A Physicist's Renewed Look at Biology: Twenty Years Later

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At the very beginnings of science the striking dissimilarities between the behavior of living and nonliving things became obvious. Two tendencies can be discerned in the attempts to arrive at a unified view of our world. One tendency is to use the living organism as the model system. This tendency is exemplified by Aristotle. For him, the son of a physician and the keen observer of many forms of life, it was obvious that things develop according to plans. Every animal and plant is generated in some definite way, runs through a cycle of development in which it unfolds its inherent plan, and succumbs to death and decay. For Aristotle, this very obvious feature of the world which surrounds us is the model for understanding our (sublunar) world. Astronomy is the exception and offers the contrast of an eternal periodic system subject to neither generation nor decay.

With the ascendance in the Renaissance of the science of physics in our modern sense of the word there seemed to develop at first a peculiar break between the living and the nonliving parts of the world. Life seemed to have unique properties quite irreducible to the world of physics and chemistry: "motion generated from within," "chemistry of a very distinct kind," "replication," "development," "consciousness"—each of these aspects of life turned into elements that became more and more foreign to the physicist, to the extent that many physicists even today look upon biology as something outside their domain.

A partial reversal of this bizarre partition of the world into the living and the nonliving came with the many proofs that living forms are not, in fact, constant but over the long range have evolved and that the family tree of this evolution can be traced. The interpretation of evolution in terms of natural selection, especially after the latter had been put into clearer perspective with the establishment of the science of genetics, suggested a unified view of life but still left uncertain the connection of life with the nonliving world. The insights of chemistry and its first inroads into biochemistry made it clear that the break between the nonliving world and the living world might not be absolute.

Molecular genetics, our latest wonder, has taught us to spell out the connectivity of the tree of life in such palpable detail that we may say in plain words, "This riddle of life has been solved." The ideas of information storage, of the replication of the stored information, and of its programmed readout have become commonplace and have filtered down into the popular magazines and grade school textbooks. The marvel that the mechanical and chemical machinery underlying all these affairs can in fact be worked out is keeping a host of scientists very happy and very busy. With one exception, I feel that there is no need to go into the historical aspects of these developments since they have been very adequately treated in the book *Phage and the Origins of Molecular Biology* (*1*).

The exception is due to the fact that the contribution to this book by N. W. Timofeeff-Ressovsky, although written, for technical reasons could not be included in the book. I hope very much that the time will not be far off when this omission can be rectified. At this moment I would like to describe briefly to what I refer. During the years 1932–37, while I was assistant to Professor Lise Meitner in Berlin, a small group of theoretical physicists held informal private meetings, at first devoted to theoretical physics but soon turning to biology. Our principal teacher in the latter area was the geneticist, Timofeeff-Ressovsky, who, together with the physicist K. G. Zimmer, at that time was doing by far the best work in the area of quantitative mutation research. A few years earlier H. J. Muller had discovered that ionizing radiations produce mutations, and the work of the Berlin group showed very clearly that these mutations were caused either by single pairs of ions or by small clusters of them. Discussions of these findings within our little group strengthened the notion that genes had a kind of stability similar to that of the molecules of chemistry. From the hindsight of our present knowledge one might consider this a trivial statement: what else could genes be but molecules? However, in the mid-thirties, this was not a trivial statement. Genes at that time were algebraic units of the combinatorial science of genetics, and it was anything but clear that these units were molecules analyzable in terms of structural chemistry. They could have turned out to be submicroscopic steady-state systems, or they could have turned out to be something unanalyzable in terms of chemistry, as first suggested by Bohr (*2*) and discussed by me in a lecture 20 years ago [reprinted in Cairns *et al.* (*1*)]. It is true that our hope at that time to get at the chemical nature of the gene by means of radiation genetics never materialized. The road to success effectively bypassed radiation genetics. Nevertheless, radiation genetics has been, through all these decades and is now more than ever, a field of great importance, most recently and depressingly so because of the possibilities of large-scale military applications entailing exposure to ionizing radiations.

To illustrate our state of mind at that time I append to this lecture (*3*) a memorandum on the *Riddle of Life*, written to clarify my own thinking in the fall of 1937, just before I left Germany to go to the United States. I found this note a few years ago among my papers. This memorandum would appear to be a summary of discussions

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at a little meeting in Copenhagen, arranged by Niels Bohr, to which Timofeeff-Ressovsky, H. J. Muller, and I had traveled from Berlin. These discussions occurred very much under the impact of the findings of W. M. Stanley reporting the crystallization of tobacco mosaic virus (*4*).

Neurobiology

While molecular genetics has taught us the proper way to reconcile the characteristics of the living world, generation, development toward a goal, and decay, with the contrasting incorruptibility and planlessness of the physical world, it has not resolved our uncertainty about the proper way to relate this language to the notions of "consciousness," "mind," "cognition," "logical thought," "truth"—all these notions, too, elements of our "world."

What is language? How does a child come to associate meaning with a word? The ability to form abstractions is undoubtedly inherent in our brain, this marvel of a computer. The study of the brain's connectivity, the study of the development of this network in the growing animal, the study of its function and potencies—all of these studies are aspects of the neurobiology of the next decade and they are very appealing ones to many of my colleagues and to many of the new generation of graduate students.

Transducer Physiology

I have two reservations concerning neurobiology. The first reservation is that we are not yet ready to tackle it in a decisive way. I believe that there is a widespread underestimation of the things we do not know and do not understand about cell biology and cell-cell interaction. It simply is not enough to know that nerve fibers conduct, that synapses are inhibitory or excitatory, chemical or electrical, that sensory inputs can be transduced, that they result in trains of spikes which measure intensities of stimuli or the time derivatives of these intensities, that all kinds of accommodations occur, and so forth. I believe that we need a much more basic and detailed understanding of these stimulus response systems, be the stimulus an outside one or a presynaptic signal.

Sensory physiology in a broad sense contains hidden as its kernel an as yet totally undeveloped but absolutely central science: transducer physiology, the study of the conversion of the outside signal to its first "interesting" output. I use the word "interesting" advisedly because I wish to exclude from the area of study which I intend to delimit, for instance, the primary photochemical reactions of the visual systems. I look upon the primary photochemical processes as something "uninteresting" because they concern the conversion of a light stimulus into what might be called an olfactory stimulus. A light quantum, in order to be effective as a sensory stimulant, naturally must, in the first instance, create within the cell a primary photoproduct which carries the business further. In thus excluding the photochemistry of the visual process from transducer physiology proper, I am excluding the beautiful work on the photochemistry of rhodopsin for which George Wald received the Nobel prize 2 years ago. Transducer physiology proper comes after this first step, where we are dealing with devices of the cell unparalleled in anything the physicists have produced so far with respect to sensitivity, adaptability, and miniaturization. Which biological material will turn out to be the most suitable for bringing us decisive insights in this field? For a number of years I have studied an organelle of the fungus *Phycomyces*, the sporangiophore, in the belief that in the field of transducer physiology, as in genetics, essential progress will require the use of a suitable microorganism. I need not detail this work here since it has very recently been critically reviewed by a group effort of those involved in this work (*5*). Let me say here only that this organelle is exquisitely sensitive to light, to gravity, to stretch, and to a stimulus which we believe to be olfactory, and illustrate it with a few slides. Others have proposed and demonstrated the suitability of other systems: chemotaxis of bacteria (*6*); olfaction in insects (*7*); mechanosensitivity of motoric cilia (*8*). We may hope that each of these systems, as well as the lipid bilayer systems, which can be made to simulate most of the astounding feats of living membranes (*9*), will contribute to the great discoveries in cell physiology which, in my opinion, are prerequisite for a truly successful venture into neurobiology.

Body and Soul

My second reservation regarding the hopes of neurobiology is more disturbing to me and also more nebulous; the eagerness with which we plunge into neurobiology overlooks an essential limitation—the a priori aspect of the concept of truth. It is well understood that a computer can be constructed so as to operate with certain axioms and formalized rules of logic, deriving in this way any number of "proved declarative sentences." We may call these sentences true if we have faith in the axioms and the rules of logic, and we may be tempted to consider the logical sum of provable sentences as the computer's definition of truth. However, our friends the logicians have made it clear to us long ago that in any but the simplest languages we must distinguish between an "object language" and a "metalanguage." The word "truth," and thus all discussion of truth, must be excluded from the object language if the language is to be kept free of antinomies. There then follows the strange result that there must be sentences that are true but not provable (*10*). Thus the notion of truth, if it is to be meaningful at all, must be distinct and prior to the system of provable sentences, and thus distinct from and prior to the computer which should be looked upon as the embodiment of the system of provable sentences.

Thus, even if we learn to speak about consciousness as an emergent property of nerve nets, even if we learn to understand the processes that lead to abstraction, reasoning, and language, still any such development presupposes a notion of truth that is prior to all these efforts and that cannot be conceived as an emergent property of it, an emergent property of a biological evolution. Our conviction of the truth of the sentence, "The number of prime numbers is infinite," must be independent of nerve nets and of evolution, if truth is to be a meaningful word at all.

Artist versus Scientist

Twenty years ago (*11*) the Connecticut Academy of the Arts and Sciences had a jubilee meeting and on that occasion invited a poet, a composer, and two scientists to "create" and to "perform." It was a very fine affair. Hindemith, conducting a composition for trumpet and percussion, and Wallace Stevens, reading a set of poems entitled "An Ordinary Evening in New Haven," were enjoyed by everybody, perhaps most by the scientists. In contrast, the scientists' performances were attended by scientists only. To my feeling this irreciprocity was fitting, although perhaps not intended by the organizers. It is quite rare that scientists are asked to meet with artists and are challenged to match the other's creativeness. Such an experience may well humble the scientist. The medium in which he works does not lend itself to the delight of the listener's ear. When he designs his experiments or executes them with devoted attention to the details he may say to himself, "This is my composition; the pipette is my clarinet." And the orchestra may include instruments of the most subtle design. To others, however, his music is as silent as the music of the spheres. He may say to himself, "My story is an everlasting possession, not a prize composition which is heard and forgotten," but he fools only himself. The books of the great scientists are gathering dust on the shelves of learned libraries. And rightly so. The scientist addresses an infinitesimal audience of fellow composers. His message is not devoid of universality but its universality is disembodied and anonymous. While the artist's communication is linked forever with its original form, that of the scientist is modified, amplified, fused with the ideas and results of others, and melts into the stream of knowledge and ideas which forms our culture. The scientist has in common with the artist only this: that he can find no better retreat from the world than his work and also no stronger link with the world than his work.

The Nobel ceremonies are of a nature similar to the one I referred to. Here, too, scientists are brought together with a writer. Again the scientists can look back on a life during which their work addressed a diminutive audience, while the writer, in the present instance Samuel Beckett, has had the deepest impact on men in all walks of life. We find, however, a strange inversion when we come to talking about our work. While the scientists seem elated to the point of garrulousness at the chance of talking about themselves and their work, Samuel Beckett, for good and valid reasons, finds it necessary to maintain a total silence with respect to himself, his work, and his critics. Even though I was more thrilled by the award of the Nobel prize to him than about the award to me and momentarily looked forward with intense anticipation to hearing his lecture, I now realize that he is acting in accordance with the rules laid down by the old witch at the end of a marionette play entitled "The Revenge of Truth" (*12*).

The truth, my children, is that we are all of us acting in a marionette comedy. What is important more than anything else in a marionette comedy is keeping the ideas of the author clear. This is the real happiness in life and now that I have at last come into a marionette play, I will never go out of it again. But you, my fellow actors, keep the ideas of the author clear. Aye, drive them to the utmost consequences.

References and Notes

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Appendix 1

Preliminary write-up on the topic "Riddle of Life" (Berlin, August 1937).

We inquire into the relevance of the recent results of virus research for a general assessment of the phenomena peculiar to life.

These recent results all agree in showing a remarkable uniformity in the behavior of individuals belonging to one species of virus in preparations employing physical or chemical treatments mild enough not to impair infective specificity. Such a collection of individuals migrates with uniform velocity in the electrophoresis apparatus. It crystallizes uniformly from solutions such that the specific infectivity is not altered by recrystallization, not even under conditions of extremely fractionated recrystallization. Elementary analysis gives reproducible results, such as might be expected for proteins, with perhaps the peculiarity that the phosphorus and sulfur contents appear to be abnormally small.

These results force us to the view that the viruses are things whose atomic constitution is as well defined as that of the large molecules of organic chemistry. True, with these latter we also cannot speak of unique spatial configurations, since most of the chemical bonds involve free rotation around the bond. We cannot even decide unambiguously which atoms do or do not belong to the molecule, since the degree of hydration and of dissociation depends not only on external conditions, but even when these are fixed, fluctuates statistically from molecule to molecule. Nevertheless, there can be no doubt that such large molecules constitute a legitimate generalization of the standard concept of the chemical molecule. The similarity between virus and molecule is particularly apparent from the fact that virus crystals can be stored indefinitely without losing either their physicochemical or infectious properties.

Therefore we will view viruses as molecules.

If we now turn to that property of a virus which defines it as a living organism, namely, its ability to multiply within living plants, then we will ask ourselves first whether this accomplishment is that of the host, as a living organism, or whether the host is merely the provider and protector of the virus, offering it suitable nutrients under suitable physical and chemical conditions. In other words, we are asking whether we should view the injection of a virus as a stimulus which modifies the metabolism of the host in such a way as to produce the foreign virus protein instead of its own normal protein, or whether we should view the replication as an essentially autonomous accomplishment of the virus and the host as a nutrient medium which might be replaced by a suitably offered synthetic medium.

Now it appears to me that, upon close analysis, the first view can be completely excluded. If we consider that the replication of the virus requires the accurate synthesis of an enormously complicated molecule which is unknown to the host, though not as to general type, yet in all the details of its pattern and therefore of the synthetic steps involved, and if we consider further what extraordinary production an organism puts on to perform in an orderly way the most minute oxidation or synthesis in all those cases that do not involve the copying of a particular pattern—setting aside serology, which is a thing by itself—then it seems impossible to assume that the enzyme system of the host could be modified in such a far-reaching way by the injection of a virus. There can be no doubt that the replication of a virus must take place with the most direct participation of the original pattern and even without the participation of any enzymes specifically produced for this purpose.

Therefore we will look on virus replication as an autonomous accomplishment of the virus, for the general discussion of which we can ignore the host.

We next ask whether we should view virus replication as a particularly pure case of replication or whether it is, from the point of view of genetics, a complex phenomenon. Here we must first point out that with higher animals and plants which reproduce bisexually replication is certainly a very complex phenomenon. This has been shown in a thousand details by genetics, based on Mendel's laws and on modern cytology, and must be so in order to arrive at any kind of order for the infinitely varied details of inheritance. Specifically, the close cytological analysis of the details of meiosis (reduction division) has shown that it is a specialization of the simpler mitotic division. It can easily be shown that the teleological point of this specialization lies in the possibility of trying out new hereditary factors in ever-new combinations with genes already present, and thus to increase enormously the diversity of the genotypes present at any one time, in spite of low mutation rates.

However, even the simpler mitotic cell division cannot be viewed as a pure case. If we look first at somatic divisions of higher animals and plants, then we find here that an originally simple process has been modified in the most various ways to adapt it to diverse purposes of form and function, such that one cannot speak of an undifferentiated replication. The ability to differentiate is certainly a highly important step in the transition from the protists to the multicellular organisms, but it can probably be related in a natural way to the general property of protists that they can adapt themselves to their environment and change phenotypically without changing genotypically. This phenotypic variability implies that with simple algae like *Chlorella* we can speak of simple replication only so long as the physical conditions are kept constant. If they are not kept constant, then, strictly speaking, we can only talk of a replication of the genomes which are embedded in a more or less well-nourished, more or less mistreated, specific protoplasma, and which, in extreme cases, may even replicate without cell division.

There can be no doubt, further, that the replication of the genome in its turn is a highly complex affair, susceptible to perturbation in its details without impairing the replication of pieces of chromosomes or of genes. Certainly the crucial element in cell replication lies in the coordination of the replication of a whole set of genes with the division of the cell. With equal certainty this coordination is not a primitive phenomenon. Rather, it requires that particular modification of a simple replication system which accomplishes constancy of supply of its own nutrient. By this modification it initiates the chain of development which until now has been subsumed under the title "life."

In view of what has been said, we want to look upon the replication of viruses as a particular form of a primitive replication of genes, the segregation of which from the nourishment supplied by the host should in principle be possible. In this sense, one should view replication not as complementary to atomic physics but as a particular trick of organic chemistry.

Such a view would mean a great simplification of the question of the origin of the many highly complicated and specific molecules found in every organism in varying quantities and indispensable for carrying out its most elementary metabolism. One would assume that these, too, can replicate autonomously and that their replication is tied only loosely to the replication of the cell. It is clear that such a view in connection with the usual arguments of the theory of natural selection would let us understand the enormous variety and complexity of these molecules, which from a purely chemical point of view appears so exaggerated.