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Changing the perception of our own nature. On the Nobel Prize in Physiology or Medicine awarded to Robert G. Edwards*

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Resum. Robert edwards és el pare de les tècniques de reproducció assistida. Gràcies a ell, han nascut al món més de quatre milions de criatures que, possiblement, no existirien si no hagués estat pel desenvolupament d'aquestes tècniques. La fecundació in vitro, inicialment una tècnica concebuda per a superar determinades malalties que provoquen esterilitat femenina, va obrir la porta a tot un seguit de noves tecnologies associades que, pel fet de posar al nostre abast els gàmetes i els embrions humans, han permès interaccionar amb aquestes entitats biològiques de la nostra pròpia espècie i modificar conceptes que fins aleshores teníem molt clars i immutables: la maternitat, les relacions paternofilials, el començament de la vida o, fins i tot, la pròpia identitat humana. Amb aquests canvis, o més ben dit darrere seu, han vingut un seguit de modificacions en els valors ètics i els conceptes legals que els acompanyen que han significat una autèntica revolució en la visió que tenim de nosaltres mateixos com a espècie i el lloc que ocupem en l'immens panorama de la natura.

paraules clau: tècniques de reproducció assistida · bioètica · fertilització in vitro

Abstract. Robert Edwards is the father of assisted reproduction techniques. Thanks to him, more than 4 million children have been born who possibly would have not existed had it not been for the development of these techniques. In vitro fertilization, a technique originally designed to overcome certain diseases that cause female sterility, opened the door to a whole series of new, associated technologies that, by putting at our disposal human gametes and embryos, have allowed us to interact with these biological entities of our own species in addition to modifying the concepts that, until that moment, had very clear and constant meanings: maternity, paterno-filial relationships, the beginning of life, and even human identity itself. These changes as well as those that followed resulted in a reassessment of our ethical values and legal concepts, which in turn has caused a genuine revolution in the way we view both ourselves as a species and the place we occupy in the vast panorama of nature.

Key words: assisted reproduction techniques · bioethics · in vitro fertilization

According to Alfred Nobel's will, the Nobel Prize was to be granted to "those who, during the preceding year, shall have conferred the greatest benefit on mankind." It is very unusual that Nobel's laureates receive their award the year after their discovery or invention—the most recent exception being President Obama, winner of the 2009 Peace Prize, who was so surprised by the announcement as to be slightly embarrassed. Indeed, the subject of this talk had to wait for 32 years to see his work acknowledged. In the interval between Edwards' discovery and his Nobel Prize (Fig. 1), Louise Brown, the first baby born after the successful application of in vitro fertilization (IVF), grew up and had a child of her own (Cameron, spontaneously conceived), while Patrick Steptoe, Edward's colleague in IVF development, died in 1988 and thus never received the full acknowledgement he obviously deserved.

Fig. 1. Robert G. Edwards. Photo: Copyright © Bourn Hall

* Based on the lecture given by the author at the Institute for Catalan Studies, Barcelona, on 16 December 2010, and at the Octubre Centre of Contemporary Culture, Valencia, on 19 January 2011 for the Nobel Prize Cycle.

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Why the delay?

But what are the reasons for the long delay between a Nobel-worthy contribution and its award? In my opinion, there are several reasons:

- A general bias in the Nobel Prizes themselves
- Intense opposition to this particular award
- Fear regarding the decision

It is generally accepted that Nobel Prizes tend to favor discoveries over inventions or theories. An example of this assertion is the fact that in 1921 Albert Einstein was awarded the Prize for his discovery of the photoelectric effect, not for his theory of relativity. The development of a new therapy, such as IVF, can be considered more an invention than a discovery; this general bias would lessen its chances of receiving the Nobel Prize allowing new and interesting discoveries to move up the eligibility list.

A furious opposition. The work of Dr. Edwards had, from the very beginning, colossal opponents and detractors. Suffice to say that the same day the Nobel Prizes were publicly communicated, a press release from the Vatican appeared in mass media all over the world. It criticized the awarding of the Nobel Prize to Dr. Edwards, based on the fact that it failed to take into account "the ethical implications of such an award" and it reiterated that IVF "is unacceptable since it implies the selection and the elimination of human embryos". The Vatican's position is clearly stated in the document 'Instruction *Dignitas Personae* on certain Bioethical questions' from the Congregation for the Doctrine of the Faith, which said (*sic*.):

> "With regard to the *treatment of infertility*, new medical techniques must respect three fundamental goods: a) the right to life and to physical integrity of every human being from conception to natural death; b) the unity of marriage, which means reciprocal respect for the right within marriage to become a father or mother only together with the other spouse; c) the specifically human values of sexuality which require 'that the procreation of a human person be brought about as the fruit of the conjugal act specific to the love between spouses.' Techniques which assist procreation are not to be rejected on the grounds that they are artificial. As such, they bear witness to the possibilities of the art of medicine. But they must be given a moral evaluation in reference to the dignity of the human person, who is called to realize his vocation from God to the gift of love and the gift of life."
> [http://www.vatican.va/roman_curia/congregations/cfaith/documents/rc_con_cfaith_doc_20081208_dignitas-personae_en.html]

This statement is undoubtedly in favor of maintaining the boundary between sexuality and reproduction which, as discussed below, IVF and related techniques have clearly dismantled.

Fear regarding the decision. The ethical and social implications of IVF and related assisted reproductive techniques (ARTs) make them provocative topics. A social revolution was aroused after the development of ARTs because they implied a new perception of the position of our own species in the context of the world. This can be envisaged as a threat but also as an opportunity for the evolution of mankind; and it is discussed later in this article as something positive. However, recognition of the controversy that the decision would likely arouse no doubt led to an unusual delay in the Nobel Prize being granted to Edwards (and Steptoe).

Reasons for an acknowledgement

In my opinion, and surely that of the Nobel Prize Award Committee, there were many important reasons for recognizing Dr. Edwards' contribution to medicine in general and to the treatment of infertility in particular:

- Traditional interest in reproduction
- The associated improvements in our understanding of reproduction
- As the basis for many other related technologies
- For its efficiency
- In setting the stage for a social revolution

Traditional interest in reproduction. Human reproduction has been a topic of fascination throughout our history. At the beginning of human civilization, this fascination became a religious matter, with fertility and related agrarian cults offering us some of the oldest human representations ever found. Images such as Willendorf's Venus (dated between 24,000 and 21,000 BC) and the Paleolithic Levantine paintings at Cogul's Cave (between 10,000 and 6500 BC) are examples of art in which male and female sexual characters are explicitly depicted and even exaggerated. Later, already in historic eras, fertility cults, such as those of the Min, Heqet, and Taweret in ancient Egypt, and Priapus and Cybele in ancient Greece and Rome, were related to agrarian and resurrection cults. During the Renaissance, this curiosity becomes more 'scientific,' as evidenced by Leonardo da Vinci's interest in the anatomy of a fetus inside the womb or the anatomy of sexual intercourse. Attention then moves to more cellular aspects, with published depictions of a spermatozoon under the microscope, the so called *homunculus* [12], or the ovum as the origin of everything (*Ex ovo omnia*) [13].

Associated improvements in our understanding of reproduction. Sir Isaac Newton famously remarked, "If I have seen further, it is by standing on the shoulders of giants." No new discovery or technology appears from nowhere; rather, previous to any advance in human knowledge there are other works and fundamental steps that pave the way for the new discovery. This was the case for the 2010 Nobel Prize in Physiology or Medicine. A quick review of these steps is as follows.

1890 First 'surrogate mother.' Walter Heape reports the transfer of rabbit embryos to a hare's uterus, resulting in two pups.

1932 Aldous Huxley imagines IVF in his novel *Brave New World*.

1946 William J. Hamilton and John A. Laing describe the development of cow eggs until the blastocyst stage [10].

1951 Collin R. Austin identifies the need for sperm capacitation in mammals before fertilization [1].

1952 Robert G. Edwards starts his PhD.

1953 James D. Watson and Francis H.C. Crick determine the structure of DNA [23].

1955 Robert G. Edwards defends his PhD: 'Growth of mouse embryos with altered chromosome complements," directed by Alan Beatty.

1959 Min Chueh Chang reports the first rabbits to be conceived by IVF; however, sperm capacitation took place in vivo [4].

1963 Ryuzo Yanagimachi and Min Chueh Chang report successful IVF in hamsters, with every step of the process performed in vitro [25].

1970 Robert G. Edwards and co-workers perform the first human IVF using oocytes matured in Vivo [7].

1971 They obtain good quality human embryos in all pre-implantation stages. Later, Robert G. Edwards will remember:

"I'll never forget the day I looked down the microscope and what I saw was a human blastocyst gazing up at me. I thought: We've done it!"

1972 Edwards and co-workers begin embryo transfers at Newmarket Hospital. The Medical Research Council denies them financial support:

"The Board accepted that Dr. Edwards was an investigator of high scientific standing, energy and originality. Board members and referees, however, all had serious doubts about the ethical aspects of the proposed investigations, especially those relating to the implantation in women of oocytes fertilized in vitro, which was considered premature in view of the lack of preliminary studies on primates and the present deficiency of detailed knowledge of the possible hazards involved. Reservations were also expressed about the procedure of laparoscopy for purely experimental purposes, and about the proposed facilities and arrangements for patient care. Recommendations:

(i) The application should be declined on ethical grounds and the reason should be conveyed to Dr. Edwards and Mr. Steptoe.

(ii) It should be suggested, without commitment, to Dr. Edwards that he might formulate an application to the Council for support of a similar programme of work on primates."

Robert Edwards remembers:

"Steptoe and I were deeply affected by the desperation felt by couples who so wanted to have children. We had a lot of critics but we fought like hell for our patients. But we had enough supporters—not many—but just enough for us to carry on our work." [2]

1973 An Australian team of Dr. Carl Wood's [6] achieves the first human pregnancy after IVF, but it ends as a spontaneous abortion.

1975 Edwards' team, using gonadotrophins to induce superovulation, successfully induces a pregnancy after transferring blastocysts, but it is ectopic and thus terminated after 10 weeks of gestation.

1977 The researchers decide to move towards natural, unstimulated cycles. On 10 November 1977, they treat a woman with tubal infertility using a single fertilized oocyte that, after transfer at the 8-cell stage, results in the birth of Louise Brown on 25 July 1978 [19] (Fig. 2, 3A).

After this first success, three more pregnancies were obtained; two of them ended as miscarriages, one because a triploid fetus; the second due to a complication of amniocentesis, which revealed a normal 46XY fetus. The third resulted in the birth of Alistair.

1984 Victoria Anna, the first Spanish baby conceived by IVF, was born; the infertility treatment had been performed at the Institut Universitari Dexeus in Barcelona (Fig 3B). This first birth in Spain led to a close and fruitful relationship between Robert Edwards and several Spanish scientists. At that time, Edwards, together with Jean Cohen, was establishing a new scientific society, the European Society of Human Reproduction and Embryology (ESHRE) dedicated to basic knowledge on the biology of reproduction as well as clinical aspects of human infertility and ARTs. They were joined by Dr. Josep Egozcue, from the Autonomous University of Barcelona, and Dr. Pere N. Barri, from the Institut Universitari Dexeus among other scientist from most European countries.

This relationship would last throughout the public career of Dr. Robert Edwards and would allow two of them (Dr. Josep Egozcue and Dr. Anna Veiga) to succeed him


Evening News

Meet Louise, the world's first test-tube arrival

SUPERBABE

Wide-eyed Louise Brown pictured in hospital 18 hours after she was born. Today she's doing well. See Page Three

Fig. 2. An example of the media coverage of the birth of Louise Brown, which made the covers of many newspapers.

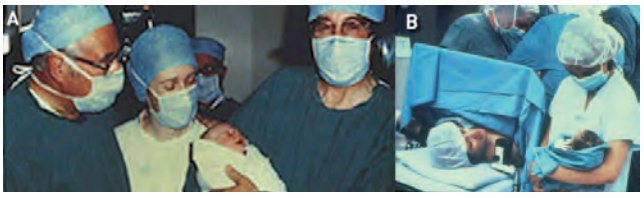

Fig. 3. A) Dr. Robert Edwards holding Louise Brown after her birth. B) Dr. Gloria Calderon holds in her arms Victoria-Anna after her birth.

Fig. 4. Dr. Edwards and Dr. Egozcue (top row, second and sixth from left to right, respectively) among other ESHRE Presidents [2]. (B) Dr. Anna Veiga, Dr. Pere N. Barri and Dr. Edwards at a dinner during the 2007 ESHRE Meeting, held in Lyon.

as Presidents of ESHRE (Fig. 4). The contribution of Robert Edwards to our basic understanding of mammalian reproduction is certainly noteworthy but his contribution to infertility treatments was groundbreaking, since IVF was followed by a long list of closely related ARTs.

"A new field of medicine has emerged, with Robert Edwards leading the process all the way from the fundamental discoveries to the current, successful IVF therapy. His contributions represent a milestone in the development of modern medicine." [9]

As the basis for many other related technologies. In an editorial by the ESHRE, it was pointed out that Robert Edwards' work provided the basis for other ARTs that would initiate a new discipline in the field of Medicine: Reproductive Medicine and even Regenerative Medicine. Let us review their primary focuses.

In vitro fertilization. IVF is based on a very simple principle: to join spermatozoa and oocytes outside a woman's body. To do so, the gametes must first be collected and then appropriately prepared. Collecting oocytes ready to be fertilized is one of the major handicaps of this technique. The procedure starts by suppressing the woman's hormonal pituitary levels and inducing a rise in FSH (follicle stimulating hormone) and LH (luteinizing hormone) by injecting these hormones according to a complex and personalized protocol. This procedure induces superovulation, yielding a higher than normal number of oocytes to be fertilized and, most importantly, controlled ovulation. The oocyte is removed by an echo-guided follicle puncture, which is followed by a short period of in vitro culture to allow the female gamete to reach the adequate degree of maturation. Spermatozoa are obtained by masturbation followed by centrifugation of the semen to remove the seminal plasma, thereby inducing sperm capacitation. Gametes can come from the two members of the couple or from gamete donors, if one or even both members cannot produce them.

Once the male and female gametes are obtained, they are incubated together in an appropriate in vitro environment for several hours until signs of fertilization are observed: two pronuclei and two polar bodies. These embryos are then cultured in vitro for 3 to 5 days after which they are transferred to the uterus, either that of the female member of the couple or that of a surrogate mother. The introduction of donors in the reproductive project has changed our notions regarding parenthood, as is discussed later on in this article.

Gamete and embryo freezing. Although the first pregnancy generated from frozen sperm dates back to 1954 [3], in 1984 the first success in freezing human embryos was described [26] while it was not until 1997 that oocyte freezing became possible [16]. Freezing gametes and embryos requires their maintenance at very low temperatures in liquid nitrogen (–196°C), which prevents all biochemical reactions. Cryoprotectants must be added to the freezing medium in order to avoid ice formation, as this would damage cellular structures. Under these conditions cells can safely be stored almost indefinitely. The ability to freeze gametes and embryos has led to the creation of banks that facilitate both the preservation of fertility, even after the donor's death and donation. The first frozen-thawed embryo successfully resulting in a pregnancy in Spain was in 1986 [21], a noteworthy event since only one cell survived after thawing.

Pre-implantation genetic diagnosis. Pre-implantation genetic diagnosis (PGD) was developed in 1989 by Handyside and coworkers [11] in order to select normal in vitro fertilized embryos before transferring them to the uterus in couples at high risk of having a child with genetic abnormalities. In Spain, PGD was first clinically used in 1993, making it the third case described in the world [22]. PGD requires the removal of a single cell from a 6- to 8-cell embryo and then genetically characterizing it by fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR) DNA amplification. However, the indications for PGD have expanded since its initiation and now include the selection of embryos for analysis based on other criteria, such as avoiding the transmission of a genetic disease to future generations [18], selecting against embryos carrying genes that predispose the future adult to developing some kinds of cancer (breast or colon cancers), selecting healthy embryos that will be compatible donors for siblings affected by genetic diseases (human leukocyte antigen [HLA] matching), or even selecting the embryo of the desired sex for social reasons (social sexing).

Intracytoplasmic sperm injection (ICSI). First reported in 1992 [15], ICSI consists of injecting the sperm into the oocyte's cytoplasm using a micromanipulator. Either ejaculated spermatozoa with low fertilizing capacity (as in oligo-, astheno-, teratozoospermia) or sperm obtained from the epididymis, deferent ducts, or even testis can be used. ICSI also can be performed, although with lower fertilization efficiencies, using round or elongated spermatides [8]. This versatility in the origin of the male

gametic material has made it a powerful technique capable of overcoming a wide variety of infertility problems of male origin.

Regenerative medicine. Regenerative medicine is based on the use of a very special type of cells: stem cells. Their undifferentiated state makes them pluripotent, i.e., they can differentiate into any kind of cells of the organism from which they were derived, in order to regenerate damaged tissues and organs from individuals (regenerative medicine). Stem cells can be obtained from adult cells either directly (adult stem cells) or by inducing their pluripotentiality (induced pluripotent stem cells, iPS) [20]. The use of cells from either source does not cause any ethical concern but some of their biological characteristics make them unsuitable for certain regenerative processes. By contrast, stem cells derived from human embryos (embryonic stem cells, ESC), prepared as described above but not used further, have the capacity to differentiate into any kind of cell and seem to be suitable for regenerative medicine, but their use has raised ethical concerns.

One of the most serious drawbacks faced by regenerative medicine is immunological rejection. To solve this problem, self-transplant has been proposed, implying the use of cells derived from the same adult organism (iPS) or of cloning technologies (somatic cell nuclear transfer, SCNT) to derive genetically identical ESC, in what has been called therapeutic cloning. SCNT technology was developed to produce transgenic animals and resulted in the birth of the first mammalian clone, a sheep called Dolly, in 1996 [24]. It consists of removing the genetic material of a recipient oocyte and replacing it with the nucleus of a donor somatic cell. After that, the reconstructed embryo is activated to initiate embryonic development, leading to either an individual (reproductive cloning) or ESC (therapeutic cloning).

Finally, there is a line of investigation exploring the possibility of obtaining gametes, both male and female, from stem cells. Preliminary results from animal models have been encouraging. If these attempts can be reproduced in humans, they could solve many infertility problems even among individuals who cannot produce gametes.

For its efficiency. The efficiency of the various ARTs are expressed as the pregnancy rate, which varies widely depending on the circumstances of the particular ART application but is typically between 20 and 50%. Comparing these figures with what is considered to be the efficiency of natural conceptions (33%) it is clear that, for those unable to conceive, these techniques can offer the same chance of reproductive success as achieved by fertile individuals. Moreover, it has been estimated that, across the world, these techniques have resulted in the birth of over 4,300,000 babies since 1978. It seems obvious thatn in this sense, Robert Edwards' work can be considered as 'a great benefit to mankind.'

In setting the stage for a social revolution. As mentioned above, the social revolution linked to the development of ARTs poses, in the opinion of some people, a threat whereas others see it as an opportunity. I belong to the latter group since I am convinced that the changes brought about by ARTs have forever altered our vision of ourselves and the place we occupy in the vast panorama of nature.

Dissociation between sex and reproduction. This social revolution is based on the complete dissociation between sex and reproduction. Of course, before the development of ARTs sex without reproduction was certainly possible, but there could be no reproduction without sex. This made maternity and virginity opposing concepts, a situation that conditioned many beliefs and even the history of Christian civilizations.

New paterno-filial relationships. By dissociating sex from reproduction, ARTs has changed our definition of paterno-filial relationships. These changes are concomitant with the appearance of new kinds of maternity, brought about by ARTs. Before 1978, there were only two kinds of 'mothers': legal and biological. After 1978, the biological mother concept was split into gestational mother and genetic mother, since gestation could be carried out by a surrogate mother or by the recipient of a donated oocyte. Moreover, in late 1990s, the use of a technique in which part of the cytoplasm from oocytes obtained from young women was transferred to older women to improve their gestation capacity resulted in the birth of a dozen children [5]. Although this technique is no longer used due to unexpected side effects, it briefly introduced the concept of the 'cytoplasmic' mother, different from the genetic mother, since it provides mitochondrial DNA from the donor to the embryo.

All these 'new maternities' can be exerted by the same person or by different ones. Furthermore, these maternities (or paternities) can be exerted asynchronously, introducing leaps among generations: embryos being gestated by their nieces; embryos without parents but with grandparents, derived from gametes obtained from ESC (which in turn would have been obtained from an embryo that has never produced an individual); embryos descended from siblings, which is essentially how clones must be considered since, from a biological point of view, they are like asynchronous homozygotic twins...

Providing a new step in human life. Before Edwards' work, human life was generally defined as comprising three major phases, fetal life, childhood and adulthood, but ARTs' ability to manipulate the preimplantation embryo provided a possible fourth phase. Therefore new biological, ethical and legal questions arose: What is a human pre-implantation embryo? What moral consideration does it deserve? What rights does it have? As stated by John A. Robertson [17]:

> "Precisely because the early embryo is genetically unique and has the potential to be more, it operates as a powerful symbol or reminder of the unique gift of human existence..."

for that reason

> "While the preimplantation human embryo doesn't have the same moral status as infants and children, it deserves special respect and serious moral consideration as a developing form of human life." [14]

Preimplantation human embryos do not have a moral status but they do have a moral value; thus, there are moral reasons to treat them in some ways and not in others. A situation similar, although not identical, as of how to treat a human corpse, since it also deserves special considerations. According to this line of reasoning, the human embryo is not considered as a person and thus it does not have an absolute value. Its moral value can be pounded by other values, i.e., health, research, and general wellbeing, such that it can and should be used only when morally relevant ends are sought.

This argument has inspired new laws, bylaws, and international treaties among developed countries that seek to reflect these social changes in their legal codes. In Spain, the most important laws are 14/2006, on Human Assisted Reproduction Techniques, and 14/2007, on Biomedical Research. Among the international treaties, one of the most relevant is the Convention on Human Rights and Biomedicine (Oviedo's Convention), enacted by the Council of Europe on 4 April 1997. Based on all these considerations, the title I chose for this article: *Robert Edwards. Changing the perception of our own nature,* I guess is pertinent and has been sufficiently justified.

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