RESEARCH ETHICS

A natural stem cell therapy? How novel findings and biotechnology clarify the ethics of stem cell research

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The natural replacement of damaged cells by stem cells occurs actively and often in adult tissues, especially rapidly dividing cells such as blood cells. An exciting case in Boston, however, posits a kind of natural stem cell therapy provided to a mother by her fetus—long after the fetus is born. Because there is a profound lack of medical intervention, this therapy seems natural enough and is unlikely to be morally suspect. Nevertheless, we feel morally uncertain when we consider giving this type of therapy to patients who would not naturally receive it. Much has been written about the ethics of stem cell research and therapy; this paper will focus on how recent advances in biotechnology and biological understandings of development narrow the debate. Here, the author briefly reviews current stem cell research practices, revisits the natural stem cell therapy case for moral evaluation, and ultimately demonstrates the importance of permissible stem cell research and therapy, even absent an agreement about the definition of when embryonic life begins.

Although one promising technology, blighted ovum utilisation, uses fertilised but developmentally bankrupt eggs, it is argued that utilisation of unfertilised eggs to derive totipotent stem cells obviates the moral debate over when life begins. There are two existing technologies that fulfil this criterion: somatic cell nuclear transfer and parthenogenic stem cell derivation. Although these technologies are far from therapeutic, concerns over the morality of embryonic stem cell derivation should not hinder their advancement.

A 37 year old mother of three comes into your clinic presenting abdominal pain, marked tiredness, and puffy ankles. The standard array of diagnostic tests suggests acute liver failure. Your patient rejects all treatment options, including radical liver transplantation surgery, and decides to wait and see how her disease state progresses. Remarkably, perhaps miraculously, six months later she shows signs of a complete recovery, despite a lack of medical intervention.

Just over a year ago, researchers at the New England Medical Center in Boston presented new data on an old cell type, pregnancy associated progenitor cells (PAPCs), which might help explain the *deus ex machina* mode of recovery in your patient.¹ As far back as 1979,² it was shown that women who give birth to sons retain some of their sons' fetal cells—for example, PAPCs, which can in turn give rise to multiple cell types along the haematopoietic stem cell (HSC) pathway of differentiation.¹

After all, the reasoning goes, the placental/blood barrier is not a perfectly selective portal, and some fetal blood and cells will cross into maternal circulation. What is surprising, however, is the ubiquity and persistence of these fetal stem cells; they can be found in maternal circulation up to 27 years after the baby is born.⁵ Additionally, these fetal stem cells were found to localise to diseased organs and repopulate them. For example, in one woman with a thyroid adenoma, biopsy revealed two populations of cells: her germline, cancerous thyroid cells were surrounded by healthy thyroid cells derived from her son's fetus. Even more strikingly, one woman with liver disease had significant repopulation of her liver with healthy fetal derived hepatocytes, the first indication of functional non-haematopoietic stem cell derived PAPCs.¹

Similarly, the liver recovery of our patient might involve some sort of natural defence mechanism whereby PAPCs patrol a mother's body and look for damaged tissues to

repopulate. The principal researchers of the Boston study concluded that:

Whatever the mechanism involved, we believe that the idea of fetal cells expressing non-hematopoietic markers is novel and may have important long term health implications for the woman who has undergone pregnancy by providing her with a younger population of cells that may have different capabilities in the response to tissue injury.¹

The natural replacement of damaged cells by stem cells occurs actively and often in adult tissues, especially rapidly dividing blood cells. This case, however, posits a kind of natural stem cell therapy provided to a mother by her fetus. Because there is a profound lack of medical intervention, this therapy seems natural enough and is unlikely to be morally suspect. Nevertheless, we feel morally uncertain when we consider giving this type of therapy to patients who would not naturally receive it. Much has been written about the ethics of stem cell research and therapy; this paper will focus on how recent advances in biotechnology and biological understandings of development narrow the debate. Here, I will briefly review current stem cell research practices, revisit our PAPC cases for moral evaluation, and ultimately demonstrate the importance of permissible stem cell research and therapy, even absent an agreement about the definition of when embryonic life begins.

Abbreviations: HSC, haematopoietic stem cell; PAPC, pregnancy associated progenitor cell

¹ Presumably this effect occurs in women who give birth to daughters as well, but because Herzenberg *et al* were screening for a y chromosome, these daughters' fetal cells could not be detected at the time.^{3,4}

Stem cells are, very basically, cells that have the potential to become any number of other cells. There are two broad categories of stem cells: embryonic stem cells derived from the developing embryo, and adult stem cells derived from more highly specified tissues. Embryonic stem cells are totipotent, implying an ability to differentiate into any type of cell, and indeed a whole organism, upon exposure to specific morphogens, chemical controller signals. Adult stem cells, such as those found in the bone marrow, are multipotent at best, not totipotent, because they have already taken a step along a differentiation pathway. A consensus on the use of these terms is yet lacking. Additionally, somewhat confusingly, adult stem cells may be derived from the fetus, since even a fetus at later stages in development achieves the sort of epithelial, haematopoietic, and neuronal regulatory control needed for survival. In fact, a fetus that has developed past the earliest stages of differentiation no longer possesses totipotent embryonic stem cells.

The promise of stem cell therapy involves targeted transplantation of these totipotent, healthy stem cells to diseased organs and tissues. If a cirrhotic liver can be repopulated with healthy hepatocytes, normal liver function can be regained. Replacement of degenerating neurons by healthy neurons in a Parkinson's patient can dramatically enhance quality of life and prolong life span. Although adult stem cells show some efficacy in repopulation studies, most researchers agree that not all types of cells can be derived from multipotent, already differentiated adult stem cells. The importance of embryonic stem cells lies in their value as totipotent cells.

There is little controversy over the morality of conducting research and therapy using adult stem cells, because these can be harvested from living donors of bone marrow and other tissues. Embryonic stem cells, however, are derived from the embryo very early in its stages of development, typically not later than five to eight days after fertilisation of an egg by a sperm, after which the embryo begins to differentiate and loses its totipotency. The fertilisation itself may occur not in the body but in a test tube; it is estimated that currently in the United States, over 400,000 frozen embryos left over from in vitro fertilisation treatments can be used as sources of embryonic stem cells.⁶ Given the limited number of stem cell lines currently available, this number, estimated from a 2003 survey by the American Society for Reproductive Medicine, seems more than adequate.⁷

Are the fetal stem cells that save our patient's liver embryonic or adult derived? Fetal stem cells that transfer across the placenta and remain in utero for decades have been identified as (adult) haematopoietic stem cells. Because haematopoietic stem cells cannot typically transdifferentiate into epithelial cells such as hepatocytes, however, the circulating stem cells in our patient are likely to be of an embryonic origin. There has been only one report of adult bone marrow stem cells repopulating a damaged liver in a mouse model, but this mode of transdifferentiation was later shown (by the same group) to require fusion between a pure HSC and an existing hepatocyte.⁸⁻⁹ In the case of our patient, however, the researchers were not able to find a single cell from the baby that had fused with his mother's hepatocytes.¹ If the researchers did not inadvertently overlook any fused cells, we can assume that all of the repopulated hepatocytes were derived from embryonic stem cells.¹⁰⁻¹¹

What seems important, then, is the potential moral objection to harvesting embryos for the purpose of stem cell research and therapy. It is less contentious to harvest embryos, often dozens at a time, for the purpose of assisted reproduction. In fact, the sheer number of left over embryos in thousands of fertilisation clinics across the United States is testament to the moral acceptability of the technology. The

procedure itself involves physically extricating multiple ova from a woman and fertilising each ovum with sperm collected from a man. The fertilised embryos are cultured in vitro for up to eight days, and the healthiest looking embryos are then implanted back into the mother's uterus. Non-implanted embryos are frozen for potential future use, but may simply be discarded if the patients decide they will not want any more children.

Those who have no moral qualms against such assisted reproduction technology may nevertheless oppose using these frozen embryos to derive embryonic stem cells for research purposes. One distinction these opponents make is the seeming unnaturalness of stem cell research.⁷⁻¹² They argue that the only natural way to give moral weight to the lives of frozen embryos is to implant them and carry the fetus through a full pregnancy. In vitro fertilisation, it is argued, is merely an assistance of reproduction, a natural phenomenon in which all healthy humans may engage. Implanting a fertilised embryo back into the mother's womb is analogous to using a respirator in assisted breathing, or implanting a pacemaker to control cardiac arrhythmia. Using a fertilised embryo for scientific research seems to disregard the natural order of things, disrespecting the sanctity of the embryo itself.

The argument for such "naturalness" is an old one: forces larger than human beings shape the external world, a higher order with which we are not to meddle. Using *naturalness* as proxy for *morality* fails, however, when we consider other, highly accepted, medical procedures. Very basically, perhaps, we keep a patient on life support despite his natural tendency to die. The pacemaker we install creates an artificial, not natural, rhythm in the heart. We induce childbirth, sometimes as early as 32 weeks, if we feel that the baby's health would suffer during a prolonged pregnancy. Indeed, in vitro fertilisation itself is hardly natural, in that it eliminates copulation from the process of reproduction. It seems that all advances in medical technology do something unnatural in order to alleviate pain and suffering, or to offer the joys of very natural procedures like childbearing. *Intent to further natural life* seems a more appropriate standard than *naturalness*. Moreover, regaining the ability to walk after severing a spinal cord, or seeing light again after years of retinal degeneration—potential benefits of stem cell therapy—surely weigh the same, on a scale of naturalness, as childbearing, to which these critics do not seem to object.

Even if we do look to naturalness for guidance on the moral status of an embryo, we see some potential contradictions. Because reproduction is required for the survival of a species, naturally much emphasis is put on proper development of embryos. Ann Kiessling, a science researcher at Harvard and Director of the Bedford Stem Cell Research Foundation, explains:

Failure to signal the mother that development is progressing within normal limits results in spontaneous maternal reversion to a non-pregnant state with expulsion of the failed conceptus. Such mechanisms to ensure the robustness of offspring are probably as important to survival of the species as the capacity for reproduction itself. Nature celebrates success and disdains failure.¹³

A large majority of fertilised eggs will follow this path to destruction through spontaneous abortion.¹⁴ If nature itself has low regard for these embryos, it hardly follows that arguments for naturalness should prevent the use of such embryos for scientific research with the potential to cure many debilitating diseases.

Furthermore, our discussion of natural embryonic development suggests multiple tiers of embryonic moral worth.

Kiessling outlines many stages in which a fertilised egg can fail to develop into a fetus in early embryonic development—for example, a sperm that penetrates the egg may fail to remodel its chromosomes, and the embryo will die within several days, just as it would if it had not been fertilised. Even if remodelling is normal, however, the development of polarity within the developing embryo is also important, and failure to develop an inner cell mass will result in spontaneous abortion. Even if the embryo can proceed past these stages of development, it might not implant itself into the uterus properly, and will be released with the mother's menses. These fertilised eggs that fail to survive the harsh climate in utero are termed "blighted ova". These blighted ova can never progress to the stage of fetal development because of major early developmental defects. Importantly, though, Kiessling notes:

An inability to develop to a healthy offspring does not, however, necessarily negate the potential of the fertilised egg to give rise to stem cells. Thus it is possible that many eggs traditionally doomed to die during embryogenesis could be utilised for stem cell production... This notion highlights the urgent need to be able to distinguish developmentally capable fertilized eggs from incapable fertilized eggs.¹³

Nature suggests, then, that not all embryos are created equal. Technology that can distinguish between a productive fertilisation and a non-productive fertilisation can be used to ensure derivation of stem cells only from embryos incapable of life. But opponents of the distinction argue that a life begins at fertilisation, and the moral worth of each embryo is equal. There are dangerous postnatal extensions, the argument goes, of evaluating life based on developmental potential. These extensions are *prima facie* tenuous, however, because there is a clear difference between a developmentally *retarded* human child and a developmentally *incapable* clump of cells that is extruded with a woman's menses.ⁱⁱ

The moral acceptability of this technology rests in this distinction between a fertilised egg and an unfertilised egg.ⁱⁱⁱ To date, no human has yet been born without the fertilisation of an egg by a sperm. The very humanness of an embryo is conferred upon it by this process of fertilisation; the sanctity of an embryo's life lies in its origins as part mother and part father: unique, whole, and complete. An embryo, in the classical sense, is the functional union of an egg and a sperm.

ⁱⁱ Whether this spontaneously aborted menstrual extrusion constitutes life is beyond the scope of this paper. Common arguments against this premise include the mysterious process of twinning, in which a single embryo asexually reproduces to become two separate monozygotic individuals. The embryo cannot be a single life until this process is complete, the argument goes, which may take up to fourteen days, long after the period when a stem cell would be harvested. Additionally, the evidence of tetragametic conception challenges the individual personhood of each early embryo, because two separately fertilised eggs may fuse after seven days of separated development to form a single individual. According to this argument, each fertilised egg cannot constitute an individual person because one such personhood would disappear in the process of fusion. For more on this nuance of personhood versus life, see Daley's lecture.⁶

ⁱⁱⁱ A report in *Nature* from October 2005 challenges this assumption. Collaborating researchers were able to derive a totipotent stem cell line in mice from a single cell taken from the blastomere stage of an embryo—without harming the embryo itself. This technique, removing a single cell from the 8 or 16 cells of a blastomere, is routinely done in human pregnancies for preimplantation genetic testing; it seems acceptable, then, to use this technique for stem cell derivation. Chung Y, Klimanskaya I, Becker S, *et al.* Embryonic and extraembryonic stem cell lines derived from single mouse blastomeres. *Nature* 2005: in press. doi:10.1038/nature04277.

An embryo is not, then, an egg that is not fertilised by a sperm. Any stem cell derivation technology that utilises an unfertilised egg avoids the entirety of the proposed moral quandary because an unfertilised egg can never become an embryo.

This argument assumes, however, that an unfertilised egg has low intrinsic moral worth. One intuitive validation of this assumption looks to each woman's completed menstrual cycle, during which an unfertilised egg is discarded as biological waste. In general, we do not confer any degree of sanctity onto this egg, nor do we mourn its loss. This argument is explicated by Michael Sandel, Professor of Government at Harvard University, when he admits that: "Human life develops in degrees".¹⁵ Like Kiessling, Sandel argues that there is an important inherent difference between an acorn seed and its more awesome oak counterpart:

although every oak tree was once an acorn, it does not follow that acorns are oak trees, or that I should treat the loss of an acorn eaten by a squirrel in my front yard as the same kind of loss as the death of an oak tree felled by a storm. Despite their developmental continuity, acorns and oak trees are different kinds of things. So are human embryos and human beings.

An acorn is, however, at least a fertilised seed. An unfertilised human ovum is not even a seed—it is a single cell like hundreds of others, of which most will die by neglect within the woman's ovaries. This unfertilised egg is on equal standing, biologically and morally, with the woman's red blood cells donated to a blood bank. Some may argue, however, that a red blood cell can never become a full human being, whereas that unfertilised egg may later be fertilised. This argument seems flawed, however, once we consider the unfertilised egg's male counterpart. Surely, a man cannot have equal moral worth to another man's ejaculate donated to a sperm bank or discarded in a condom, even though each sperm has the potential to become a new human being.

Therefore, even if fertilisation marks the beginning of an inviolable life, embryonic stem cells may yet be derived from an unfertilised egg without moral compromise. But because this nomenclature becomes confusing, it is perhaps appropriate to abandon usage of the loaded modifier "embryonic," and instead use "totipotent". In other words, totipotent stem cells must not necessarily be embryonic in origin. There are at least two recent advances in biotechnology that demonstrate how unfertilised, non-embryogenic eggs can be used to create potentially totipotent stem cells. The first process involves a reproductive method most commonly associated with bees: parthenogenesis.

It has been known for quite some time that some species do not employ fertilisation in order to propagate every member of the species—for example, in the honey bee fertilised eggs become female worker bees, and unfertilised eggs develop into male drones. Human beings cannot employ parthenogenesis as a means for reproduction. Nevertheless, unfertilised human eggs do sometimes spontaneously activate, divide, and propagate. This pathological process may result in a rapidly dividing, ectopic mass of cells that implants itself into random sites in the body. These tumours are termed "teratomas" and can differentiate into any organ tissue because of the ovum's original totipotency. Teratomas explain, for example, how a tumour mass filled with teeth and hair can be found in such ectopic sites as the uterus.¹⁶

Although the natural process of parthenogenesis in human females results in such a highly disturbing pathologic state, the idea of totipotent stem cells derived from an egg activated parthenogenically *ex vivo* is appealing because it obviates the

moral debate regarding embryonic stem cells. Even if we accept that the life of an embryo begins with fertilisation, there are several nuances that make parthenogenic stem cells morally permissible. Firstly, because these stem cells do not derive from a fertilised egg, no life is compromised in the harvesting process. Nevertheless, some may argue that since bees reproduce parthenogenically, these parthenogenic stem cells should be viewed as potential human embryos. I have, however, explained above how an unfertilised human egg cannot ever proceed to the stage of development that might give rise to an embryo: and since many cleavage events are egg specific and do not require sperm involvement, parthenogenesis is valuable as a tool for studying stem cells without creating an embryo.¹³ Additionally, parthenogenic stem cells are totipotent in the sense that they may ultimately differentiate into any cell of the postpartum human body. Unlike a true embryonic stem cell, however, they do not have the capability to differentiate into *placental* cells, making it impossible for a parthenogenic stem cell to ever transdevelop into an embryo.¹⁷ Since placental cells are critical to embryonic development from its very earliest stages, parthenogenic stem cells have the ability only to mimic life, but not to develop into life.

We have acknowledged that accepting the use of unfertilised, parthenogenically activated eggs for stem cell derivation assumes that there is no inherent moral value of an unfertilised egg.¹⁵ If this is true, other technologies may also be permissible for derivation of stem cells—for example, the cloning of the first mammal, Dolly the sheep utilised a technique known as somatic cell nuclear transfer. In this process, an unfertilised egg is collected from an ovary and its DNA mechanically removed. Unlike parthenogenesis, the egg is activated by replacing its haploid DNA with the diploid DNA of another cell type—for example, skin cell DNA. The resulting renucleated egg is activated electrochemically and cultured in vitro. At this stage, the dividing egg can follow either of two paths. The first, which was performed for Dolly and most scientists agree should never be performed for any human, involves transplanting this renucleated egg into the mother's uterus for stimulation of embryonic development. The second path involves keeping this renucleated egg *ex vivo*, on a culture plate, for derivation of totipotent stem cells.

This latter pathway, often referred to as “therapeutic cloning” or “research cloning”, has garnered much negative press recently because the word “cloning” is “loaded with the spectre of eugenics and genetically engineered individuals”.¹³ It is important to distinguish, however, between reproductive cloning, as in the case of Dolly, and a technology so divorced from cloning of individuals that it does not even produce a fertilised embryo. In any strict sense, the renucleated, dividing cell created by somatic cell nuclear transfer is not an embryo because, like a parthenote, it is never fertilised by a sperm: and because it is never implanted into a woman's womb, it does not have even the potential to become an embryo.¹⁸ We know that parthnotes cannot develop placental tissue, and so could never develop into a human being; similarly, renucleated cells can be modified to prevent placental differentiation. Alexander Meissner and Rudolf Jaenisch, researchers at the Massachusetts Institute of Technology, have used nuclear transfer to create stem cells in mice that are totipotent yet cannot implant into the uterus because of a disruption in placental formation.¹⁹ They used a technology to selectively degrade the gene products of the *Cdx2* gene, preventing the renucleated egg from forming the trophoblast layer of a normal developing embryo. Like a parthenote, the renucleated egg has no potential for becoming a human being. And because it is never fertilised, it does not constitute human life at any point during its derivation. The potential implications are profound. Kiessling expounds:

Once the technology is perfected to generate insulin-secreting cells, or spinal cord compatible neurons from hpPS (parthenogenic stem) cells, such women could be treated with cell lines derived from their own eggs. In many ways, this type of treatment is more closely related to autologous blood transfusion than to reproductive biology.¹³

In this vein, we can imagine in the case of our patient with acute liver failure that one therapeutic intervention might involve: extrication of one of her unfertilised eggs; denucleation and successive renucleation with healthy hepatocyte DNA; derivation of totipotent stem cells via electrochemical manipulation, and retransplantation of stem cells into her diseased liver to facilitate repopulation. In many ways, this process is much more “natural” than the heterorepopulation of her liver by her son's fetal stem cells because it is more autologous. These are entirely components of her own body, after all, that are used in her therapy; and, once the efficacy of autologous stem cell therapy is refined, it does not seem a large leap to recognise the value of heterologous stem cell therapy, codifying into medical practice what our patient's son's fetal stem cells do for her naturally.

But heterologous stem cell therapy, whatever the harvesting method, is still far from therapeutically efficacious. I realise that many of the technologies described here are still in their nascent stages of development. Although an exciting idea, it is still unproven that PAPCs can be stimulated to repopulate and cure diseased organs in any inducible manner. And to date, no parthenogenic stem cells have been derived using human eggs. Nevertheless, it is important to consider the implications of such technologies before they are fully ready. For if we realise that such stem cell research is immoral after it has already been developed and used, we have failed in our quest for moral rigour. A recent, somewhat related, example from the medical arena concerns the controversy over rofecoxib, a COX-2 inhibitor.²⁰ At issue in this controversy is not the science—the large scale studies were conducted in an ethical and scientifically sound manner—but the way science was used.²¹ The data—particularly the risk of adverse cardiovascular events—was not fully disclosed to physicians or the public, resulting in improper prescription that risked adverse cardiovascular events in up to 100,000 patients.²²

On the other hand, it is equally important to realise the great value of scientific research; we must take pains to prevent the throttling of good science. David Sarnoff, the founder of Radio Corporation of America, has said that “Freedom is the oxygen without which science cannot breathe”.²³ Furthermore, the history of medicine is wrought with examples of life saving technologies that were developed despite fierce initial opposition. Vaccine development—for example, faced myriad challenges a hundred years ago. Public opinion was so polarised that Edward Jenner was forced to try his cowpox vaccines on his own family before public deployment of an effective vaccine. The idea of injecting a virus (albeit a mere fragment or particle) into a healthy body to gain some uncertain future benefit smacked of quackery. Nevertheless, the poliovirus vaccine quickly and safely eradicated a crippling childhood disease from modern America. Barry Furrow, a professor of law, relates his experience:

The development of the Salk polio vaccine in 1953, and later the Sabin vaccine in 1956, was a major public health development. I remember standing in line in elementary school in rural South Dakota to drink a small cup of the Sabin polio vaccine. In the 1950s in South Dakota we were well aware of the effects of polio, seeing parents of our friends crippled by the disease and forced to use leg

braces, crutches and other aids to move around. The polio vaccine was a harbinger of the increased power and pervasiveness of medicine.²⁴

The increased power and pervasiveness of medicine rescued millions of children from debilitating disease. Its awesome healing effects do not make vaccination automatically immune to criticism; all revolutionary medical advancements deserve due moral evaluation. As with the polio vaccines, however, those advancements that are efficacious and promising, and that preserve the sanctity of our accepted morals, deserve attention, support, and positive employment.

In this paper I have shown that stem cell research that does not use fertilised eggs clearly meets both of these criteria, promising efficacy and preserving morality, without risking the paradox of harming life. In terms of efficacy, the description of a natural stem cell therapy provided to a mother by her son's fetal embryonic stem cells heralds the potent therapeutic value of a similar but heterologous stem cell therapy. In terms of morality, although there may be no consensus on when a fertilised egg becomes a life, I have argued that an egg that never becomes an embryo can in no circumstances constitute life. Several technologies, including those utilising parthenogenic stem cells and renucleated eggs, fall on the rectitudinous side of this moral bright line. If no life is harmed in the process of stem cell derivation, it would be morally irresponsible to ignore the promise of stem cell therapy. Like vaccination had the power to save generations of children from crippling disease, stem cells have the power to cure many of medicine's current and future plagues.

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ECHO

Prescription for ethical approval

Please visit the *Journal of Medical Ethics* website [www.jmedethics.com] for a link to the full text of this article.

Young aspiring researchers now have some novel criteria by which to steer their research proposals through scientific ethics committees.

Three of their more experienced peers, self confessed “veterans of rejection,” have, tongue in cheek and in the style of Cochrane, devised four standardised indices to be calculated for each submission to an ethics committee. High scores for these objective measures denote appropriate committee performance. These indices are needed, the veterans say, because ethics committees, now representing every minority interest, have become a formidable obstacle.

The first index—the ethics ratio—compares the lengths of ethics submission and the successful grant application; ideally, the ratio should be greater than 5 to assure approval within months, anything under 3 risks rejection as being too lightweight. The ethics committee correction index and the researcher frustration index take in such esoteric aspects as the age and sex of committee members; number of grammatical errors found by subcommittee; and value of the research grant. Finally, the odds ratio for obligatory resubmission (OR²) can be reduced by applying a few commonsense principles—ensuring that the ethics submission is heavyweight, at least 758 g per copy; the lay summary is simplified to assume a reading age of 12 years; proof of funding and potential monetary and public relations benefits to the hospital are highlighted; and references to clinical and research governance in the method are maximised.

And the reaction of the researchers' local ethics committee? Seemingly, underwhelmed.

▲ Fitzgerald DA, *et al.* *Archives of Disease in Childhood* 2005;**90**:1249–1250.