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A FEW REMARKS ON THE IMPACT OF BIOCHEMISTRY ON GENETICS

(history of biology, social values)

ERWIN CHARGAFF

Department of Biochemistry,
Cell Chemistry Laboratory
Columbia University
630 West 168th Street
New York, N.Y. 10032

I

Since in this cosmos of ours all hangs together, you can find an impact of any natural science on any other, if you wait long enough. The collision between biochemistry and genetics, although slow in coming, had far-reaching effects, once it took place. This will not be a historical lecture--I have a rather low opinion of what now masquerades as history of science--but we shall have to go back a little time, say, 25 years or so. In 1952 a man with whom I was quite friendly and for whom I had a lot of admiration, though I did not share his philosophical outlook, wrote a book to which he gave the title: "The Biochemistry of Genetics". This was J.B.S. Haldane. There was a lot of genetics in that book, but little biochemistry. Some of the names that were soon to acquire so much importance in our thinking appear in it, *e.g.*, Avery or George Beadle. More names are absent. At the same time we must consider that, with a few exceptions, the great discoveries in biochemical genetics occurred in the forties: infectious TMV-RNA, transforming principle, chemical proof of the existence of many different nucleic acids, base-pairing, etc. Of all this, there is almost nothing in Haldane's book. This merely shows that the times were not yet ripe for the utilization of all the new material that lay open, but was not perceived. By the time Haldane's book was published in 1954, the Watson-Crick structure of DNA and the Hershey-Chase experiments were also in print; but I am sure, even if they had been in time for the book, they also would not have been mentioned.

II

Speculations on the nature of the unit of heredity, later designated "the gene", must have begun soon after genetics was rediscovered or reformulated at the beginning of this century. I do not believe that in the beginning one thought of these units in chemical terms, as substances; just as now, even if we could posit a unit of memory, we should not be inclined to assign it a chemical structure. The notion that all events of life must participate in a dimension of chemistry as well as one of physics arose later. Of course, the existence of hereditary conditions that expressed themselves in biochemical phenomena must have long been known. The genetically determined disease hemophilia had been described quite some time ago, and "inborn errors of metabolism" were studied before this designation had become popular.

When biochemistry came into its own and it became possible to isolate and characterize the various more or less complicated components of the cell, such as the proteins, the polysaccharides, the complex lipids, and finally the nucleic acids, it became fashionable to choose as the pretender to the role of hereditary determinant always the class of compounds that seemed to be the most diversified and complicated at that time. Mostly the proteins, and among them the enzymes, were put forward, because they seemed to offer the greatest possibilities of specificity; but when type-specific polysaccharides were discovered, they, too, became candidates. All this was, however, much empty talk. Two sciences--in our case biochemistry and genetics--cannot impinge on each other before the areas of their contact are sufficiently broad.

It is quite clear that this contact could not be established as long as *Drosophila* remained the principal organism of the geneticist. This changed, however, in the 1940's with the introduction of *Neurospora* and of *E. coli* and its bacteriophages into genetic research. By far the greatest impulse came from the work of Avery's laboratory on the transforming principle in *Pneumococcus* which was shown to be a deoxyribonucleic acid. The proof that DNA was the carrier of hereditary information introduced an enormous forward step in biological thinking. It led to the chemical demonstration of the existence of very many DNA varieties of different chemical composition; it led to the discovery of base-pairing; it led to the structural model of DNA as a double helix; it led to an incredible expansion of understanding as marked by such terms as replication, transcription, genetic code, etc. Were I to go into all this, my brief talk would turn into a huge book on the recent history of biology.

III

While the instrumentarium of biochemical genetics is getting more and more varied, the scientific basis, or, if you want, the strategy, of almost all the work is rather simpleminded. The seat of all biological information, the communications center of all of living nature, resides in a relatively primitive array of four nucleotides in the DNA. Changes in certain crucial nucleotide sequences, or their deletion, are the cause of mutations; and as these changes are inheritable, so are the mutations.

But is this all true; and if it is true, how far does its import reach? This has become a field in which it is extremely difficult to separate the gold from the sand. We are all drowning in a flood of verbiage.

The genetic signals which, let us grant, reside in the DNA of a cell, an organ or an organism, are all related to the chemical materials of the body, in the first place, to the proteins and the nucleic acids. These are two of the four plastic constituents of the cell. As for the other two, *viz.*, the polysaccharides and the lipids, one must resort to a rather long-winded explanation, in order to tie them to the nucleic acids. But even if we could extend this reasoning to all the vitamins, and the hormones, and the pigments, the membranes and the organelles, and so on, is this enough to explain the uniqueness of any living being, let alone man, the crown of them all? What is the biochemistry of our fingerprints, of our autoimmune reactions? Is there a genetics of individuality, and how is it guided? We seem still to be lacking an entire dimension; and I do not even have a name for it. Even as simple a contraption as the automobile is not explicable through its material make-up only. What is it without fuel and, even more, without a driver?

IV

But it was not really my purpose to supply you today with a stringent critique of the biochemical basis of genetics. I should prefer to dwell on some of the consequences of this union of two scientific disciplines.

To begin with, we are often told that pure science or basic science is value-free; it is morally neutral. This was, for instance, claimed by the great sociologist Max Weber, one of the founders of what now has unfortunately become a pseudo-science. But was this true in Weber's time and is it true now? I doubt it. I might even ask, was it ever true? Perhaps for single and rare individuals in very unusual circumstances. The ancient myth of Prometheus and his punishment for bringing the fire down to earth shows how deep the misgivings were even in those early times. And if the liver of Prometheus is no longer being devoured by the eagles of Jove, but by cancer, he still remains a victim of civilization which, I am told, is unthinkable without technology which, in turn, is unthinkable without science.

In any event, for many centuries the various scientific disciplines, as they evolved gradually and very slowly, could be regarded as being as innocuous, as value-free as, for instance, poetry or music or painting. That is, they could occasionally be misapplied by malevolent or mindless people, but essentially they existed unmolested in the crevices of a society that had entirely different worries. Scientists may have been looked at as queer people, minding their own business which nobody else was interested in. But there were so very few of them and they cost very little money. Some were teachers, others had odd occupations: Kepler a calendar-maker and astrologer, Spinoza an optician. In a way, professionalism did not exist, there were no "experts" or "specialists": they were all, more or less, devoted amateurs or dilettantes.

Another thing worth noting is that for a very long time the several different scientific disciplines developed separately, each operating under a somewhat different "code of honor". It was only in the last century that some of them began to get together and, in some instances, to coalesce. First, perhaps, physics--the science of states--and chemistry--the science of substances. And the glue which held them together was always provided by mathematics. When chemistry was found to be the most practical, the most applicable of the sciences, colonization began in a greater style. And this is how, among several other sciences, biochemistry came about, roughly 100 years ago. Genetics is even much younger.

When togetherness set in, bedlam broke loose. The old story of the Tower of Babel repeated itself. Only through their coalescence was the tremendous power inherent in science finally revealed: much more, in my opinion, a power for evil than for good. Only then could technology begin its amok run towards the annihilation of mankind, towards death and destruction. And of the great abominations, the great misdeeds, of our days--the nuclear bomb, the landing on the moon--it is difficult to say where science ends and technology begins. They are one gigantic conglomerate, always fulfilling ever greater needs which they themselves have created. The devilish serpent, when it promised my primordial ancestors that they would be like gods, knew what it was doing. What it did not tell them, however, was how to get rid of radioactive wastes, nor how to create energy without being consumed in the process.

Incidentally, if science is really, as so many wise men of the 19th century claimed, a machine for the destruction of mankind, it is no wonder that so many scientists I know are misanthropes. Humanity leaves when statistics enters.

V

Another consequence of the force-feeding of science in the last 30 years or so has been to make it into a mass occupation. A concomitant of this has been the deplorable fact that science has become extremely expensive. This has delivered us into the hands of the government with its huge and mindless bureaucracy. So far, we do not yet have to pay page charges for our thoughts; these are still supposed to be free. But thoughts are not of much use in science--sometimes I have the impression they are an obstacle--you must also be able to implement them; and this costs now a lot of money. Moreover, we are being told ever more frequently in the universities in what direction to think; we are instructed to gather money where the action is; and the loudest nitwits play the tune. It has become almost impossible to discover the unexpected.

This has produced a frantic search for stunts, though always in the framework of the fashionably accepted models. For the rule seems to be: "No breakthrough without a handout"--and also the counterpart: "No handout without a breakthrough". And this is, unfortunately, the playground on which that child of the shotgun marriage between biochemistry and genetics, namely, molecular biology, pushes his hoop. This started, perhaps, with the double helix, the first scientific hypothesis promoted by Madison Avenue. Since then, the sloganification of science has made tremendous strides. And now there is no peep that does not carry its pithy, preferably ungrammatical, label. It began when most unassuming soups were called "shockates".

VI

It is, therefore, not surprising that this child prodigy--or should I say, this prodigal child?--molecular biology, got the itch to be extremely useful. (Here I should insert parenthetically that I am not particularly fond of the frequently advanced argument of the usefulness of science. I draw the same consequences from reading a good scientific paper as from listening to a Mozart piano concerto. They are as they are. To understand nature more fully may fill me with delight; but this is all).

This is, of course, not the reaction of normal people. Regular scientists are supposed to operate under what I once called the Devil's Maxim: "*What can be done, must be done.*" and a lot can, unfortunately, be done. Looked at it this way, the impact of biochemistry on genetics may turn out disastrous. The work on specific sequences in DNA, on the highly specific restriction enzymes, on the ligases, on the insertion of home-made DNA chimeras into plasmids, and their propagation in bacteria may well have reached a stage where the urge to make over man, to improve him according to an undisclosed model, becomes overwhelming. The battle cry of "genetic engineering" or "genetic surgery" goes to the head, and even more the overhead, of every money-grabbing administrator. It also appeals to many ambitious molecular biologists, for after all this is the only form of engineering or surgery that can be done by a Ph.D. The orgy has barely begun, but when we are through with it, Auschwitz may look like a kindergarten.

Feeling, as I do, that our so-called progress, namely, towards the maximum of moral entropy, and perhaps also of thermodynamic entropy, cannot be stopped, it was with a sensation of deep melancholy that I read about the "Council of Asilomar". There, the elders of molecular biology got together from all over the world. Deliberating in devout isolation they condemned the heresies of which they themselves had been guilty in the first place. The theses listing the various prohibited items of genetic malpractice read like a guide to what the future will bring us. "Well," I said to myself, "arsonists are known to join fire brigades, but this must be the first case in history when they have formed one of their own".

Erwin Chargaff at the Symposium