

Preface to a Grammar of Biology

A hundred years of nucleic acid research.

Erwin Chargaff

I

Darwin's *Origin of Species*, probably one of the most influential books in the history of science (1), was published in 1859. The loud-mouthed, pompous, and insincere admiration of natural science, so characteristic of our time, began much later. It was, for example, possible for wise old Peacock, who in his youth had been Shelley's friend, to let two of the principal figures of his last novel, published in 1860, converse as follows.

"Lord Curryfin: . . . We ought to have more wisdom, as we have clearly more science.—The Rev. Dr. Opimian: Science is one thing and wisdom is another. Science is an edged tool with which men play like children and cut their own fingers. If you look at the results which science has brought in its train, you will find them to consist almost wholly in elements of mischief. . . . The day would fail, if I should attempt to enumerate the evils which science has inflicted on mankind. I almost think it is the ultimate destiny of science to exterminate the human race" (2).

Now that we have come so much nearer to this destiny, who would still dare write thus? It is not pleasant to be denounced by dark times as a *vir obscurus*. Still, Jean Paul took this risk in his "War Declaration against the

War," part of that odd and wonderful book whose publication cost so much trouble; 137 years before the explosion of the first atom bomb:

"And who can guarantee, seeing the immense developments in chemistry and physics, that there will not be finally invented an infernal engine which similar to a mine will start and terminate a battle with one shot; so that the enemy can do no better than to deliver the second, and towards evening the entire campaign is finished?" (3).

I should like to start this essay with one of the quiet in the land, with Friedrich Miescher, who a hundred years ago, in 1869, discovered the nucleic acids, somehow between Tübingen and Basel. As was to be expected, nobody paid any attention to this discovery at that time. The giant publicity machines, which today accompany even the smallest move on the chessboard of nature with enormous fanfares, were not yet in place. Seventy-five years had to pass before the importance of Miescher's discovery began to be appreciated. For that it required the appearance of another quiet man whom I shall mention soon.

II

I should like to place these brief remarks under the protection of two sayings. The first comes from an ancient Greek poet who is being credited with the invention of the iamb, Archilochos from Paros, who said: "The fox knows many things, but the hedgehog one big thing" (4). The second word

comes from Kierkegaard, who in 1849 noted in his diary: "A single man cannot help his time, he can only express its collapse" (5).

I use the first saying in reference to Miescher, the second applies to our time. It is now exactly a hundred years ago that Friedrich Miescher in 1869 discovered the nucleic acids. First from the nuclei of lymphocytes, and later from the spermatozoa of the Rhine salmon, he was able to isolate what we now would designate as DNA, deoxyribonucleic acid. Miescher himself—and this appears clearly from his correspondence and from the tone of his compact papers—was well aware of the importance of his observations (6). They failed, however, to make much impression on his time; and how little echo there was can perhaps be deduced from the fact that even today the best history of the natural sciences, in the volume devoted to the 19th century and published in 1961, mentions the name of Darwin 31 times, that of Huxley 14 times, but Miescher not at all (7). There are people who seem to be born in a vanishing cap. Mendel was one of them and Willard Gibbs and David Keilin, and so was also Miescher. They all were no foxes, and Archilochos would not have hesitated to classify them as hedgehogs.

It is almost impossible to retrace the course of the history of science to an earlier stage, for not only should we be required to forget much of what we have learned, but much of what a previous epoch knew or believed to know has simply never been learned by us. We must remember that the natural sciences are as much a struggle *against* as *for* facts. Every 30 years, a new growth makes the old forest impassable. Hence, I shall not even attempt to depict the scientific and intellectual climate in which the first faltering steps of biochemistry occurred. It is, in general, true of every scientific discovery that the road means more than the goal. But only the latter appears in the ordinary scientific papers. Probably, this is mostly to be welcomed, since otherwise there would be no end to

The author is professor of biochemistry and chairman of the department at the College of Physicians and Surgeons, Columbia University, New York. This is a translation of an article published in *Experientia* 26, 810 (1970), which was adapted from the Miescher Memorial Lecture delivered on 30 May 1969, in the aula of the University of Basel on the occasion of the 25th anniversary of *Experientia*.

the chatter. In the case of Miescher, however, we should have liked to know more. The decision to investigate the chemistry of the cell nucleus testifies to an unusual foresight, but also to a bold disregard of the consequences with which too fast a pioneer must reckon.

A few years ago, I attempted to describe this dilemma facing the scientific outsider, and each pioneer is *eo ipso* an outsider.

"The natural scientist is often faced with a series of observations, a set of phenomena, into which he attempts subsequently to introduce some sort of chronological or causal order. He determines several points and connects them to a curve; he measures certain values in a number of samples and estimates the averages and deviations; he constructs a reaction chain or postulates a cycle: whatever he does, there remains much darkness between the few points of light. Whether he emphasizes the light or dwells on the obscurities will depend upon his temperament, but even more upon the temper of the times and upon a form of ever-changing vogue or fashion which acts as a censor forbidding him to be ahead by more than one or two steps. If he runs too fast, he disappears from our sight; if he goes too slowly, he joins the 18th Century. For most people, this is not a problem: they are where all the others are" (8).

This is exactly what Miescher did not do: he found himself, when he began and also when he ended, not where all the others were; and for this reason, only very few paid him the attention that he deserved. One might ask, however, how many of the world-shaking discoveries, bestowed on us in the last 10 or 15 years, will prove worthy of centenary remembrance. This brings us to a problem in the value theory of science—in what actually constitutes the value of a scientific observation—and these are considerations that I should prefer to avoid here (9). What makes the study of nature so magnificent is its very givenness: it is because it is; it is as it is; and "*tolle, lege!*" remains its eternal admonition.

In the case of the nucleic acids it is not at all difficult to describe the significance of their discovery. Quite apart from their important biological functions, recognized within the last 25 years, which I shall mention later, the nucleic acids are unique among the four principal classes of cellular constituents—the proteins, the nucleic acids, the lipids, and the polysaccharides—in that their discovery can be dated precisely. Here is *one* man,

one place, *one* date; and this man is Friedrich Miescher, 1844 to 1895. He died young. The frontispiece to his collected papers shows a fine and shy, perhaps a sad face; as if the shortness of his life had thrown a shadow over it. I have often asked myself what such a man would have done in our ghastly time.

The discovery of DNA by Miescher was followed soon after by the description of ribonucleic acid (RNA) in the laboratory of Hoppe-Seyler in Tübingen. Then began the long road—in this case nearly 80 years—which every biologically important, complicated chemical substance must travel: first its structure, then its function. Since in the nucleic acids we have to do with extremely complicated structures, composed of a very large number of four or five simpler substances, the gradual advance of our knowledge progressed somewhat differently, namely in three principal stages: (i) investigation of the primitive structure, that is, identification of all chemical substances that participate in the architecture of the macromolecule; (ii) formulation of their biological functions as carriers of genetic information; (iii) recognition of their species-specific character and of their detailed structure. This work was carried out by many, and there would be little sense in offering a long catalog. A few names should, however, be mentioned. In the first stage there were, following Miescher and Hoppe-Seyler, Piccard, Kossel, Altmann, Neumann, Jones, Steudel, Feulgen, P. A. Levene, Thannhauser, Hammarsten, Jorpes, Gerhard Schmidt, Dische, and Gulland. In the second stage: in addition to Brachet and Caspersson, especially Avery; in the third stage: my own laboratory, Wilkins, Crick, and Watson. Many different personalities were involved, different temperaments, different characters; and the many little chips that they unearthed gained significance and color only in the mosaic of the whole.

The generally antlike character of the natural sciences is made particularly evident in this history; only that by now the ants have become rather more obtrusive (10). Also, we deal less with a mosaic than with a jigsaw puzzle in which it is not necessary for all pieces to fit perfectly, as long as the image, expected or permitted by present-day opinion, is reproduced approximately. The so-called exact sciences often are not as exact as is commonly

believed. How often do they infer the existence of a hat from the emergence of a rabbit! Nowadays it is not seldom that an intensive search, or only an intensive assertion, produces what looks like truth: This is what could be called *veritas creata*. But there is something much higher, namely, *veritas creans*.

III

At this point, I should like to indulge in a short digression. Nature can be explored on many levels; none is more or less profound, none is more or less correct, but they are different. Which one you choose depends upon inclination, talent, accident, but most of all, unfortunately, upon fashion. Now one could say, at the risk of some superficiality, that there exist principally two types of scientists. The ones, and they are rare, wish to *understand* the world, to know nature; the others, much more frequent, wish to *explain* it. The first are searching for truth, often with the knowledge that they will not attain it; the second strive for plausibility, for the achievement of an intellectually consistent, and hence successful, view of the world. To the ones, nature reveals itself in lyrical intensity, to the others in logical clarity, and *they* are the masters of the world. Goethe was certainly wrong and Newton right; but somehow I cannot escape the feeling that, as long as humanity lasts, the dispute will never be entirely resolved. The laughter of Spinoza, as he watched two spiders battling each other, can still be heard. It is almost an intrinsic part of our concept of science that we never know enough. At all times one could almost say: We can explain it all, but understand only very little.

Most scientists, therefore, are what Archilochos would have called foxes, and they know many things. And then there still is a subdivision, much on the ascendant in biology, and these wish to *change* the world (11). With them I do not wish to deal here, for I am convinced that the attempts to improve or outsmart nature have almost brought about its disappearance; just as the all too frequent performance of intelligence tests is more likely to make the testers more stupid than the tested more intelligent. That the end sanctifies the means has for more than a hundred years been the credo of the sciences; in actual fact, it is the means that have diabolized the end.

IV

Physiological chemistry, still in its infancy, was the first science to become interested in the nucleic acids, and somewhat later organic chemistry, already highly developed at that time, took up the study. The constituents, the purines and pyrimidines and their sugar derivatives, which form the actual components of the nucleic acids, that is, the nucleosides and the nucleotides, were isolated and characterized; better methods for the isolation of the nucleic acids from tissues were developed; and finally rather complicated studies led to the identification of the two sugars, deoxyribose and ribose, which are characteristic of the two types of nucleic acid. At a still later date there began the synthetic and analytic work which was followed by the description of several more or less specific enzymes. I have mentioned before the principal names of those that participated in this work, but I should like to add the names of several organic chemists who took part in the first basic attempts at synthesis, namely Emil Fischer and Traube, Wheeler and T. B. Johnson, and much later Alexander Todd.

What was known about nucleic acids at the end of this stage? Much and little. Their qualitative composition was more or less understood, that is, it was possible to give a list of the types of molecules which were liberated by the degradation of the nucleic acids. These were in the case of DNA: (i) deoxyribose, a pentose sugar; (ii) two nitrogen-containing substances belonging to the purine group, adenine and guanine; (iii) two related nitrogenous substances belonging to the group of pyrimidines, cytosine and thymine; and finally (iv) phosphoric acid. RNA was found to be very similar to DNA in its ultimate constituents. It contains: (i) another pentose, ribose; (ii) the same two purines as DNA, adenine and guanine; (iii) two pyrimidines, of which one is identical with a DNA constituent, cytosine and uracil; and again (iv) phosphoric acid.

Further work demonstrated that in the nucleic acids each of the purines and pyrimidines carries a sugar moiety—these derivatives are called nucleosides—and that each nucleoside carries a phosphate; these nucleoside phosphates are designated as nucleotides. This is then the primary structure of a nucleic acid: a chain of nucleotides

linked to each other *via* phosphate bridges, a polynucleotide. It will simplify the following discussion if a few simple abbreviations are introduced, namely, the initials of the various purine and pyrimidine nucleotides. In speaking of A, G, C, T, or U we designate the corresponding nucleotides containing adenine, guanine, cytosine, thymine, or uracil.

For many decades the formulation of a DNA looked very simple, for instance: (AGCT)_n. One postulated the existence of a compound composed of all four building blocks, a so-called tetranucleotide, which was repeated several times in a nucleic acid. No firm assertion could be made as to the size of this value *n*, though it was considered as quite small. The notion of the occurrence of giant molecules, polymers, even in the living cell, prevailed only slowly, first perhaps with regard to the proteins. How enormous the leap into the present actually is may be seen from the fact that the molecular weight of a chain composed of ten tetranucleotides is about 12,000, whereas now the molecular weights of various DNA species are computed as many millions, and even billions. Had in the early days the nucleic acids been considered as a text—actually, one was far from it—it could be said that in less than 30 years a short aphorism has grown into an immense epic.

Although it was known that both nucleic acid types, DNA and RNA, occur in all living cells, no conception of their function, nor even of their actual structure, had emerged.

V

This brings us to a period, 75 years after Miescher's discovery, to the year 1944. At that time there appeared a publication by Avery and collaborators (12) on the mechanism of the so-called Griffith phenomenon, the transformation of one pneumococcal type into another. The final sentence of this remarkable paper, which was disregarded in the widest scientific circles, reads as follows:

"The evidence presented supports the belief that a nucleic acid of the desoxyribose type is the fundamental unit of the transforming principle of *Pneumococcus* Type III."

As this transformation represents a permanently inheritable alteration of a cell, the chemical nature of the substance responsible for this alteration

had here been elucidated for the first time. Seldom has more been said in so few words. The man who had written them, Oswald Theodore Avery (1877–1955), was at that time already 67: the ever rarer instance of an old man making a great scientific discovery. It had not been his first. He was a quiet man; and it would have honored the world more, had it honored him more. What counts, however, in science is to be not so much the first as the last.

This discovery, almost abruptly, appeared to foreshadow a chemistry of heredity and, moreover, made probable the nucleic acid character of the gene. It certainly made an impression on a few, not on many, but probably on nobody a more profound one than on me. For I saw before me in dark contours the beginning of a grammar of biology. Just as Cardinal Newman in the title of a celebrated book, *The Grammar of Assent*, spoke of the grammar of belief, I use this word as a description of the main elements and principles of a science. Avery gave us the first text of a new language, or rather he showed us where to look for it. I resolved to search for this text.

Consequently, I decided to relinquish all that we had been working on or to bring it to a quick conclusion, although the problems were not without interest and dealt with many facets of cellular chemistry. I have asked myself frequently whether I was not wrong in turning around the rudder so abruptly and whether it would not have been better not to succumb to the fascination of the moment; but these biographical bagatelles cannot be of interest to anybody. To the scientist nature is as a mirror that breaks every 30 years; and who cares about the broken glass of past times?

I started from the conviction that, if different DNA species exhibited different biological activities, there should also exist chemically demonstrable differences between deoxyribonucleic acids. From the very beginning I drew an analogy to the proteins in assuming that the biological activity of the nucleic acid probably rested on the sequence specificity of its constituents—on the order in which the four different nucleotides were arranged in the macromolecule—rather than on the occurrence of new, as yet unrecognized constituents. The prototype of this difference then would be "*Roma-Amor*" and not "*Roma-Rosa*." This has proved to be correct.

There existed, however, a difficulty which appeared almost unsurmountable: the lack of any method for the precise chemical characterization of a nucleic acid. The development of suitable procedures took 2 years, 1946–48. The results were most surprising. They showed that the old and unfounded tetranucleotide hypothesis was wrong; that there existed an enormous number of different deoxyribonucleic acids whose composition was constant and characteristic within the species and within all organs of the same species; in other words, that the different DNA species differed from each other, as is the case with the proteins, through the different arrangement of their constituents, through different nucleotide sequences. This was strictly speaking the beginning of the notion, so commonly accepted in the meantime, of the “information content” of DNA.

Retaining the previously defined abbreviations, a DNA molecule could no longer be formulated as $(AGCT)_n$ but as $(A_m G_n C_o T_p)$, with m , n , o , and p representing not only very high values, but values characteristically different in DNA preparations isolated from different species. This placed the nucleic acids for the first time on the same level as the proteins.

But there emerged also something much more surprising, which distinguished the nucleic acids from the proteins, namely, a sort of equipoise between the several DNA constituents, as had not yet been observed in any other natural polymer. This is the relationship between adenine and thymine on the one hand, guanine and cytosine on the other, to which I first referred as complementarity, but which several years later, under the name of “base-pairing,” became the fundamental slogan of a new science. These observations were reported in several lectures in 1949 and published at the beginning of 1950 (13).

These were the observations: If the total formula of a DNA molecule is written as $(A_m G_n C_o T_p)$, as has been done above, we find in many differently composed DNA species that the values m and p are equal, as are the values n and o , and that the sums $(m+n)$ and $(o+p)$ show equality as do the sums $(m+o)$ and $(n+p)$. To put it in words, the DNA constituents are paired as follows: (i) adenine with thymine; (ii) guanine with cytosine; (iii) purines with pyrimidines; (iv) the substances classified chemically as

6-amino derivatives (adenine and cytosine) with the 6-oxo derivatives (guanine and thymine).

VI

The natural sciences are furiously writing on second volumes of which there exist neither the first nor the last. Nothing is ever finished in this slippery world. But the second volume containing the observations outlined above can be considered as concluded. In referring to this work as historical I use a synonym for oblivion.

Before turning to the further course of our history I should mention a second subterranean branch of the great river for which unfortunately nobody has come up with a more sensible name than “molecular biology,” namely, the early work on bacteriophages, principally *Escherichia coli* phages. The names of Delbrück and Luria, S. S. Cohen, and Hershey are connected with these studies.

These investigations on viruses had the merit of making available simple and clearly perceivable systems. Many studies would have come to nothing, had they been limited to plant or animal cells or only to bacteria. Like every reformation this one too was also a deformation; it has served to push the major part of research into an area of which it is not even clear whether it represents a microcosmic image of living nature. What happens so frequently in the natural sciences has happened again: depth engenders restriction. In the end, we know nearly all about nearly nothing.

What was essential in these findings was the demonstration that the proliferation of bacterial viruses in the infected bacterial cell is mediated solely through the DNA of the phages. These results, therefore, confirmed Avery's previously mentioned seminal observations.

What has, consequently, become evident is that DNA, at least under certain conditions, can be considered as the carrier of “biological information”; that this information must be based on sequence specificity; and that the DNA molecules are distinguished by peculiar and unusual regularities of their composition. The newer history is again connected with a series of names, of which a few should be mentioned: Watson and Crick, Monod and Jacob, Holley and Nirenberg. But this newer history of biology is also connected

with something else, and this could form the subject of an apocalyptic intermezzo.

VII

The last 15 years have witnessed an event that, I believe, is unique in the history of the natural sciences: their subjugation to, their incorporation into, the whirls and frenzies of disgusting publicity and propaganda. This is no doubt symptomatic of the precarious position assigned by present-day society to any form of intellectual activity. Such pursuits have at all times been both absurd and fragile; but they become ever more ludicrous when, as is now true of science, they become mass professions and must, as homeless pretentious parasites, justify their right to existence before a period devoted to nothing but the rapid consumption of goods and amusements. These sciences were always a *divertissement* in the sense in which Pascal used the word; but what is their function in a society living under the motto *lunam et circenses* (14)? Are they only a band of court jesters in search of courts which, if they ever existed, have long lost their desire to be amused?

End of the World through Black Magic was the title Karl Kraus gave to one of his books. (At that, his time was, compared with ours, still bucolic; but the great prophets always live in the future.) The black magic of our days, these mass media concerned with both the production and the distribution of so-called news; these forever titillated and nauseated intimacies, splashing all over us from newspapers and magazines, from radio and television; this bubbling and babbling emptiness of deadened imagination: they have all taken hold of science, as of all other intellectual products of humanity, they have swallowed it up. It is not difficult to understand why our youth experiences a revulsion from all these synthetic celebrities strutting on the television screens of the world, from the ever-increasing pollution of our intellectual and our actual atmosphere; and if, at least in America, there begins to be noticeable a distinct aversion to the natural sciences on the side of the students, this is certainly due in part to the fact that these sciences appear to form part of the discredited trappings of a hated history. Hiroshima is more than the name of a destroyed city.

Since the end of the second world war—but especially since the Russian successes in space flight—the financial resources, especially in the United States, being pumped into the natural sciences have augmented in a manner that would have been unimaginable before. This has given rise to a popularization, but also to an enormous vulgarization, of science. Its achievements have begun to take on the form of a spectator sport, and young scientists start like race horses. Science has been perverted by public opinion to a sort of Hollywood and has begun to adapt itself to this brutal standard. The noise, enormous even before, has increased with the restriction of available funds (15). The old joke about the conversation between two Pavlovian dogs could be modified slightly: “Every time, when I ring the bell, there comes a guy and gives me a prize.”

Still, it is always surprising that in such bad times—somehow between Auschwitz and Vietnam—so much good science has been produced. I do not know, though, what to conclude. (Times not so bad, sciences not so good?) That in our days such pygmies throw such giant shadows only shows how late in the day it has become.

VIII

On the basis of the x-ray work on DNA by Wilkins in London and of the chemical observations of my laboratory, Crick and Watson in 1953 made a very fruitful proposal with respect to the macromolecular architecture, the secondary structure, of DNA (16). This model—a double helix consisting of two intertwined DNA strands held together by specific hydrogen bonds, namely those predicted by the above-mentioned principles of base-pairing—forms an important part of the grammar that the title of this paper has alluded to. It is, in any event, the most intelligent explanation of the regularities discovered by us: of base-pairing, the equivalence of purines and pyrimidines, and so forth.

The model of a double-stranded DNA suggested immediately a possible pathway for nature to bring about the replication of a DNA molecule with the conservation of its innate biological information, based on its nucleotide sequence. The old strand A makes the new strand B, the old strand B makes the new strand A; positive makes negative, negative makes positive, and so

on *ad infinitum*. This process has been realized in vitro enzymically; but the living cell, with its confounded multidimensionality, still presents us with many question marks. Nevertheless, one may say that the problem of the *conservation* of hereditary biological information is relatively well understood, though this is less true of the mechanisms through which such information can be changed. The insight into the *transmission* of the text coded into DNA, that is, its transcription into complementary RNA and the translation of this RNA into different proteins, encounters greater difficulties, and these processes are understood only in vague outlines. The first step consisted in the demonstration of enzyme systems (RNA polymerases) which, with the use of a DNA as an obligatory template, are able to synthesize RNA molecules of complementary composition and nucleotide sequence.

These RNA molecules belong to several different classes. We encounter here, among others, the comparatively high-molecular species of ribosomal RNA, then the small molecules of transfer RNA, at least one type for each of the amino acids occurring in proteins, and finally a very large number of different so-called “messenger RNA” molecules—substances that transmit the instructions of the DNA concerning the structure of enzymes and other proteins to the ribosomes where the synthesis of proteins takes place. Each of these messengers carries the cipher for at least one protein, read from a section of the DNA of the genome. The RNA of plant viruses and certain RNA-containing bacteriophages presumably contain the code for several proteins whose synthesis is induced by the infection.

From all this, and from many other things for which I have no room here, we have learned that the range of what is considered as biological specificity is always in danger of being underestimated. If DNA is really our thread of Ariadne, the labyrinths out of which it is expected to lead us are truly inscrutable. When in biochemistry we employ such an innocuously sounding expression as, for instance, that a certain protein, an enzyme, “recognizes” a specific nucleotide sequence, do we as much as suspect how much of an anthropomorphic hypostatization we have undertaken?

All the schemes, which in several

versions represent the “central dogma” that “DNA makes RNA and RNA makes protein,” would not have carried us far, had it not been possible to demonstrate, more or less conclusively, that RNA really contains nucleotide triplets, each of which forms the code word for a given amino acid, as, for example, UUU for the amino acid phenylalanine. I do not wish to discuss here how valid these assignments really are, but prefer to limit myself to admiring the magnitude of the cryptographic achievement, rejoicing in the fact that nature seems so much better than Shakespeare whom Dr. Johnson reproved for not having been able to write “six lines together without a fault.”

IX

These then, sketched with reprehensible superficiality, are the elements which made possible the first step to a “grammar of biology.” If the French saying “*Il n’y a que le premier pas qui coûte*” were correct, the rest ought to be easy. In other words, today the smallest of the small bacteriophages, tomorrow the brain that conceived *Die Zauberflöte*. But in my laboratory there exists an old house proverb saying “The first success in an experiment comes from the devil; but then the way drags on.” And truly, it will still take a long time from the relatively primitive structures, such as phages and viruses, with which molecular biology is principally concerned, to the higher unicellular organisms, let alone the multicellular ones.

Total knowledge requires a limited universe, but the realm of life has no boundaries recognizable to us except death itself. This has had the consequence that, as we cannot define it, life as a category has practically disappeared from modern biology. We really still are very far from an actual grammar of the living cell, not to speak of that of an organ, an organism, or, even more, a thinking organism. It is not by accident that the grammar of the tower of Babel was not written. The processes of cell differentiation, morphogenesis, and cellular organization still are entirely obscure. One could almost say that we have remained as far from the goal as ever. For it still remains our goal to understand nature, not to talk it to death.

Do we really understand the world? We designate what we understand as

the world. Humanity has an enormous capacity to disregard the incomprehensible. There are many peculiar expressions to be read in our journals. A phage is said to "commit suicide," an infected bacterial cell to "abort." I myself may have been heard to say that a nucleic acid chain is being read, copied, or even translated: that it is the carrier of biological information, of a message acquired through transcription and transmitted as a translation. Are these all not expressions which, if we try to think them to their end, make the epistemological twilight of our sciences appear even more livid? We posit intelligence where we deny it. We humanize things, but we reify man. I am afraid our sciences have not escaped the process of alienation, of dehumanization, so characteristic of our time. The attempt to describe life in its generalized contours leads to an automatization before which everything—the leap of the cat or the Goldberg variations—appear equally incomprehensible.

In the study of biology, the several disciplines exist next to each other, but they do not come together. We have no real idea of the inside of a living cell, for we lack what could be called a science of compressed spaces, we lack a scientific knowledge of a whole; and while a sum can be subdivided, this is not true of a whole. I know full well, science progresses from the simple to the complex. I, too, have been taught that one must begin at the bottom; but shall we ever emerge at the top?

I look out of the window. There is a dog; he barks; he wags his tail. What is his molecular biology? The new doctrinaire biology has won great triumphs and caused great damage. By its readiness to explain all, it has blinded us to the fact that we understand only little. It has furnished us the key to a very small lock; but the door it has opened for us, is it perhaps merely a door to a castle in the air? Somehow I cannot rid myself of the feeling that we still lack an entire dimension that is necessary for the understanding of a living cell; and I am not thinking of the *vis vitalis*.

Our biology no less than our technology is a product of capitalism, governed by unwritten rules of supply and demand. Just as the ones poke around the moon, the others ransack life. The slogan always is: *Eritis sicut diaboli, scientes bonum, facientes malum*. I believe, we have not reflected sufficiently on the real goals of these new natural sciences. When I began my studies the battle cry was "knowledge"; now it is "power." It was much later that I discovered that already in 1597 Francis Bacon had announced the identity of these goals. But what is "power" in biology? The type of answer I get promises, for instance, the production of heaps of thoroughly healthy Einsteins. But is this desirable? Who will sew the pants for these Einsteins and, still more important, who will write the newspaper articles about them? But, really, these are only jokes. Since not even the most primitive of the smallest bacteriophages has been unraveled, this type of debased creation will still require much time; and warners and offenders will long before be buried in one and the same Nirvana of oblivion. Perhaps—but I have little hope—humanity will in the meantime have become more intelligent.

Faced with this enormous throng of sorcerer's apprentices, I should like to add only one remark. It would seem to me that man cannot live without mysteries. One could say, the great biologists worked in the very light of darkness. We have been deprived of this fertile night. The moon, to which as a child I used to look up on a clear night, really is no more; never again will it fill grove and glen with its soft and misty gleam (17). What will have to go next? I am afraid I shall be misunderstood when I say that through each of these great scientific-technological exploits the points of contact between humanity and reality are diminished irreversibly.

References and Notes

1. Biological hypotheses are in general accepted by the public much more readily and rapidly than chemical or physical discoveries. Thus, the index to the Schlechta edition of Nietzsche's works records 33 references to Darwin, one mention each of Robert Mayer and Virchow, and none of Helmholtz, Clausius, or

- Liebig. In his enormous receptiveness Novalis is a great exception among German thinkers.
2. Thomas Love Peacock, *Gryll Grange*, chapter 19.
3. Jean Paul, "Dämmerungen für Deutschland," in *Sämtliche Werke* (Reimer, Berlin, 1862), vol. 25, p. 91. A not dissimilar passage already may be found even in Montesquieu, in the 105th letter of his *Lettres persanes*.
4. E. Diehl, *Anthologia lyrica Graeca* (Teubner, Leipzig, 1949–52), No. 103.
5. Taken from the German translation: Sören Kierkegaard, *Die Tagebücher* (Brenner-Verlag, Innsbruck, 1923), vol. 2, p. 33.
6. Friedrich Miescher, *Die histochemischen und physiologischen Arbeiten*, 2 volumes (Vogel, Leipzig, 1897). The letters contained in the first volume and also the introduction by Wilhelm His are particularly worth reading.
7. R. Taton, Ed., *Histoire Générale des Sciences* (Presses Universitaires de France, Paris, 1961), vol. 3, pt. 1.
8. E. Chargaff, "On some of the biological consequences of base-pairing in the nucleic acids," in *Developmental and Metabolic Control Mechanisms and Neoplasia* (Williams & Wilkins, Baltimore, 1965), p. 7.
9. I should like to venture one remark. One gains the impression that nowadays the value of a piece of research is being measured in terms of its potential for productive unemployment relief: He who gives something to do to the greatest number of idling scientists is a great man. For this purpose we have now, for instance, a citation index from which one can ascertain how often he has been cited by others. This is a worthless standard. Meissonier and Bouguereau certainly were mentioned, and bought, more often by their contemporaries than Cézanne and Sisley. If, on the other hand, the value of a scientific observation is to be appraised on the basis of its unexpectedness, its originality, this requires a distance in time, a sort of bird's-eye view. This is true of the sciences no less than of the arts. We only have to think of the lack of appreciation with which Jean Paul or Hölderlin were treated by Goethe and Schiller; except that a scientific Hölderlin would not even have achieved a publication. Unappreciated geniuses in the natural sciences remain unrecognized; for them there is no posterity.
10. J. D. Watson's *The Double Helix* (Atheneum, New York, 1968) depicts the hectic climate of present-day research quite adequately.
11. This is surely not the kind of change contemplated by the young Marx in his 11th Feuerbach thesis.
12. O. T. Avery, C. M. MacLeod, M. McCarty, "Studies on the chemical nature of the substance inducing transformation of pneumococcal types," *J. Exp. Med.* **79**, 137 (1944).
13. E. Chargaff, "Chemical specificity of nucleic acids and mechanism of their enzymatic degradation," *Experientia* **6**, 201 (1950).
14. I have resisted the temptation to translate this phrase, more expressively, as *moondoggle*.
15. Not infrequently, quite banal discoveries, especially in the field of virus and phage genetics, are being celebrated with a newspaper and television ballyhoo that would have deserved a better soap. Although these are mostly pseudo discoveries, not even applicable to unicellular organisms, one uses press conferences, interviews, and the like, to allude to the imminent "synthesis of life" or to impending cures by "genetic engineering." The public, which forgets rapidly, retains the pleasant taste of the greatness and vigor of the sciences.
16. J. D. Watson and F. H. C. Crick, "Molecular structure of nucleic acids," *Nature* **171**, 737 (1953).
17. This passage alludes, of course, to the first lines of Goethe's celebrated song *An den Mond*: "Füllest wieder Busch und Tal / Still mit Nebelglanz. . . ."