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IN THE PIPELINE:
A WAVE OF VALUABLE MEDICAL TECHNOLOGY

by William B. Schwartz

Prologue: Americans have long been fascinated with high-technology medicine. This is reflected in our taste for science fiction as well as in our appetite for health services and our growing medical costs. In this paper William Schwartz hints at some of the promising new technologies that are in the development pipeline—technologies that will make such advances to date pale by comparison, he asserts. The most exciting of these have to do with molecular and cell biology, which open the door to treating the causes and origins of disease, not simply the consequences. Schwartz believes that in the short term (over the next five to ten years) such technologies are likely to add to the cost of health care. In the longer term, however, costs may go down as a result of technologies now in development, which could bring about less expensive treatments or even cures for maladies that are now very expensive to treat. Schwartz, a physician, has had a long and distinguished career in medicine, academic medicine, and health services research and economics. He received his medical degree from Duke University. Previously he served as chief of the Division of Nephrology at New England Medical Center, and was physician-in-chief there for several years. He has held two endowed chairs in medicine at Tufts University and now is Distinguished Physician of the Department of Veterans Affairs and professor of medicine at the University of Southern California. Schwartz served as principal adviser to the RAND Health Services Program for more than a decade. He has participated in the activities of the National Institutes of Health and was president of the American Society of Nephrology. He is an elected member of the National Academy of Sciences’ Institute of Medicine, and has published frequently in Health Affairs and a wide variety of medical and health economics journals.
Abstract: Technologic change has proceeded at a rapid pace during the past twenty years, and advances that are even more remarkable are in sight over the next decade. These changes will be driven largely by advances in molecular and cell biology, imaging techniques, and tissue engineering. Therapies directed toward causes rather than consequences of disease could conceivably produce inexpensive cures and thus slow the rise in medical costs. A more likely scenario envisions a continued rise in costs as advances in technology produce many expensive interventions that extend life but are not curative.

About half of the rise in health care costs over the past several decades has been attributable to advances in medical technology. Twenty years ago we could exhaust our diagnostic and therapeutic efforts at low cost because there were very few effective interventions. All of this changed during the 1970s and 1980s as the list of valuable but expensive interventions rapidly expanded. But this is history. Policymakers now must ask how rapidly technologic change will continue and whether such change will produce an ongoing increase in health spending.

This paper focuses on the first of these questions. It summarizes evidence indicating that rapidly expanding insights into molecular and cell biology and other scientific disciplines will lead to a flood of medical advances within the next five to ten years. In prospect is a technologic revolution that will shift therapeutic attention from the consequences of disease to its causes. We also can anticipate important advances in diagnostic capabilities, driven in large part by new techniques for medical imaging. The economic impact of these changes cannot be forecast with certainty, but the most likely scenario envisions a continued upward pressure on costs.

Cell Receptors And Drugs

Researchers are now focusing their efforts on designing drugs that have the specific ability to interact with a particular type of cell receptor. Such interaction sets into motion a cascade of events that stimulates or inhibits cell function and that is responsible for the drug’s therapeutic effects. Drugs that target a single type of receptor produce far fewer undesirable side effects than do older agents that act less specifically.

The potential value of agents that stimulate receptors is well illustrated by Sumatriptan, a new drug for the treatment of migraine headaches. Sumatriptan acts on a receptor that constricts the dilated vessels responsible for the migraine attack, and, in the great majority of patients, it promptly relieves all symptoms, usually without side effects. Inhibiting receptor activity also can have powerful therapeutic effects. Ondansetron, a new drug of this type, is highly effective in controlling the nausea and vomiting that occur with chemotherapy and in postoperative patients. It exerts its effect by blocking a receptor that causes the muscles of the
intestinal wall to go into spasm. New drugs focusing on specific receptors are likely to be available by the year 2000 for the treatment of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis.

Receptors in the brain are also of great interest because of their potential role in the treatment of a wide range of disturbances such as obesity, depression, schizophrenia, manic-depressive disorders, memory loss, sleep disorders, obsessive-compulsive behavior, anxiety, panic reactions, and impotence. The goal of research in this area is to find drug molecules that can stimulate or inhibit a particular receptor’s activity. New imaging techniques (for example, positron emission tomography, or PET scanning) will make it possible to identify areas of the brain associated with a given disorder and thus direct the search for the receptors involved.

Receptors stimulated by a drug over a long period may eventually lose their capacity to respond. Attempts to restore the exhausted receptors’ responsiveness are now at the cutting edge of receptor research.

Autoimmune Diseases

Normally, the immune system reacts only to foreign proteins such as bacteria or viruses, destroying them to protect the organism. The major players in this immunologic defense system are white blood cells called lymphocytes. The body produces billions of lymphocytes, each capable of recognizing a specific protein. The two major types of lymphocytes are B-lymphocytes, which produce antibodies against foreign proteins, and T-lymphocytes, which send out chemical signals that activate a variety of defense mechanisms. As a person’s pool of lymphocytes grows, those cells with the capacity to recognize and destroy the person’s own tissues are screened out. This screening process allows the immune system to become tolerant to “self,” while retaining its ability to destroy foreign proteins.

Many serious illnesses stem from a curious phenomenon in which the immune system self-destructively turns on the body’s own tissues. In such autoimmune diseases, some lymphocytes mistakenly recognize certain normal tissues as foreign. For example, when lymphocytes destroy the insulin-producing cells of the pancreas, they cause diabetes; when they destroy the surface proteins of joints, they cause rheumatoid arthritis. Other common autoimmune diseases include multiple sclerosis, certain types of hyperthyroidism, and some kidney and blood-vessel disorders.

The current treatment of autoimmune disorders is designed to inhibit the action of the disease-causing, abnormal lymphocytes. Prednisone and other immunosuppressive agents are used for this purpose, but they are less than ideal because they also inhibit the function of normal lymphocytes needed for defense. Consequently, infections can complicate immunosuppressive
therapy. Agents that are more specific in their action, destroying or blocking only “anti-self” lymphocytes, would be highly desirable therapeutic agents. By the year 2000, drugs will be available that either block receptors on the cells of healthy tissue that are under attack or prevent rogue lymphocytes from reaching their targets. Rheumatoid arthritis is a particularly attractive target for such efforts. Attempts are already being made to prevent the entry of inflammatory cells into body joints by blocking the receptors that white cells use to move out of the bloodstream into tissues.

Other research is directed toward the underlying factors that elicit the autoimmune reaction. Recent studies on juvenile-onset diabetes (Type 1) show promise of preventing this disease. The story starts with the discovery of a link between Type 1 diabetes and the Coxsackievirus, a cause of sore throats and meningitis in children. The Coxsackievirus has on its surface a protein that is similar in structure to a protein found on the insulin-producing (islet) cells that are attacked by the immune system in diabetes. This suggests that the immune mechanisms that are mobilized appropriately to defend against the Coxsackievirus mistakenly attack and destroy the islet cells. Recent experiments in animals suggest that this is indeed the case. Promising methods to thwart the proliferation of T-lymphocytes that can damage islet cells are already under study.

Genetics And Disease

Advances in molecular and cell biology are opening a new era in clinical medicine. Screening for genetic disorders, gene therapy, and powerful new drugs for cancer and heart disease promise to radically improve the quality of medical care. At the heart of our new understanding of disease lies the fact that all information determining the structure and function of each human cell is embedded in segments of deoxyribonucleic acid, or DNA, that make up a particular gene. Each gene specifies the production of a given protein. The information contained in a gene is transferred by a messenger (messenger ribonucleic acid, or mRNA) to sites where the specified protein is synthesized. Even the slightest change in the structure of the gene can lead to the production of an abnormal, disease-producing protein. Such abnormalities may be inherited, such as sickle-cell anemia, or result from genetic damage caused by chemicals, radiation, and other environmental toxins. Some of these advances in molecular biology have profound implications for the treatment of genetic disorders and diseases.

Gene therapy for genetic disorders. The first efforts at gene therapy have, as has been widely reported, been directed toward correction of genetic errors by insertion of normal genes into the defective tissue. One promising method is the packaging of the normal gene into a virus that has
been rendered harmless by molecular technology. The abnormal lungs in patients with cystic fibrosis are a major focus of such efforts. In this case, the “therapeutic” gene is inserted into a harmless virus that can take up residence in the cells of the lungs and produce the normal version of the protein that is defective in cystic fibrosis patients. If successful, this work will open the door to the treatment of a wide range of hereditary abnormalities. But the prospects for gene therapy range far beyond such diseases. Gene therapy promises to be of value in the treatment of a variety of disorders such as malignancies and heart disease and in facilitating organ transplantation between animals and humans.

**Screening for cancer and other diseases.** The recent isolation of a gene linked to a common inherited form of colon cancer (responsible for 10 to 15 percent of all colon cancers) promises to allow the identification by mass screening of persons who are at high risk of developing bowel malignancies. More than one million people are thought to carry the gene and thus to face a 70 to 90 percent risk of developing colon cancer. New genetic screening techniques will make it possible to identify the population at risk, many of whom can be expected to develop cancer before the age of fifty—an age far younger than average for contracting the nonhereditary form of the disease. Those found to have the genetic abnormality will be candidates for preventive dietary measures and for regular colonoscopies, starting when they are in their twenties or thirties. Colonoscopy will allow early identification and removal of premalignant polyps.

Over the longer term, genetic screening for diabetes, hypertension, and other diseases also may become routine. However, such genetic screening may not be straightforward, as exemplified by recent experience with the cystic fibrosis gene. A variety of mutations have been identified in this gene. Moreover, the correlation between a given mutation in the gene and the presence and severity of the disease is not high. This may be due to the role of an as yet unidentified additional gene that modulates the behavior of the cystic fibrosis gene. These findings bear witness to the complexity of cystic fibrosis and indicate that screening procedures will be far more difficult than was originally anticipated.

**Genes and cancer therapy.** Chemotherapy for cancer relies in most instances on the destruction of rapidly dividing cells. Because rapid cell division is not specific to cancer, however, therapeutic efforts often are severely impeded. For example, chemotherapy often damages normal cells, such as those in the bone marrow, and creates serious complications.

Research on cancer treatment has been shifted in new directions by insights into the role of mutant genes in the genesis of cancer. These mutant genes cause cells to grow wildly. To control the flow of misinformation from these genes, several strategies are being explored. One approach
focuses on drugs to render the mutant gene inactive. A second method uses "anti-sense" drugs that inactivate messenger RNA that provides the blueprint for the production of the abnormal, disease-producing protein. Another promising strategy uses a naturally occurring enzyme to chop the RNA into its component segments, thereby blocking the transfer of harmful misinformation. In other cases, drugs that can bind to the abnormal protein (typically an enzyme) and inhibit its action will be used. These blocking tactics offer impressive new avenues for the treatment not only of cancer but also of a wide range of other diseases.

Another prospect for cancer therapy comes from research on genes that inhibit malignant transformation of cells—the tumor-suppressor genes. Dysfunction of one such gene, the p53 gene, is thought to contribute to the development of as many as half of all cancers. Several approaches to correcting the failure of this gene to control abnormal cell growth are under way. Normal tumor-suppressor genes are being inserted into cancer cells. Attempts also are under way to revitalize suppressor genes whose protective functions have failed. The most recent study of the gene has shown that it exerts its protective effect by stimulating production of a protein that is responsible for normal cell growth. This finding has important clinical implications; it may be possible to develop drugs that mimic the function of the p53-induced protein and thus inhibit cancer cell growth.

On another front, progress is being made in dealing with life-threatening tumors that have spread to other organs from their original sites. One intriguing approach to controlling such metastases is to starve the tumor by cutting off its blood supply. Drugs that can do this—anti-angiogenic agents—are now undergoing clinical trials. Colon and breast cancer would be particularly promising targets for this therapy. The recent discovery of a gene that suppresses the spread of metastases has opened the way to still another therapeutic strategy, but too little is known to predict its value.

A variety of other approaches to cancer therapy are also in progress. For example, antibodies to specific tumors are being coupled with toxic agents. The intent is to use the antibody to seek out the tumor so that it can deliver its destructive agent selectively without harming normal cells. Another strategy uses customized vaccines made from a person's own cancer cells to stimulate the immune system to attack and destroy the tumor.

Genes and heart disease. When coronary arteries are injured by cholesterol or angioplasty, they release growth factors that cause a proliferation of their smooth muscle cells, thus narrowing the vessel and reducing blood supply. Research is focusing on methods to break the link between injury and cellular overgrowth in the artery. Efforts are being made to design drugs that will inactivate the growth-factor gene and thus block the synthesis of the factors themselves. In other research, genes that cause production of a
protein that protects against proliferation are inserted into a benign virus that is then introduced directly into coronary vessel cells. If the technique is successful in protecting coronary vessels in animals, it could find wide use in patients with symptomatic coronary disease and even early asymptomatic disease. Investigations also are under way to make use of similar techniques to prevent the cardiac enlargement and heart failure seen in cases of prolonged, inadequately treated hypertension.

**Genes and the transplantation of animal organs into humans.** Until recently, the antigenic differences between humans and animals have posed an apparently insuperable barrier to successful transplantation of animal organs into humans. However, the successful insertion of human genes into pigs gives reason to believe that this obstacle can be surmounted. Investigators believe that clinical trials of such animal-to-human transplants (called xenografts) may be feasible between now and the end of the decade. The success of xenografts would help to eliminate the current shortage of some 60,000 transplantable organs.

On a parallel track, the problem of organ replacement is being pursued by the new discipline of tissue engineering. Researchers are, for example, attempting to create an artificial implantable liver that can serve as a permanent liver replacement. Techniques also are under development for implanting insulin-producing cells of the pancreas as a replacement for the pancreatic cells that have been destroyed in patients with diabetes.

### Advanced Imaging Techniques

Improvements in computed tomography (CT) scanning and magnetic resonance imaging (MRI) will greatly enhance the diagnostic power of these devices and expand the volume of scanning procedures. Scanning of the heart is a dramatic example. The moving heart has previously defied accurate definition by CT scans and MRI, but new techniques will soon allow the motion of the heart to be “frozen” so that sharp images can be obtained. With refinements in these methods, the detection of even the early stages of coronary artery disease will be possible.

Advances in MRI, PET scanning, and magnetoencephalography also will provide new tools for evaluating mental illness and other brain disorders and for assessing the effectiveness of treatment.

Two imaging techniques that are nearing clinical application promise significant advances in diagnostic capabilities. The first, coherence interferometry, provides detailed images of the top few millimeters of a given organ by capturing the faint light that is reflected off the tissue. Preliminary studies suggest that the degree of detail can come close to that which is now obtained with stained histologic tissue sections. Such “optical biopsies” will
open a wide range of diagnostic possibilities for organs whose surfaces are readily accessible, such as the eye, colon, and coronary arteries. The technique should be particularly useful in the diagnosis and management of eye disorders such as glaucoma and retinal disease. A second technique, new and sophisticated methods of transillumination, promises to add significantly to diagnostic capabilities by its ability to recognize subtle tissue abnormalities. Imaging of brain bleeding, brain tumors, and oxygen deficits in the brain are already in clinical trials. Transillumination also promises to be useful in imaging the breast, prostate, and testicles and to identify structures within cells (for example, nuclei and mitochondria).

In the more distant future lie the medical applications of “virtual reality.” Work now in progress suggests that it will be practical to use virtual reality techniques to obtain a precise spatial perspective on internal body organs. High-speed computers in combination with ultrasound will be used to create a “virtual hole” in the patient’s body that will display a given organ in three dimensions. By looking into an ultrasound “peephole,” surgeons will be able, for example, to perform amniocentesis and many types of biopsies with great precision. This method also will create three-dimensional images for the surgeon working inside an organ. When used preoperatively, the virtual reality technique will enable the surgeon to plan operative strategy with simulated body structures.

Policy Implications

The foregoing brief summary of the medical advances in the pipeline provides strong evidence that drastic technologic changes are likely to take place over the next five to ten years. These potential advances raise a serious question for policymakers: Will technologic advances be a powerful force that drives costs upward, or will these advances attenuate or eliminate the cost spiral? In trying to answer this important question, one can envision two different scenarios with radically different policy implications.

History argues for the view that rapid technologic change, in the aggregate, fuels a relentless upward pressure on health spending. But it also is conceivable that history is not about to repeat itself. If treatment of genetic diseases such as cystic fibrosis proves successful, the cost of care for such illnesses might be sharply reduced. Fundamental, rapid advances in molecular and cell biology could lead to the prompt discovery of curative therapies for some patients with major illnesses such as cancer and coronary artery disease. As a result, the cost spiral might be sharply attenuated during the next five to ten years.

The second and far more likely scenario envisions a future in which the historic pattern-cost increases driven in large part by new technology-
continues for at least the next decade. New drugs, curative in some instances, may convert many rapidly fatal diseases to chronic diseases, imposing heavy financial burdens for hospital, home care, and other services. For decades insulin has played this role in diabetes; more recently, new drugs have had a similar impact on acquired immunodeficiency syndrome (AIDS). The same pattern could well be encountered with cancer. Insights into the genetic mechanisms that allow unchecked cell growth will stimulate a host of new therapies, each with a different mode of action and each tailored to a particular type of cancer. Some dramatic cures are likely, but in many patients the new therapies may simply chip away at the disease, as has frequently been the case in the past. The care of many serious autoimmune diseases might well evolve in the same fashion.

With other diseases (such as Alzheimer’s), long-term, expensive therapies might lead to only marginal improvements. The barely measurable slowing of Alzheimer’s disease produced by the new drug Tacrine is one example. With still other illnesses, a marginal gain will be achieved at high cost when an expensive treatment replaces an inexpensive one. The use of tissue plasminogen activator (TPA) (which costs $2,200) in place of streptokinase (which costs $200) for the treatment of a single heart attack is a good example. The one-percentage-point improvement in mortality rate produced by the use of the former agent may be a harbinger of many other advances that are medically worthwhile but substantially more expensive.

On another front, it is likely that further advances in surgery that reduce risk and pain (such as laparoscopy and arthroscopy) will open the door to many more surgical procedures. Patients with less severe illnesses and those for whom traditional surgical procedures pose an excessive risk will become suitable candidates for new therapies. Increasingly sophisticated diagnostic imaging, as well as radically new imaging techniques, also can be expected to add substantially to costs. Because virtually all new imaging devices are noninvasive, they practically eliminate risk and pain; thus, their use becomes medically warranted even when the likelihood of obtaining useful information is small. Cost per unit of service will drop, but any savings will almost certainly be overwhelmed by volume increases.

A continued rise in costs driven by new technology would confront policymakers with a choice between diverting an ever-larger fraction of national resources to the health care system or containing costs by rationing services. Squeezing waste and inefficiency out of the system, often advanced as a panacea, has recently been shown to have little promise of effectively limiting cost increases. ²

Given the uncertainties, prudence requires that policymakers prepare to deal with the possible need for rationing. The mechanisms that might be employed, and their pros and cons, are beyond the scope of this paper.
Suffice it to say that such cost increases are likely to be slowed only by premium limits or budget caps or by a more subtle strategy that uses tax policy and reimbursement mechanisms to discourage investment in new technologies—a kind of "silent" rationing. The social cost of this latter policy would be high in forgone medical benefits and the failure to exploit our decades of investment in the fundamental science that underpins current advances.

Even if over the next decade we do not achieve the optimistic goals of scenario one, the prospects for the long term—say, twenty-five or thirty years—look promising. Screening for a wide variety of illnesses, either at birth or in early childhood, should be possible within the next five to ten years. In the case of juvenile-onset diabetes, for example, early detection of those prone to the illness will lead to preventive measures based on insights on the role of Coxsackie infections and thus to considerable savings in health care dollars. In the case of diseases that most commonly appear in adulthood or later in life—hypertension, coronary artery disease, Alzheimer's disease, and many forms of cancer—the payoff from preventive measures will probably be long deferred. However, it seems highly probable that by the year 2020 or 2025 an ever-deeper understanding of cell biology will lead to substantially more effective prevention and treatment of most serious illnesses and may well slow or even eradicate the rate of cost increases. Unhappily, such progress will exert its own high price. A growing population of older persons will bring a predictable spectrum of economic and social problems. In the short term, cost is the paramount issue; in the long term, the successes of biomedical research are likely to produce even more serious problems.

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