The Reshaping of Healthcare
By Jeff Goldsmith
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For most of this century, the American healthcare system has been organized around the acute illness: a life-threatening Act of God. The role of the healthcare system was to rescue us from the illness and to take custody of us until we were well again.

We have used a casualty model of health insurance to finance healthcare, attempting to spread the cost of intervention across as broad a pool of "risk" as possible. We have built a vast and costly apparatus around this acute-care model, premised on the fundamental unpredictability of disease.

As chronic illnesses -- degenerative diseases correlated closely to the aging process-replaced the acute infection as our most significant health problem, the "fit" between our healthcare needs and the health services framework worsened significantly. The acute-care framework was shaken during the past 15 years by rapid advances in diagnostic and therapeutic technologies that enabled caregivers to intervene earlier in chronic disease processes like heart disease and cancer, and to manage more patients on an ambulatory basis (prior to an episode of acute need) without hospitalization.

Changes in the next 15 years will demolish what remains of the acute-care paradigm and force our health insurance system and society to confront the increased predictability of disease risk Unlike the "revolution" in healthcare delivery during the Eighties, which arose from the imaging and surgical suites, the impending revolution will originate in the pharmacy and clinical laboratory.

Parallel advances in predictive genetics and immunology will converge during the next 15 years, making it possible to predict chronic disease risk in many persons before symptoms emerge.

The paradigm of diagnosis and treatment will be replaced by one of prediction and early-stage management of illness, rendering much of our current armada of diagnostic and curative technologies obsolete. "Acts of man" will be increasingly implicated in our health status, rendering the casualty model of health insurance fundamentally untenable.

Unraveling the genetic roots of illness

Most acute infections are visited upon us by foreign agents like bacteria, viruses, or other parasites. By comparison, most chronic diseases originate within our genome-our complex genetic programming. Each cell in the human body contains about nine feet of DNA, containing the genetic recipe for a human being.

Some 3-4,000 human diseases can be traced to defects in a single gene, and many other major diseases, such as diabetes and cancer, are probably the result of multiple, interacting genetic flaws, triggered by environmental or behavioral events. Evidence of these genetic links was uncovered by studying patterns of inheritance of diseases in multiple generations of the same family through population genetics.

During the mid-Eighties, a confluence of events in human genetics enabled scientists, for the first time, not only to locate (or map) within a specific chromosome the genetic flaws linked to major illnesses such as cystic fibrosis, but to decode (or sequence) the specific gene at issue and identify the protein product of that gene.

Wedded to the powerful new diagnostic technologies such as the genetic probe, identification of specific genetic roots of disease is leading to rapid development of predictive tests that can tell prospective parents if their child-to-be has inherited defective genes that will predispose him or her to a specific illness later in life. While disease risk is obviously mediated by both environment and behavior, comprehensive risk assessment based upon the genetic makeup of an individual will be possible within 15 years.

Human Genome project

During the next 15 years, geneticists around the world will be conducting a massive cooperative research effort called the Human Genome project. Its goal is to completely map and at least partially sequence the entire human genome. Scientists do not even know how many genes a human possesses (the best estimate is 50,000-100,000).

By the conclusion of this project, the form and function of most of our genes will have been established-and a new dimension of medicine will have emerged. Instead of "diagnosing" disease late in disease processes, we will be predicting disease risk based upon our genetic inheritance, and attempting to manage that risk before symptoms emerge.

The Human Genome project has been called a biological version of the Manhattan project, which produced the world's first atomic device. This is an apt analogy, since the information yielded by the Human Genome project will detonate like a nuclear device in our society. Few institutions will be the same afterward.

The Genome project will destroy the population-based actuarial framework on which our health and life insurance industries rest, and it will touch off a violent struggle over the control of genetic testing information and our privacy rights.

The Genome project will lead to a capacity to provide prospective parents detailed information on the physical character, personality, intelligence, and life chances of their future child as early as six cell divisions after conception. It will even be possible for a woman to sort through her "inventory" of eggs to find the most "desirable" or heartiest egg for future conception.

It will provide parents of young children with potentially devastating information on the risks they have passed on to them. Genetic screening technologies will probably be inexpensive enough to be applicable to broad populations, enabling us to locate those with the highest prospective disease risk in order to focus our preventive resources on them.

These exciting genetic breakthroughs raise a major question: How will we manage this information and its impact on our thus "empowered" lives?

The end of insurance?

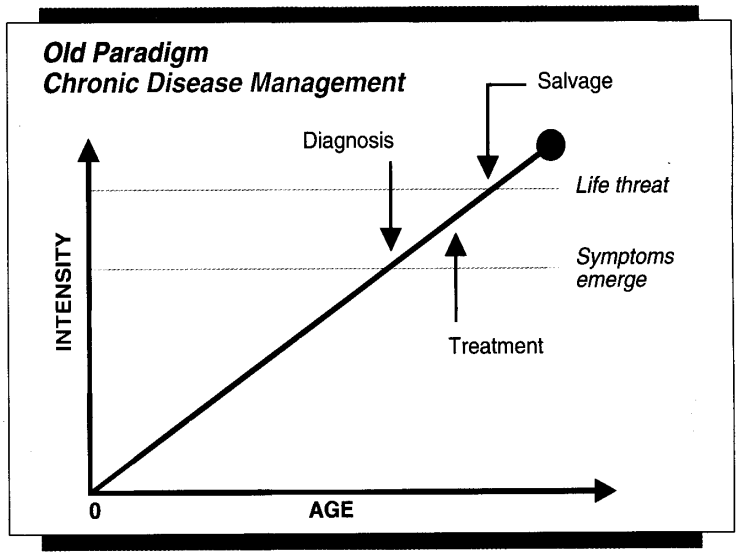
The premise of illness as an unpredictable casualty or Act of God will be invalidated by genetic screening. Some such illnesses or occurrences like trauma or viral infection will still remain, but they will be a small portion of our total burden of illness. And though understanding our genetic inheritance will not predict with perfect certainty the likelihood of disease occurrence or premature death, it will dramatically narrow the uncertainty.

For health and life insurers, who have made underwriting decisions based upon actuarial estimates of group risk or life expectancy, genetic prediction represents a cataclysm. If individuals knew, even with 40 percent certainty, that they would contract an expensive or life-shortening illness, they could purchase life or health insurance at a much lower price than their actual risk would suggest. If a significant population did so, insurers would be bankrupted. Because of adverse selection, they would pay out in claims far more than they collected in premiums.

Yet would it be socially responsible to pay out claims for avoidable or manageable illnesses that individuals, having known the risks, did nothing to ameliorate? Could we continue to pretend that illnesses that are predictable or likely consequences of identified genetic flaws are simply "Acts of God" and pay for care for them as if they were accidents?

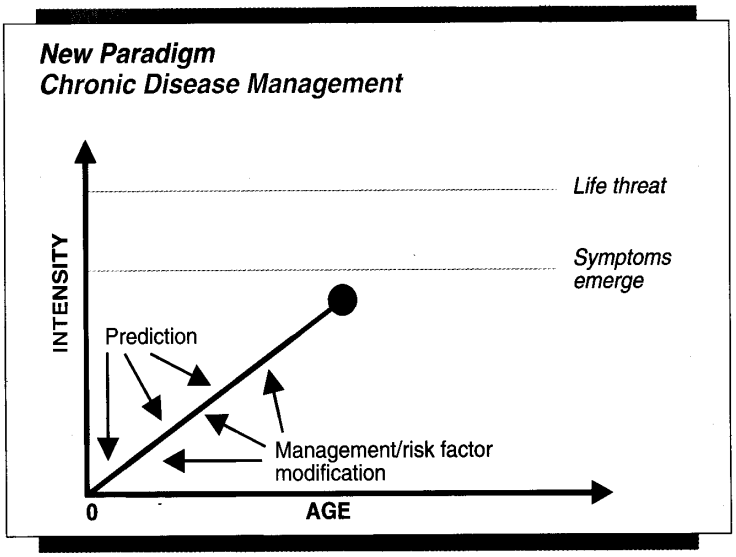
Under present rules (or lack of them), insurers could demand genetic screening information and use it to exclude individuals from coverage, or mandate that specific actions be taken as a condition of insurance. Parents whose unborn child was found to have a high likelihood of expensive illness could be mandated to abort the child as a condition of continuing to receive family coverage. Or specific therapy could be mandated to ameliorate the identified risk.

Americans are likely to rebel against the use of genetic screening information to restrict their freedom. But who will negotiate the "treaty" between individual rights and the insurance industry? How will publicly financed health insurance programs like Medicare or Medicaid, or their successors, manage genetic information on their covered populations? What is the appropriate balance between individual and societal responsibility for the resultant cost of care? Will life and health insurance underwriting be socially viable in the biotechnological future?



Source: Health Futures

Figure 1



Source: Health Futures

Do-it-yourself eugenics

Even if these problems are resolved satisfactorily, how individuals will behave in response to this information may be even more problematical. The decision to abort a fetus that carries the genes for Huntington's disease may be a morally and socially responsible decision, but what about the decision to abort a fetus with only a 30 percent risk of say, colon cancer, which might not even occur until age 70? American society has a high intolerance of risk of any kind, so why should genetic risk be any different?

What is to prevent parents from aborting if their future child is not going to be tall, blond, and intelligent, or if it carries the genes for a "difficult personality"? Unimpeded by societal

restrictions, tides of fashion could sweep through our gene pool, eliminating diversity for those with sufficient resources to afford the intervention, and potentially heightening existing social class or racial differences or life chances. In a way, it is fortunate that such an intense debate is taking place about how we feel about abortion, because the new information prospective parents will acquire will only make the decisions and societal consequences that much more difficult to manage.

It does not take a Rhodes scholar to predict a critical scarcity of human geneticists and genetics counselors by the end of this decade, or the birth of a multibillion-dollar new industry of genetics testing and counseling. Nor does it take a crystal ball to predict a worsening of societal conflict over abortion and reproductive rights and access to prenatal and postnatal care as well as to the costly, emerging therapies to correct genetic abnormalities.

Genetic therapy may trail definitive predictive genetics by as much as a generation, providing a lengthy period of anxiety and perhaps over-reaction to genetic screening information. American society is appallingly unprepared to face these issues.

Opportunities to reduce illness

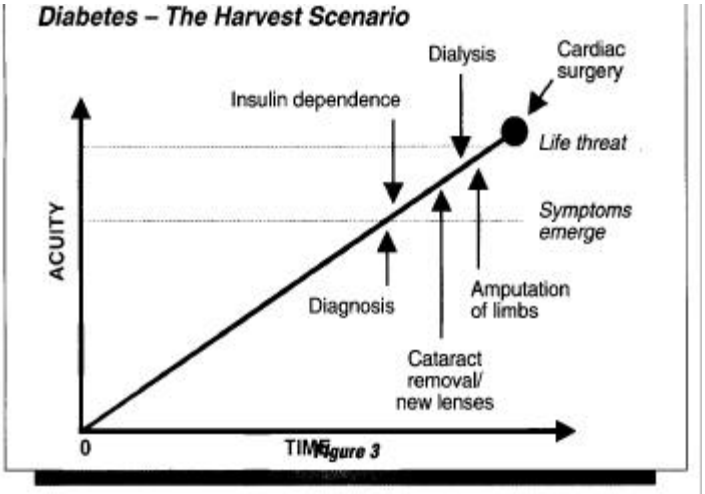


Figure 3

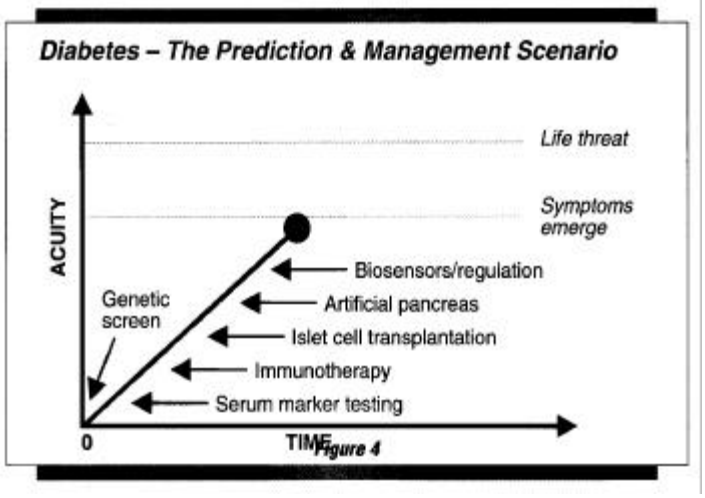


Figure 4

The eerie gap between the advent of genetic screening and the availability of genetic therapy does, nevertheless, present significant opportunities to reduce needless illness. Broad-based screening of large populations will enable the healthcare system to focus its efforts on those with the highest identified health risks. Genetic screening will lead to regular, disease-specific prospective monitoring based upon inexpensive diagnostic tests and custom tailored to the genetic risks for individuals.

For many diseases, periodic screening for protein "markers" in the blood or urine of "at risk" children or adults will provide clues to the early onset of the actual disease process. Such markers have been discovered for juvenile onset diabetes (specific antibodies circulating free in the blood signal the body's misguided immune response to its own beta islet cells, which, when destroyed, render the patient diabetic). Serum markers have also been discovered that signal the beginning of some forms of cancer.

Controlling environmental and behavioral risk factors that accelerate the genetically determined disease risk will be even more important during the next 15 years than it is today. Specifically identified vulnerabilities may increase the saliency of avoiding risky diets and lifestyles. Parents can thus tailor their child-rearing strategies to minimize the impact of inherited risks. Obviously, dietary and behavioral risk factors that may uncover or trigger disease-specific genetic flaws will get much attention.

The "liquid nervous system"

By far the most complex organ in the body is its immune system, a "liquid nervous system" capable of recognizing and defending against literally a trillion foreign substances the body has never seen before. For more than a generation, scientists have dreamed of enhancing the body's remarkable defense mechanisms as a too] in fighting disease.

Instead of introducing foreign substances into the body, immunotherapy's goal is to selectively stimulate or suppress the immune response to specific events such as viral infection, trauma' or organ transplantation. Given the complexity of the immune system, progress in development of immunotherapy has been slow, and it will be incremental, rather than "revolutionary," in nature.

A major goal of immunotherapy is controlling the function of strategic substances that shape the immune response. These substances, called cytokines, are the chemical messengers that not only activate the immune system but heal the body's wounds and guide the growth and repair of its organs and tissues. These cytokines include epidermal and nerve growth factors, blood cell growth factors like EPO and G-CSF, and the interferones and interleukins-an increasingly familiar set of human substances at center stage in biotechnology.

Until the advent of genetic engineering, scientists were reduced to bizarre schemes in their attempts to extract from vast quantities of human blood or urine tiny amounts of these naturally manufactured substances to study their disease fighting impact. The advent of genetic engineering changed everything.

Now it is possible to take the gene that codes to these complex proteins and splice it into bacteria and grow bathtubs full of them. In ten or 15 years, we will take the same genes and splice them into algae and grow designer proteins in ponds, or splice the genes into cows and harvest their protein products out of the milk. The price will fall as technology improves and the initial high costs of development are paid down.

The explosion of biotechnology stock prices during 1991 was the result of the first wave of genetically engineered cytokines, initially EPO and G-CSF, making their way into pharmacies. These two substances cause, respectively, red and white blood cells to regenerate rapidly. EPO is a substance produced in the kidneys to correct for anemia, which reduces the red blood cell count and oxygen-carrying capacity of the blood. G-CSF causes the white blood cells to regenerate after bone marrow transplantation or whole body radiotherapy for cancer. That is how it restores immune system function, shortening the dangerous period of infection risk after these radical therapies.

These two substances are the first of a wave of new biologicals that will speed the healing process. Epidermal growth factors will speed healing and reduce scarring from burns and major trauma. Nerve growth factors promise to regenerate damaged nerve tissues and restore loss of function from trauma or degenerative diseases like Alzheimer's or Parkinson's disease.

New immunosuppressants will control the body's natural tendency to reject a transplanted organ. Instead of shutting down the entire immune system and exposing the transplant patient to a whole range of infections, the goal in transplantation is to induce organ-specific, donor-specific immune tolerance, leaving the rest of the immune system intact. Pursuit of this prize remains

elusive, but significant incremental improvements have been made in immunosuppression with new substances like OKT-3 (a man-made antibody), FK506, and rapamycin.

Man-made antibodies

There are two types of immune response. One is the production of hunter and killer cells, which scavenge the bloodstream and organs and destroy diseased cells and foreign substances. The other is the production of antibodies, which bind to specific threatening substances, blocking their action against the body and subsequently destroying them. The human body contains almost 10 million different antibodies, which are constantly differentiating in response to new threats.

A major breakthrough in biotechnology was the ability to create man-made antibodies using a mouse as an antibody "factory." In 1975, scientists stimulated a mouse to produce antibodies to a particular foreign substance (called antigen), isolated the antibody by dissecting it from the mouse's spleen, and fused it to mouse cancer cells, which enabled them to grow quantities of that specific ("monoclonal") antibody in a petri dish.

The discovery of this technology has led to widespread anticipation of rapid progress in the fight against cancer. By manufacturing specific antibodies to recognize a particular cancer cell, and fusing it to the antibody substances that could destroy the cell once contact was made, scientists expected major breakthroughs in cancer therapy.

This early optimism has not been home out. In fact, it took 15 years before the first two major man-made antibodies, neither of which are cancer drugs, made their way through the FDA approval process. These are the immunosuppressant OKT-3 and the antisepsis drug Centoxin.

Using animals as antibody-producing "factories" is time-consuming and expensive. It also yields substances that can trigger immune rejection by the human immune system because they are recognized as foreign and attacked. Advances in genetic engineering may soon make it possible to replicate the entire human antibody library in a colony of bacteria, making possible rapid location and replication of the desired antibodies.

This will markedly reduce the cost of antibody production and enable pharmacists to concoct specific combinations of antibodies for individual patients or for classes of illness. Eventually, scientists hope that hybrid man-made antibodies that both identify and chemically destroy specific cells will be used in a wide range of therapies including treatment of viral illnesses like AIDS and hepatitis, as well as cancer.

Conquering auto-immune diseases

Two of the most widely prevalent chronic diseases-diabetes and arthritis-are believed to be auto-immune diseases. This means that they arise from a malfunction in the immune system that causes the body's natural defenses to attack the body's own cells as if they were foreign. Short-circuiting this inappropriate immune reaction could be the key to preventing these diseases.

There has been sharply rising optimism that these diseases may be prevented by selective immune suppression. In the case of juvenile-onset diabetes, it may be possible, by anticipating the body's attack on the insulin-making beta islet cells in the pancreas, to snuff the process with aggressive immunosuppression.

The more widely prevalent adult-onset version of diabetes, which results from a loss of sensitivity to insulin, may be a more difficult nut to crack.

With arthritis, the very substances that are key to stimulating the immune response-interleukins I and 6, and a substance called TNF (tumor necrosis factor)-have been implicated in the destruction of cartilage and bone in arthritis. These substances even play a role in osteoarthritis, which is no longer thought to be a completely mechanical process, but increasingly a chemical or metabolic one. Understanding what releases these substances into the joints and blocking their release or their uptake into the cartilage and bone holds the key to curing arthritis.

This goal, which would liberate tens of millions of arthritis sufferers from increasingly painful disability, appears to be within realization by the end of the decade or the beginning of the next one.

Naturally occurring substances that block inflammation may have wider applicability than merely controlling arthritis. Inflammation is a signal that the body's immune system is actively responding to a threat to our health, but inflammation sometimes flares out of control, as in the gram-negative bacterial infections that bring on septic shock. The body manufactures substances that block inflammation by blocking the inflammatory cytokines, such as the interleukins. Controlling interleukin release and action may be an even more powerful tool for fighting septic shock than the controversial antibody Centoxin.

Begged questions

Societal readiness to use these powerful new tools is, alas, highly questionable. Some new biologicals are staggeringly expensive (Centoxin will cost $3,700 per dose) and challenge the system to rationalize their use. Others, like the new generation of bioengineered vaccines, may not only cost less but avert massive costs in broad populations by depriving viral agents of a foothold.

Genetic screening and serum marker testing, as well as monitoring devices like biosensors that detect changes in key body chemistries, are likely to be inexpensive enough to be used broadly across society without bankrupting an already strained healthcare budget. Biotechnology is not synonymous with "costly."

The ability of people to adopt a "life cycle" approach to their disease risk will require marked changes in societal values-lengthening time horizons and encouraging responsible healthy behavior. While the sharp reduction in the number of smokers does suggest that health promoting value and behavioral change is possible, a depressingly large fraction of contemporary illness could be prevented without technological assistance.

Changing societal values is the essential task, and one which requires both public health and political leadership.

Further, the millions who lie outside our present health insurance system do not get access to primary-care physicians or other caregivers who can identify early disease risks and counsel individuals or families on how to avoid them. America is experiencing mini-epidemics of

nineteenth-century diseases like measles, tuberculosis, and syphilis, because immunization rates are falling and basic public health measures are not being followed.

If these trends-poor primary-care access and erosion of public health effort-persist, the new advances will only accentuate the already disgracefully large variation in health status and life chances existing between rich and poor. But if access to primary care or neighborhood level healthcare services were improved, the emerging armada of new biological tools could dramatically improve the health of those at the highest risk.

Most important, however, will be devising a new way of thinking about illness. It will be morally and fiscally untenable to continue to think of disease as an inexorable Act of God. Our health insurance system will have to find a new rationale for assessing healthcare risk and setting premiums.

To the extent that illnesses become predictable and manageable, our passive, reactive approach to financing and delivering care must give way to a proactive approach that implicates the patient, family, and society in appropriate measure in both the avoidance and ultimate financing of care.

Some way must be found of balancing the individual and societal obligation to promote good health with the responsibility for providing needed care for unavoidable or unmanageable conditions. Americans need not be passive victims of disease.

The healthcare system's new tools will permit it to transfer both power and moral responsibility to families and individuals to manage their own health more effectively.

Genetic therapy:
Look for the weakest link

The complexities of genetic therapy are daunting. The challenge is somewhat like rewriting a complex computer program while the program is running -- except the program is perhaps the most complex in biological history. Besides, the genetic flaws are repeated in literally every cell of a person's body. Replacing damaged or defective genes may become the "holy grail" of genetic therapy, only to remain as elusive as its namesake.

A more likely approach than gene replacement is to infuse into the body genetically altered cells carrying instructions to make proteins the body itself cannot make because of genetic damage. These proteins will enter the life process, correcting for genetic damage.

Imagine, for example, a woman with genetic damage that predisposes her to arteriosclerosis: She receives infusions of genetically altered endothelial cells (cells that line the blood vessels) that produce TPA (a clot-dissolving agent) or nitric oxide (which causes blood vessels to relax). These cells would take root in the patient's arteries and medicate them continuously.

Imagine infusing a man who has a hereditary immune deficiency with a genetically engineered virus that "transfects" him with new genes that produce antibodies or enzymes his body was unable to manufacture on its own. These approaches are being tested as we write.

The rush to isolate "stem cells" in the bone marrow, the precursor cells to our entire immune system, has been stimulated by their potential strategic importance as a therapeutic tool. Genetically altered stem cells may be the most powerful possible vector of genetic therapy, since the entire immune system grows out of those cells and they circulate so widely in the body. The ability to use genetically altered stem cells therapeutically may eventually render bone marrow transplants unnecessary.

The key question with most diseases will be this: What is the weakest link in the chain of events or accidents that spring from our genetic programming and ultimately result in disease? It may not be cost-effective to correct the root cause-flawed genetic programming. And to understand the full chain of events that unfolds in a particular illness may take much longer than to merely identify the involved genes.

-Jeff C Goldsmith

Suggested reading

Bishop, J, **and Waldholz, M.** ***Genome,***

Touchstone Books, 1990. A comprehensible treatment of the breakthroughs in human genetics that led to the Human Genome project.

Hood, L. **"Biotechnology and Medicine of the Future,"** Journal of *the American Medical Association,* March 25, 1988. A more technical treatment of the instrumentation and technology that underlies the Genome project.

Biotechnology in **Perspective,** Industrial Biotechnology Association, Washington, DC, 1990. A **primer on the** basic techniques of biotechnology, including recombinant DNA **and monoclonal antibodies,** and their broadbased applications in medicine and agriculture.

Eisenstein, B. **,"The Polymerase Chain Reaction: A Now Method of Using Molecular Genetics for Medical Diagnosis,"** *New England Journal of Medicine,* January 18, 1990. A review article on the *most* powerful gene probe technology, and *bow PCR* is being applied to diagnosing viral and parasitic illness as well as genetic defects linked to disease.

Jaret, P. "Our **Immune System; The Wars Within,"** *National Geographic,* June 1986. A spectacular *and* readable primer on the functioning of the immune **system.**

Nossal, G. **"Immunology: The Basic Components of the Immune System,"** *New England Journal of Medicine,* May 21, 1987. Amore systematic and technical treatment of immune system function.

"What Science Knows About AIDS," *Scientific American,* October, 4988. An entire issue devoted to this ***subject lays*** **out the** scientific impasse, avenues of attack, and the medical and societal impact of AIDS.

Part 2 of this article (which will appear in the Healthcare Forum Journal, *July/August 1992) will explore ways in which the emerging capacity of biotechnology to predict and manage healthcare risk will affect the healthcare delivery system and further transform the role of the hospital.*

The Reshaping of Healthcare – part 2
Healthcare Forum Journal (July/August 1992)

Over the next seven to ten years, biotechnological innovations are likely to bring about changes that will force managers and professionals to reinvent the healthcare system. Although intervening events, like major economic dislocations or draconian restrictions on healthcare spending, could postpone the predicted events, these changes are, in my judgment, likely to be both inevitable and irreversible.

The advances in biotechnology will have dramatic impact on critical care, allowing the sickest patients to heal more rapidly and sharply reducing lengths of stay, on the treatment of heretofore hopeless diseases such as Alzheimer's and Parkinson's (see "Neurosciences-The next frontier") and on cancer therapy (see "Cancer treatment -- The long wait may be ending"). And the new predictive tools in genetics will *result in* a major paradigm shift with profound implications for healthcare delivery.

First fruits-critical care

The most immediate changes wrought by biotechnology are already unfolding in the critical-care arena. Critical-care patients will benefit from dramatic improvements in immune suppression, chemotherapy for radical cancer treatment, burn care, and other arenas. The emergence of bioengineered human growth factors, such as EPO, G-CSF, and the epidermal growth factors, all of which speed regeneration of vital human cells, will enable the sickest patients in hospitals to heal much more rapidly, reducing lengths of stay in critical-care settings.

Advances in immune suppression for organ transplantation have been slow but steady. The workhorse immunosuppressant, cyclosporin, is giving way to a new generation of agents less toxic to the liver and kidneys, less dependent on heavy accompanying doses of steroids, and less likely to cause hypertension.

In the early Nineties, lengths of stay for organ transplantation are already falling rapidly. At the University of Chicago, kidney transplant patients are often sent home after only a week's stay, compared to five to six weeks just five years earlier. Sixty to 70 percent reductions in length of stay for other categories of organ transplantation appear within reach.

For burn patients, the epidermal growth factors, combined with the ability to culture the patient's own skin for replacement of burned tissue (avoiding the risk of graft rejection), promise not only more rapid healing but markedly reduced scarring and residual skin damage. The same growth factors will speed healing from major trauma and surgical wounds, enabling these patients to return home sooner. Epidermal growth factors also promise to improve (or indeed make possible) healing of peripheral wounds and pressure sores in diabetics, forestalling the need for amputation and containing infection risk.

Quantum improvements can also be expected in the management of hospital-borne infections. Presently, about 3 percent of those admitted to American hospitals acquire hospital-borne infections, and as many as 60-100 thousand patients die of them every year. Future therapy for hospital-borne infections will probably be three-pronged: antibiotics to fight the infection itself,

antibodies to control the toxins they release, and anti-inflammatory agents to control inflammation. Timely, coordinated use of these multiple agents promises sharp reductions in death rates from hospital-borne infections, reduced ICU stays, and better results for these classic "outlier" patients.

Critical care has been a major contributor to census growth in hospitals during the past 20 years. As a consequence, many larger institutions have steadily expanded their critical-care bed capacity. While admissions of critical-care patients will continue to rise during the Nineties, reductions in length of stay will more than compensate, leading to significant overcapacity in criticalcare services by the end of the decade.

Length of stay will also be reduced by more effective utilization control, managed care growth, and the increased use of living wills. Providers contemplating major critical-care expansions should weigh carefully both their volume forecasts and the cost-benefit relationships before proceeding.

These gains will come at a price: explosive growth in drug costs, which in some cases may offset any savings from reduced length of stay. Forecasts of cost for the antisepsis drugs awaiting FDA approval have ranged as high as $3,700 a dose. The new growth factors can cost thousands of dollars for a course of treatment. Unchecked use of these new biologicals could cause cancerous lesions in many hospital pharmacy budgets.

The obvious challenge to medical staffs and pharmacy managers is to control the use of high-cost therapeutic agents through clinical protocols or practice guidelines that protect the patient and the institution from inappropriate use of these expensive new tools. Protocols will emerge from collegial interaction and therapeutic experience.

Such protocols will encourage consultation prior to use and specific, verified clinical indications that justify administration of multi-thousand-dollar drugs. To say these drugs must be rationed misses the point; their appropriate use must be established and controlled for the patient and the health system to benefit.

Early warning systems

The emergence of powerful predictive genetic tools will make possible continuous monitoring of genetically linked disease risk such as the risk of cancer. Our genetic programming, or genome, is not written in stone; indeed, our genetic makeup is constantly altered not only by environmental and lifestyle factors such as stress and toxins but also by random mutation and (recently discovered) natural DNA amplification and repair. The genome is a living "text" altered by the process of life itself. Taking a comprehensive assay of our genome with powerful new "gene probe" tests will assist in identifying genetically inherited disease risks-but it will tell us little about the timing associated with those risks.

Identifying the genetic roots of a disease is the first step in unraveling the chain of biochemical events (creation of proteins, enzymes, and so forth) that lead to disease. As this chain is unraveled, researchers are discovering "serum markers"-antibodies specific to diseases like juvenile-onset diabetes, prostate and ovarian cancer-present in the blood or urine that tell us the disease process has begun well before it can be detected by imaging or biopsy.

Presently, only a few dozen tests have evolved that link genetic damage to disease risk. By the end of this decade, it is possible that this list will have grown to a few thousand diseases. Only a handful of diseases have yet yielded serum markers that enable very early detection. By the year 2000, we may have hundreds of serum markers for serious chronic disease, early warning signs of the triggering of genetic or autoimmune health threats.

It will be possible (at relatively small expense) to screen individuals with inherited risks of contracting disease for "serum markers" that indicate the onset of disease. Evaluating disease risk *will* thus be a two-stage process: (1) assaying periodically the genetic baseline, and (2) carrying out customized screening for identified disease risks.

As the range of illnesses that can be prospectively evaluated grows, a new multi-billion-dollar industry *will* be born, powered not only by human curiosity and desire to protect our children but by insurance firms and managed care plans anxious to protect their insureds (or themselves) from preventable illness and avoidable costs. Perhaps an even bigger industry than the testing itself *will* be counseling families on how to manage the identified risks, not only treatment planning but also coping with the power*ful* emotional impact of the new and unwelcome knowledge.

The issue of who will control this industry will emerge as a strategic concern in the late Nineties. Promising candidates are pediatricians and obstetricians working together or through their affiliated hospitals, children's hospitals (which are likely to have the early edge in genetic therapy for many of these conditions), group practices (prepaid or otherwise), and freestanding genetic testing centers that *will* affiliate or contract with the above actors both for referrals and therapeutic follow-through.

Altering the surgical landscape

Though it is still uncertain how rapidly these advances *will* come and how precise the new tools of genetic prediction and serum marker testing will be, the prospect of screening and early intervention in diseases like diabetes, cancer, and arthritis could alter the surgical landscape of the next century.

Presently, surgical management bulks large in the later stages of all of these diseases. Diabetes eventually results in amputations, intraocular lens replacement, and open-heart surgery. Arthritis results in joint replacement. Surgical intervention is a staple of laterstage management of cancer. Many procedures (angioplasty, open-heart surgery, joint replacement) are redone after a number of years, adding to demand. The ability to anticipate and arrest or postpone these major degenerative diseases could produce sharp reductions in surgical incidence rates for their complications.

Given the explosive growth of laparoscopic surgery and the likely expansion in the surgical franchise it will produce, it is reasonable to expect surgical incidence rates to continue increasing through the mid-Nineties, with the vast majority of the growth in ambulatory or subacute surgical demand. As a result, as much as 85 percent of all surgery could be ambulatory by the end of the decade.

However, it is entirely possible that early-stage intervention in chronic disease will result in a decline in surgical incidence rates by the late Nineties. Managed care pressure for alternatives to surgery and rising co-payments will also exert a braking influence.

The American health system already has a surplus of surgical capacity in most communities, some of which are probably experiencing an epidemic of invasive procedures. Despite the superficial appearances of a boom, surgery is already a mature market, even given the growing elderly population. Providers contemplating expansions of surgical capacity should carefully evaluate these trends as well as their community's specific surgical demand curve (adjusted for age) before committing the capital.

Inpatient service in decline

Inpatient hospital use leveled off in the US during the last three years of the Eighties, after declining by 20 percent during the previous five years. The compound influence of the changes discussed above should be a further 20 to 30 percent reduction in inpatient use in the 1990s. Demand for acute care will not disappear, but it will be increasingly focused on trauma, serious infection, and care for the fragile elderly. United States hospital use rates, already the lowest in the world, will decline from the low eight hundreds to the low six hundreds in days per thousand by the early part of the next century.

While the downpayment on this reduction will come from laparoscopy and alternative treatments for prostate disease, reductions in long-stay cases in tertiary centers (trauma, transplantation, radical cancer therapy) will have a disproportionate impact later in the decade. Better planning and management of chronic diseases will yield 40 to 60 percent reductions in hospital utilization rates among the elderly. Rates will also decline most rapidly in the East, which has inpatient use rates double those in the West, owing to a delivery system dominated by specialists and academic health centers.

Dawn of prospective medicine

Since its inception in the Thirties, "managed care" has principally meant averting (typically through queuing or alternative therapy) hospitalizations for acute episodes. While lip service has been given to prevention, contemporary managed care still means "event"-driven cost avoidance, not health status improvement.

The Nineties have seen a welcome emphasis on evaluating the outcomes of clinical care and on proving the efficacy and cost effectiveness of therapy. However, in classic acute-care fashion, practice guidelines or clinical protocols usually begin with a medical incident. Thus, these two "progressive" forces in medicine-managed care and the outcomes movement-remain captive of the acute-care paradigm.

The emergence of a capacity to predict and manage disease pre-symptoms will provide a powerful set of new tools not only to anticipate medical problems before they arise but to empower individuals and families with knowledge to help them improve their own health status. Managed care will become truly prospective, as predictive tools free us from event-driven medicine. The initiating event will be a human event, not an "Act of God." Community-wide screening and tracking of disease risk will begin with a genetic assay and be followed by periodic, low-intensity contact between the "patient" (where is the illness?) and the health system.

Each person will have a genetic risk profile, identifying the major behavioral and environmental risk factors that must be controlled by the "patient" and his or her family to

minimize disease risk. This risk profile will lead to development of a customized screening protocol to track the emergence of potential disease threats.

The profile will also identify potential clinical interventions at the points where chemoprevention or treatment (genetic therapy or immune therapy) is likely to be most cost-effective. The clinical record comprising genetic assay, risk profile, and screening updates with clinical indications will follow the patient (perhaps in microelectronic records on the patient's insurance ID card) and be periodically updated as the person is screened.

These technologies will enable health plans and public sponsors to sharpen their identification of the highest-risk persons in the community and focus their attention on ameliorating their health risk. These technologies will therefore make possible a new goal structure: maximizing the health status and life chances of people, minimizing the need for institutional care, and postponing life-altering chronic disease symptoms for as long as practicable. This goal structure, which harmonizes well with what most of us want for ourselves and our parents, is diametrically opposed to the historic goals of the contemporary American hospital and nursing home system, which has sought to maximize the number of people in custody on a given evening.

Hospital's changing role

The contemporary acute-care hospital is not the logical center of a prospective health-promoting social system. Indeed, the hospital is a blunt instrument in improving the public health. Acute-care demand will not cease, and hospitals must organize more effectively to provide it. But acute care must not remain the centerpiece of the American health system. While hospitals can act as catalysts for system change, the ultimate control points for health services use will lie outside the hospital.

Planners and public officials have realized that community-based healthcare systems, whether founded on a public health model or medical group practice or some fusion of these two, are the foundation upon which an effective system of health status improvement must be built. A hospital-centered, specialtyoriented medical care system will continue to "wait" for the interesting cases to come to them *in extremis.*

Simultaneous invention of the community-based system is taking place both in the public and private sectors. In self-defense, overburdened public health systems in such diverse places as Dallas and New York City are attempting to rebuild or build new community-based health services anchored in primary care to stanch the flow of patients into hospital emergency rooms. On the private-sector side, health plans, group practices, and some hospitals are sponsoring dispersed networks of primary-care sites, fused in some places with diagnostic and therapeutic technologies, to accommodate managed care and fee-for-service patients in non-institutional settings anchored in neighborhoods.

The worsening shortage of primarycare physicians and the difficulty of supporting primary medical practice in inner cities and rural areas pose a major threat to the ability to complete the transformation to a community-based system. The shortages of personnel will compel innovation in healthcare organization. Multidisciplinary approaches that extend limited physician cadres and dissolve the increasingly questionable barrier between medical care and human services will become essential.

Stripped of its ideological baggage, and armed with new tools, that War on Poverty workhorse-the community health center-will arise anew in the Nineties with new sponsorship and a new relevance to community needs. A new architecture of health professionals imbedded in neighborhoods and anchored to primary care will be needed to leverage the new predictive technologies effectively, and to promote patient and family education, behavioral modification, and disease risk management.

The emerging capacity to predict and manage illness will also alter the terms of the clash of perspectives between advocates of prevention and traditional medical care. The predict-and-manage approach to prevention is more muscular and technologically potent than the conventional prevention model. But by avoiding custodial care and distributing responsibility for alleviating identified disease risk between families and the health system, it challenges the traditional medical model-and the primacy of providers as definers of illness. In the

new model, the role of the provider is recast from custodian to counselor, and clinical intervention is not the first recourse. The hospital will be the relief pitcher, not the starting pitcher, in the health services rotation.

The medical and socio-behavioral models must be melded into a new framework that effectively manages identified health risks and uses interventional technologies only when most appropriate. Properly employed, new information and treatment options will empower individuals and families to manage their own disease risk, rather than making them passive wards of the health system.

Cancer treatment-The long wait may be ending

Nowhere in clinical medicine has the gap between biotechnological promise and performance been larger than in cancer treatment. Almost as if in mockery, the declaration of a war on cancer in the early Seventies was greeted with a nearly 20-year-long drought in the discovery of effective new therapeutic agents. Cancer death rates continued rising during the Eighties, fueled largely by the epidemic of lung cancer.

Optimism in the early Eighties about the promise of cellular therapy for cancer patients gave way to a decade of frustration as cancer researchers confronted gaps in their fundamental knowledge of the process of cell growth and differentiation. Drug research in cancer prior to the late Eighties had a depressingly random aspect. Chemical agents were screened more or less at random to determine if they killed cultured cancer cells, then to determine if they could be tolerated, even marginally, by healthy cells in the human body.

Advances in understanding of the genetic and cellular origins of cancer, and parallel advances in drug design, have fundamentally changed this process. Researchers now look for the vulnerable sequence of molecular events in cancer, and try to intervene to alter the course of the disease. The goal is more elegant therapy that minimizes side effects.

Several strategic targets in. cancer growth have shown the first signs of vulnerability. Angiogenesis (growth of blood vessels) is a vital process in solid tumor growth, since a tumor cannot grow beyond the size of a BB without access to its own blood supply. Blood vessels grow into tumors because cancer cells release chemical agents into adjacent healthy tissues that

promote infiltration of blood vessels. Once this is accomplished, the tumor uses the new blood vessels not only as a source of oxygen and nutrients but also as a pathway for metastasis, spreading into other areas of the body and, almost inevitably, killing the patient.

Researchers at Harvard Medical School discovered, by happy accident, a fungus that prevents angiogenesis and arrests tumor growth cold in a variety of animal models of solid tumors. A synthetic analog of this fungal agent, fumagillin, has shown striking effects in limiting tumor growth without toxic side effects in animals, and is entering human trials.

Research at the National Cancer Institute has revealed that metastasis, the conclusive phase of cancer, is controlled by genes, just like oncogenesis (the initiation of cancer cell growth), and that a specific class of enzymes is vital to the capacity of cancer cells to tunnel their way into the bloodstream.

This discovery has opened the way not only to technologies that "freeze" the genes responsible for metastasis but also chernopreventive agents, which block the enzymes (called metalloproteinases) that chemically breach tissue membranes and open the door for metastasis. The blocking agents for metastasis are also entering clinical trials.

Another exciting potential therapeutic approach has emerged at the M.D, Anderson Cancer Center in Houston in the study of the anti-cancer properties of retinoic acid, an analog of vitamin A, Not only has cisretinoic acid (in combination with interferon) had dramatic impact in reducing late-stage solid tumors, it has also prevented precancerous cells from evolving into mouth cancer.

This may be the most exciting potential discovery of all, since people at risk of contracting cancer, at least in the soft tissues, may be treated with "chemoprevention" and achieve a restoration of normal tissue growth.

The chemotherapeutic leg of the traditional cancer treatment "triad" appears poised for an explosive advance, perhaps at the expense of surgical management. Much of this therapy will be infusion dependent, since many of the new

therapeutic agents are "large molecule" proteins that cannot survive the digestive tract's assault. Day hospitals and homecare will expand dramatically to absorb the new therapeutic modalities, as most of them will not require hospitalization. The next generation of agents will be "smaller molecule" analogs, however, which may be administered orally. The proportion *of* cancer treatment that requires hospitalization will probably continue shrinking during the Nineties, as it has during the past 15 years.

Such discoveries place a premium on early detection of cancer cell growth. Cancer screening will move far beyond the primitive but important tools of the Pap smear and mammogram during the Nineties, and become a major part of effective community medicine.

These new tools will be placed in the hands of primary care physicians and community health workers, enabling a quantum advance in prevention of disease.

Neurosciences— next frontier

Few events in terms of health status are more irrevocable than nervous system damage due to trauma, strokes, or degenerative diseases like Alzheimer's or Parkinson's. Innovation in the clinical neurosciences promises not only to control the amount of damage, but eventually to restore lost function by regrowing damaged nerve tissues. The Nineties have been proclaimed the "decade of the brain" by Presidential decree. By the end of the decade, the grim neurosciences may have moved tangibly toward the goal of becoming restorative disciplines.

The past 30 years have seen sharp reductions in mortality from spinal cord injury, from 30 percent in the Sixties to as low as 6 percent currently in some centers. During the past 18 months, new hope for trauma patients has come from the discovery that aggressive treatment immediately after injury with steroidal anti-inflammatory agents can limit nerve damage and restore some motor function.

Research on stroke patients points to the possibility that powerful antioxidants like superoxide dismutase (SOD) administered quickly after a stroke may be able to limit permanent brain damage. Indeed, it may not be oxygen deprivation from the stroke itself that kills the nerve cells, so much as flooding the brain with destructive free radicals when blood resumes flowing. These anti-oxidants have been dubbed (somewhat breathlessly) "lazaroids" because of the illusion they create of bringing damaged cells back from the dead. If their clinical effectiveness is established, these new substances would be administered, like streptokinase, in the immediate wake of a catastrophic event.

For patients who have already sustained nerve injury, it may prove possible to regrow damaged nerve tissues by injecting cultured nerve cells and/or human nerve growth factors into the damaged area. In experiments at Sweden's Karolinska Institute, infusing nerve growth factor into brain tissues damaged by Alzheimer's disease has apparently promoted regrowth of nerve cells and some restoration of memory.

Neuroscientists have also achieved some success by grafting fetal nerve cells into damaged areas to achieve restoration of function. These research efforts have been virtually halted in the US by die federal government's ill-conceived ban on fetal cell tissue research. Future technological progress may enable surgeons to use cultured nerve tissue prepared with human nerve growth factors, bypassing the need for fetal tissue.

The prospect of restoring long-damaged tissues from past injury, or reversing damage from devastating neurological disorders like Parkinson's or Alzheimer's, could provide hope for millions of seriously impaired people and open up huge new markets for neuroscience centers. Neurosurgical restoration will eventually replace cardiac surgery as the key differentiator of a tertiary center.

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