Johann Gregor Mendel in the 21st Century: Genetic Science Fiction is Alive Today

In the Winter 1998 issue of The Permanente Journal, we reviewed the present role of Kaiser Permanente in clinical genetic care. We now attempt to bring the recent spectacular advances in genetics into practical focus, and to offer a glimpse of the future.

Our purpose is not to present an academic analysis with an extensive bibliography but rather to update the clinician on aspects of recent genetic breakthroughs that will interface with daily clinical practice. A brief reading list is appended. We would like all of you to be at least one step ahead of your patients, who often obtain medical information from the news media and from the Internet.

Mapping the Human Genome

By the year 2003, researchers expect, 99.9 percent of the nucleotide sequences—containing 3.1 billion base pairs per nucleotide—will have been identified.

With the mapping of the human genome, part of an effort which is currently incomplete, the practice of medicine will change forever. This mapping of the human genome is just “the end of the beginning;” full annotation of the human genome will probably require at least several decades. Given that genes and their interaction with the environment play a role in all diseases, physical disorders will be defined not on the basis of signs and symptoms but on underlying genetic variations, which interact with the environment and lead to disease. Diagnosis will be made before symptoms occur, and this advance timing will allow preventive measures to be taken. Treatment will be based on each person’s individual genetic makeup, thus maximizing therapeutic effect while minimizing untoward reactions.

Gene Chips

The basis for these medical miracles will be a “gene chip,” which will determine 5000 to 10,000 genes or DNA variations per person. A second gene chip will then guide the physician to a precise diagnosis and person-specific treatment. These high-tech weapons might seem to lead to a perfect health care system, but they are two-edged swords: New problems will arise concerning ethics, invasion of privacy, discrimination in employment and insurability, high costs, and the prospect of eugenics (in a medical context, the practice of “weeding out” the weakest, most disease-prone persons from a population).

Diagnosis and Prevention

This era of genetic research will introduce us to new forms of preventive health, diagnosis, and intervention as well as an entirely new medical approach and vocabulary. We must become familiar with techniques such as pharmacogenomics, cloning, gene and stem cell therapy, preimplantation diagnosis and treatment, and prevention of birth defects. Some of these activities are already in use and deserve illustration here.

Medical researchers have been using information from the federally sponsored Human Genome Project to help diagnose about 1000 rare syndromes (eg, Prader Willi, myotonic dystrophy, Friedreich’s ataxia) and are beginning to apply this new knowledge to more common disorders, such as breast cancer, ovarian cancer, and colon cancer. This technology can be used for current diagnosis and to help predict disorders that may manifest later (eg, presymptomatic diagnosis of both Huntington’s disease and predisposition to breast cancer). Insufficient space exists here to address the issues of stigmatization or genetic discrimination, although these are genuine concerns.

Pharmacogenomics

Every medication we take is metabolized according to our individual enzyme systems, which in turn are related to our genes and DNA. Ideally, choice of medicine and dosage should be based on each person’s genetic profile. Reactions to medication may be predicted according to analysis of single nucleotide polymorphism (SNP)—“snippets” of DNA that vary among individuals. In each of us, these SNPs occur once in about every 1000 nucleotides or base pairs. Using these new techniques in gene analysis will allow us to predict toxicity of powerful medications, such as those used in chemotherapy and psychiatric disorders. For example, certain psychotherapeutic medications, although extremely useful for schizophrenia, are toxic in certain individuals.

Some reactions to medications can currently be predicted genetically. For example, researchers have shown that 10 percent of people have a mutation in the gene that codes for the enzyme thiopurine methyltransferase and that this mutation prevents inactivation of azathiaprine; the mutation thus can lead to severe side effects. More extensive discussion of appropriate modifications of medication dosage, and the potential for untoward reactions, is available in our reading list.

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effects and even death. Molecular testing for this mutation can thus predict whether a person can or cannot take azathiaprine safely.

Of course, the genetic predisposition of certain individuals to have severe toxic reactions to specific substances is not news. From empirical evidence, clinicians have known for many years that red blood cells in certain persons and ethnic groups are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD). This genetic defect causes severe hemolysis to develop after affected persons ingest fava beans, aspirin, sulfonamides, and other substances. New genetic techniques will allow identification of many other genetic defects before their corresponding idiosyncratic reactions occur.

Because pharmacogenetics has potential for efficacy in management of common chronic disorders, such as diabetes, hypertension, and asthma, this field will have a large clinical impact on future medical practice. Two patients with hypertension might each receive different therapeutic agents on the basis of their genetic profile.

To take advantage of these technical advances therapeutically and commercially, 14 major pharmaceutical companies, five academic centers, and the Wellcome Trust (in Great Britain) have formed a consortium. The purpose of the consortium is to create a giant map of genetic landmarks, which can become a potent tool for predicting certain diseases and drug reactions. An SNP map encompassing at least 300,000 markers will be developed for linkage studies. This map will permit personalized pharmacotherapy based on genetic makeup. Predisposition to major chronic disease (eg, diabetes, coronary disease, neurogenetic disorders) will be identifiable on the basis of “gene array” and variation in SNP patterns. To prevent commercial chaos, the pharmaceutical companies have agreed to keep all information in the public domain and nonpatented.

Cloning

The prospect of making exact copies of ourselves has exciting as well as frightening implications and allows for a free range of fantasies appropriate for science fiction, horror movies, or both. For now, we are still impressed by Dolly the Sheep and her bovine counterparts. But take heed: today the sheep, tomorrow the shepherd.

The current situation may be an improvement on the Austrian-housepainter-turned-German-dictator, but the specter of eugenics rears its ugly head even though most of us doubt the likelihood of “designer babies.” The genetics of behavioral traits (eg, intelligence) is probably too complex, and cloning will therefore probably be used for more practical problems.

Until recently, scientific dogma held that cloning requires use of early pluripotential embryonic cells (perhaps before two weeks of fetal life). Dolly changed all that with a new technique that used mammary skin cells. This new cloning methodology involved four steps:

1. A donor nucleus is extracted from adult somatic or fetal cells.
2. The donor nucleus containing the genes is made dormant.
3. The inactivated donor cell nucleus is placed in a recipient cell (the “cell shell”), the nucleus from which has been removed.
4. The donor nucleus containing the genome is then reactivated by electrofusion, which synchronizes the growth cycle of the donor and recipient cells. When the genes have been “turned on,” the dividing cells are placed into a surrogate mother and voilà—Dolly, Molly, and Polly.

Cloning technology is already being used for medical purposes and for commercial advantage. Using this technology in combination with gene therapy has provided us a new avenue of therapy. The human gene for anti-hemophilic factor (factor IX) has already been introduced into the milk protein gene of fetal sheep. Similarly, in the case of George and Charlie—the bovine equivalents of Dolly the Sheep—the human gene for albumin has been placed into the milk protein gene of the cow. The future holds even greater potential: production of pluripotential stem cells (which could form the basis of a “body repair kit”) and treatment of infertility through DNA cloning of only one parent. Cloning technology could also allow use of animal organs for human tissue transplantation: Human genes will be introduced into cloned animals so that their organs can be used, without rejection, in human transplantation (xenotransplantation). How about calves being the donors for human liver transplantation, instead of just forming the basis for liver and onions?

Ethical Concerns

But the concerns about cloning present a formidable counterbalance. Here the specter of eugenics arises again, as do ethical issues about the sanctity of life. Use of human embryos for “tissue farming” is certain to engender strong opposition. As for the problem of safety, will we see an increase in congenital anomalies or cancer?
Cloning techniques, though impressive, are imperfect. Dolly was the only success in an experiment involving 277 donor nucleus and recipient cells. We could see loss of genetic variation and restriction of the human gene pool. Although cloning would select for traits that have been successful in the past, would these traits adapt to an unpredictable future? Will we be setting ourselves up for the equivalent of a measles virus, which caused only limited disease in European immigrants but wiped out large populations of Native Americans and Pacific Islanders?

Although we are proceeding at full speed with cloning research in humans and animals, real and potential dangers exist for which we must be prepared.

**Stem Cell Therapy**

Use of pluripotential stem cells to create any type of body cell—or even, theoretically, a whole person—is one of the most controversial aspects of the new genetics. The degree of concern is such that federal funds cannot currently be used in stem cell research. This situation could soon change, however. The National Institutes of Health has recently developed a draft proposal to relax prohibition of federal funding for stem cell research. A jointly sponsored bill is currently pending before Congress.

Stem cells can be created in a number of ways. One technology involves removing a nucleus (usually from an early fetal cell) transferring the nucleus to an egg cell, and inducing the new cell to divide. The dividing cell is then converted to a “primordial” (or “pluripotent”) cell by addition of a gene to produce telomerase, an enzyme that continues the process of cell division indefinitely. This primordial cell is “instructed” to become the type of tissue needed by the patient and is then transplanted into the diseased tissue to reproduce and replace the abnormal cells.

**Utility of Stem Cell Technology**

The following is a partial list of possible uses of these “body repair kits”:

1. Replacement of damaged brain cells in Alzheimer’s, Parkinson’s, and Huntington’s diseases.
2. Introduction of nerve cells to repair spinal cord injuries.
3. Production of bone marrow transplant cells for cancer and gene therapy.
4. Repair of myocardial damage by production of new, healthy heart cells.

Considering the magnitude of these therapeutic possibilities, stem cell research is bound to continue despite current limitations and concerns.

**Vitamins and Birth Defects**

Of more immediate practical interest than cloning is the possibility of using vitamin therapy to avoid birth defects. Demographic and clinical evidence show that neural tube defects are related to folic acid deficiency early in pregnancy; and the US Centers for Disease Control and Prevention (CDC) has recommended that women should take at least 0.4 mg folic acid daily before and during pregnancy. To help ensure adequate folic acid intake among prenatal women whose diet is inadequate in folic acid, this vitamin has been added to wheat flour and to other food substances. Recent advances have clarified the mechanism by which folic acid prevents neural tube defects, and this mechanism might play a role in preventing other birth defects (eg, cleft lip and palate, congenital heart disease, and Down syndrome). Researchers have recently clarified the molecular basis by which abnormalities in folic acid metabolism can lead to the birth defects mentioned above. The culprit in this scenario appears to be reduced levels of methylenetetrahydrofolate reductase (MTHFR), a key enzyme of folic acid metabolism. Although the mechanisms appear to be somewhat different, some evidence suggests that abnormalities of folic acid metabolism due to MTHFR deficiency play a role in development of neural tube defects, cleft lip and palate, congenital heart disease, and possibly nondisjunction (the basis of trisomy 21, commonly known as Down syndrome). The mechanism which causes trisomy 21 seems to be DNA hypomethylation and abnormal chromosomal segregation caused by defective folic acid metabolism. Conotruncal heart defects have been reduced 40 percent through use of periconceptual multivitamins, including folic acid. The defect in the MTHFR enzyme gene is in the C-to-T substitution at nucleotide G77 (G77C→T).

**Preimplantation Diagnosis and Treatment**

Preimplantation diagnosis for couples known to be at risk for genetic disease has been available for decades, but preimplantation treatment is still in the experimental stage. Preimplantation diagnosis is currently available for four types of “at-risk” couples:
1. Both parents are carriers of a similar autosomal recessive gene (e.g., Tay-Sachs disease, cystic fibrosis, sickle cell disease, and thalassemia).

2. One parent carries an autosomal dominant disorder (e.g., Marfan syndrome, myotonic dystrophy, and Huntington’s disease).

3. X-linked disorders (e.g., Duchenne-Aran muscular dystrophy, hemophilia).

4. One parent carries a balanced translocation (e.g., the 14/21 balanced translocation that causes a form of Down syndrome).

Transgenic Gene Therapy

To respond to preimplantation diagnosis, new technology, still imperfect, raises the possibility of transgenic gene therapy. This therapy involves in vitro fertilization using eggs and sperm, followed by removal of the blastomere in the morula stage (two-three days after conception). Polymerase chain reaction (PCR) then amplifies the DNA from each blastomere. Molecular study of the DNA raises the possibility of correcting the genetic defect.

This technology creates a number of risks, including the risk of embryo damage or death and risk of contaminating the DNA. Another potential problem is allele dropout (ADO), a situation in which PCR amplifies only one of two alleles and thus causes misdiagnosis of a gene mutation. As technology advances, however, imperfections in technique are likely to be resolved, thus opening up the likelihood of effective transgenic therapy.

No End in Sight

As we enter the 21st century, we stand on the shoulders of giants: We are beneficiaries of the 20th century explosion of genetic knowledge, an explosion which began with the discovery of the DNA double helix and which will end who-knows-where. ❖

Representative Reading List


Possibility

“They don’t see the same world that the rest of us see. They see possibility.”

Malcolm Gladwell, “The Tipping Point,” Little, Brown, and Company