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BIOLOGY IN PROFILE

A GUIDE TO THE MANY BRANCHES OF BIOLOGY

Edited by
P. N. CAMPBELL
Courtauld Institute of Biochemistry
The Middlesex Hospital Medical School
London, England, UK

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GENETICS

by

Professor Joshua Lederberg
(President of The Rockefeller University)

The science of living things is too complicated both in method and in objective to yield to tidy classifications. It is wrong to think of genetics as a distinct branch of biology: this would imply the existence of other compartmented branches. Rather it is a particular way of looking at almost every aspect of biology. Genetics is centered on the question of heredity: how does a given organism derive its characeristics from its ancestry and pass them on to its progeny. It thus focusses on the intrinsic quality of an organism. This in turn can be understood only in relation to how its development responds to the extrinsic environment that it experiences.

The methods used by geneticists embrace those of all the other biological specialities; and the object organisms that illustrate genetic principles range from viruses to the human. Particular emphasis is placed on morphological methods that display the chromosomes, and chemical ones for DNA, since these objects are the material carriers of information in heredity. Organisms used for genetic study may be chosen primarily for their convenience in the laboratory, e.g. bacteriophages (bacterial virus), *E. coli*, drosophila or inbred mice. Or, as in the case of plant breeding or human genetic disease, vitally important economic and medical practical objectives may be at stake.

Most geneticists thus find themselves also attached to one or even several other biological specialities covered elsewhere in this volume. On the one hand the geneticist will probably have specialized on a given group of organisms (see "Handbook of Genetics" by King in reading list). On the other hand he or she may have in mind any of the themes like molecular biology, physiology, nutrition, ecology, behavior, medical sciences or evolution. The methods of biochemistry, biophysics and structural biology can hardly be avoided. Some aspects of genetics also make heavy call on demographic and statistical analysis.

Genetics was founded on the observations made by Mendel over a hundred years ago. Using the garden pea for his observations, he found that hereditary traits followed regular rules of transmission: the now familiar Mendelian Laws. We now know that these laws are manifestations of the usual behavior of chromosomes during the "reduction divisions" of gamete-forming cells in higher plants and animals. Many exceptions to these rules are now known; but in 1865 they enabled Mendel to postulate the existence of the genes as relatively autonomous particles underlying heredity.

For many decades genes were invisible and beyond chemical analysis. Since the identification of DNA as the genetic material, by Avery, MacLeod and McCarty, in 1944, the task of genetics has been to integrate the study

of the gene into the overall framework of the chemical biology of the cell. This integration, now largely successful, still presents formidable challenges to all of experimental biology.

Future challenges

Genetics has moved so rapidly in the past decade that it is unlikely that we can reliably foresee even the most fruitful and rewarding directions of advance over the next 20 years. The scientific objectives of genetics are scarcely distinguishable from those of molecular biology as applied to DNA, the structure of chromosomes, and the mechanisms by which genetic information is transcribed and translated into protein and the formation of more complex structures. Genetic aspects of evolution require an even more complex synthesis of these principles into the global panorama of evolutionary development. At the present time, evolutionary theory is still founded mainly on the most simplified models of genetic change. Thus it takes little account of more complex forms of variation. Some of these involve the transfer of blocks of genetic information from different species, and other modifications of DNA more complex than the change in a single nucleotide base. The limitations here are both in the inherent chemical complexity of DNA changes themselves, and the almost intractable mathematical complication of the comprehensive theory to model the changes. For these reasons the logical completeness of our present theory of evolution is still controversial. To put this another way, can we demonstrate that four billion years was enough time for evolution from the primeval ooze to contemporary humankind?

This question also opens up extensions of genetics to such issues as (1) what were the actual steps in the original evolution of life on earth from inorganic matter? and (2) what can be said about the distribution and diversification of life on other planets in the solar system and beyond? I have no doubt that many more missing links are still to be found among the species inhabiting earth; except for the most primitive initial exploration of Mars, of course, questions of the extraterrestrial distribution of life (exobiology) hardly go beyond intelligent and informed speculation.

As to the connections of genetics with developmental biology: rather detailed information is now available about the mechanisms that regulate gene expression in microorganisms. At least a number of provocative model systems have been put forward. There is nevertheless grave doubt whether these models account for gene regulation in eukayotic organisms. Hence the fundamental problem of embryology -- how cells differentiate -- remains obscure in molecular terms. The recent illumination of DNA-switch mechanisms in bacteria must make us wary even of insisting that the DNA in the nuclei of different differentiated cells remains absolutely identical, as has been presumed for the last 75 years.

Very powerful tools have been developed, quite recently, that encourage much optimism about our ability to attack these fundamental scientific questions. The most cogent of these is DNA-splicing, or recombinant-DNA technology. This enables us now to isolate specified pieces of DNA from the nucleus of one organism and implant them into a convenient vector, be it a bacteriophage or plasmid. In consequence bits of DNA of specified structure and function can be amplified: that is to say, grown in bulk and treated like chemical reagents.

If we keep in mind that there are probably of the order of 100,000 functional genes in the nucleus of a higher organism and that perhaps 10,000 of these are active in any given cell, we get some conception of the complexity of the task ahead. It is likely that, in order to gain a comprehensive understanding of cell biology, we will need to identify and understand the functioning of at least several thousand gene products, both as individual entities and how they relate to one another. The effect of DNA change, that

is genetic variation, on the respective gene products has been one of our most powerful tools for analyzing cell structure and function and will probably play an even more important role in future research.

It is perhaps easier to foresee areas of vital practical application during the next 20 years than it is to anticipate the fundamental discoveries which are always likely to come as a surprise.

Besides its importance as an analytical tool, recombinant-DNA technology is already well on its way to spurring an industrial and medical revolution in the production of specialised biological products like interferon, vaccines, polypeptide hormones, antibodies and other vital proteins. Industrial microbiology of course embraces still larger fields of production of chemicals, antibiotics, amino acids and other essential nutrients. Inexpensive replacements for sucrose, and a host of other large scale chemical industrial processes are being influenced in the most exciting and constructive ways by these new approaches to genetic modiciation of microbial strains. The role that industrial microbiology may play in the development of energy sources is perhaps more problematical. We already have the example of gasohol; and new genetic strains may be expected to play at least a modest role in the conversion of biomass residues that would otherwise present problems of waste disposal. There is little doubt about the economic justification for the application of sophisticated microbial processes when the end-product is expensive, i.e. valued in £ per kilogram or even gram. For cheaper products valued in £ per tonne a more careful appraisal of the economic justification is needed to ensure that the sophisticated techniques are applied to the most fruitful processes for energy and materials conversion on a large scale.

The application of Mendelian genetics to plant breeding has long since demonstrated its immense practical impact in developments like hybrid maize in the United States, and dwarf rice and wheat in the agriculture of developing countries. The fact that for many years farmers in developed countries have faced problems of too much rather than too little grain may have impeded the more urgent application of still more sophisticated scientific methods in plant breeding. Besides the possible extension of DNA-splicing to plant cells we have the already demonstrated approach of fusing somatic cells of plants in culture. Peter Carlson has combined this approach with the selection of desirable properties in cell cultures of the tobacco plant. Although cell fusion still has limited applicability among plant species by current techniques, there can be little doubt that this approach has opened up revolutionary alternatives in the development of plant types for use as crops. As the cost of petrofuel based fertilizers rises; as we become more conscious of other costs of energy in crop production; and particularly as the pressure of the world's growing population on food resources continues its apparently inexorable rise, the need for rapid development of more efficient modes of agriculture becomes obvious. In this sense the development of new crops capable of more efficiently exploiting marginal land resources assumes geo-political significance. This is accentuated by portents of climatic change that may place grave pressures on the agricultural self-sufficiency of the Eurasian land mass.

Somewhat similar remarks can be made about animal production: poultry have been developed that are efficient converters of plant nutrient into meat. However, even more desirable would be the efficient utilization of pasture and other fodders that are inherently unsuitable for human consumption. The task of development of improved breeds of cattle and other large animals with the use of sophisticated genetic approaches is, for obvious reasons, more formidable than poultry development; but large strides have already been made and enormous ones may be anticipated, including the most aggressive exploitation of the existing diversity of germ plasm.

Geneticists face the paradox that the very success of plant breeding tends to drive out wild strains of crop plants. Yet these are a precious and unrenewable resource to provide diverse "germ plasm", needed for disease

resistance, productivity under harsh conditions, and other special adaptations. Geneticists are actively involved in field expeditions and in policy and political discussions in efforts to preserve these resources.

More generally, under pressures of economic efficiency, and resource and energy depletion, we need to be able to make more rationally based choices on the balance between the dangers and economic advantages of toxic products of industry and energy generation. Cancer and genetic defects are recognized as the most insidious of these dangers, and genetic methods have already played an important part in the quick screening of chemical substances for their possible environmental hazard.

The reliability of screening methods using bacteria or small animals raises profound questions of comparative biology and genetics. The differences between these species and the human include differences in the metabolism of potentially toxic substances, in immune and repair mechanisms, in many aspects of cell biology. Historically, toxicology has developed as an applied science, which has not in the past used genetic and evolutionary concepts in extrapolating the effects of substances on simpler organisms to estimate their risks to the human. Comparative toxicology presents challenges of the deepest interest to basic science and social policy alike.

If we turn now to the applications of genetics to human affairs, especially to disease: within a few years after the rediscovery of Mendelism in 1900, Archibald Garrod had identified a number of human metabolic diseases which were clearly under genetic control. In fact these studies, which began from a clinical perspective, were the foundations of physiological genetics: that is to say the explanation of gene action in terms of enzymes. For he was able to identify diseases like albinism and alkaptonuria as defects in specific enzymes under genetic control. Since then several thousand genetic syndromes, most of them very rare, have been found and characterised.

In addition, there are a number of unfortunately more common chromosome defects like Downs Syndrome and Klinefelter's. In specific populations, single-gene defects like the thalassemias (southern Europe) and sickle cell disease (among African blacks) are all too prevalent. We have understood for some time that these are a by-product of evolution with heterozygote advantage but have been rather helplessly unable to do very much about it. Around the management of these genetic diseases a sub-profession of genetic counselling has emerged and in the United States this is beginning to be recognized as a professional specialty in its own right. What the genetic counsellor needs to know is how to diagnose specific diseases using cell culture or tissue samples often from amniocentesis, then to provide sensitive counselling to parents who wish to know the prospects of genetic damage and what steps they can take to ensure that they may have healthy children. At issue may be advice about a prospective abortion in the case of a child at risk during pregnancy. This is obviously a grave decision that must be governed by many personal factors, and also by the highest standards of technical realiability about the diagnosis.

New methods for the diagnosis of genetic disease from amniotic fluid cell samples have been developed: the most oustanding recently is Y.W. Kan on the molecular diagnosis of sickle cell disease. For the first time, despite the hullabaloo of a decade ago, it is now possible to advise parents at risk about the prospects that a particular pregnancy will be subject to this highly disabling disease. They may then elect preemptive abortion with a view to ensuring that they can, in further pregnancies, have children with the healthy life-prospect that should be everyone's birthright.

Most single-gene diseases in man are very rare but these have been the only ones which could be carefully studied. There remains the fact that between 20% and 50% of human disease is subject to more subtle variations in propensity or susceptibility. We have had only very primitive methods of studying the genetics of such multifactorial diseases as schizophrenia, heart disease, diabetes or cancer. The Kan methodology now enables the compre-

hensive mapping of the human chromosome set. From that we can anticipate very rapid leaps to the understanding of the genetic components not only of these diseases but of many other aspects of human longevity and personality. (Much of what's been said until now is hardly more than conjecture because methods like twin comparisons are so unreliable that only the lack of alternative methods can justify their use in research).

Some people are seriously questioning how far we should go in genetic typing for fear of some obvious forms of special abuse. But every advance in genetic insight takes us further and further away from the concept of genetic fatalism and offers more alternatives and options of dealing with the medical problems presented.

Finally, there is little doubt that DNA changes, which is to say genetics at the somatic cell level, are of central importance in the very nature of cancer, ageing and developmental defect. The analytical tools of modern genetics, especially those involving DNA splicing, DNA cloning, the sequencing of DNA, will be our most powerful resources in attacking cancer, heart disease, psychiatric illness: the major scourges of mankind in developed countries at the present time.

The rest, that is most, of the world's population faces a different set of problems that can be summarized as population, famine and plague. Geneticists do not directly intervene in population change, but their skills are indispensable for understanding its consequences for the human condition. The development of new crops is already an important factor in economic development. As to plagues, the most important communicable diseases in the world today are no longer the bacterial and viral infections familiar in developed countries. It is malaria, schistosome and other worm infestations, trypanosomes, Leishmania, and other protozoa, that are the scourges of hundreds of millions of people today. But these very organisms are fascinating objects of basic biological inquiry, presenting a challenge that parallels that of the bacteria a century ago. One of the main frontiers now being reached is the application of the most sophisticated tools of modern molecular biology and genetics to the eukaryotic microbes and worms that are the major public health problems of the developing countries.

Further reading

Judson, Horace, *The Eighth Day of Creation: Makers of the Revolution in Biology*. London: Jonathan Cape, 1979.

Jacob, Francois, *The Logic of Life: A History of Heredity*. London: Allen Lane, 1974.

Whitehouse, H.L.K., *Towards an Understanding of the Mechanism of Heredity*. New York: St. Martin's, 1973.

McCusick, V.A. and Claiborne, R. (eds.) *Medical Genetics*. New York: HP Publ. Co., 1973.

King, R.C. (ed.) *Handbook of Genetics*, Vols. 1-5. London: Plenum, 1974-76.

Vogel, F. and Motulsky, A.G. *Human Genetics*. New York: Springer-Verlag, 1979.

Bodmer, W.F. and Cavalli-Sforza, L.L. *Genetics, Evolution, and Man*. San Francisco: W.H. Freeman, 1976.

The most comprehensive oversight of the field is offered by *Annual Review of Genetics*, published by Annual Revs., Inc., Palo Alto, Calif.