50 YEARS OF CURRENT SCIENCE—GLEANINGS

INTERACTION OF PHYSICAL AND BIOLOGICAL SCIENCES*

At one time the segregation of the physical and the biological sciences could scarcely have been more complete. But the lines of demarcation are gradually vanishing, and a fusion between the two is occurring in many places, *e.g.*, the interpretations of nerve action in terms of ionic flow, and of cortical events in terms of spatio-temporal patterns of neuronal activity; the analogies between the working of the brain and the operations of electronic calculators; all these and many more have for a long time compelled the simultaneous study of widely different fields of science.

The relation of molecular structure to properties is a major chapter of science and now forms a body of doctrine built up over a century. Through the stimulus, partly industrial, of the intensive work on polymers—those huge molecules now made almost to a predetermined specification of properties—this study today embraces some of the chief constituents of the living cell.

Natural compounds of very high molecular weight, formed at low temperature and under the directing influence of existing cell structures, have normally a much more regular configuration than the chains randomly formed in polymerizations initiated by free radicals at high temperatures. The gap between the natural and the artificial has been significantly narrowed by the recent discoveries of Ziegler and of Natta. By the use of new catalysts based upon aluminium alkyls and titanium or vanadium chlorides, beautifully oriented polymers of regularly repeating structures are formed. The initiation mechanisms may well be ionic, and the regularity is almost certainly due to the guiding influence of a heterogeneous catalyst.

The closer approach of this mechanism to that used in the cell is very suggestive. Substances closely resembling natural rubber and guttapercha (which stand in a *cis-trans* relation to one another) have indeed been made by such means. The properties of these regularly ordered polymers are profoundly different from those of the less ordered forms, and during 1956, Natta, Corradini and Dall'Asta, in a study of crystalline polypropylene oxide, have commented on the notable analogies between their product and the fibroin of silk.

In this general connexion, the recent work of Ballard and Bamford is highly suggestive. These authors find that in the polymerization of DL-phenyl-alanine-N-carboxy λ-amino-acid anhydride initiated by polysacrosine dimethylamide, the polysarcrosine chain is able to catalyse the reaction between the base and the anhydride in a marked degree. They justly point out the analogy between this phenomenon and an enzyme reaction.

Work continues in many laboratories on the fibrous and globular proteins and on nucleic acids (and models have recently been shown to the Royal Society of the beautiful structures which the X-ray crystallographers are beginning to propose for these vitally important substances).

The problem is enormously complicated, but its attraction depends, of course, largely upon the belief, widely held on good grounds, that these structures are fundamentally concerned in the processes of heredity. Nevertheless, the view that nucleoproteins are the basis of genes which could be self-replicating in isolation and merely in virtue of their structure is probably a dangerous over-simplification.

In the chemistry of inanimate Nature the study of structure alone is quite insufficient and must be undertaken in conjunction with that of function; in other words, reaction mechanisms are as important as molecular structures.

That the properties of living things are an emergent result of contributions from finite, if large, numbers of structural units of genes, that the genes are rather stable though not immutable, that in proper circumstances they change their associations in accordance with the laws of probability, are among the major basic principles of science. Recent work has, however, widened the view of the ways in which hereditary characters are transmitted. Besides sexual unions there are transmission by infective agents, by transduction and by Pontecorvo's parasexual mechanisms. Moreover, the combinatory phenomena that are so important in the Mendelian system cannot play much part in micro-organisms which multiply by binary fission. Fruitful as the reference of cell properties to the structure of genes has been, the body of doctrine which rests on this assumption is in some important respects incomplete, as indeed every chapter of science must be incomplete by itself. The picture presented is essentially static. The phenomena of growth, adaptation and reproduction need a dynamic one.

No one structure is likely to be autosynthetic in isolation; even the viruses require as hosts more or less intact cells, the machinery of which they can exploit. The building blocks of the cell, wonderful though they may be as structures, are useless by themselves. Cell function depends upon the rhythm and harmony of their reciprocal actions: the mutual dependence of protein and nucleic acid; the spatial and temporal relations of a host of elementary processes which with

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their sequences and bifurcations make up the reaction pattern of the cell. A system of mutually dependent parts each of which performs something like enzymatic functions in relation to another, will, as can easily be shown, in the steady state appear as a whole to be autosynthetic. No individual part need be credited with a new and mysterious virtue by which to duplicate itself. Thus the picture widens beyond the structural units to their quantitative proportions, to their reciprocal dependence and to their rate of growth. This fusion of physical chemistry and biology leads to conclusions about the nature of adaptive processes, the automatic attainment of maximum growth-rates, and mechanisms for the choice of the most favourable metabolic patterns (as in the Pasteur effect).

The reality of the dynamic picture is sometimes called in question because there may be alternative explanations of particular phenomena. For example, the important phenomenon whereby drug resistance develops is often referred exclusively to selection of random mutants, although it is easy to show on the basis of very general physico-chemical assumptions that the effect should demonstrably occur as an automatic response, the adapted cells having reorganised their reaction patterns. This conclusion in its turn in no way denies the possibility of spontaneous resistance due to structural mutations. Nor, on the other hand, does the occasional demonstration of mutations leading to resistance rule out automatic cytoplasmic adjustments.

Normally, mutations, apart from those caused by radiation or special chemical agents, have been supposed to occur only when cells divide. This view itself seems to be changing. Some years ago, Baskett made a number of observations individually and collectively indicating that during the long delay which attends the first growth of *Bact. lactis aerogenes* on D-arbinose, there is in fact a physiological adaptation of the cytoplasm, and not the selection of mutants. Generally similar results have been found by Dean for cells initially reluctant to use lactose.

Somewhat analogous observations in a more spectacular form were reported by Akiba, and more fuly by Szybalski. Bacterial strains exposed to streptomycin for a number of days in a buffer not supporting growth were found eventually, if they had survived at all, to have become resistant to the antibiotic. Szybalski, however, quotes what he calls "tentative evidence" that the changes occur in a nucleus. The conclusion, however, seems to be far from certain, since the relations found in crossing drug-resistant with sensitive organisms are usually very complex. In genetic analysis with micro-organisms the number of parameters which can be adjusted is considerable, and illusory effects of sharp segregation phenomena are sometimes produced by the process of dividing continuous variables such as rate or time of growth into arbitrary domains such as 'slow' and 'fast' or '*plus*' and '*minus*'. That a high percentage of non-dividing cells should suffer nuclear mutations making them resistant precisely to that drug to which they are being exposed seems much harder to explain than the alternative of a dynamical change by which the cell as a whole reacts to the presence of the drug in an almost predictable way. The same general comments might be made about the 'spontaneous mutations' in the absence of division, to histidine-independence of a bacterial strain recently studied by Ryan.

In spite of some alarm, physico-chemical mechanisms of cell adjustment need not be in any conflict at all with valid principles of genetics. But it is a misapplication of the latter when they are used to exclude all mechanisms except selection of random mutants or of favourable gene combinations. Random mutations to drug resistance may indeed be shown by the relatively rare examples where the Lederberg technique of replica plating has given positive results. Nature, however, presents us with a vast hierarchy of systems: sub-atomic units (in a vast and confusing array), atoms and molecules, micelles, chromosomes, nuclei, cells, colonies, tissues, individuals and communities of individuals. Nobody can suppose that all phenomena have their origin at any one particular level.

The disentangling of the complicated and fascinating relationships met with in this field will demand close co-operation of the physical and biological sciences, which in other words, only means that to the highly ingenious models of structure must be added equally illuminating models of function. Whatever the answer may be to the controversial problems of today, that is what the future in one way or another will surely bring forth.