Medicine

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Summary. Advances in hepatitis and immunology illustrate the influence of basic research and technologic innovation in shaping the past, present, and future of medical care.

Nothing expresses as effectively and as succinctly the course of American medicine since World War II as Aaron Wildavsky's provocative observation that we are "Doing better and feeling worse" (*1*). The immense scientific and technological developments that have characterized medicine during the 20th century account for our "Doing better." Paradoxically, the same developments also account for our "feeling worse," and are related to technology's dominant influence in shaping the past, present, and future of medical care.

Before World War II, some giant steps had, of course, been taken. Such steps include the introduction of anesthesia, Claude Bernard's concept of the body's internal milieu defending itself against a vast and motley world of stresses, the recognition of foxglove as a source of digitalis, still an invaluable cardiovascular drug, the empirical validation of vaccination, the identification of the major human blood groups, the usefulness of liver in containing the manifestations of pernicious anemia, and the isolation of insulin for the control of diabetes.

More recently, advances in our understanding of human genetics have led to what is doubtless only the beginning of genetic medicine. Much has been learned about human chromosomes and the genes they carry, making it possible now to identify many inherited diseases in utero. Well more than 100 genetically determined inborn errors of metabolism are known and several can be treated. Phenylketonuria (PKU) is an example. Insights into the major hemaglobinopathies or blood disorders including sickle cell anemia and thalassemia, which afflict large numbers of people, are leading the way to new therapeutic intervention. Judicious use of recombinant DNA technology may one day enable us to cure some of these diseases at the molecular level, replacing defective genes with normal ones.

But fundamental advances, actual or anticipated, occur erratically and infrequently; often they do not affect the general nature of medical practice, which depends heavily on the "art" of medicine, a skill that still lies in the physician's ability to make the patient feel better and that does not always depend on the physician's knowledge of medical science. However, the character of medicine *has* changed in many substantial ways since World War II, owing in large measure to the technologic concepts and technological innovations that have dramatically improved specific aspects of medical care while, at the same time, inducing repercussions. Modern medical technology enhances our well being and also compromises it. And it has made the physician both healer and technician (*2*).

Many new medical technologies are designed to extend the doctor's ability to make a diagnosis. Fiber optics, nuclear imaging, and sensitive tests for biochemical analysis of body tissues and fluids are invaluable to refined diagnosis of disease. Perhaps most conspicuous among the new diagnostic armamentarium is computerized axial tomography—CAT or CT scanning—and its radiologic offspring that make it possible to "see" lesions in the brain and deep in other recesses of the body. That these technological advances are achieved at great economic cost to society and also tend to depersonalize the patient is a subject of growing discussion within the medical community and society at large, but cannot go without mention in even a brief review.

Costly, depersonalizing, and often truly life-saving technology has assumed a major place in patient care that mirrors technological developments in diagnosis. The heart-lung machine has made possible astonishing surgical feats, including of course the transplantation of organs. The array of equipment that is now so familiar a part of intensive care units sustains lives that previously would have been lost. Renal dialysis, a million dollar business and billion dollar federal program, enables many kidney disease patients to lead productive lives but can also needlessly prolong the lives of the terminally ill. We have learned full well that technological pluses have negative aspects too.

Infectious Disease

Medicine's biggest triumph has been the virtual control and, sometimes, the eradication of infectious disease. This control, some argue, has been achieved more by improved sanitation and nutrition (*3*) than by the doctor and his bagful of antibiotics and vaccines. But surely the doctor deserves some credit. Only within the past decade, for example, have researchers identified viruses and bacterial toxins (often from coliform organisms) that are responsible for various types of tropical diarrhea, but the morbidity and mortality associated with such diseases, especially in infants, are best reduced by an adequate diet and sound hygienic practices. Medicines may be more harmful than otherwise. Conversely, the virtual elimination in the United States of polio by 1964, after a record number of 35 cases per 100,000 population in 1953, must surely be credited to basic research in understanding polio virus and to the development of an effective vaccine. The marked decrease in the frequency of tuberculosis provides an example of joint influences at work: public health measures on the one hand and new drugs (streptomycin, aminosalicylic acid, isoniazid, ethambutol, and rifampin) on the other.

Although infectious diseases are reasonably well contained, pockets of resistance remain. Malaria in particular is still prevalent in many parts of the world, as is schistosomiasis. "New" viral and bacterial infections (Legionnaire's disease is an example) continue to appear. But one can suppose that in each case, progress will be made through appropriate application of present principles of identification, environmental and sanitary control, vaccines, and drugs. Fur-

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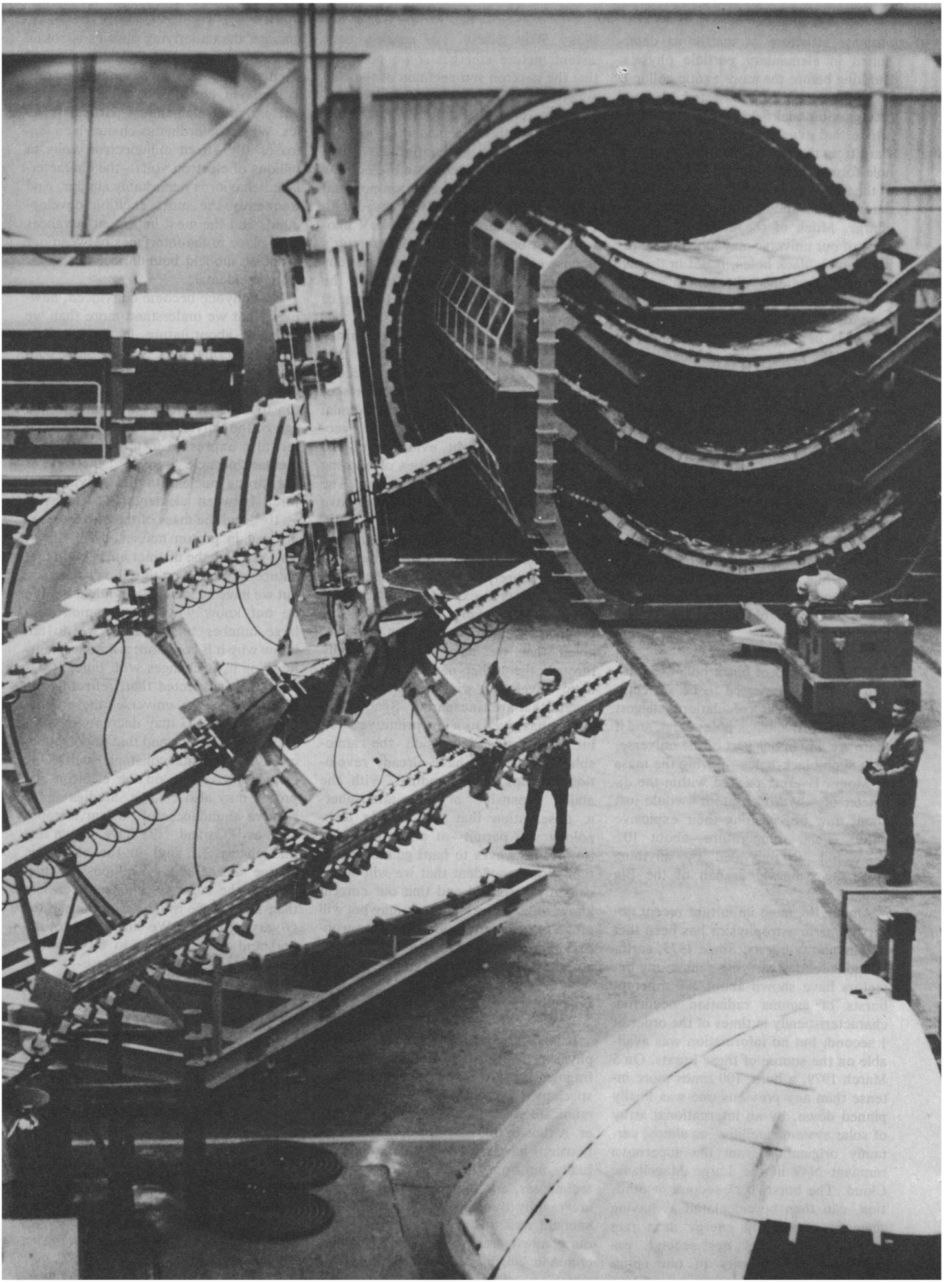
←*Metal airplane parts bonded with polymer adhesives are cured in a giant autoclave.* [*Courtesy of Lockheed Corp.*]



thermore, new therapeutic approaches to the control of viral infections are on the horizon. Amantadine is recognized as one of the first useful antiviral drugs. Interferon, now the object of intense public interest, may well turn out to be a potent antiviral protein. First identified in 1957 (*4*) as the body's natural antiviral agent, interferon, which has been isolated recently from human blood cells, has been used successfully in experimental therapy of hepatitis and severe herpes infections (*5*). It is certain that before long researchers will have made interferon in sufficient quantity (most likely by using gene-splicing techniques) that intensive studies of its properties will be possible. Whether it will live up to its reputation as a striking new anticancer agent remains to be seen, but its usefulness in treating viral diseases seems predictable.

Despite the progress that has been made in the control of infectious disease, fear of epidemics persists. Witness the alarm created by the idea that recombinant DNA technology would let loose in the world some ultravirulent and uncontrollable agent that might kill people by the thousands. And the ill-fated swine-flu vaccination effort shows how an entire nation may respond to the threat of a viral infection in a manner that in retrospect appears not only irrational, but hysterical.

It is somewhat ironic, in view of our remarkable successes in protecting the population at large from the threat of widespread epidemics, that the danger of infection to a limited but important group of patients has been enhanced by medical efforts. Because of immunosuppressive measures that are employed for transplant patients, individuals with cancer, and persons with a variety of other diseases, a large pool of patients especially susceptible to infectious agents is being created iatrogenically. Not only are these patients highly vulnerable to known pathogens, they are also susceptible to opportunistic infections by microorganisms not ordinarily infectious in human beings. In these patients such organisms can cause overwhelming infection and death. Because the number of patients with iatrogenically suppressed immune systems can be expected to increase, decreased resistance in man rather than increased aggression by bacteria and viruses may account for an increasing persistence of infectious diseases, although one cannot discount the problem of organisms becoming resistant to the very antibiotics that have proved to be such potent weapons against them.

No discussion of medicine during recent decades that does not encompass volumes can be comprehensive; a sensible author refrains from even attempting such a goal. But it is possible to point to a couple of areas in some detail that, in addition to fields already mentioned, stand out as examples of what is most characteristic of medical science as I have known it and that show most clearly where basic research and medical practice connect with one another. These are hepatitis and immunology, particularly the HLA system.

Hepatitis

Description during the past 15 years of the various forms of viral hepatitis is an exciting tale, garnished by serendipity, some danger, painstaking serological and microscopic studies, ethical problems, and Nobel Prizes for two Americans. On the basis of observations made during and after World War II, infectious hepatitis was divided into two types, each tentatively attributed to viruses. One type, classified as ordinary infectious hepatitis or hepatitis A, principally affects children and young adults. It is characterized by fecal-oral transmission, a short (weeks) incubation period, and a benign course. The other, called post-transfusion or type B hepatitis was attributed to parenteral transmission of blood or blood products. It has a long (months) incubation time, tends to affect older persons, and runs a more severe and sometimes lethal course.

In 1965, a geneticist named Baruch Blumberg was studying the antigenic profile of various human plasmas by exposing them to the many antibodies found in the blood of patients who have received multiple blood transfusions. By this means, he identified an unknown antigen in the blood of an Australian aborigine (*6*). Blumberg called it Australia antigen. The subsequent observation that Australia antigen is found in the blood of patients believed to have hepatitis B (*7*) precipitated a landslide of research leading to the identification of Australia antigen as the surface coat of the hepatitis B virus (designated as HB_sAg for hepatitis B surface antigen). Other hepatitis-related serological markers (*8*) have been described, including the hepatitis B core antigen (HB_cAg), which is thought to be an integral component of the virus itself, and antibodies to these antigens. Presence of the antigens has been demonstrated by immunological techniques; virus particles and fragments in tissues and blood have been visualized by electron microscopy. The hepatitis surface B antigen has been further divided by subtype determinants labeled a, d, y, w, and r. These subtype determinants do not appear to affect the clinical course of hepatitis but are epidemiologically provocative in that most hepatitis B in the Americas and Europe manifest subtype adw, and that in the Orient, subtype adr. Another antigen associated at times with HB_sAg is HB_eAg (e antigen); the presence of both of these antigens indicates a particularly infectious form of the disease in which the liver is likely to be involved.

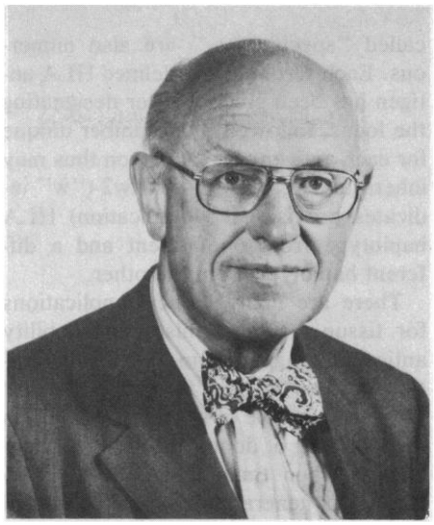
Similar developments have elucidated hepatitis A. The responsible virus particles have been discovered in the stools by electron microscopy; the antibody can be identified in blood immunologically. But it is now apparent that many cases of hepatitis are neither type A nor type B. These cases are labeled non-A, non-B, or type C hepatitis (*9*). Although non-A, non-B is a cumbersome description, it is preferable to hepatitis C because further study will probably reveal that the viral etiologies of the "new" hepatitis are several if not manifold.

Further delineation of the viral forms of hepatitis may be expected. Past and present advances along these lines may not necessarily be therapeutically useful but will provide major public health benefits and new diagnostic tools. Prevention rather than treatment is facilitated. Blood donors, for example, can be screened to eliminate persons who are chronic carriers of hepatitis B. As a result of screening out hepatitis B, most cases (80 to 90 percent) of post-transfusion hepatitis today are ascribable to non-A, non-B virus. Furthermore, present knowledge should permit the development of appropriate vaccines, and progress is being made in this regard.

During the years in which knowledge about hepatitis was expanding rapidly, an ethical cause célèbre developed over an experimental protocol designed by Saul Krugman who was studying hepatitis in mentally retarded children at New York State's Willowbrook hospital (*9*). Since most of these children, like others living in an institutional environment, became infected with hepatitis spontaneously, Krugman saw no harm in deliberately exposing them to hepatitis virus by oral or parenteral means. Krugman's experiments were invaluable in the delineation of the types of hepatitis, but they caused a furor among the burgeoning ethical conscience of the late 1960's and early 1970's. Today they could not be repeated.

Yet ethical questions remain. Personnel in hemodialysis units are probably at

risk for hepatitis B because of their frequent exposure to blood and needles. Those who work in oncology units also are at increased risk because so many of their patients, immunosuppressed as part of their cancer therapy, carry hepatitis B or non-A, non-B virus. Do such personnel deserve special consideration? Even more important, how should those doctors, nurses, dentists, and other health workers who are hepatitis B carriers be managed? Should they be encouraged or even required to change jobs so they will not expose their patients to the virus? The issue at present remains unsettled.



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Immunology

If Nobelist Blumberg discovered HB_sAg, another Nobelist, Rosalyn Yallow, made possible the measurement of HB_sAg and other hepatitis-related antigens and antibodies by inventing, with the late Solomon Berson, the radioimmunoassay (*10*). By this remarkable technique, femtogram (10^{-15} gram) amounts can be detected and quantified in various biologic materials. The competitive inhibition principle of the radioimmunoassay technique can be summarized as follows. Unlabeled antigen in unknown samples competes against labeled antigen for binding to antibody and thereby diminishes the binding of labeled antigen. To determine the concentration of antigen in an unknown sample, the degree of competitive inhibition observed in the unknown is compared with that observed in known standard solutions.

The radioimmunoassay is but one of the fantastic clinical advances made possible by basic immunologic research. Immunology deals with the recognition of self and its defense against non-self. A vast and complex antibody system, of which HB_sAg is a single example, is responsible for what is known as humoral immunity. Humoral immunity, which confers passive and temporary protection against various infectious processes, depends on the presence and normal function of B lymphocytes and on their related plasma cells. These cells elaborate the immune globulins (Ig) found in human plasma and designated IgA, IgG, IgM, and IgD. These Ig molecules are largely responsible for conferring passive and temporary protection against infection. IgA is the principal immunoglobulin in gut secretions. IgE plays a major role in the immediate hypersensitivity that characterizes anaphylactic reactions.

The other major group of lymphocytes consists of what are known as T cells. Derived from the thymus gland, these cells are responsible for cellular immunity, including delayed hypersensitivity, and manifest themselves clinically by such phenomena as the skin tests for tuberculosis and the rash that appears after exposure to poison ivy. T cells have been classified according to their immunological function as "inducer," "helper," "suppressor," "effector," and "killer" subtypes (*11*). Helper T cells promote the formation of humoral antibodies by B cells, suppressor T cells decrease the formation of humoral antibodies by B cells, and effector T cells participate in delayed hypersensitivity reactions. Cytotoxic lymphocytes may play a role in the rejection of transplanted organs. The various types of immunoregulatory T lymphocytes can be separated by analysis of their functions in vitro, and, in some cases, by glycoprotein markers on the T cell surface.

Clinical Disorders of the Immune System

Numerous clinical disorders express abnormalities of the immune system. Some, consisting principally of immune deficiencies, are genetically determined and primarily affect infants and children. But immunodeficiencies may be acquired at any age. Their pathogenesis with respect to lymphocyte activity is often complex; a deficiency of B cell formation, as found in several types of hypogammaglobulinemia, may reflect impaired production of B cells, decreased availability of "helper" T cells, excessive activity of "suppressor" T cells, or a combination of all three mechanisms (*12, 13*).

Because various other permutations of abnormal lymphocyte function exist, and because other serum factors (complement, for example) affect the immune process, the varieties of immunodeficiency are many. However, their total prevalence is low. Study of the immunodeficiency syndromes therefore helps to disentangle and elucidate the intricacies of the immune process. Knowledge so gained may in the future lead to therapeutic interventions that can, as appropriate, promote or inhibit a specific immune function.

Far more common than immunodeficiencies are sicknesses characterized by excessive or misdirected immune reactions. Two outstanding examples are the disorders ascribed to (i) autoimmunity and (ii) the deposition in tissues of "immune complexes." In some autoimmune diseases, host cells are altered by viruses or drugs and act as foreign antigens that stimulate an immune response that destroys the altered host cells and perhaps similar but normal host cells as well. In other instances, immune processes appear to be subverted so that they fail to recognize normal cells and attack them.

Clinical examples of diseases believed to be based on autoimmunity include hemolytic anemia, myasthenia gravis, certain thyroid disorders, and some types of chronic hepatitis. Autoimmune hemolytic anemia may be precipitated by a number of drugs and some neoplastic diseases.

In those diseases characterized by the formation of immune complexes, crucial components of various organs accumulate deposits consisting essentially of antigen, antibody, and complement. An occasional case of viral B hepatitis is, for example, complicated by glomerulonephritis; in such cases complexes containing Hb_sAg, antibody to Hb_s, and complement have been identified by immunofluorescence on the basement membrane of the glomerulus.

Various phenomena characteristic of autoimmunity have been described in patients with inflammatory disorders of joints. Rheumatoid arthritis, for example, is associated with the development of "rheumatoid factors" in the blood and in the synovial fluid. "Rheumatoid factors" are complexes consisting principally of IgM and IgG antibody. Even more convincing evidence of autoimmunity is found in systemic lupus erythematosus (SLE), a multiple organ disease. Processes believed to affect autoimmunity are evident on histologic, serologic, and clinical examinations. Deposits of immune complexes are found in

various tissues, and the serum of patients with SLE teems with antibodies to nuclear substances including deoxyribonucleic acid (DNA). Among the clinical manifestations that occur are hemolytic anemia, glumerulonephritis, inflammation of the blood vessels (vasculitis), and arthritis. Unfortunately, except in the case of drug-induced autoimmunity, the etiologic agents that initiate autoimmune disorders are poorly understood. Current treatment therefore remains chiefly symptomatic. In severe cases, immunosuppression with corticosteriods or the cytotoxic drugs azathioprine or cyclophosphamide may be used, but such agents are themselves hazardous. The challenge for the future is the development of measures that arrest deranged immune reactions without damaging those that are normal. One possibility currently under study is the preparation and use of antiserum directed against various lymphocyte fractions.

The Histocompatability System

Although disorders of the immune system are difficult to treat, increased knowledge of this system has mitigated at least one troublesome problem: the rejection of transplanted organs. The technical virtuosity is now available to transplant not only kidneys and hearts, but also livers, bone marrow, pancreatic islet tissue, and others. To obtain appropriate donor organs in sufficient numbers, however, requires the use of allogeneic sources, a procedure that invites transplant rejection because of a lack of histocompatability between donor and recipient. Discovery and elucidation of the histocompatability (HLA) system have improved allogeneic graft survival and have shown that susceptibility to various diseases is influenced by our genes (*14*).

The HLA antigens, each of which is genetically determined by an allele situated in loci of the short arm of chromosome 6, are found on the surface of practically all nucleated cells of the body. Histocompatability loci that have been identified are labeled A, B, C, D, and DR (D-related).

The pattern of histocompatability in tissues (the phenotypic haplotype) can be identified serologically by the HLA antigens produced by the A, B, C, and DR loci; typing of D antigens requires in addition the use of specially prepared lymphocytes. Because a great variety of alleles may occupy each locus, the corresponding serologically defined antigens, called "specificities," are also numerous. Each serologically defined HLA antigen has been given a letter designating the locus, followed by a number unique for each antigen (*15*). A person thus may inherit an A1, B8, Cw4, DRw2 ("w" indicates provisional identification) HLA haplotype from one parent and a different haplotype from the other.

There are many clinical applications for tissue typing of histocompatability antigens, ranging from the demonstration that two different fathers sired a pair of twins in a case of superfecundation to the matching of donor and recipient haplotypes when transplantation is undertaken. In general, allographs obtained from close relatives of the recipient survive longer when the donor and recipient HLA-A and HLA-B specificities match; but survival of cadaveric transplants appears to depend to some extent on the matching of D or DR specificities (*16*). Identification of additional specificities may be expected and should improve the outlook for transplants obtained from cadavers, a necessary development in view of the limited number of organs that can be supplied by the recipient's parent, sibling, or children.

Analysis of HLA haplotypes has proved helpful in ethnic studies of population groups, but the most exciting development has been the finding of an association between some diseases and certain HLA specificities (*17*). The most striking association is found in patients with ankylosing spondylitis; nearly 90 percent of them have the B27 antigen. Since B27 occurs in only 7 percent of the white population, a white person with a haplotype containing B27 runs a 12-fold greater risk of having ankylosing spondylitis than the white population at large. Other disorders associated, although less strikingly, with various HLA antigens include Reiter's syndrome, gluten-sensitive enteropathy (celiac disease), juvenile diabetes mellitus, myasthenia gravis, multiple sclerosis, and some diseases of the thyroid and of the adrenal glands. Associations of this sort naturally lend credence to the hypothesis that many of mankind's illnesses can be ascribed not only to invasions of external origin, but also to the genetically determined susceptibility of the host. Time and further research will reveal the validity of this hypothesis and the extent to which it is applicable.

An intriguing but still relatively mysterious field is the influence of immunological processes on neoplasia. Neoplasia is accompanied by the appearance of tumor-associated cellular neoantigens in a large number of carefully studied models. Why, then, does the host not mount an effective immunologic defense? Many explanations have been advanced, including the presence of blocking factors such as antigens shed by tumor cells or antigen-antibody complexes in the serum. More recently, it has been proposed that uncontrolled host suppressor cell activity may undermine effective antitumor immune responses and enhance tumor growth (*17*). An understanding of suppressor cells in neoplasia may induce reassessment of the effects that various commonly used immunotherapeutic agents, such as BCG (tuberculin) organisms, exert on the immunoregulatory system of patients with cancer. The general failure of immunotherapy in neoplasia with these agents may have resulted in part from the demonstrated capacity of the agents to activate suppressor cells. New immunotherapeutic strategies which incorporate recent insight regarding the suppressor cell might make it possible to help patients with cancer by selectively activating the host cells involved in the defense against neoplastic growth while nullifying the suppressor cell system.

Clearly, medicine still has a long way to go; the advances that contribute to "feeling good" are likely also to continue to create instances of "feeling worse." Nevertheless, one recognizes that if attention is focused on certain serious organic diseases—infectious, immunologic, even malignant—the contributions of science and technology to modern medicine have been truly wondrous, giving confidence for the future.

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