SPECIAL ARTICLE

Functional Genomics

Clinical Effect and the Evolving Role of the Surgeon

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The genetic and molecular revolution that has occurred over the last 2 decades has dramatically increased our understanding of basic disease processes and will undoubtedly lead to improved detection methods and treatment. This will occur at an even more rapid rate after the completion of the Human Genome Project in the next 2 to 3 years. While these remarkable technological advances offer great hopes for novel therapeutic modalities, complicated medical, ethical, and legal issues will need to be addressed. This article briefly describes the advances that have occurred and their future ramifications for the field of surgery. Most assuredly, we will all be affected by these changes. Surgeons have the opportunity to be active participants and real leaders in the research and complex decisions regarding the optimal treatment of patients. However, formal training in these techniques and their potential applications will be required. Surgeons, as well as all physicians, must rise to the occasion or, otherwise, we will be relegated to a bystander status with clinical and moral decisions being made by nonclinicians. *Arch Surg. 1999;134:1209-1215*

Surgeons have always been at the forefront of technological and scientific medical advances. For example, at the turn of the 20th century, surgeons were actively involved in the development of antiseptic techniques and antibiotics, which have made operative procedures safer and more feasible. Our current knowledge regarding the physiologic basis of shock and the methods for resuscitation were made possible by surgeons. Moreover, the field of transplantation, which has completely revolutionized medicine, was forged by surgical investigators. With the explosion of molecular techniques and research in the past decade, surgeons once again have the opportunity to be leaders and active participants in the genetic revolution and the implications that this new information will have on the clinical practice of medicine. With the completion of the Human Genome Project (HGP) at the turn of the 21st century, there will be dramatic changes in the overall care and treatment of our patients and a better understanding of the cellular mechanisms responsible for a number of diseases. However, in addition to the potential benefits, this futuristic technology will bring new dilemmas and ethical concerns that have never been faced.

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THE HUMAN GENOME PROJECT

The scientific community put aside its differences to embark on a great journey that stretched across an almost endless set of genomic base pairs to achieve what no scientist had done before—the identification and sequencing of the estimated 100 000 human genes.[1] This endeavor was initially envisioned in the 1980s, but came to fruition with the collaboration between the National Institutes of Health and the Department of Energy. The partnership allowed for better coordination of the research and technical activities related to the HGP. Since its inception, great strides have been achieved ahead of schedule, and it is now anticipated that a "working draft" of the human genome DNA sequence will be generated by the year 2001. A complete and highly accurate reference sequence is expected to be available by the year 2003. If successful, the completion of the human DNA sequence in 2003 will coincide with the 50th anniversary of Watson and Crick's description of the fundamental structure of DNA.[2]

On completion, the HGP is expected to have a major effect on the field of medi-

cine, providing physicians with an unprecedented arsenal of genetic information that will hopefully lead to better understanding and treatment of approximately 4000 genetic diseases. One example is the discovery of single nucleotide polymorphisms in the genetic code that occur about once every 1000 bases along the 3-billion base human genome. Single nucleotide polymorphisms are thought to serve as genetic markers for identifying disease genes by linkage studies in families or from the discovery of genes involved in human diseases such as asthma, diabetes, atherosclerosis, schizophrenia, and cancer.[3-6] These findings may lead to better screening and help implement preventive medical therapy in the hope of reducing the development of certain diseases in patients found to have predisposing conditions.[7-9]

All surgical disciplines will be directly affected by the information obtained from this project. In this article we will focus on a few of the areas in which we foresee major developments occurring that will greatly influence our clinical care and surgical treatment.

THE POTENTIAL EFFECT OF THE HGP ON SURGICAL TREATMENT

Transplantation

For many years, transplantation of human tissues and organs has been performed to save the lives of individuals suffering from organ failure and other serious diseases. Despite the advancements in transplantation and immunology, the Food and Drug Administration estimated that approximately 48 000 people were on the waiting list for suitable organs for transplantation in the United States in 1996. This level of organ and tissue demand cannot be met by organ donation alone, and it is expected that patients will die while waiting for suitable organs or tissues for transplantation. The suitability of tissues and organs for transplantation is a major clinical consideration.

Rejection may occur in transplanted organs and will usually occur when the organ is recognized as foreign by the patient's immune system. The more closely the transplanted tissue matches the patient's own tissue type, the smaller the risk of rejection. To overcome this problem, patients are treated with drugs that suppress the immune system, but this type of intervention is still fraught with many complications (eg, toxic effects of drugs, opportunistic infections, and malignancy). Xenotransplantation has been proposed as a possible solution to the problems of organ availability and suitability for transplantation.[10,11]

Xenotransplantation is the transplantation of tissues or organs from animals into humans. Experiments in xenotransplantation were pioneered in 1905, but most transplantations involving animal organs into humans have been made since the 1960s, aided by advances in the understanding of the immune system and the availability of new drugs. Although this technique is considered to be a leading-edge technology, most patients receiving cross-species transplants have not survived for longer than 1 month following the operation. Data obtained from the HGP will enable transplant surgeons to genetically engineer animals to have specific combinations of human antigens. This would allow animals to be engineered with organs having human antigens precisely matching those of a transplant patient. Xenotransplantation could then be performed routinely without the associated risk of hyperacute rejection. The patient's immune system would not require modulation with immunosuppressive medications and thus eliminate complications currently known to exist with immunosuppression. The problem with organ availability would then become a point of historic interest rather than a current point of mortality.

The shortage of human organs for transplantation has pushed the field of engineering technology to develop temporary novel machinery to assist patients waiting for organs. This presents engineers with the problem of creating other devices to substitute for the needed organs (eg, heart, eyes, lungs, kidneys, and liver). For a successful artificial organ, the design must be complex to perform the desired function, but compact and simple enough to be placed in the human body. Most artificial organs are large external devices and tend to be more successful than their counterparts, the internal devices, partially because they are left outside the body where there is no size limitation. Nevertheless, the downside to these machines is that they are normally used for only short periods, such as during surgery, and are not practical for long periods of use. The HGP will provide engineers with the genetic tools to better design human organs and eliminate the need for mechanical, external devices.[12-14]

Organ cloning offers humanity the best hope for identical organ matches and the elimination of immunosuppression and its complications. Recent investigations using organ cloning have been implemented as a possible method to procure much-needed organs. In 1996, we witnessed the cloning of the lamb Dolly, based on the revolutionary somatic cell nuclear transfer technique, developed by researchers from the Roslin Institute in Edinburgh, Scotland. The nucleus was substituted for the chromosome normally provided by the sperm and egg at fertilization. Cloning has been practiced for a number of years in plants and mammals, and Dolly's birth simply followed an orderly progression of cloning techniques. Broadly defined, cloning is asexual reproduction resulting in a genetically identical organism. The first successful mammalian cloning by nuclear transfer was reported in 1986. It was performed by using cells from cleavage-stage sheep embryos fused with unfertilized sheep eggs. Fetal fibroblasts also have been used as a source of donor nuclei to produce live lambs. When genetic technology becomes established, cloning may be used to produce unique animal genotypes for agriculture. The most common procedure for the production of transgenic mammals uses a microinjection of DNA into 1-cell zygotes. Although appealing, the efficiency rate is still very low and its high cost has placed restraints on its use.[15-18]

Theoretically, by identifying the stem cells of interest, the information gathered from the HGP could enable scientists to develop organ cloning techniques that will revolutionize the field of genetics and transplantation. Stem cells have the ability to divide without limit and to give rise to specialized cells. Human development begins when a sperm fertilizes an egg and creates a single cell that has the potential to form an entire human being; it is therefore *totipotent*, meaning that its potential is total. As de-

velopment progresses, the embryo enters a new stage and is referred to as the blastocyst. The blastocyst is characterized by the formation of a hollow sphere of cells. This hollow sphere has an outer layer of cells, and inside the hollow sphere resides a cluster of cells called the inner cell mass. It is this inner cell mass that gives rise to the pluripotent stem cells that are capable of producing many but not all types of cells. The pluripotent stem cells undergo further specialization into stem cells that are committed to giving rise to cells with a specific purpose. Once a pluripotent stem cell specializes into a liver cell, it cannot change course. Pluripotent stem cells are not capable of producing totipotent stem cells. With the identification of these stem cells, it may soon be possible to develop the countless organs needed.[19-22]

Oncology

The use of genetic information in the treatment of cancer will influence the practice of all oncology surgeons in the next century. A key point of genetic screening is that the presence of these genes does not imply that the patient has one of the genetic conditions associated with the expression of the genes. It does, however, become important if that patient not only carries the genetic marker, but also has a family history of that type of cancer and/or has a close relative with cancer. The surgeon must be trained in all aspects of genetic data interpretation and be familiar with providing counseling to additional family members who are identified to be at risk.[9,23]

All forms of cancer have a genetic origin since mutated genes can trigger the neoplastic process. However, only a small percentage of cancers are actually inherited. Mutations are carried in reproductive cells, passed on from one generation to the next, and are therefore present in every cell throughout the body. Most cancers are generated from random mutations that have developed in somatic cells during one's lifetime either as a mistake during cell division or in response to injuries from environmental agents such as chemicals or radiation. Progression of a normal cell to malignancy appears to follow a series of defined steps, each one influenced by a different gene or set of genes. Several types of genes have been implicated in this progression, and it is here where the HGP will have its greatest influence.

Oncogenes normally encourage cell growth, but when mutated or overexpressed, they can trigger cells to continue to proliferate. Tumor-suppressor genes normally restrain cell growth; when missing or inactivated by a mutation, they allow cells to grow and divide uncontrollably. The DNA repair genes (ie, "proofreader genes") appear to affect neoplastic transformation by failing to correct mistakes that occur as DNA copies itself. This allows mutations to accumulate at thousands of sites and predispose to malignant transformation. The identification of disease-related genes has led to an increase in the number of available genetic tests that detect diseases or an individual's risk of disease.[24-30]

Genetic testing is available for many disorders, including Tay-Sachs disease and cystic fibrosis. New tests are being developed to detect predispositions to Alzheimer disease, colon cancer, breast cancer, and other conditions. The HGP will provide an unprecedented and powerful modality to increase our ability to screen high-risk groups and the general population. With the identification of certain high-risk groups for the development of cancer, surgeons will play an ever-increasing role in both genetic screening and ultimate therapy. Prophylactic surgery may soon become more prevalent as a first-line treatment in the fight against cancer, as demonstrated in patients with familial adenomatous polyposis and children with the multiple endocrine neoplasia syndrome type 2 (MEN 2).

The inheritance of familial adenomatous polyposis is mendelian dominant and can be inherited by either sex in equal distribution. The identification of the adenomatous polyposis coli (*APC*) gene has led to the development of genetic testing programs that are currently being evaluated. Following the identification of an *APC* mutation in a patient, unaffected family members will need to be tested to determine whether they too carry the mutated allele. Patients with mutated *APC* will develop colon cancer sometime in their lifetime; therefore, they will require colonic resection. The only points of controversy are the need for removal of the rectum and the timing of the surgery. A recent investigation[26] from the Netherlands suggests that the risk of rectal cancer was approximately 3 times higher in patients with *APC* mutations located after codon 1250 compared with patients with mutations before this codon. It is their recommendation that patients with an *APC* mutation before codon 1250 undergo a total proctocolectomy with permanent ileostomy or an abdominal colectomy and ileorectal anastomosis. Those patients with mutations after codon 1250 are candidates for an ileal pouch anal anastomosis. These findings will require further evaluation.

The discovery of the association between mutations of the RET proto-oncogene and hereditary medullary thyroid carcinoma has allowed surgeons to identify patients who will eventually develop medullary thyroid carcinoma. Genetic screening for RET proto-oncogene mutations in patients with MEN 2 allows prophylactic thyroidectomy to be performed in RET mutation-positive patients at an earlier stage of the disease process than does traditional biochemical screening. The current English-language literature concludes that a considerable number of children with MEN 2A or MEN 2B, who have clinical or biochemical evidence of medullary thyroid carcinoma before thyroidectomy, have persistent or recurrent disease after long-term clinical follow-up and supports the importance of prophylactic surgery.[25,31,32]

Prophylactic mastectomy in patients with a family history of breast cancer and the presence of the breast cancer susceptibility genes (*BRCA1* and *BRCA2*) has been suggested in certain instances.[30,33-35] However, the specific role of prophylactic surgery in patients with *BRCA1* and *BRCA2* mutations has not yet been clearly defined. This may be because *BRCA* mutations are rare, and the positive predictive value of the genetic test is less than 0.2% in the general population. To better define the role of prophylactic surgery with genetic testing, surgeons and oncologists will need to develop and support a registry that follows up patients who have had the test performed.[36-39] This will provide a considerable amount of data on which to base these important clinical and ethical decisions.

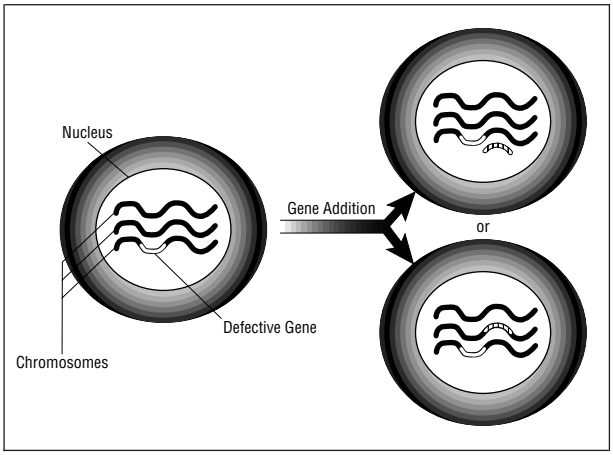

Figure 1. *Gene addition seeks to compensate for a defective gene by providing cells with a corrective gene. Most delivery systems introduce corrective genes into the cell's nucleus, where they remain only transiently. Other methods integrate genes into the chromosomes. Integrated genes can be passed on to progeny cells in the course of normal cell division, which may provide long-term therapeutic benefits. Figure 1 is adapted from Kmiec EB. Gene therapy.* Am Scientist. *1999;87:240-247. Copyright 1999, Sigma Xi, The Scientific Research Society.*

Wound Healing

Successful wound repair involves a complex interaction between cells, extracellular matrix molecules, and cytokines. The healing response in connective tissues has been investigated and has been found to be analogous to wound healing in the skin. Previous studies have provided evidence supporting a crucial role for cytokines in wound healing. Wound repair occurs in a temporal and organized fashion, beginning with degranulation of platelets at the site of injury. This degranulation leads to the release of a host of cytokines, including platelet-derived growth factor, transforming growth factor β, fibroblast growth factor, epidermal growth factor, and insulinlike growth factor. Growth factors such as transforming growth factor β, platelet-derived growth factor, and fibroblast growth factor are thought to play critical roles in wound healing. They are thought to attract cells into the wound, stimulate their proliferation, and have a profound influence on the extracellular matrix deposition. A fine balance between these growth factors and cytokines will determine the composition and appearance of any wound.

A number of surgeons have been pioneers and leaders in the field of wound care and have also been involved in investigating the use of topically applied agents. The results to date have not been as promising as originally expected. This may be because wound healing involves many local and systemic mediators, and the addition of topical agents is not sufficient to overcome the humoral response. For example, adult fibroblasts have been demonstrated to have a relative excess production of cytokines compared with fetal fibroblasts. This excess cytokine production is thought to contribute to suboptimal wound healing in adult wounds compared with the scarless healing of fetal wounds. With the use of the HGP database, it is foreseeable that surgical wound care could involve the use of skin substitutes that would temporarily alter the local milieu in favor of wound healing. Fibroblast and collagen inhibitors could be designed to prevent excess scar formation. Another application may involve genetically enhanced epithelial cells that undergo a more proficient number of cell divisions, migrate faster, and lead to a large skin reservoir. These types of genetically enhanced cells or tissues will benefit a number of surgical patients, including those who have sustained severe burn injuries.[40,41]

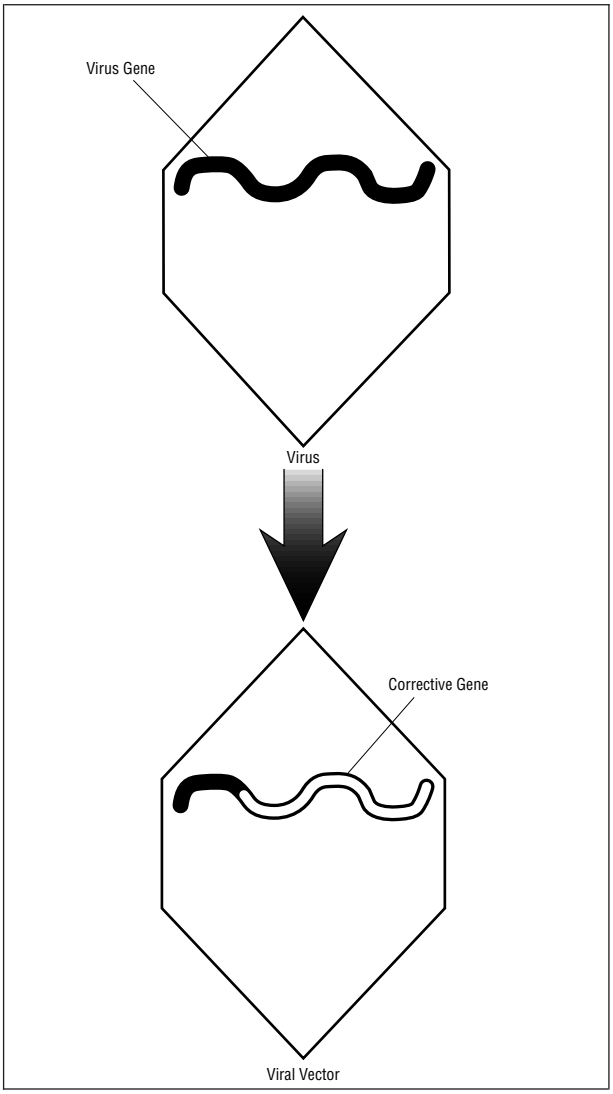

Figure 2. *Viruses are used as gene delivery vectors to target the cell's nucleus and potentially provide a corrective gene. Figure 2 is adapted from Kmiec EB. Gene therapy.* Am Scientist. *1999;87:240-247. Copyright 1999, Sigma Xi, The Scientific Research Society.*

Pediatric and Fetal Surgery

Since the advent of prenatal screening, identification of fetuses at risk for identifiable genetic diseases or traits has been a primary goal. Using amniotic fluid, fetal cells, and fetal or maternal blood cells obtained during amniocentesis, prenatal testing is currently being performed. Other methods employed include α-fetoprotein assays, chorionic villus sampling, and ultrasound tomography. Fetoscopy, a new tool in the treatment of birth defects, uses a camera on a needle inserted in utero to view the fetus. It is currently being used in ultrasound-guided invasive fetal therapy, including multifetal pregnancy reduction, manipulation of amniotic fluid,

Description of the Main Gene Delivery Systems*

Vectors	Characteristics	Disadvantages
Retroviruses	Relatively high titers (10^6-10^7 CFUs/mL) Broad cell tropism Stable gene expression No toxic effect on infected cells Total insert capacity in the virion is in the range of 10 kb Only infect dividing cells	Random insertion of viral genome, which may possibly result in mutagenesis Possibility of replication-competent virus formation by homologous recombination
Lentiviruses	Can infect nondividing cells Can be pseudotyped with retroviral or VSV G envelopes; therefore, they also have broad cell tropism Stable gene expression Total insert capacity in the virion is in the range of 10 kb	Serum conversion to HIV-1 Possible proviral insertional mutagenesis in target cells Presence of tat and rev regulatory proteins (the early lentiviral vectors also have some HIV-1 accessory proteins)
Adenoviruses	Very high titers (10^{10} PFUs/mL) Transiently high levels of gene expression Can also infect nondividing cells Large DNA inserts can be accommodated in the vector (7-8 kb)	Host immune response Not suitable for long-term expression owing to the lack of integration into host genome Complicated vector genome
Adeno-associated viruses (AAVs)	Wide range of cells can be infected, including cells that do not divide Ability of the virus to establish latent infection by viral genome integration into cell genome Viral integration specific for human chromosome 19 (only for wild-type AAV) Nonpathogenic, nontoxic Small genome (5 kb)	High titers of pure virus are difficult to obtain This vector system is still not well characterized Limited capacity for foreign genes (about 4 kb) The AAVs require a helper adenovirus or herpesvirus for replication Lack of specific integration for recombinant AAV vectors
Cationic liposomes	Are not infectious Theoretically, there is no limit to the size of DNA Low degree of toxicity	Targeting is not specific Low transfection efficiency Only transient expression Difficult in vivo applications

**The table is adapted from Romano G, Pacilio C, Giordano A. Gene transfer technology in therapy: current applications and future goals.* Stem Cells. *1999;17:191-202. Copyright 1999, AlphaMed Press. CFU indicates colony-forming unit; kb, kilobase; HIV, human immunodeficiency virus; VSV, vesicular stomatitis virus; G, glycoprotein; and PFU, plaque-forming unit.*

drainage and shunting procedures, fetal transfusion therapy, operative fetoscopy, and finally, in utero stem cell transplantation. The HGP will increase research and activity in the field of fetal surgery by expanding the current knowledge of genetic diseases and the rate of fetal surgical intervention, using not only the current techniques, but also the combination or use of somatic gene therapy. In utero manipulation of identifiable genetic defects may soon become as common as a breast biopsy or inguinal hernia repair.[42,43]

GENE THERAPY

Gene therapy will be another area that will benefit from the HGP. All surgical disciplines may eventually benefit and use gene therapy in the comprehensive treatment of patients. It is a new and emerging technology that employs the process of understanding and manipulating genes—the biological units of heredity. Gene therapy is setting the stage for scientists to alter patients' genetic material to fight or prevent disease. A major goal of gene therapy is to supply cells with healthy copies of missing or mutated genes (**Figure 1**). Instead of giving a patient a drug to treat or control the symptoms of a genetic disorder, physicians attempt to correct the basic problem by altering the genetic makeup of some of the patient's cells. Hundreds of major health problems are influenced by altered gene function; therefore, gene therapy could be used to treat many of these conditions.[44,45]

Chen et al[46] and Ettinghausen and Rosenberg[47] have investigated the genetic modification of tumor-infiltrating lymphocytes in an effort to increase their therapeutic efficacy. Tumor-infiltrating lymphocytes isolated from patients were transfected with a retrovirus vector containing the gene for either tumor necrosis factor α or interleukin 2. This genetic manipulation was designed to enhance the immunoreactivity of tumor-infiltrating lymphocytes toward tumor cells and avoid the systemic cytotoxicity of the cytokines. It is possible that this technique could also be used to alter germ cells to prevent a genetic defect from being transmitted to future generations.

Gene therapy could also be used as a drug delivery system by inserting a gene that produces a useful product into the DNA of the patient's cells. As medicine focuses increasingly on the molecular level, using gene therapy for drug delivery could potentially save much effort and expense. It may also be a shortcut in the complicated process of collecting large amounts of a gene's protein products, purifying the product, formulating it as a drug, and administering it to the patient.

There is a wide array of vector systems that have been used to deliver DNA or oligonucleotides into mammalian cells, either in vitro or in vivo (**Figure 2**). The most common vector systems are based on retroviruses, adeno-associated viruses, adenovirus, herpes simplex virus, cationic liposomes, or receptor-mediated polylysine DNA complexes (**Table**). The stage of development of vectors is still not sufficient to be efficiently applied in wide-

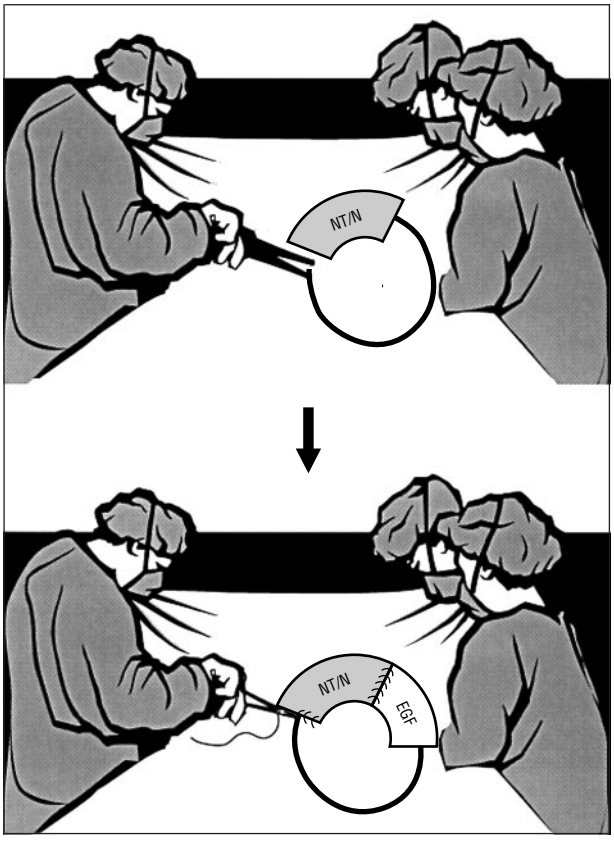

Figure 3. *The surgeon of the future will need to be knowledgeable in the techniques and applications of genetic research.*

spread therapy. The difficult tasks of vector design have to deal with safety issues, improvement of in vivo gene delivery efficiency, and gene regulation after cellular transduction. However exciting and appealing this may appear, gene therapy is still in the experimental stages.[48]

ETHICAL, PSYCHOLOGICAL, AND LEGAL IMPLICATIONS

The applications of the HGP will open doors to a new world of discoveries that in the past had only been a dream. These promising discoveries will also give rise to uncertainty and debate concerning how this knowledge should be applied and who should have ownership of its products and effects. Our understanding of the human genome, technological advances, and ethical, psychological, and legal issues surrounding genetic testing will influence the translation of genetic information into medical applications.

As the scope for genetic testing extends beyond testing for single genetic disorders to testing large sections of the population for genes associated with common disorders, it is important to consider the ethical dilemmas that will arise. One such issue deals with genetic information. Should everyone be allowed to have access to genetic databases? Is this information part of the patient's medical record and thus subject to protection? Do insurance companies and employers have the right to access these records to protect themselves from future liabilities? These are but a few of the questions yet to be answered and the answers will certainly have an enormous effect on society.

Since current genetic testing is only capable of detecting a patient's predisposition but not necessarily implying 100% penetrance of every genetic disorder, is it right to subject patients to information about their "possible future disease pattern" if no current therapy is available to cure them? These issues will also need to be considered when contemplating pregnancy. That is, what is the risk of passing negative genetic markers to subsequent generations? Society may soon be faced with yet another difficult question involving genetic screening and therapy. Once this technology is readily available, who is to have access to it, and should society pay for this type of therapy? Indeed we may find individuals pushing the edge of genetic technology in the hopes of developing or creating the "perfect human."[49-53]

Finally, physicians will have to deal with many new legal ramifications. Physicians may encounter allegations of negligence in reporting genetic results to patients if the physician is not prepared or properly trained to advise both the patient and family members of their potential risk. The physician may be at risk for presumably not adequately advising the patient or family or conducting the proper interventions based on the relevant clinical information.[54-58] Surgeons will need to be trained properly if they decide to use genetic testing in their practice. There will also need to be planning and preparation of appropriate protocols for the safekeeping of genetic material. These data also will need to be protected from third-party reviewers who may wish to use this information as a means to discriminate against patients with certain health conditions.

CONCLUSIONS

There is no question that in the next decade, the clinical treatment of patients will be radically altered. The following hypothetical, surgical patient illustrates a potential (and not entirely far-fetched) scenario.

Bob, a 40-year-old construction worker, presents with a symptomatic right inguinal hernia for which he desires elective repair. Bob's family history is notable for colon cancer and heart disease in first-degree relatives. In the preoperative workup, a cheek swab DNA sample is obtained. In a comprehensive assessment of the future development of cancer and preoperative risk factors (eg, coronary artery disease), the sample is quickly analyzed using DNA chip technology, also called microarrays, that can simultaneously analyze thousands of genes to detect abnormal expression patterns or gene mutations. In the year 2010, this analysis is as common as blood and urine tests. Findings from the genetic screening show that Bob has an increased risk for developing colon cancer; therefore, future screening for this possibility is advised, which in his case is a cost-effective method for detecting polyps that may eventually develop into cancer. In addition, the genetic screening shows that Bob is at an increased risk for coronary artery disease; therefore, a medical regimen, including a gene-therapy cocktail, is prescribed to try to prevent future problems with myocardial infarction. With this information, Bob wishes to speak further with genetic counsel-

ors who specialize in fetal assessments. Bob and his wife are contemplating future pregnancies and using germline gene therapy, and they would like to correct any underlying genetic defects, such as the future risk of colon cancer or coronary artery disease, so that these tendencies would not be passed on to their offspring.

The possibilities of genetic-based medicine are exciting and offer physicians and scientists the ability to truly understand, from a mechanistic standpoint, the pathophysiologic characteristics and origins of a number of disease processes. Clinical practice will be radically altered and will require physicians to become formally trained and knowledgeable in these techniques, their applications and limitations, and the effective counseling of patients and their families. In the past, surgeons have been at the forefront of exciting medical advances. There is no reason why surgeons should not continue in this proud tradition. The surgeon of the future will not only need to be adept at the techniques of cutting and sewing organs and tissues, but also knowledgeable in the cutting and splicing of genes that may be used for adjuvant genomic approaches in the comprehensive treatment of surgical diseases (**Figure 3**). In the next decade, we will witness the development of more major advancements in the field of medicine than have occurred in the last century. Surgeons must be ready and able to assume active leadership roles in the decisions regarding the best options in the treatment of our patients who present with surgical diseases.

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