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Reminiscences on learning about morals and ethics in biomedicine

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Abstract Learning about ethics requires a knowledge of moral philosophy. Until recently, scientists paid little attention to moral philosophy or ethics during their training. Many of them, and especially biologists, made their first acquaintance with these classic topics as they began their PhD. Their learning depended on whether their Professor or Supervisor was knowledgeable in these disciplines, even if self-trained. Medical students were obviously more aware of the ethical aspects of their work. As a dedicated scientist, I had undertaken a PhD in developmental genetics of mouse embryos which demanded injecting hormones, operations, autopsies, and examining blastocysts and fetuses for imbalanced chromosomes. Stress laid on ethics and moral philosophy by my professor, Conrad Waddington in Edinburgh University, proved enormously helpful as I moved to human IVF, stem cells and preimplantation genetic diagnosis and maturing oocytes *in vitro*. No-one else was interested, neither in these topics, nor their ethics. This situation changed as I telephoned Patrick Steptoe, inviting him to join us. His brilliant laparoscopy was essential as we worked together on human IVF. We helped establish an Ethical Committee to guide us. Today, IVF scientists and clinicians are deeply aware of their ethical responsibilities to their patients. They face a challenging future as new developments transform their field of study.

KEYWORDS: ethics, history, IVF, moral philosophy, reminiscences

Introduction

It is an honour to come to Istanbul, meet my Turkish and other colleagues and discuss serious moral aspects of reproductive science in this Second Meeting on the Moral Philosophy and Ethics of Assisted Human Reproduction. First, I wish to describe the ethical background as we introduced human IVF, stem cells and preimplantation genetic diagnosis (PGD). Opening studies leading to human fertilization and preimplantation embryology *in vitro* were faced with issues concerning the very basis of human life. They involved such fundamental aspects as fertilization and embryo growth *in vitro*, the early morphology of human embryos and the activation of numerous genes including those causing human diseases. The essentials of fertilization and early development had been clarified in animals long before human IVF was invented. Why did it take so long to move to human fertilization *in vitro*, introduce it into clinical medicine, and debate its ethical implications? Many investigators working in the 19th and 20th centuries dealt with major aspects of the science and medicine of human infertility such as donor insemination, yet they never really faced the underlying scientific facts, and restricted ethics to such well-known clinical issues as donor insemination and abortion. I believe that today other scientists, e.g. molecular biologists, do not pay sufficient attention to the ethics of their own work. Interfering with DNA obviously demands strict ethical inquiry, yet as IVF was introduced in the 1960s, many scientists, including molecular biologists, were very ready to criticise Patrick Steptoe and myself without ever having faced their own ethical issues.

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Brief history of the emergence of moral philosophy and ethics of science and medicine

Medicine has been well to the forefront when debating ethical and moral issues. It differs from science in that it has long been driven by the daily need to treat patients, assess the effects of complex operative techniques and prescribe expensive medicines. Many queries with allied ethical problems can emerge on each day of their practice. Medical ethics has also had to face issues connected with reproduction. Abortion, for example, has long raised immensely complex problems in history. It is an awful task for doctors and surgeons to undertake, and is practised legally in most European countries which have passed Abortion Acts. Artificial insemination using donor spermatozoa has also been a matter of debate among clinicians over several centuries. Debates on its legitimacy were published in clinical journals in the 18th and 19th centuries. It was bitterly opposed in the early 20th century by a committee headed by the Archbishop of Canterbury, UK. Today, it is accepted as a major means of overcoming infertility and a serious ethical aspect of human reproduction. Its significance has grown since oocyte donation is now widespread and can involve patients aged up to 65 years.

Complex ethical issues in medicine are often adjudicated through established standards of care as regulated by organizations such as the General Medical Council in London. The Council has to judge harshly and publicly in some situations, even striking doctors off the medical register. Clinicians are aware from their days in Medical School that they may have to face such situations; this has been the case since the earliest days of medicine, even back to the Grecians and the Romans, and perhaps to the Ancient Egyptians.

Scientists have taken many years to examine their work ethically. Why is this so? One reason concerns the relative insignificance of science during previous centuries, except in relation to studies on astrology and mathematics. The Renaissance was driven by pioneers such as Leonardo da Vinci. Subsequent expansion of science has been due to its rational approach to inquiry by the experimental verification of new hypotheses. Its rational thinking opened Pandora's boxes in several scientific disciplines, and the ethical implications of many discoveries have not been properly assessed by moral philosophers until recently. Yet, over many years, physicists ridiculed moral philosophy as being an insignificant topic which obstructed scientific progress. Perhaps a major stimulus in a particular discipline was needed to alert them to the significance of ethics. Wartime provided many stimuli. These included the development of sophisticated weaponry and more clinical matters such as the safety of anaesthetics in the First World War or the outcome of the atomic bomb in the Second World War.

Inventing nuclear weapons was accompanied by the famous ethical battle between Edward Teller and James Oppenheimer over whether this bomb should be made and dropped on Hiroshima. Other serious aspects of modern science received very little moral attention. James Watson and Francis Crick clarified the structure of DNA, without too much attention to its ethical implications for humanity. Yet Watson attended many scientific and political meetings in the early days of IVF. There, he criticised me for what I was doing, yet I never heard him criticise himself for what he was doing. I recently spoke with him when he invited me to his laboratory at Cold Spring Harbor in New York, in a most beautiful area of the United States. On a return visit to Bourn Hall, near Cambridge, UK, he told me his fears about IVF had been related to the possibility of reproductive cloning. He had also decided to appoint two moral philosophers to his staff, which could well be potentially a new ethical breakthrough into the ethics of advanced genetics. We were now thinking in unison. I reckoned our brief contact was a major philosophical advance since somebody high up in science had become aware that he had to face the ethical music, if I may put it that way.

The advance of biomedicine and its increasing moral significance

A series of events led to my entry into biomedicine. Biomedicine is a huge topic today, and I can speak only to my own field of research, namely developmental genetics. My science began when, as an ex-soldier, I mistakenly studied agriculture for 3 years, then struggled into genetics. I never regretted moving to Edinburgh University to join Professor Conrad Waddington, who became my professor. Until then, I had been fascinated by the great science pioneers, including Mendeleef, Rutherford, Darwin and Howard (an early meteorologist). Ethics rarely crossed my mind except for occasional forays into the Greek philosophers, as with many other scientists. Among those four pioneers, Charles Darwin was the most significant for me, as I learnt of his amazing advances in understanding genetics, palaeontology and evolution. This fascination persists today, and in a sense, drove me to understanding the moral philosophy of my research as it headed inevitably from animals to humans. Waddington was fascinated by scientific ethics. He enjoyed debating the significance of science and religion with bishops and priests, and stacked a whole bookshelf in the library with books on moral philosophy and ethics. I have often wondered

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if he knew that one of his students was heading into major ethical issues! My PhD work on chromosomes in mouse embryos demanded obeying the UK laws on animal experimentation, an initial step into the ethics of my field, but little else of an ethical nature. I was interested in means of allowing parents to choose the sex of their babies, but this project failed until achieved by Joe Schulman and Karabinus (2005).

Nevertheless, there could be no doubt that ethics was knocking on my door as I moved on to mature human oocytes *in vitro*, ready for fertilization. Ideas on human fertilization *in vitro* had emerged in the National Institute of Medical Research in Mill Hill, London where I met many doctors. They informed me of the enormous number of infertile patients, which stimulated my interest since the techniques developed for studying animal embryos in Edinburgh would be relevant to solving some problems of the infertile. For example, knowledge on chromosomes became highly valuable when some human beings were discovered as possessing non-diploid numbers of chromosomes. Studies on mouse blastocysts were closely related to studies on human blastocysts, and were later incorporated into my early studies on embryonic growth and the preimplantation genetic diagnosis of inherited disorders.

Moving to Cambridge and Glasgow Universities led to my interest in maturing and fertilizing human oocytes *in vitro*, growing them to blastocysts, and then transferring the best embryos to their mothers' uteri. John Paul, Robin Cole and I also began work in Glasgow leading to the first studies on embryo stem cells and their therapeutic properties (Cole et al., 1966). Achieving fertilization *in vitro* in Cambridge in 1969, working with Barry Bavister and Jean Purdy, sent a signal that assisted human conception was near. We needed a medical colleague, and reading of his prowess with laparoscopy led me to phone and invite Patrick Steptoe to join our small team. He worked in the Oldham and District General Hospital (ODGH), and I was fated to travel there over a 10-year period to achieve the birth of Louise Brown. Until this time, advice on the ethics of my research had been decided in debates with my professors. Moving to human patients stressed the need for ethical advice since the ethics and moral philosophy of assisted reproduction, and the necessity to counsel patients, were now essential. An Ethical Committee would provide necessary background moral support and set standards of care. They are highly familiar to medical men, and I first read about them when reading papers from US doctors. A Committee in Oldham could be consulted about successive discoveries through the stimulation of ovarian follicles by administering exogenous hormones, the induction of oocyte maturation and fertilization *in vitro*, the growth of embryos to blastocysts *in vitro* and the transfer of blastocysts to their mothers' uteri. The ODGH agreed to establish an Ethical Committee to oversee our work. Usually immensely helpful, such Committees are only as strong as those who sit on them; members can include clinicians, business men, religious officials, patients, scientists and others.

Our own Committee was fundamental for our work as opposition to IVF emerged from various sources. I well remember Professor Bunny Austin, my own Professor in Cambridge University, who was always helpful, whereas Professor Thaddeus Mann opposed any research on human embryos. Such differences were presumably to be expected as our research produced human embryos growing *in vitro*, ready for transfer. Opposition was also inevitable from the Pope and other religious organizations. It also came from some philosophers and certain scientists including James Watson, Anne McLaren, Leon Kass, and others. Even some of my graduate students made their distaste very clear, yet some of them opened IVF clinics after the birth of Louise Brown! Patrick and I would not bend to opposition from people who failed to understand our intentions, or from religious sources who asserted that we were immoral, illicit, dishonest, illegal, etc., whatever these terms meant. It was also fascinating to watch as many scientists joined Ethical Committees as IVF became practised in hospitals and spread throughout the UK.

Ethics of the IVF pioneers

As our work progressed, we increasingly believed that we could help millions of people worldwide with various forms of infertility. This condition afflicted up to 10% of couples. Our work leading to preimplantation genetic diagnosis and the therapeutic use of embryo stem cells promised to help many thousands more. In 1963, we had watched rabbit stem cells differentiate into blood, muscle, neurons and virtually every tissue in the body. They promised, even in the 1960s, to offer future therapeutic help to millions of sick people. Our introduction of the preimplementation diagnosis of genetic diseases in 1968 had involved choosing male or female rabbit embryos for transfer and correctly diagnosing the sex of all the offspring. We still awaited the Genome Project, which would enable hundreds of disease genes to be averted in IVF offspring, a procedure which is now expanding very rapidly. Indeed, programmes devoted to eliminating some inherited human disorders are proving highly successful, and might spread rapidly since the Genome Project now allows thousands of genes to be diagnosed.

These astonishing possibilities convinced us of the significance of the clinical imperative. Each of these topics depended on a source of healthy human

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blastocysts which had been proved to be normal as shown by the birth of one or more healthy IVF babies after the embryos were replaced in their mothers. We were determined to achieve this first birth and decided to maintain our ethical stance unless something seriously wrong emerged in our work. No such problems emerged, so I therefore began the journey to and fro from Oldham, 184.2 miles from Cambridge, to treat our patients with Patrick Steptoe. The succeeding decade in my life involved lecturing in Cambridge from 9 till 10 am, then dashing out to a car to be driven fast to Oldham and my tiny laboratory there. Patrick had already stimulated patients with human menopausal gonadotrophin and human chorionic gonadotrophin (HCG) to stimulate many ovarian follicles to grow and their oocytes to mature. Knowing that follicles would ovulate at 37 h post-HCG, we timed the final stages of oocyte maturation to occur at 3 pm, providing sufficient time to get to Oldham from Cambridge.

Our adoption of the clinical imperative and the inalienable rights of couples to have their own child convinced us that our ethical stance was legitimate provided we did no harm. I was concerned about the lack of scientists in our ODGH Ethical Committee, and few if any of them could cope with scientific advances in the laboratory. Nevertheless, the Committee stood by us until Louise was born and we prepared to move to Cambridge. We also continued with our own ethical defence, attending Press Conferences, TV interviews and writing papers on the ethics of IVF. For example, Dave Sharpe, a US lawyer, and I wrote the first paper on IVF ethics which was published in *Nature* in 1971 (Edwards and Sharpe, 1971). We asked for a regulatory authority to be established by Parliament to provide advice and help on complex scientific, medical and ethical issues. This request was granted when the UK Parliament established the Human Fertilization and Embryology Authority (HFEA) 15 years later. I also wrote on science, law and ethics of IVF in a leading US journal (Edwards, 1974).

It was also essential to respect the role of the British government, since it had a major stake in certifying the origins of its citizens. Just before Louise's birth, her mother, Lesley Brown, expressed a wish for her birth to be recorded on film for posterity. The Government denied her this right since the Oldham and District Hospital was a part of the National Health Service. Believing her rights were being overridden, her lawyer telephoned the British Cabinet in London, threatening to issue a writ against them in 5 minutes time unless they changed their mind. The Minister responded within 3 minutes, and gave consent to the filming! This little episode revealed that ethics and rights are clearly very important matters to be sustained on behalf of our patients.

Ethics after the birth of the first IVF babies

The birth of Louise Brown surprised everyone, since her birthdate had been kept confidential in order to avoid excessive attention from the Press. Even so, the world soon understood that science had entered decisively into early human life, and that it progresses ever further, year on year. The widening ethics of IVF led to the Prime Minister then in power, Margaret Thatcher, requesting that ethics of IVF should be debated in the House of Lords. This ancient House has been totally modernised. It now includes people of wisdom including the UK's leading doctors, scientists, industrialists, religious leaders, and people who have made contributions to society. It is indeed a house of wisdom, and they voted by 3 to 1 that the work on IVF already done in Oldham and later was fully legitimate. The House of Commons also accepted future aspects of IVF such as oocyte donation, research on human embryos and surrogate mothers after some hesitation but with a similar majority, so our politicians had granted us their support. Lady Warnock was appointed to produce a report which proved to be very liberal and has helped to sustain IVF in many countries outside the UK. Even though a philosopher, Lady Warnock stated that she did not use philosophy to come to terms with IVF. This fact has always worried me. If philosophy is not needed at this level, why do we bother to consult them? After all, we had published a somewhat similar paper in *Nature* 15 years earlier (Edwards and Sharp, 1971), requesting such a committee which made me wonder what philosophers actually did.

The HFEA was established by the UK Government to assess new advances and the ethical regulation of IVF. It was a sort of barrier between the State, the Press and IVF professionals, and its judgements were overall fair, despite some surprising errors. We maintained our own ethical activities, publishing an ethical paper for every 3–4 of our scientific papers. We also continued attending conference after conference, large and small meetings, or even question time, to debate our ethics. During these years, we opened Bourn Hall Clinic and achieved 1000 babies in 8 years.

Modern lessons from moral philosophy and ethical practice

What lessons about moral philosophy and ethics do we learn from all this experience? First, it is time that ethics has a larger place in scientific courses. Human IVF was based on earlier studies in mice. We published many papers showing how ovarian stimulation could induce mice to ovulate up to a hundred oocytes. After mating, these females implanted an average of 25 or more fetuses per pregnancy. Later, Carl Gemzell and others stimulated

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amenorrhoeic patients with pituitary extracts, and produced multiovulations which resulted in human quadruplets, quintuplets and even higher multiple pregnancies. The clinicians involved were unaware of our results in mice, yet it was surely morally essential to assess animal data before proceeding to human studies.

In my opinion, moral philosophy and the ethics of modern biomedicine are still insufficient. This is why the first meeting in this series was held in London in 2004, and proved to be among the best ethical meetings I have ever attended. Lectures from moral philosophers outnumbered those delivered by scientists and clinicians. Discussions were outspoken, and should provide an excellent basis for teaching reproductive biomedicine and its ethics to third years or older graduate students. It is essential that students entering medicine, and especially those entering the applied biological sciences, should have a clear idea of ethical concepts. I attempted to train our Cambridge students in the ethics and moral philosophy of biomedicine. The course proceeded so well that many medical students wished to attend in preference to their other lecture courses! I believe it is still running.

Future outlooks

A stage has been reached in reproductive biomedicine where microarrays and gene technologies involving labelled RNAi (RNA interference) now enable studies on embryos or tissues involving thousands of genes. The Genome Project has classified virtually all of our human genes. Disease genes can be measured in single blastomeres removed from human embryos, so every disease gene can in theory be controlled via preimplantation genetic diagnosis. It may cost £5000 to avert a single disease gene in an embryo, but the savings at birth and during childhood and adulthood must be 50 times greater. Santiago Munné et al. (2004) showed how chromosomes could be counted in blastomeres extracted from an embryo, to provide information on anomalies threatening the embryo. Approximately 50% of human preimplantation embryos were found to inherit chromosomal imbalance. This astonishing work implies that the ethics of PGD were well based in the clinical imperative. The question emerges as to why a woman ovulates so many 'dud' eggs while paying the biological costs of her menstrual cycles. And why are human spermatozoa so disgraceful? A value of 10% normal spermatozoa is considered to be fertile, so why produce the remaining 90%? These are matters for scientists, moral philosophers and evolutionists to discuss.

Another issue concerns the high cost of IVF. One half of its costs are for hormones manufactured to stimulate ovarian follicles and oocyte maturation. The cost of IVF would be radically reduced if the cost of hormones could be decreased to one-third of the current value. Recent advances in maturating human oocytes *in vitro* after giving small levels of these priming hormones promises an excellent supply of mature oocytes at a much lower cost. Their cryopreservation by vitrification could enable women to cheaply store many of their eggs for use after their menopause. This greater reproductive freedom for women is welcome, and will lead to many complex ethical decisions in IVF clinics.

Other developments promise to change IVF procedures. Embryos might be made from stem cells, rather than from eggs and spermatozoa. Even more extreme, haemopoietic stem cells may be converted to embryonic stem cells or to oocytes, as in mice, although this work requires confirmation (Johnson et al., 2005). Will the menopause become redundant as post-menopausal couples become pregnant after these oocytes are thawed and fertilized by their husband's spermatozoa? What can be done in mice may not be possible in humans, so human cloning may also lead to a dead end.

Biologists are not on the edge of destructive items such as the atom bomb. We are pro-life, although some recent ideas in biomedicine imply that it is time to learn a little more about ethics and moral philosophy. Remember what Jacques Monod wrote about our living in a universe which fails to listen to our music. We are essentially isolated and must devise the best medical treatments for members of our species, while ensuring the highest standards of ethics and moral philosophy.

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