of *in vitro* [3] maturation of human oocytes in a paper published in 1965, "Maturation *in vitro* [3] of Human Ovarian Oöcytes." The article provoked controversy over the ethics of IVF, which some viewed as a threat to the natural reproduction. After publishing the 1965 article, Edwards started his next set of experiments aimed to fertilize human eggs matured *in vitro* [3]. This research led him to partner with Patrick Steptoe [30], a gynecologist working at the Oldham District and General Hospital in Oldham, England.

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Subject

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