On The Unity of the Sciences

Interreactions among the physical and biological sciences show that unification is progressive.

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It was only 16 years ago that the seeds were sown which led gradually to what is now so clearly a revolution in the biological sciences. In 1944 it was announced by Avery, MacLeod, and McCarty that nucleic acids may possess biological activity; that they can direct and orient inheritance in bacteria. This now classic paper created a storm of protest, and the conclusions were vigorously opposed by many reputable authorities. It was nearly eight years before the full significance of this astonishing discovery was generally recognized, and it took almost another eight years for the revolution it initiated to come into full flower. In the interval, several Nobel prizes were awarded, though not to the original discoverers, for remarkable advances in knowledge which were closely related either to nucleic acids or to their genetic activities.

This revolution in the life sciences has produced results almost as remarkable and as unexpected as those of the revolution in the physical sciences that was initiated by the discovery of radioactivity. The formal lines between the several disciplines have disappeared in biology just as they were broken down in the physical sciences. It is no more possible now to make a clear distinction among cytologists, geneticists, immunologists, and virologists than to make one among chemists, physical chemists, and physicists. They attend each other's meetings, present papers on associated problems, and utilize materials, techniques and instruments that, ten years ago, they either had no interest in or had not heard of. Most importantly, they have come to speak a nearly common language, and thus to understand one another.

Such, then, is the force of a new and sweeping concept, which embraces all of biology, from viruses to whales, in a single unifying principle. With the discovery that nucleic acids are the chemical basis for heredity and that the biological phenomenon, identified as the gene, is in fact attributable to a specific polynucleotide sequence, molecular biology became a reality, and the long-hoped-for marriage between the biological and the physical sciences commenced.

Analysis of a Crystal

To exemplify this synthesis among scientific disciplines that have long had too little in common, I present here a single figure, which I have selected with some care (Fig. 1). A glance at this lovely gem, more valuable than a diamond, reveals that it a physical entity —a nearly perfect crystal with many sides. The magnification is low, and the crystal probably could be seen with the naked eye.

A crystallographer would undoubtedly assign a long name to this object, but despite the extraordinary power and resolution of his instruments, it is doubtful that he could precisely identify it.

A chemist would find that the crystal is composed of but two molecular species, one protein, the other nucleic acid, and could show that the nucleic acid is of the ribose type and makes up about 30 percent of the substance. But it is doubtful that he would establish the nature of the crystal.

A physical chemist would find that the ribonucleic acid has a molecular weight of about 2 million, the protein a molecular weight of a few hundred thousand. He could also demonstrate that the crystal is entirely composed of like units with a particle weight of many millions, and he would infer that each particle contains both protein and nucleic acid. If he were very clever he could separate the two components that make up the particles, without destroying either, but he might need a biochemist to help.

An electron microscopist would find that the crystal is made up wholly of very tiny spheres, about 27 millimicrons in diameter, and he just might be able to discern that the central portion of each sphere had a slightly higher electron density than the peripheral area. He would not be able to visualize any limiting membrane, but, if he had had much experience with similar objects, he might begin to suspect the identity of the material. Certainly he would establish that the crystal contained several billion identical particles, for he could count them without great difficulty.

An immunologist would find that the crystal contains antigenic material and that it could stimulate the production of several kinds of antibodies in a number of different animal species. He would do well not to test it in this way in man or in monkeys, however, for if he did, and if he were a really competent immunologist, he could certainly identify the substance!

A virologist would make the startling discovery that the crystal is composed of type 1 poliomyelitis virus and that even a relatively small number of the particles, perhaps no more than 30, could induce severe paralysis in man or other primates. If, now, he obtained the ribonucleic acid that had been carefully separated from the protein component by the biochemist, he would find that it, too, is infective. Thus, he would have in his hands an *infective molecule* (how odd these two words seem when used together!)—one that can guide and direct the synthesis of more molecules like itself and ultimately lead to the production of disease.

A geneticist would find that the virus or the infective nucleic acid (the distinction has become merely semantic) possesses heritable properties which can be identified as genes, that it may undergo mutation as do other biological entities, and that the mutants have heritable properties which probably re-

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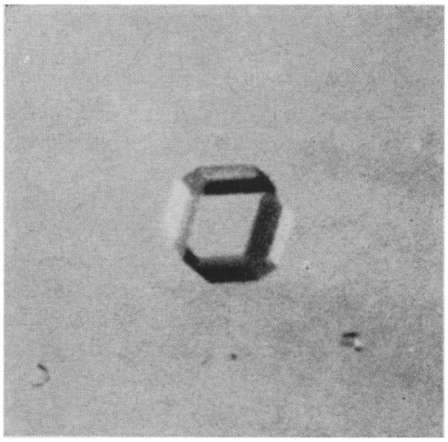

Fig. 1. A single large crystal of Mahoney poliomyelitis virus (× 80). [R. L. Steere and F. L. Schaffer, *Biochim. et Biophys. Acta* **28**, 241 (1958)]

flect alterations in the fine structure of their nucleic acids.

The lovely crystal has been found to have some surprising attributes. It is one of the first ever to be prepared with an animal virus, and I wish to acknowledge indebtedness to Wendell Stanley of the Virus Laboratory of the University of California for this excellent reproduction. To analyze in depth this seemingly simple object has required the kinds of professional competence that previously were distributed among some eight different scientific disciplines, both physical and biological. Because of the large significance to broad understanding that material of this kind contributes, biologists have recognized their need to acquire more than a nodding acquaintance with the physical sciences; at the same time, many in the latter disciplines have recognized the importance of knowing more biology. The results of this new community of interest—of the rebirth of the natural philosopher, if you will—have been both unexpected and remarkably rewarding.

Some Results

Not only are we confronted now with a number of infective molecules (some of the deoxyribonucleic acid type have recently been obtained from tumor-inducing viruses), but also we can no longer escape a new biological concept—that of *infective heredity*. Certain bacterial viruses induce heritable changes in the bacteria they infect, as, too, of course, do several viruses that induce tumors in animals. A striking example is the diphtheria bacillus, which is led to produce a new protein—that is, diphtheria toxin—as a result of infection with a bacteriophage.

New genes now can be introduced into certain cells; genes previously present can be masked or overridden, and biological material is beginning to acquire a made-to-order aspect that recalls the remarkable achievements of synthetic organic chemistry. Heredity has acquired wholly new aspects, and the possibility that it may be controlled and guided seems no longer to be merely visionary.

Cytology and fine anatomical structure are being re-evaluated through systematic application of the electron microscope. Cytoplasm no longer appears to be simply a structureless jelly and has been revealed as a complex maze of channels and organelles with distinctive metabolic functions.

Chromosomes have been assigned individual designations, and aberrations in their number and variety are now associated with certain abnormalities in sexual development as well as with some congenital malformations—for example, mongolism. The mitotic apparatus has been separated from cells and studied as an independent entity. Why chromosomes cannot be visualized during the intermitotic interval remains a mystery.

The precise amino acid sequence of some proteins—for example, insulin and ribonuclease—is established, as is that of certain pituitary hormones. That the chemical structure of the latter substances had been exactly understood was proved when they were synthesized and shown to possess predicted biological activity. One type of human abnormal hemoglobin which is genetically determined is known to differ from the normal respiratory pigment only in respect to a single amino acid.

Immunology, possibly one of the most important and also one of the most underdeveloped among the biological disciplines, is rapidly coming of age; recognition of the existence of so-called autoimmune mechanisms, the exquisiteness of the distinction between "self and non-self," to use Burnet's terms, and the remarkable advances in understanding homograft rejection are indicative of what lies ahead in this field. That immunology, like so much else in the life sciences, is shown to be directly under genetic control—control which is now known to be definable in molecular terms—is illustrative of the encouraging advancement and the progressive unification of scientific knowledge that is taking place.

Significance

I have emphasized the revolution that has occurred recently in biology in part because it is exciting but chiefly because of what it implies for understanding. The accumulation of seemingly unrelated technical details that has plagued and often discouraged the student of the life sciences is beginning to aggregate in a meaningful way, and much of it now hangs together in a framework of principles that are solidly based.

The discovery that a nucleic acid molecule can reproduce itself in a biological environment, that it carries in its chemical structure as much coded information as can be found in more than 100 textbooks, and that by virtue of chemical necessity it controls the synthesis of its complementary partner with such precision that mistake—that is, a mutation—occurs less than once in a million replications is not only impressive but far-reaching.

Biology, like chemistry, is in a position to discard many of its descriptive shackles. The unifying principles that emerged from knowledge of the structure of the atom, which so changed ideas in the physical sciences, now have their counterparts in new knowledge of the structure of the gene, which is, of course, the elementary basis for the continuity of life.