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The promise of cloning for human medicine

Not a moral threat but an exciting challenge

The production of a sheep clone, Dolly, from an adult somatic cell[1] is a stunning achievement of British science. It also holds great promise for human medicine. Sadly, the media have sensationalised the implications, ignoring the huge potential of this experiment. Accusations that scientists have been working secretively and without the chance for public debate are invalid. Successful cloning was publicised in 1975,[2] and it is over eight years since Prather *et al* published details of the first piglet clone after nuclear transfer.[3]

Missing from much of the debate about Dolly is recognition that she is not an identical clone. Part of our genetic material comes from the mitochondria in the cytoplasm of the egg. In Dolly's case only the nuclear DNA was transferred. Moreover, we are a product of our nurture as much as our genetic nature. Monovular twins are genetically closer than are artificially produced clones, and no one could deny that such twins have quite separate identities.

Dolly's birth provokes fascinating questions. How old is she? Her nuclear DNA gives her potentially adult status, but her mitochondria are those of a newborn. Mitochrondia are important in the aging process because aging is related to acquired mutations in mitochondrial DNA, possibly caused by oxygen damage during an individual's life.[4] Experimental nuclear transfer in animals and in human cell lines could help elucidate mechanisms for many of these processes.

Equally extraordinary is the question concerning the role of the egg's cytoplasm in mammalian development. Once the quiescent nucleus had been transferred to the recipient egg cell, developmental genes expressed only in very early life were switched on. There are likely to be powerful factors in the cytoplasm of the egg that make this happen. Egg cytoplasm is perhaps the new royal jelly. Studying why and how these genes switch on would give important information about both human development and genetic disease.

Research on nuclear transfer into human eggs has immense clinical value. Here is a model for learning more about somatic cell differentiation. If, in due course, we could influence differentiation to give rise to targeted cell types we might generate many tissues of great value in transplantation. These could include skin and blood cells, and possibly neuronal tissue, for the treatment of injury, for bone marrow transplants for leukaemia, and for degenerative diseases such as Parkinson's disease. One problem to be overcome is the existence of histocompatibility antigens encoded by mitochondrial DNA,[5] but there may be various ways of altering their expression. Cloning techniques might also be useful in developing transgenic animals—for example, for human xenotransplantation.

There are also environmental advantages in pursuing this technology. Mention has been made of the use of these methods to produce dairy herds and other livestock. This would be of limited value because animals with genetic diversity derived by sexual reproduction will always be preferable to those produced asexually. The risk of a line of farm animals prone to a particular disease would be ever present. However, cloning offers real prospects for preservation of endangered or rare species.

In human reproduction, cloning techniques could offer prospects to sufferers from intractable infertility. At present there is no treatment, for example, for those men who exhibit total germ cell failure. Clearly it is far fetched to believe that we are now able to reproduce the process of meiosis, but it may be possible in future to produce a haploid cell from the male which could be used for fertilisation of female gametes. Even if straight cloning techniques were used, the mother would contribute important constituents—her mitochondrial genes, intrauterine influences, and subsequent nurture.

Regulation of cloning is needed, but British law already covers this. Talk of "legal loopholes"[6] is wrong. The Human Fertilisation and Embryology Act may need modification, but there is no particular urgency. A precipitate ban on human nuclear transfer would, for example, prevent the use of in vitro fertilisation and preimplantation diagnosis for those couples at risk of having children who have appalling mitochondrial diseases.[7] Self regulation and legislation already work well. Apart from any other consideration, it seems highly unlikely that doctors would transfer human clones to the uterus out of simple self interest. Many of the animal clones that have been produced show serious developmental abnormalities,[8] and, apart from ethical considerations, doctors would not run the medicolegal risks involved. Transgenic technology has been with us for 20 years, but no clinician has been foolish enough to experiment with human germ cell therapy. The production of Dolly should not be seen as a moral threat, but rather as an exciting challenge. To answer this good science with a knee jerk political reaction, as did President Clinton recently,[9] shows poor judgment. In a society which is still scientifically

illiterate, the onus is on researchers to explain the potential good that can be gained in the laboratory.

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Reducing morbidity from chest drains

Knowledge of basic principles and use of appropriate equipment would help

The insertion of an intercostal chest drain to relieve the pleural cavity of unwanted air or liquid is a common procedure. It is simple to perform and should be associated with a low mortality and morbidity. However, unnecessary problems are often encountered, both during and after the procedure.

Most hospital doctors will, at some stage, insert a chest drain, either urgently in cases of trauma or electively for a pneumothorax or pleural effusion. An adequate understanding of the anatomy and pathophysiology of the pleural space is vital, as is proper teaching of the technique of insertion and subsequent management of chest drains.[1-3]

The aim of drain insertion is to restore and maintain the negative intrathoracic pressure necessary for lung expansion and drainage of the pleural cavity.[4] The physiological mechanisms maintaining full expansion depend on removal of excess liquid and gas from this space. The basic principle of chest drainage is to ensure this by re-establishing the negative intrapleural pressure. When at rest (that is, at functional residual capacity), the elastic forces of the chest wall and lung try to separate the visceral and parietal pleural layers, and create a negative intrapleural pressure of -2 to -5 cm of water. During inspiration, the negative intrapleural pressure increases to about -35 cm of water. Full expansion of the lung will also allow reactivation of the surface forces that hold the visceral and parietal pleuras together.

Pneumothoraces are caused by a breach in the continuity of the pleural sac (either via the lung or chest wall), allowing positive pressure air into the cavity from the alveoli or the atmosphere. The negative intrapleural pressure is lost, causing the lung to collapse and fall away from the chest wall. A one way airflow mechanism, usually via an underwater seal drainage system, is necessary for managing a chest drain.

The addition of suction (10-20 cm of water) to this system increases the negative intrapleural pressure. If suction is to be used it must be at high volume and low pressure. A low volume pump (such as a Roberts) should not be used as it will not be able to handle a large air leak and will allow air to accumulate, worsening the pneumothorax.[5] Suction should be instituted according to individual need, but, on the whole, the more the patient can comfortably tolerate, the sooner re-expansion will occur.

There is no virtue in siting a "low" drain, even for liquid. A drain of appropriate size in any position in the pleural cavity will restore negative pressure and re-expansion of the lung, expelling excess pleural contents. Accurate placement of the tip of the drain, once inserted, will expedite the process but is not essential. Insertion in the fifth intercostal space in the anterior axillary line is safe and should avoid the risk of abdominal penetration. As for size, a 28 French gauge or larger drain should be used for blood to minimise blockage. However, a 24 French gauge is adequate for air or low viscosity effusions.

A major subject of concern is the standard of equipment with which medical staff are expected to insert a drain safely and efficiently. What is provided, even in cardiothoracic wards or accident and emergency departments, is almost universally inadequate. This is a correctable contributor to the morbidity associated with chest drainage. Few items are needed to establish safe, efficient chest drainage, but they are seldom provided. Usually, a "trolley" is set up containing some local anaesthetic, skin antiseptic, and drapes, a small dressings set containing plastic forceps, a scalpel, a chest drain with trocar, a 2/0 (or smaller) suture, and the underwater drainage system. These items alone do not allow safe access to the pleural cavity and will cause undue discomfort for the patient. The trocar is often wrongly used to gain access to the pleural cavity, making this a dangerous procedure.[6]

These problems can be avoided by providing appropriate equipment. We recommend that a trocar should never be used and that access to the pleural cavity must be attained by blunt dissection. To achieve this, metal instruments are needed (such as a pair of artery forceps), with which the incision through the intercostal muscles can be widened to allow passage of a finger. The finger should then be used to establish access to the pleural cavity. The artery forceps should be applied to the inside tip of the chest drain in parallel, thus creating a firm, blunt tip. This rigid arrangement can safely be passed into the pleural cavity via the previous breach in the parietal pleura and directed either apically for air or basally for liquid. It should then be connected to the underwater drainage

system. To secure the drain, a suture of number 1 or greater (silk or nylon) should be used to allow firm tying and avoid breakage. The tube should then be taped to the side of the patient, avoiding the large quantities of strapping often seen.

Perhaps the most commonly encountered error in chest drain management is clamping of the tube. There is no definite indication for clamping a chest drain, and it may be highly dangerous, potentially converting simple pneumothoraces to life threatening tension pneumothoraces.[7] Unfortunately, drains continue to be clamped, even on "specialist" units. This usually occurs during transfer to the radiology department or between units by nursing staff. It must be discouraged.

As a result of our observations, we have designed a prepacked chest drain set for our hospital containing the basic items needed for the safe insertion of chest drains (see box). We advocate the application of the principles of advanced training in life support[1] and encourage inexperienced practitioners to seek help early. Standardised methods of inserting and managing chest drains would be of benefit to both patients and medical staff.

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Discrimination, informed consent, and the HIV infected clinician

We must ask whether patients' rights to avoid the remotest of risks should override clinicians' rights to practise as long as their skills remain unimpaired

In the middle 1980s a central ethical challenge posed by the AIDS epidemic entailed the issue of whether doctors were obliged to care for patients infected with HIV regardless of the small but ineliminable risk that they might become infected as a result. Without exception, those who considered the issue from an ethical perspective concluded that doctors were morally obliged to provide care even in the face of risk; that professional duty took precedence over personal fear or preference.

It was within that context that a small closed meeting was convened in 1988 at the Hastings Center, a research institute just north of New York, devoted to the study of medical ethics. The aim of the meeting was to examine a related but quite different issue: whether patients have a right to avoid contact with doctors infected with HIV. Two leading advocates of the rights of people with HIV, who were at the same time well known for their defence of patients' rights, were asked to address this issue. To the surprise of many at the session, both concluded, with great difficulty, that clinicians who engaged in invasive procedures had a duty to avoid exposing their patients to even the remotest of risks and should stop practising if they became infected.[1]

Despite this conclusion they adamantly opposed mandatory HIV testing to identify infected health care workers, a position that many suggested was inconsistent with their exclusionary posture. Further confounding the discussion was the observation of a conservative professor of law that the exclusion of HIV infected doctors was an irrational but predictable consequence of a regulatory philosophy that assumed that consumers had a right to be protected from risks that were vanishingly small.

I recall this meeting that occurred almost a decade ago because it may shed light on the complex issues involved in the case of Dr Patrick Ngosa, the British obstetrician recently barred from practising medicine because he delayed being tested for HIV despite suspecting that he was infected. The case has produced a paroxysm of anxiety and calls for mandatory HIV testing of health care workers.[2]

The discussions at the Hastings Center took place before the wave of consternation over the American dentist David Acer, several of whose patients developed HIV infection. The precise mechanism of HIV transmission in that dental office has never been resolved. But it was the near death testimony before Congress of one patient, Kimberly Bergalis, in which she denounced those who had failed to protect her, that forced the issue of infected doctors on to the agenda of AIDS policy.

It mattered little that the estimates from the Centers for Disease Control of the risk of HIV transmission—1/40 000 to 1/400 000 from HIV infected surgeons and 1/200 000 to 1/2 000 000 from HIV infected dentists[3] —were vanishingly small (the risk of a fatal reaction to anaesthesia in surgery is 1/10 000). Infected doctors became a symbol of dread. It was not surprising that those who believed that the struggle against AIDS had been subverted by a cabal of civil libertarians and gay activists used the occasion to call for draconian measures.[4] Nor was it surprising that

those who had opposed simple measures like needle exchange for injecting drug users—a policy that might have prevented thousands of infections—suddenly argued that any measure that might prevent even one infection (such as testing all doctors and debarring all those who were seropositive) was morally imperative. What was surprising was that the case of Dr Acer produced a fissure between those who had been allies in the struggle for sound, effective AIDS prevention and in efforts to overcome the shameful pattern of discrimination that had punctuated the history of the epidemic. In that clash we can come to appreciate the most difficult challenge posed by the healthcare worker who is infected with HIV.

Several prominent ethicists argued that the principles of medical ethics, which established the right of informed consent, provided ample grounds for claiming that patients had the right to determine whether they should assume even the remotest of risks of HIV transmission in the course of their treatment. Furthermore, they argued that in the previous 20 years medical ethics had evolved away from an objective standard (determined by doctors) of which pieces of information about risk needed to be shared with patients as part of an informed consent, to a "subjective" or patient centred standard. In short, it was for patients, not the experts, to establish the norms of risk disclosure.

For those who opposed the imposition of practice limits on infected healthcare workers, the picture was very different. They argued that the remoteness of the risk of HIV infection rendered practice limitations unnecessary and the demand for disclosure about HIV an unwarranted invasion of privacy. This perspective was in keeping with the historic effort to protect people with disabilities from irrational discrimination. At its core was a determination to prevent subjective fears from overwhelming objective evaluation of the prospects of injury. Fears about exceedingly remote risks could not justify acts of discrimination in medicine or elsewhere. Hence, given what was known about HIV transmission from healthcare workers to patients, exclusionary policies entailed a profound violation of individual rights. What was needed were practice guidelines, such as the introduction of universal precautions, that would reduce the risk of all nosocomial infections. [5]

Between the logic of informed consent and the logic of antidiscrimination there is a deep conceptual chasm, one that ought not to be papered over. Nevertheless, both perspectives help to illuminate the problems posed by physicians like Dr Ngosa. The central issue is not whether healthcare workers should be subject to mandatory screening. It is whether those who are infected should be deprived of the right to practise medicine. In confronting that question, it is essential that we ask whether the rights of patients to refuse to subject themselves to the remotest of risks should trump the rights of doctors who are confronting their own AIDS related mortality to care for patients as long as their skills remain unimpaired. Quiet and careful deliberation, not noisy clamour, is what is needed.

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Removing bias in surgical trials

New surgical procedures will continue to lack credibility unless assessed by properly randomised trials with objective outcome measures

Before a new drug is introduced into clinical practice it has to be shown, by randomised double blind clinical trials, to be at least as effective as currently available treatments. The same has not been true of new surgical procedures. The safety and efficacy register of new interventional procedures (SERNIP),[1] recently set up by Britain's Academy of Royal Medical Colleges, provides a framework that should go some way to remedying the defect, but it is still voluntary rather than compulsory. Although comments such as "the personal attributes of surgeons differ from those needed for collaborative multicentre research"[2] are unhelpful generalisations, there has been a tendency for surgeons to rely on series of operations without objective assessment of their value. In a careful study of 10 international journals from 1988 to 1994, Hall *et al* found that, of the few randomised controlled trials that were published, less than half included objective methods for assessing outcome.[3] For surgical trials to have credibility, it is vital that assessments are seen to be unbiased and that those taking part are appropriately blinded to which procedure has been done.

Blinding of patients and doctors is necessary in the following three situations. Firstly, when the expectations of patients and their carers are such that they could influence the outcome; for example, when there is enthusiasm for a new surgical prodecure. Secondly, when the outcomes are based on patients' own assessments, such as quality of life scores. Thirdly, when the treatment is primarily for symptoms.

It was possible to compare three different operations for duodenal ulcer in the famous Leeds-York trial in the 1970s because the incisions were the same and patients were randomised in the

operating theatre and the physician assessing them afterwards was unaware of which procedure had been performed.[4] A similar randomised study found that wound compression pads applied immediately after operation were not effective at reducing postoperative bruising or formation of haematoma.[5]

Comparing operations through different incisions is more difficult. In a comparison of laparoscopic and small incision cholecystectomy, patients and nursing staff were blinded (single blind) by the use of identical blood or iodine stained opaque dressings irrespective of which operation was performed.[6] It was possible therefore to assess the time taken to postoperative feeding and length of hospital stay eliminating bias caused by the expectation of staff that patients treated by the laparoscopic approach should recover quicker. Similar methods must now be used to assess other laparoscopic procedures such as inguinal hernia repair and appendicectomy.

The ultimate means of blinding in surgical trials is to use a placebo operation. In the 1950s ligation of the internal mammary artery became popular for treating angina because it was thought to divert blood to the heart. The procedure was introduced into practice without proper evaluation. Later, a trial was performed in which half the patients underwent ligation while the other half had the same incision but no ligation. No difference was found in the relief of symptoms between the two groups.[7] A sham operation was also used in the evaluation by the United States Veterans Administration of the role of prophylactic sclerotherapy for oesophageal varices, in which patients were randomised to either endoscopy and injection of sclerosant into the varices or endoscopy with sham injection.[8]

When surgery is being compared with non-surgical treatment it is impossible to blind the carers or the patients at the time. In such cases it is essential that the assessment on follow up is performed by someone who is unaware of the procedure, and the patients must be told not to divulge details to the assessor. Examples include comparisons between bilateral oophorectomy and tamoxifen,[9] and between adrenalectomy and aminoglutethimide plus hydrocortisone in metastatic breast cancer.[10] Studies that used objective end points (such as mortality, Q wave myocardial infarction, and stroke), when blinding is not so important, include the prospective comparisons of angioplasty and surgery for coronary artery disease.[11]

Funding of randomised trials is a problem. Whereas research grant committees are often prepared to fund apparatus and laboratory animals, they may be reluctant to fund an operating theatre list once a week and a dedicated outpatient session for assessment and follow up. Yet these are what good prospective surgical trials require. Most drug trials are funded by pharmaceutical companies, but where an operating technique rather than an instrument is being assessed such commercial funding is not available. Funding bodies of all kinds must be sensitive to the need for surgical trials, and it is hoped that the Culyer recommendation on support funding for research in England will help to address these problems.

In most cases it is ethically desirable to obtain permission from patients before randomisation. Patients usually find this easy to accept. However, when the patient's knowledge of possible treatment options may confound the assessment, gaining informed consent may bias the study or make it impossible to perform. A particular example concerns the evaluation of the effect of different types of support on the prevalence of psychiatric morbidity in patients after surgery for breast cancer.[12] Patients were not informed that they had been enrolled in this study, and informed consent was not sought.[13] Although this trial has been criticised for lack of informed consent,[14] the authors argue that it is important to perform research in all relevant patients rather than in the self selected group of patients who would have consented to be enrolled in such a study.[13] However, the current view is that all research subjects should be consulted before being enrolled into any study.[15]

Unless assessments of surgical procedures are seen to be unbiased, properly randomised, and with objective assessment of outcomes they will continue to lack credibility. Health services will then be burdened on the one hand by the introduction of new operations that are of unproved value and may be more expensive, and on the other hand by the persistence of old procedures that should have been abandoned years ago.

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Ultrasonographic "soft markers" of fetal chromosomal defects

Detecting them may do more harm than good

Most women in Britain have at least one ultrasound scan during their pregnancy. Aside from confirming viability and establishing gestational age, ultrasound may also indicate the possibility of an abnormality. An obvious structural problem, such as anencephaly, will have predictable consequences that can be discussed with the patient with some confidence. Less straightforward is the case in which a scan identifies a so called "soft marker"—a minor, usually transient, structural change which may indicate a risk of serious fetal anomaly but which in itself is probably inconsequential.

Ultrasound imaging has improved vastly in quality, and for this reason, and because first trimester scans are now performed more often, the frequency with which "markers" are observed has risen correspondingly. Some markers may well have disappeared by the time of the "routine" scan at 18-20 weeks.

Of those markers indicating pathology, most are associated with an abnormal karyotype. The presence of two or more markers makes this much more likely, although some markers, such as nuchal translucency, have a significant association with chromosomal anomalies even when they occur alone.

Measurement of nuchal translucency has now been refined to the point where risk can be calculated with some precision.[1] When the test is performed between 10 and 14 weeks, one study suggests that about 6% of low risk and 16% of high risk women will be positive and merit further investigation by invasive prenatal diagnosis.[2] The sensitivity for aneuploidy is about 85%.[2] However, about half of those with a chromosomal disorder are likely to undergo spontaneous abortion,[3] which throws uncertainty over the precise value of the test. It may be less appropriate for widespread clinical use than was first anticipated, and certainly, other groups have found nuchal translucency screening to be less effective.[4]

Choroid plexus cysts have also caused controversy. Found in about 1% of fetuses examined before 20 weeks, these structures may, when found in isolation, indicate an overall risk of trisomy of about 1 in 150.[5] But their most common association is with trisomy 18, which is almost universally fatal. The residual risk of Down's syndrome is therefore about 1 in 880, so the need for confirmation by invasive prenatal testing cannot be an automatic assumption; maternal age, together with the presence of other risk factors, must be taken into account.

Another marker, minor dilatation of the fetal renal pelvis (pyelectasia), has a background incidence of about 1% and was originally thought to be fairly strongly associated with Down's syndrome.[6] Although this association holds when pyelectasia is found with other markers,[7] the risk in isolation may be small. However, identification of this marker may confer other long term advantages, since its presence may indicate a baby at subsequent risk of urinary tract abnormalities.[8]

Ultrasonically echoreflective bowel (bright gut), short femurs, clinodactyly of the fifth digit, and oddly shaped heads have all been identified as soft markers associated with an increased risk of trisomy. The risk associated with any one of these may be little greater than that conferred by maternal age, but if other markers are also present the likelihood of a karyotypic problem rises dramatically.

The problem with soft markers is that, even when karyotypic abnormalities are excluded, the mother and her obstetrician will remain in doubt as to their significance—a cause of considerable anxiety.

Information about ultrasonographic markers is relatively new. Many of the background data come from referral units and are therefore biased. These markers promise to be useful in screening for chromosomal abnormalities when considered alongside maternal age. But such screening may not be feasible when searching for soft markers requires more time and probably better equipment and training than a standard scan; and it may not be ethically acceptable when identifying these markers increases anxiety, usually unnecessarily and often without prior counselling.

The role of ultrasonographic soft markers and their relation to serum screening is therefore unclear. If markers are to form part of the routine ultrasound examination three criteria must be fulfilled: the complexity of diagnosis must be matched by technical skills and equipment; the counselling offered must be detailed and of high quality; and the costs must be justified by the benefits to women.

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