

Ethical issues in molecular medicine of relevance to surgeons

Mark Bernstein, MD, MHSc;^{*†‡} Joseph Bampoe, MB ChB;^{*} Abdallah S. Daar, DPhil (Oxon)^{†‡§}

The technology associated with the care of surgical patients and the level of sophistication of biomedical research accompanying it are evolving at a rapid pace. Both new and old bioethical issues are assuming increasing levels of prominence and importance, particularly in this age of molecular medicine. The authors explore bioethical issues pertinent and relevant to surgeons. Four specific areas that are exemplary by presenting both major scientific and ethical challenges are briefly addressed: privacy of information, stem cells, gene therapy, and conflict of interest in biomedical research. All of these can be generalized to all surgeons. As bioethical issues today play a greater role in surgical practice than they did even a decade ago, it is hoped that this brief review on ethical issues in molecular medicine will help stimulate present and future generations of surgeons in thinking about the ethical dimensions of their work.

La technologie associée aux soins des patients en chirurgie et le degré de perfectionnement de la recherche biomédicale connexe évoluent rapidement. Les enjeux anciens et nouveaux de la bioéthique deviennent donc de plus en plus importants et évidents, particulièrement à l'ère de la médecine moléculaire. Les auteurs examinent les enjeux de la bioéthique pertinents aux chirurgiens. Quatre domaines en particulier sont exemplaires parce qu'ils posent des défis scientifiques et éthiques. Ils sont considérés brièvement : la confidentialité des renseignements, les cellules souches, la thérapie génétique et les conflits d'intérêts en recherche biomédicale. Tous peuvent être généralisés à tous les chirurgiens. Les enjeux de la bioéthique ont aujourd'hui une plus grande importance dans la pratique chirurgicale qu'il y a une décennie à peine. Espérons que ce bref examen des enjeux de la bioéthique en médecine moléculaire aidera à stimuler la réflexion des générations actuelle et future de chirurgiens sur les dimensions éthiques de leur travail.

Molecular medicine encompasses several research and clinical disciplines. Here we briefly address 4 important areas that are topical and relevant to surgeons as well as to molecular scientists: privacy of information; stem cells; gene therapy; and conflict of interest in biomedical research. Each can be generalized to all surgeons, and each presents us with great scientific and ethical challenges. For the interested reader, Table 1 highlights issues related to the first 3 topics, with a

special focus on the ethical principles they contain.

The role of bioethical issues in surgical practice continues to grow. This brief review on ethical issues in molecular medicine was written to encourage consideration of the ethical dimensions of surgical work.

Privacy of information: databases, tissue banks and genetic information

Important developments have re-

cently come together to make privacy of information one of the most hotly debated issues in modern biomedical research, particularly in the field of genetics and genomics.¹⁻⁹ Of specific interest to the surgeon and the molecular investigator is the use of banked or fresh tissue for research purposes.^{10,11}

The rapidity of scientific advances, for example the sequencing of the human genome, has put enormous power in the hands of researchers. Information technology, including

From the ^{*}Division of Neurosurgery, Toronto Western Hospital, and the [†]Joint Centre for Bioethics, [‡]Department of Surgery and [§]Department of Public Health Sciences, University of Toronto, Toronto, Ont.

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Correspondence to: Dr. Mark Bernstein, Division of Neurosurgery, Toronto Western Hospital, 399 Bathurst St., 4W451, Toronto ON M5T 2S8; fax 416 603-5298; mark.bernstein@uhn.on.ca

Table 1

Ethical issues in molecular medicine

Ethical issue	Justifying principles	Problems
Patenting of human genetic material (or animal life of any sort)	<p>Provides biomedical industry with the opportunity to recoup research and development costs and make profits.</p> <p>Places control over genetic material in the hands of an identifiable entity or person who is then responsible for quality control (efficacy of tests) and the ethical use of the genetic material.</p> <p>Justified by principles of justice and responsible treatment of finite resources.</p>	<p>Bioprospecting, biopiracy, biocolonialism.</p> <p>Profit incentive results in premature implementation and inappropriate use of genetic testing.</p> <p>Possible decreased availability of tests and their benefit to the public.^{2,4,5}</p>
Regulation of human body parts and products (problems with creating tissue and DNA data banks)	<p>Facilitates research on gene function and interactions.</p> <p>Large collections would make genetic epidemiology studies possible.</p> <p>Some conflict between principles of public beneficence and autonomy of contributors.</p>	<p>Rigorous consent requirement reduces the number of entries; resolved to some extent by using opt-out mechanisms and anonymization.</p> <p>Security, control of and access to genetic information, especially when linked to patient records.</p> <p>Informed consent not possible for future (unforeseen) use of tissue.</p> <p>Informed consent not possible or practicable for use of large institutional archival tissue.^{10,36,39,40,50}</p>
Studies of genetically defined (homogeneous) populations or patients with rare diseases	<p>Rare opportunities for studies of genetic linkages.</p> <p>Opportunities to exploit tissues or their products commercially, e.g., the creation of unique cell lines.</p> <p>Some conflict between principles of societal benefit versus patient autonomy and justice.</p>	<p>Do patients or subjects of these studies have property rights and thus, rights to profits that accrue from these studies?</p> <p>Charges of deceit or, at best, conflict of interest could be made against clinicians and scientists working in such studies.^{5,69,73}</p>
Proliferation of commercial genetic testing, especially during the antenatal period or as part of (marriage) counselling	<p>Medical imperative: the burden of the disease and the desperation of afflicted patients mandates the development of techniques for early detection of disease or carriers.</p> <p>Some conflict between patients' right to know (particularly when effective therapeutic measures can be instituted) and relatives' right not to know.</p>	<p>Responsibility of physicians to be aware of the existence of tests, their efficacy and availability. Failure to do this could result in liability for wrongful-birth or wrongful-life claims based on negligence or lack of informed consent.</p> <p>Lack of consensus on indications for testing asymptomatic patients with adult-onset, genetically heterogeneous disorders.</p> <p>Potential adverse psychological effect on patients or relatives, or genetic discrimination in employment or insurance, particularly when effective treatment of disorders is not yet available, e.g., Huntington's and Alzheimer's diseases.^{2,32,33,55}</p>
Neuronal cell transplantation	<p>Medical imperative: desperation of patients after failed treatment.</p> <p>Justified by principles of beneficence and non-maleficence.</p>	<p>Diffuse conditions such as Alzheimer's disease are less amenable to transplant therapy than focal conditions such as spinal-cord trauma or stroke.</p> <p>Modifications of the host's brain by cell grafting and rewiring raises issues about alteration of personhood.</p> <p>Current lively debate about stem-cell supply; new sources of neuronal stem cells such as clonal expansion from mature tissue of the host could be exploited.^{5,20,40,57}</p>
Gene therapy	<p>Medical imperative: used for conditions with a grave prognosis despite optimal conventional treatment, such as malignant glioma.</p> <p>Hazards of somatic gene therapy are not limited to the host being treated; e.g., germ-line gene therapy is considered unacceptable because of its unknown effect on future generations.</p> <p>Justified by principles of beneficence: possible eradication of serious inheritable and other disorders.</p>	<p>Limitation of the technique: gene-delivery problems are still prohibitive.^{5,20,40,57}</p>

the emerging field of bio-informatics, makes it much easier to gather, store, analyze and disseminate information such as genomic and complementary DNA sequences and expressed sequence tags (ESTs), and to apply patent such material.¹²

The mounting commercialization and private-venture capital-based funding of research puts increasing pressure on researchers to behave within boundaries of ethical acceptability. Meanwhile the tension between ethical guidelines, well-established common law and emerging health information legislation makes it increasingly difficult and confusing for researchers to define and navigate the boundaries of acceptable behaviour. The growing number of research projects puts enormous pressure on institutional review boards, which are often unprepared to deal thoroughly with many of the applications due to inadequate knowledge or available time.¹³

Genetic information

Ethicists have argued whether genetic information is any different from any other type of medical information. In public surveys in Canada, the vast majority of people polled responded that genetic information is different and that access to it should be more strict than, say, information about diseases and their treatments.¹⁴ Focus groups have revealed a deep conviction that genetic information is fundamentally personal and private.¹⁴ How can we best protect personal and public interest while obtaining maximal research utility from genetic databases?

Since Hippocrates, medical information has been considered private and meant to be treated confidentially. The power of genetic information, its emerging sensitivity and potential misuse in employment and insurance, and its implications for genetic relatives makes the discussion of privacy and confidentiality particularly sensitive.^{15,16} The basic ethical

requirement on use of such information is the need to obtain *informed consent*, which is based fundamentally on respect for autonomy, individual self-determination and human dignity.¹⁶⁻²¹

Consent is an ongoing process and not just a matter of signing a form. It has 3 elements; the first is *disclosure and comprehension*. The physician caring for a patient, or researcher interacting with research subjects, is obligated to disclose all material information, especially that concerning potential health risks. The information must be comprehensible and imparted in appropriate language. The physician or researcher must ensure that the patient or study subject has understood the benefits of and risks associated with the procedure and the gathering and sharing of the data that derive from the study.

Second is *capacity*: the subject must have the capacity to comprehend fully. If not, then either the subject is unfit to participate, or the prevailing law may allow for proxy consent, which must be obtained with the same provisos of disclosure and comprehension.

Third is *voluntariness*: the subject must come to the decision freely, without coercion or manipulation.²⁰ Ultimately, the physician or researcher must act at all times in the best interests of the subject.

What do we do when the future nature of the research is not known? An emerging issue is the inadequacy of the informed-consent model with respect to the future use of information databases or banks of biological materials. The consent obtained cannot a priori be fully informed because all risks and benefits are not as yet known and therefore unknowable at the outset. One proposal has been to use broad or blanket consent, which would empower the researchers or keepers of the data or tissues to use the material in any way they see fit with no conditions applied.²² However, most legal and eth-

ical experts would likely contend that such a blanket consent would not stand up to scrutiny in a court of law or in the court of public opinion, not only because of the undefined and general nature of the provisions but also because of the asymmetry of power between the clinician/researcher and the patient/subject.²²

Others have advocated a form of layered or tiered consent. The national Heart, Lung and Blood Institute,²³ for example, has advocated a 3-tiered consent in which an individual is offered the option of consenting to the current study (first level), a study with goals broadly related to the area of the original study (second level), and/or a study with goals unrelated to the area of the original study (third level). Tiered consent has also been adopted by investigators conducting various genetic research studies.^{24,25}

We believe, however, that any form of consent as currently understood may be inadequate. Instead, we favour an authorization model for future indescribable uses of DNA data collected in the context of population genetic databases.²⁶ In this model, participants in genetic databases are able to exercise some control over future uses of genetic material by giving permission and discretion to researchers; this preserves their autonomy but promotes research.²⁶

Why are such safeguards necessary? Let us illustrate with an example relevant to orthopedic surgery. There is interesting research showing that the severity of certain types of arthritis can be predicted by genetic analysis of serum.²⁷ What if a person whose future career depends on heavy physical work volunteers his/her blood for a research study and these genetic predictors are found? Because the individual's probable future health problems are now known, this information in the hands of a prospective employer might become an obstacle to the person's being hired.

It is possible to overcome the con-

fidentiality issue by using mechanisms that de-link personal identifiers from the information in databases. This can be done either by coding (e.g., the name, age, sex, hospital number) or, more drastically, by anonymization — by completely removing the identifiers. Common sense holds that the utility of the information will diminish in direct proportion to the extent of de-linking. Furthermore, anonymization would make it difficult or impossible to identify the subject to offer life-enhancing or life-saving advice based on information from the research, or where appropriate to share the information with genetic relatives at risk. A neurosurgical example was the discovery that a germline mutation in the *hSNF5* gene on chromosome 22 predisposes offspring to malignant posterior-fossa tumours of infancy.²⁸ An important example in general surgery and oncology is the relationship between the presence of the *BRCA1* and *BRCA2* genes and the incidence of breast cancer in relatives.²⁹

Further careful thinking, research and public engagement is required to formulate the policies that are ethically most appropriate. Ultimately, fundamental ethical requirements to respect the subject's dignity, autonomy and self-determination must be observed.

Stem cells

Few areas of public discourse in biomedical research have been as controversial in recent times as the use of stem cells, particularly embryonic stem cells.^{30,31}

Some of the debate has conflated several different issues, including those relevant to abortion and cloning. Often, delicate but important nuances that are so crucial to determining what constitutes ethical behaviour in such complex areas have been ignored in the debate. This dilemma is important to resolve, as stem cell research has potential major implications for the treatment of seri-

ous disorders such as neurosurgical (examples include spinal cord injury³² and Parkinson's disease³³), general surgical (liver failure),³⁴ cardiac (ischemic heart disease),³⁵ urologic and plastic surgical (urologic organ regeneration),³⁶ orthopedic (bone and cartilage repair)³⁷ and many other degenerative conditions.

There are essentially 2 classes of stem cells: adult and embryonic. There is little controversy associated with the former.

Embryonic stem cells are derived from early embryos at about the 5–7-day blastocyst stage.³⁰ They have the potential to replicate in culture indefinitely, but also (with appropriate signals) to differentiate into many different cell types and tissues.³⁸ They are thus considered to be pluripotent. The controversy surrounding them is heated mainly because the blastocysts must be destroyed in order to harvest the stem cells. The main issue of contention here relates to when human life begins. If it begins at conception (in other words, at fertilization), then destroying a blastocyst is terminating a human life.³⁹ However, not all people agree that life begins at fertilization; within the world's great religions there are notable differences in the definition of when life begins.^{39–42} Members of the public are also likely to have diverse opinions in this matter, irrespective of religion.

In the United States, a debate has centred around the issue of using federal funds for research using embryonic stem cells. President George W. Bush has decreed that federal funding cannot be used for embryonic stem cell research except when using cells already in existence on August 9, 2001 (when the declaration was made), and only those cell lines whose derivation adhered to strict requirements of informed consent.⁴³ However, the USA has a strong private sector doing advanced molecular biological research, and at present the presidential ruling affects neither private-sector work with embryonic stem cells nor research fun-

ded at state levels.⁴⁴ Attempts by the US Congress to pass laws that would apply to all researchers have so far, as of this writing, failed.⁴⁵

Others have focused instead on the source of the embryo. They argue that when the source is excess embryos, as often occurs following in vitro fertilization, it is ethically justifiable to use them to derive embryonic stem cells because these embryos would be destroyed anyway.

Various jurisdictions are contemplating legislation that would regulate the use of embryonic stem cells, but so far, no country has enacted legislation as permissive as that in the United Kingdom.^{46,47} In Canadian draft law on reproductive technologies, using excess embryos to derive embryonic stem cells would be allowed, but not the creation of new embryos specifically for research or for therapeutic purposes.⁴⁸

Therapeutic cloning (somatic-cell nuclear transfer)

One of the most exciting developments in molecular medicine is the application of embryonic stem cell and other technologies in what is becoming known as *regenerative medicine*. This entails, among other things, bioengineering to repair, replace or regenerate failing organs and tissues.^{32–37,49} It is theoretically possible to generate such tissues from stem cells that are genetically identical to the patient in need, thus obviating the problem of rejection of tissues transplanted from allogeneic donors. It would involve the insertion of the patient's nuclear DNA from differentiated adult (somatic) cells into an enucleated ovum, which then begins to divide. Any stem cells removed from this blastocyst, and therefore any subsequent tissue or organs derived from it, would be genetically identical to the patient and would not, therefore, be rejected.

This is ethically unacceptable to those who believe that human life begins at fertilization and who would

also argue that although fertilization is traditionally defined as the fusion of an ovum with a sperm, nuclear transfer is the same as fertilization or conception. In somatic-cell nuclear transfer (SCNT), the conditions are very different and an argument can be made that this is, in fact, not strictly fertilization; some might even argue that since an embryo is by definition derived from fertilization, that the single cell entity from SCNT is not, therefore, an embryo. Nomenclature is becoming crucial to the whole debate surrounding the use of embryonic stem cells. For others, SCNT is more acceptable, especially when one considers the potential to heal large numbers of people with conditions such as end-stage organ failure (e.g., of the kidney, liver or heart), Parkinson's disease and Alzheimer's disease.⁵⁰

In Canadian surveys, the public is supportive of embryo research.¹⁴ One must not confuse therapeutic cloning with reproductive cloning, which is almost universally considered unethical.⁵¹ There is now a large body of literature on reproductive cloning and the ethical issues surrounding it, and it is important for the differences between reproductive cloning and therapeutic cloning to be borne in mind when discussing stem cells.

Adult versus embryonic stem cells

If adult stem cells were found to have the same properties as embryonic stem cells, few people would want to use embryonic stem cells for research or therapeutic purposes. Recent reports describing multi-potent adult progenitor cells (MAPC), which appear to have many but not all the characteristics of embryonic stem cells, have sharpened the debate.^{52,53} However, this has yet to be reproduced by other researchers, and in fact other papers have appeared that cast doubt on the versatility or plasticity of adult embryonic stem cells.⁵⁴ In any case, MAPC will not address the other major reason why

scientists wish to do research on embryonic stem cells, namely to unravel the mysteries of human developmental biology.

Gene therapy

Patients with inherited genetic disorders and neoplastic conditions are among those who would be expected to benefit the most from this interesting new field.⁵⁵ Other fascinating and wide-ranging potential applications of this technology include spinal fusion, presently in the experimental stage.⁵⁶

The main problem to date with gene therapy has been the difficulty with gene targeting and vectors for gene delivery. In the 1990s, it appeared as though successful gene therapy for single gene defects would be achievable. Indeed, the successful treatment of a few children with severe combined immune deficiency did raise hopes.⁵⁷ But despite considerable research funding, there has been little positive translation into clinical results in the treatment of cancer, including primary malignant brain tumours, which are almost always fatal.⁵⁸ The major stumbling block is inadequate gene-delivery vehicles, although improvement is ongoing.⁵⁹

The limited success of gene therapy forces us to call into question the ethics of any experimental treatment having a low yield for potential benefit. Herein lies a delicate tension between well-intentioned researchers attempting to translate scientifically sound and exciting concepts into clinical trials for patients with incurable conditions, and the reality that as yet, a given technique may simply be unable to keep abreast of theory.

The other major ethical issue has revolved around the regulatory environment: do commercial interests and investigator conflicts of interest (COIs) cause real harm to patients or tarnish the scientific objectivity of the research findings?⁶⁰ The case of the young man, born with an inherited

metabolic defect but leading a fairly normal life, who was subjected to an experimental gene therapy at the University of Pennsylvania that killed him, illustrates many of the issues and pitfalls related to the effective translation of gene therapy theory into practice.^{61,62} This patient ultimately died from an adverse immunological reaction to the adenoviral vector being used to try to overcome his inborn error of metabolism. As a consequence, and following Food and Drug Administration (FDA) inspection, the Institute of Gene Therapy at the University of Pennsylvania was instructed to stop and not initiate any more clinical trials, and at present the future of gene therapy trials is guarded.⁶³

Conflict of interest in molecular medicine research

One of the most important changes in research in the past decade has been the increasing participation of private interests in biomedical research. Around 70% of all funds spent on clinical drug trials in the USA comes from industry rather than from the National Institutes of Health.⁶⁴ Venture-capital money and money from well-established multinational corporations alike is being poured into research at all levels.⁶⁵ Traditional funding agencies are more frequently requiring matching funds from private industry. At the same time, clinician-scientists and other researchers are increasingly involved in establishing private companies, based often on the commercial potential of the intellectual property deriving from their research. Universities are setting up business development departments to help commercialize research and protect patents and other intellectual property.

The reduction in university funding from traditional sources such as governments has meant that many universities must now attract more private funding to function in a very competitive environment. Research-

ers move easily from academia to industry and back. In the US, one of the key developments was the passage in 1980 of the Bayh–Dole Act, which transferred intellectual property rights to researchers funded by federal research monies.⁶⁶

Is all this good for research? There are concerns that the direction and prioritization of types of research may be affected, away from basic science toward more applied research, and publication of findings may be withheld for longer than was the norm in the past. However, very good research is coming out of private industry laboratories, and there is some evidence that the Bayh–Dole Act has increased innovation in the United States.⁶⁷ In any case, it seems that this particular change is inevitable and perhaps unstoppable. We therefore must find ways of dealing with the potential COIs for both institutions^{68–72} and individual investigators. Personal COIs for clinicians performing research are complex, involving nonfinancial benefit as well as monetary interest, and constitute a constant source of ethical tension that all clinician investigators must confront honestly.^{18,73–77}

Some commentators believe that if the potential financial rewards to the institution are of consequence, there is a strong case to be made that such COIs should be avoided in the first place; even a pilot trial should not be conducted in an institution that has a salient financial interest in the outcome.⁶⁹ Full disclosure of the COI is a minimum and essential requirement, and recusal from the trial would seem appropriate if the COI looks unmanageable.⁶⁹ (The most extreme step, recusal, may not be necessary if the financial interest is modest, in other words, is deemed unlikely to have an influence on decisions about patient care or research; but there is no standard for what constitutes a minimal financial interest, and any such judgement may be subjective.)⁶⁹ *Full disclosure* means that

- a. All patients must be informed of the COI, and this information must be included in the consent form.
- b. The financial interest/COI must be disclosed to the institutional review board.
- c. The same must be done for all those who have supported the research, including all collaborators, co-investigators, institutions and other persons.
- d. All publications, including oral presentations and abstracts, must also disclose the institutional financial interest.
- e. Every safeguard that has been put into place to deal with the COI must be disclosed.⁶⁹

The best safeguard might be to establish an external committee to monitor the COI.⁶⁹ This is cumbersome, and there may be resistance to it, especially as it is not yet common practice. If an institution establishes such a committee, it should ensure that its members are knowledgeable enough to review the research. At the outset, the external committee should review the research design; later, it should review the data generated and have the power to require modifications or stop the trial. Its members should not have any financial interest, direct or indirect, in the outcome(s) of the trial. They should not be paid beyond reasonable compensation for expenses incurred. The members might include a biomedical researcher, a lawyer and a bioethicist.⁶⁹

We believe that apart from constituting the ethically correct way to proceed, the safeguards recommended, especially the appointment of an external monitoring committee, will in the long run work to the institution's advantage. There is a risk that, as more accountability is required of institutions, regulatory agencies may come to insist that data from trials conducted at institutions having financial COIs be inadmissible as evidence for drug and device approval.⁶⁹ This would be “strong medicine,”

but would ultimately set a high ethical and scientific standard that would upgrade the quality of research and therefore benefit institutions and, of course, patients.

Summary

As we move further into the age of molecular medicine, surgical patients with diseases such as breast cancer, myocardial ischemia and osteoarthritis (to name a few) stand to benefit enormously from recent advances in molecular biology such as genetic testing, stem cell research/manipulation and gene therapy. Whereas previous eras in surgical patient care have been characterized by drug development, restoration of physiological parameters and technical advances in surgical instrumentation, the epoch of molecular medicine will be marked by unique advances and at the same time challenges that stimulate all of us to contemplate important questions about the origins of life and the use of biologicals from other patients. In this review, we have tried to articulate some of the bioethical questions related to molecular medicine, especially as they relate to surgeons.

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