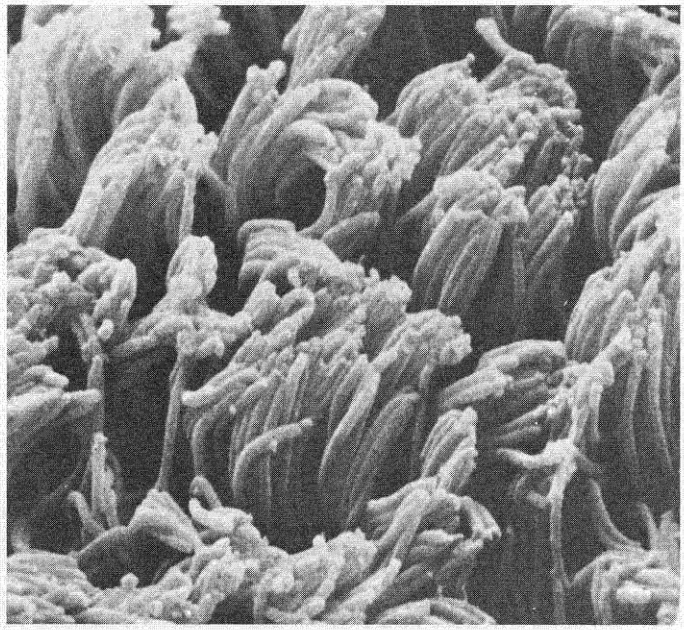
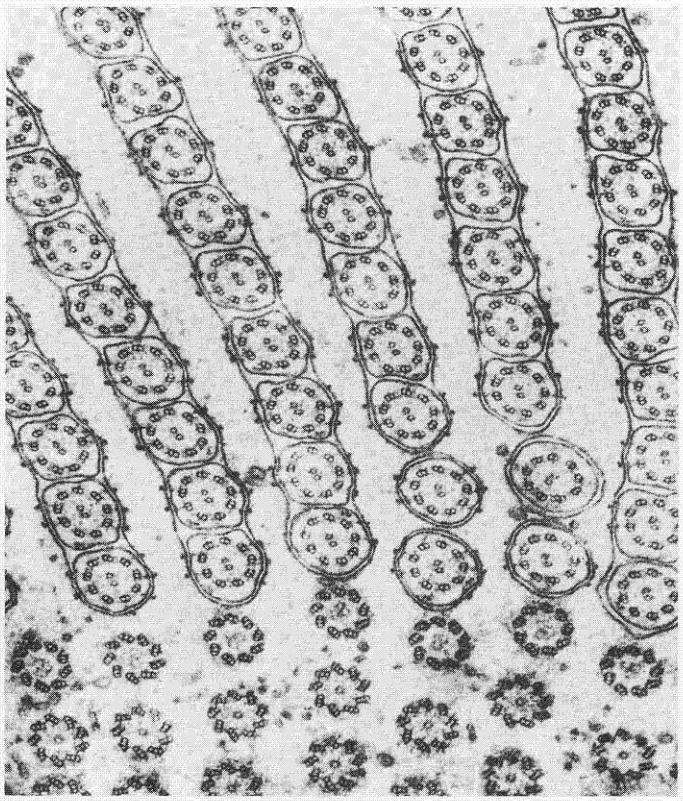
The Implications of Recent Advances in Biology for the Future of Medicine

by Robert L. Sinsheimer



The cilia that line the trachea can be observed in detail with the use of a scanning electron microscope.



A cross section through a bed of cilia shows even deeper levels of structure with the transmission electron microscope.

I cannot resist an inner smile at the pretentious title which adorns this talk, for I know very well of what fragile threads is such conceit woven. Of all our human conceits surely our persistent resort to prophecy must be among the most droll in the light of our abysmal record of success. The very persistence of the prophetic trait must I think be ascribed to some innate human urge—to a curious pride in our enlarged perception of time or perhaps to a nascent evolutionary drive to extend the craft of biological adaptation into a new dimension.

But the urge is real and the pace is swift and the future we really do believe to be written in the past and present, if only we have the wit to read. What then may we see if we stand today on the frontier of biology and look about us with the eyes of the healer?

I think we will see that we are surf-riding just behind an immense wave of progress in fundamental biological knowledge—a wave that began slowly to take form nearly a century ago and whose momentum will in the near future sweep away very many of the ancient obstacles to medical progress. In so doing it will provide the physician with unprecedented skills, unprecedented powers, *and* unprecedented responsibilities—responsibilities whose very weight may well reshape many of our enduring values.

For physicians it has been the better part of wisdom since Hippocrates to acknowledge that each cell in the body is far better informed as to its function than we are in any conscious sphere—and that the genius of innate homeostasis, accumulated in the long course of evolution, far exceeds our capacities to intervene. And thus derived the well-founded belief in the healing power of nature, if not tried too sorely, and the wisdom of the physician's restraint—his bent to facilitate the natural recovery.

But in our time the balance is beginning to tip. Analytical biology, founded a century ago in the work of Pasteur, Darwin, and Mendel, has developed with ever increasing momentum. It has received powerful and essential support from the great discoveries of physics and chemistry in the early part of this century, which revealed the basic nature of matter, inorganic and organic. It has penetrated to the core of the living cell, and it is now

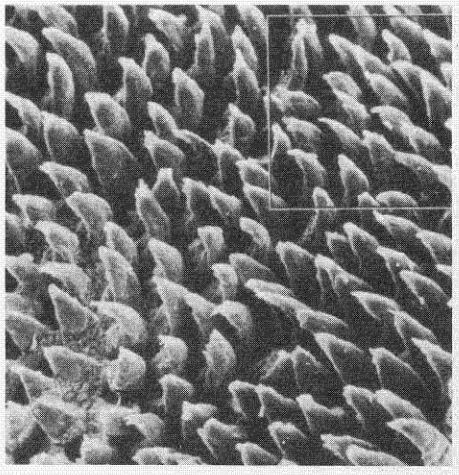
providing us an insight into the substance and nature of life, into the genesis and pattern of function—and malfunction—that can begin to bear comparison with the silent wisdom of the body.

In this conscious knowledge, infused with intelligence, are the seeds of a newer medicine, a medicine impelled to a more active philosophy that will—soberly and thoughtfully, but deliberately—seek to improve upon nature's design. For nature makes mistakes; the elasticity of homeostasis is all too finite, and two billion years of evolution have not yet achieved perfection.

In recent years we have adapted the powerful tools of modern physics and chemistry to probe ever deeper into the special architecture of life. We have thereby revealed with increasing clarity and detail the remarkable forms underlying the remarkable functions, so long known but so long mysterious. And at every level we find both order and intricacy, and we have gained both insight and aesthetic delight.

For instance we have known that the trachea is lined with cilia to control the passage of errant particles. The scanning electron microscope enables us to observe these in unprecedented detail (left). Deeper levels of structure can be seen in cross sections (below left) in the transmission electron microscope. Cilia of course beat in a synchronized motion. In this delicate and elaborate design must lie the secret of this function—or occasional malfunction.

The tongue is lined with minute papillae with which we taste. Here again we can now see (below) unexpected nuances of detail—although I should emphasize we are of course not yet at the level of molecular discrimination.



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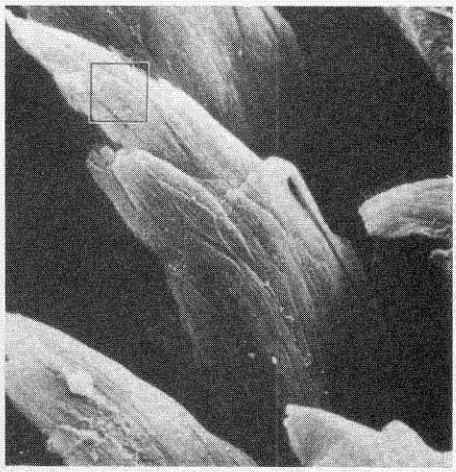

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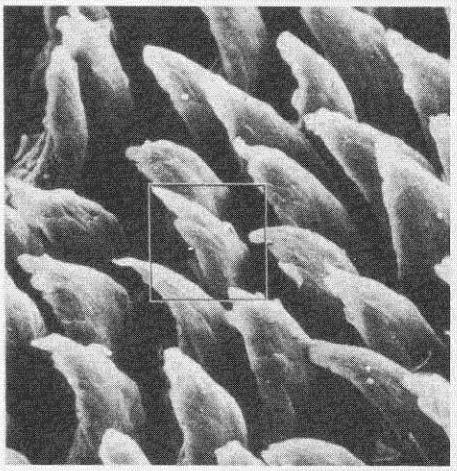

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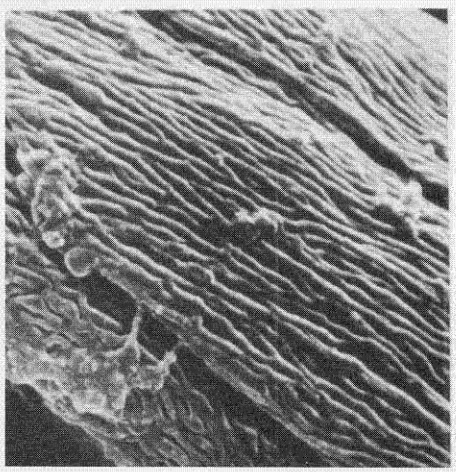
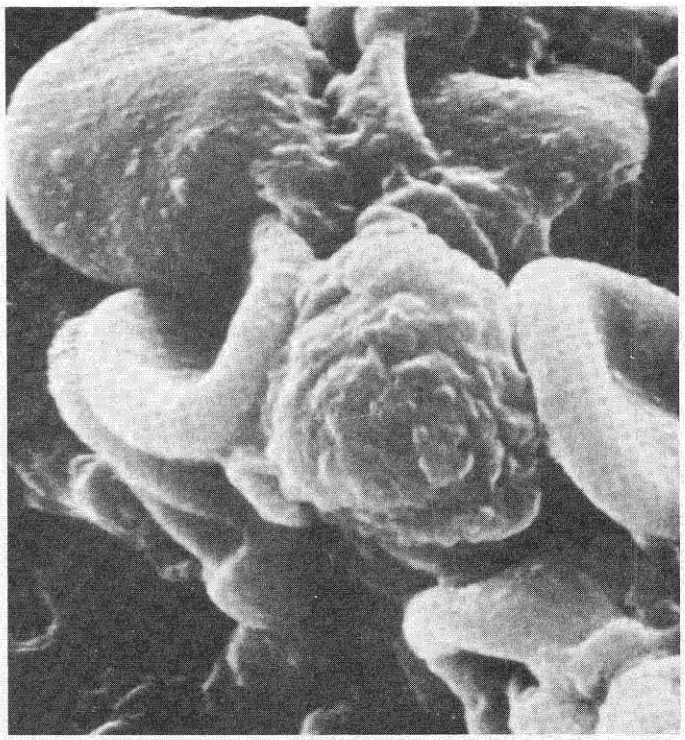
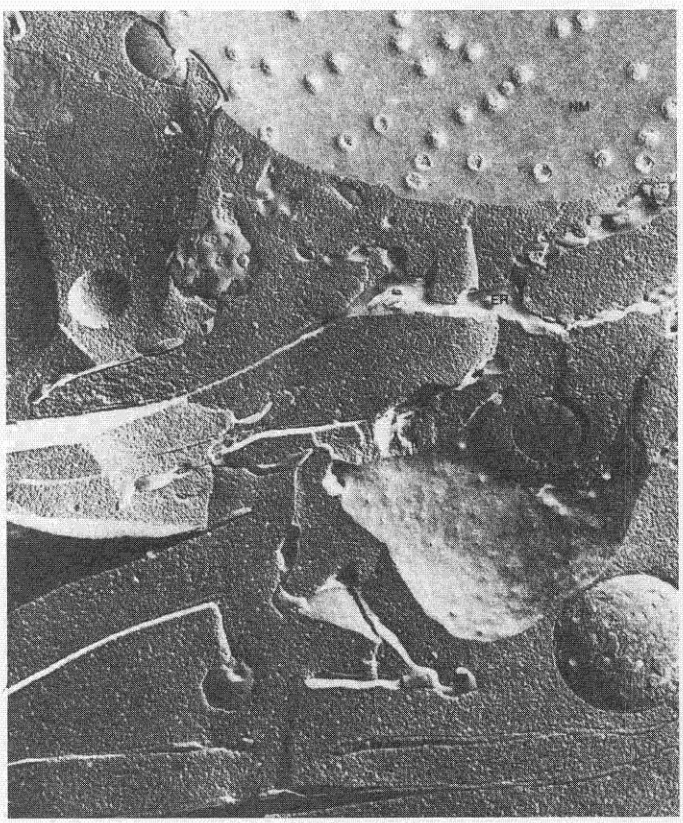


X7,000

The tongue is lined with minute papillae with which we taste. Shown here at increasing magnification are the papillae of a rabbit tongue.



The textured surfaces of red and white blood cells can be understood more clearly when magnified 9,000 times.



The inner world of a cell (shown here in cross section) is strangely reminiscent of the moon and, until recently, was just as unfamiliar.

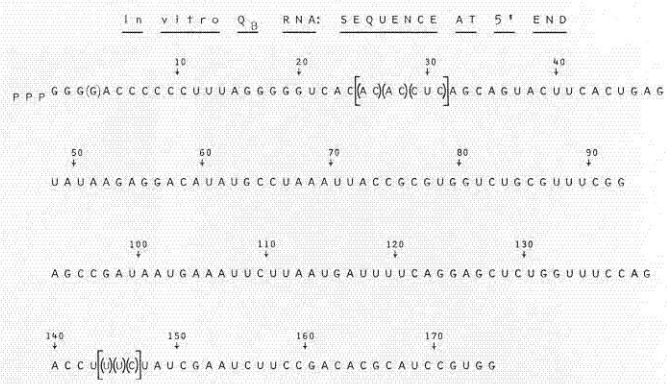
In the textured surfaces of the red cell and the white cell (left) we can begin to see hints of important design —although we cannot yet discern the sodium pump of the erythrocyte membrane, nor the antibody we know to be present on a lymphocyte.

If we slice across a cell (below left), we can see an inner world strangely reminiscent of the moon and until recently as unfamiliar to us, but now increasingly mapped and charted.

In our search to understand the nature of life we seek ever deeper levels until we reach down to the molecules and the atoms. And then we know we have come to the end of the quest. For carbon atoms are carbon atoms— and in this scale function must arise in spatial structure and temporal disposition.

If a molecule of viral DNA is put into a host cell, it will generate hundreds more just like itself. Should we call it alive? Although we cannot see them, we know this DNA ring is in fact a linked chain of subunits.

We cannot yet penetrate to that level with our visual aids. We can, more indirectly, deduce their pattern through

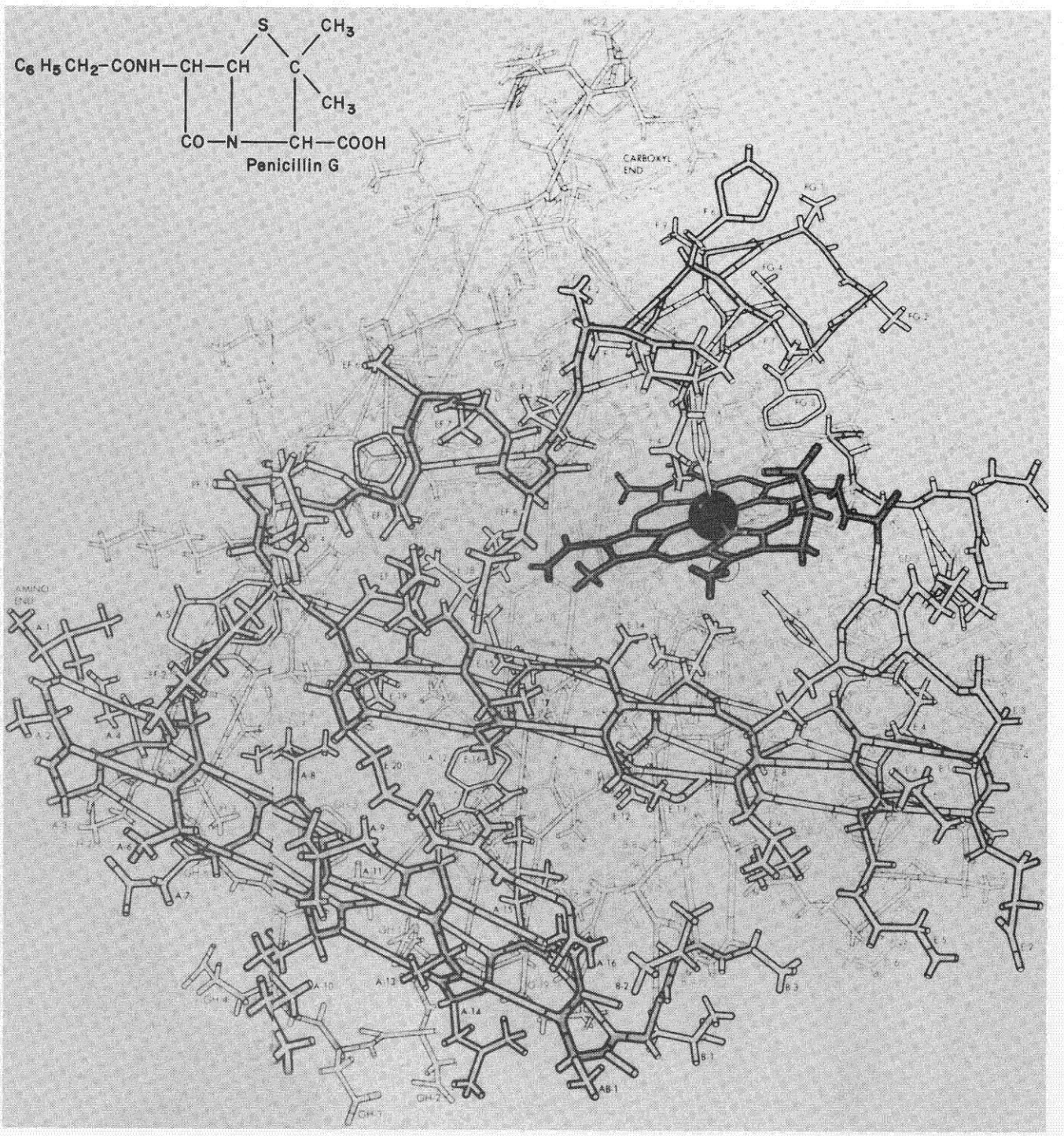


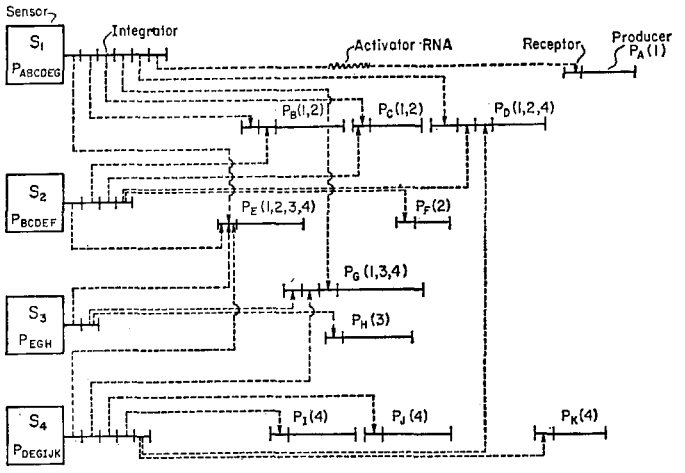
the arts of chemistry (above). Or at this level we can resort to another subtle technique borrowed, with adaptation, from physics—that of X-ray diffraction analysis. From the measured scattering of X rays by the atoms of a crystal we can reconstruct the positions of the atoms in the crystal and thus the three-dimensional structure of the molecules into which the atoms are grouped, even one so complex as the protein myoglobin (right).

This technique has been used to deduce the three-dimensional structure of an enzyme, a biological catalyst, ribonuclease and to probe its interaction with its substrate. This is leading at long last to a detailed chemical understanding of the mystery of the catalytic interaction, a process that underlies and is essential to the maintenance of life under physiological conditions.

We are not only exposing the ingenious structures underlying biological function, we are also unraveling the complex interrelations between these structures that integrate the many functions into a self-contained, self-

This three-dimensional model of whole myoglobin was reconstructed using a technique borrowed and adapted from physics—X-ray diffraction analysis.





In this proposed model of interactive gene control, the dotted lines represent the diffusion of activator RNA from its sites of synthesis to the receptor genes. The numbers in parentheses show which sensor genes control the transcription of the producer genes, and at each sensor, the producer genes activated by that sensor are listed.

controlled organism. We have found complex cycles of chemical reactions, and we are discovering interlaced hierarchies of control. Some are intracellular; other similar networks must exist at intermediate and higher levels within the body and within the brain.

These are but examples. Upon this base of knowledge we can even now begin to see disease, its cause and cure, in a very different perspective. We might usefully reclassify disease into the classes shown on the chart below.

Classes of Disease

The microbial diseases	**viral**
The molecular diseases →	**biochemical**
The cybernetic diseases	**immune**
	genetic

The *microbial* diseases (for example, pneumonia, syphilis, influenza, scarlet fever) have been recognized and understood for some time. They are the consequence of invasion by our microscopic foes, and we have developed a variety of moderately simple agents for their therapy.

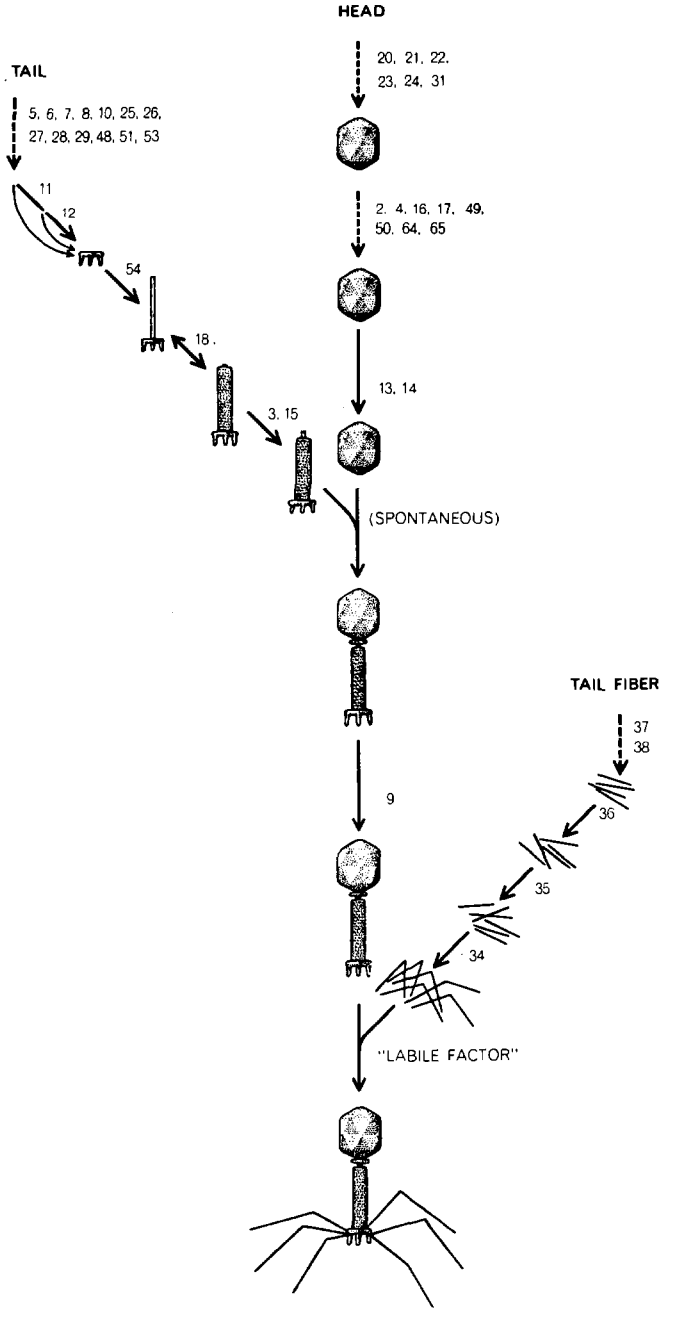
The basic principle that underlies the action of these agents—penicillin, streptomycin, sulfanilamide—is that they interfere with a metabolic process either unique to or of far greater importance to the microorganism than to man. Thus we may tolerate doses lethal to the microbes. It is fortunate that the metabolism of these species is in some respects sufficiently different from our own that this crucial distinction can be made with relatively simple chemical molecules of modest complexity.

The *molecular* diseases comprise that set of malfunctions which are the consequence of the presence—or sometimes absence—of critical molecules. I include the viral diseases (such as polio, measles, mumps, kuru) in this category because I find it more consistent to consider a virus as a self-reproducing particle within a living environment than to consider it as an autonomous life form.

Indeed it is precisely the subtle nature of the interaction of the virus with its host cell that has so far frustrated our attempts to find or devise agents that could make, as with the microbes, an effective distinction between the viral biochemistry and the host biochemistry and thus provide a selective basis for therapy.

I believe such a distinction can and will be made, but it will require a more intricate subtlety. If we contrast the structure of a penicillin and the structure of a myoglobin, we may see what will be needed. The synthesis and assembly of a virus particle requires delicate and precise interactions between molecules of this degree of complexity, interactions which specifically recognize other virus components and which, also specifically, exclude the omnipresent normal components of the host. In these interactions can lie the Achilles heel of the virus, for with understanding we should be able to devise anti-viral agents, molecules of an intermediate complexity specifically designed to interact with the viral components and block their normal function and assembly, yet, like the viral components, of sufficient specificity that these agents do not interact with the cell components and block vital functions.

The design and application of such sculptured molecules to combat viral disease—or to affect the other molecular diseases—is potentially feasible. It will require the development of a new sector of biochemistry, even of what might be called bioengineering, for it is the engineering of matter into new and complex forms for a specific purpose. But actually this has already begun. The synthesis of the adrenocorticotropic hormone, ACTH, a polypeptide of 39 amino acids, has been accomplished. The synthesis of the enzyme ribonuclease, a chain of 124 amino acids, has been achieved, admittedly in very low yield at this time. But the possibility for the design and the construction of a vast variety of biologically active enzymes, and hormones, or their analogs, and anti-viral agents, and anti-tumor agents at this new level of complexity is at hand. This achievement is certain to open whole new vistas in medicine.



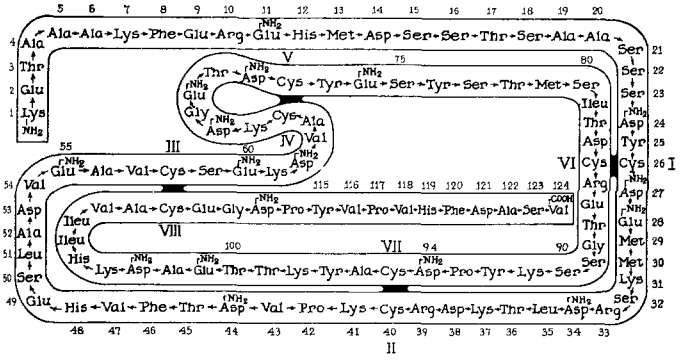
This diagram of the stages in the assembly of T4 virus shows the three different branches that lead independently to the formation of heads, tails, and tail fibers, which then combine to form complete virus particles. The synthesis of such a virus particle is a step toward devising antiviral agents specifically designed to interact with the viral components.

The *biochemical* diseases are today often of uncertain etiology. It may be that in time many will be traced to genetic origin or to external cause—to malnutrition or trauma—but at this time we recognize them as a biochemical surplus, a deficit, an imbalance, or an abnormality. There may be a hormone deficiency, an excess of uric acid or cholesterol, an under-supply of dopamine, an unusual degree of cross-linking of collagen; and they result in opacities of the eye, in stiff joints and clogged arteries, in palsy, and in aberrant behaviors.

That these are still prevalent diseases attests to the partial state of our knowledge here. I did *not* cite scurvy, which *was* a molecular disease. But further knowledge will bring understanding and in that understanding will, in the sense I have been describing, lie therapy.

I do not wish to oversimplify this issue. Some of these problems—such as the deposition of cholesterol—may well be the long-term consequence of basic imperfections in our biochemical program. We call such imperfections aging. We were not designed to live forever. And while we may invent palliatives to slow such deposition, a true solution may require some far-reaching changes of biochemical design for which we are hardly yet equipped. But the basic problems are clearly written in molecular language, and with knowledge we surely will be able to mitigate the more extreme syndromes and to slow the erosion of time.

The *immune* diseases (exemplified by allergic encephalomyelitis and lupus erythematosus) are a consequence of a biochemical perversion whereby one of the principal agencies of the body for defense against invasion is turned against normal body components. Our immune system becomes sensitive to one or more of our own molecules and may then seek out and destroy that component throughout. The rarity of this circumstance is a consequence of the normally remarkable capacity of our immune system to distinguish between the indigenous and the foreign. This distinction in each animal dates from an early developmental stage in which a tolerance is created for the indigenous molecules—the cells potentially



The design of molecules to combat viral disease is feasible, although it will require many advances in bioengineering. Already, however, the enzyme ribonuclease has been synthesized.

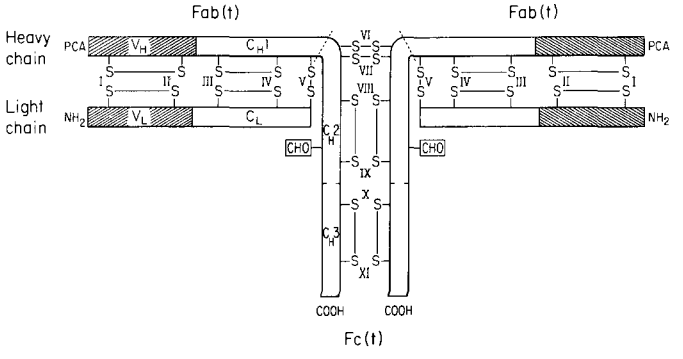
capable of forming antibodies against the normally available antigens of the individual are at this time killed off—to leave only a set programmed to respond to foreign antigens.

The occasional failures of tolerance which result in the autoimmune diseases, and our desires—whetted by the potential of transplants but currently frustrated by their rejection—to be able to host foreign tissues or substances for long periods, all emphasize our ignorance of the biochemistry of tolerance and immunity.

We *are* learning. The general structure of antibody molecules is now established (below). The origins of antibody diversity are still debated, but the decisive experiments are in sight. The specific proliferative response to antigen to form clones of antibody-producing cells is well documented but not yet understood. Here and in the equally obscure tolerance response are the keys to the induction of specific tolerance to specific antigens. When that door is opened, we will see the demise of immune disease and the resolution of immune rejection, whether of self- or alien-antigen.

And whenever it is that the skill of the surgeon can be wedded to this specific control of rejection, we can then easily foresee a golden age for surgery. The extension of life or the repair of defect or injury by the transplant, or the artificial implant, will then become a routine medical practice.

The *genetic* diseases are very simply those that we can trace directly to the inheritance of a defective gene or genes, or to an abnormal complement of chromosomes. And as we have become more knowledgeable in this field, the roster of genetic disease has markedly increased—phenylketonuria, hemophilia, histidinuria, Lesch-Nyhan disease, Tay-Sachs disease, Huntington's chorea, Downs disease, Kleinfelter's syndrome. The list is long and growing.



The general structure of the immunoglobulins (the antibody molecules present in blood) is now established.

The defect here is most basic, and therapy correspondingly is as yet more remote. If—as in hyperlipidemia—the disease is likely a consequence of an abnormal enzyme, we might be able specifically to inhibit it. If—as in other instances—the disease is a consequence of an enzyme deficit, we shall have to supply either the enzyme or the gene. Either is conceivable. The gene might be supplied via a transplant when that becomes feasible, or it may be supplied by the deliberate introduction of a specifically designed beneficial virus. To design a virus is a step beyond the molecular engineering I mentioned before, but it is not beyond our reach.

As we scan yet another sector of human frailties, we can see their origins in what I have called the *cybernetic* diseases. Not all of our concepts come from physics and chemistry. Another major source of insight to modern biology has been the development of computers, information science, and the science of control systems. In our analysis of living organisms we have become increasingly aware of the importance, the vital necessity, of control mechanisms—within the cell, within the embryo, within the body, within the brain—to maintain proportion and stability and yet permit growth and response and adaptation.

And one of the principles we can learn from cybernetics—the theory of control—is that complex control systems involving branch points and multiply interconnected feedback loops can often exist in a variety of alternative metastable states. As the result of some previous trauma or upheaval, such a system may well be in a state that may be far from optimal for its function but with no direct path available to it to return to a more effective condition. Nothing is intrinsically wrong in this condition; all the elements are working according to design, but the system is—unless and until jolted by some cataclysm—trapped in an ineffective state.

I think it is not unlikely that we will come to recognize some of our disease states as aberrations of this class: that some forms of cancer may represent such a derangement of the control mechanism of the cell to an alternative state; that some forms of hormonal imbalance are similarly self-perpetuating; and particularly that some forms of mental disease—depression, neurosis, psychosis—may be a reflection of such a cerebral circumstance. To what

therapies such insight may lead in these cases remains to be seen. We must first understand the inner cycles and identify the critical interactions. But when this is done, we should be able to simulate mathematically such a disease state and to locate the most favorable points for intervention.

Life usually outwits our efforts to classify, and some pathologies may well encompass several of these categories I have described. Cancer may in some instances be a viral disease; in others, a genetic disease, a consequence of somatic mutation; in others, as I have suggested, a cybernetic aberration. Regardless of etiology, there is increasing evidence that the appearance of cancer signals a breakdown of some sector of our immunological defense. In such complex circumstances the design of therapy may well require refinement of our pathological analysis, and this in turn the design of new techniques for such purpose.

I have here considered principally what biology may contribute to the future of medicine. I believe there will be a flow of knowledge and insight in the other direction as well. Biology has quite naturally directed its attention to the most general principles and phenomena. Medicine is inherently concerned with the individual.

Medicine can contribute to biology not only its knowledge of pathology—which often illuminates the normal from a new direction—but also, through its concern for the individual, it can emphasize the importance of biochemical individuality. It can emphasize the influence upon the integrated human being of the *cumulative consequence of numerous small departures* from the statistical norms. A sense of this uniqueness of the individual will become particularly important as we extend our interests into the basic biology of the mind—the most adaptive and hence the most distinctive organ of all. In our study of the biology of mind we shall of course continue to seek for very general principles, but we shall have to discover these behind the enormously varied faces of human experience.

I have been trying to survey for you the frontiers of biology as I imagine they might appear to the eyes of the healer. It is an unprecedented view. In every direction one can see the groundwork for truly new approaches to avert and to relieve the long-standing trials of man. Through foresight, understanding can bring prevention as well as therapy.

It is in a sense a poignant view. We have always known our earthly frailty and mortality. Familiarity has bred a reluctant acceptance. But there is now for us an added poignancy in the sober realization that with added knowledge—and now not so very much more—in some not-so-future time, disease will not cripple for so long and death will not come so early for so many.

Indeed someone is sure to ask: "Must death come at all?" And feasibility aside, the resounding echoes of that question should jar us to perceive that a medicine equipped with the full power of modern science would be as far beyond, and as different from, the medicine of this time as is the medicine of today from the tribal witchcraft of old.

As the discoveries accumulate, as new means of biological intervention arise, we can envision such possibilities as the almost indefinite prolongation of life for at least a few, as the deliberate predetermination of sex, or the design of human genetic change for varied purposes. With these will come the necessity for multiple social decisions of the most profound consequence. We are already faced with grievous decisions of the allocation of limited medical resources. This trend can only grow, for we have learned—as, for example, in the great lunar expeditions—how to focus the combined talents and efforts of vast numbers of men behind the deeds of a few. The same no doubt can be done in medicine. But who shall pay the cost, and who shall be the beneficiaries? Who shall make these decisions? I cannot say. But I can easily envision the physician at the focal point of responsibility.

There are now in our society three groups to whom we have traditionally delegated the grave concerns of life and death: the military, the judiciary, and the physicians. The military is like the dinosaur, obsolete although clearly not yet gone. In more humane societies the power of the judiciary over life and death has been progressively curtailed. But the concerns of the physician seem destined to expand and with them his role in the social order.

The aim of the physician has been simple—to preserve and extend human life by all means and at almost all cost. This has been a clear mandate—and feasible because in truth his capacities to do so have been cruelly limited. With greater abilities will come greater responsibilities. The equation is ineluctable. In the future the physician will have each day cause to consider the quality of the life he may extend or he may bring into the world and the effects of his decisions upon all our futures. For, to reflect John Donne's phrase, "No man is an island"; not only does each man's death diminish every man, but on a small planet each man's life touches every man.