Ciba Foundation Symposium 66 (new series)

HUMAN GENETICS: POSSIBILITIES AND REALITIES

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In honour of Sir Gordon Wolstenholme

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Sir Gordon Wolstenholme, Director of the Ciba Foundation, 1949–1978.
(Portrait by June Mendoza, owned by the Royal Society of Medicine, London.)

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Introduction

SYDNEY BRENNER

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I would like to repeat Dr Porter's welcome to you all, and particularly to those who attended the Ciba Foundation symposium on the *Biochemistry of Human Genetics* nearly 20 years ago. Our subject has undergone enormous development since that time, with the introduction of a range of new methods and new concepts.

To introduce the symposium, I should first note that it is a particularly appropriate time to discuss genetics and human biology. The great technical advances of the past few years, not the least of which has been the ability to clone and analyse DNA sequences, have begun to throw new light on the organization of genes in higher organisms. The discovery of several instances of what might be called spaced-out genes, that is coding sequences which are not continuous but are interrupted by other sequences, offers the first clear insight into the relationship between primary RNA transcripts in the nucleus and the messenger RNAs into which they are processed. We now know that this processing involves the precise excision of the intervening region. There are already cases where a single DNA sequence can ultimately produce more than one protein by different excision events. Whether this novel step in information transfer is used for control is still an open question, and one which is bound to attract wide attention in the coming years. No doubt there will be discussion on this question during the meeting.

The possession of these very powerful methods for molecular analysis of gene sequences will be crucial for the development of the genetics of higher organisms, particularly man. Together with somatic cell genetics, we now have the tools for tackling many problems in human genetics which have so far been totally intractable. But, as some of the papers will show, there is still more to come. Cloned DNA sequences can be inserted into cells and the value of the sequences assayed. Furthermore, since the sequences can be modified

in a directed manner, recloned and assayed again, this will allow the analysis of a function of any particular region of the DNA sequence. Genetics will, in principle, be freed from the search for rare mutational events, although I for one will regret the passing of that exciting laboratory pastime—the great mutant hunt! And that other great blood sport, the vast compendium of human haemoglobin variants, will be minuscule compared with the variants that will be produced in the test tube in the next few years.

The great ease with which molecular information can be collected on the genomes of higher organisms will tempt many. We can inevitably expect vast compendia of sequences but, without functional reference, these compendia will be uninterpretable, like an undeciphered ancient language. Many people and many computers will play games with these sequences, but we will have to find out by experiment what the sequences do and how the products they make participate in the physiology and development of the organism. Thus, although the analysis of the genotype has been taken care of, we still need better ways of analysing phenotypes. Many of us are ultimately interested in the causal analysis of development and the reduction of the complex phenotypes of higher organisms to the level of gene products. This is still the major problem of biology. We must understand what cells can do because all of what we are is generated by cells growing, moving, and differentiating. Here too, powerful tools are becoming available, among which the capacity to produce monoclonal antibodies is certain to become a major method for the analysis of the phenotypes of cells in higher organisms.

These experimental forays have naturally led to speculation on whether anything could be done to manipulate the genomes of the somatic cells of man or, in the extreme case, to alter the genetic constitution of the human population. As many of us know, the study of human genetics is opposed by some because of the fear that information acquired and techniques developed for what might be the purest of scientific motives may come to be misapplied in the future. Many of the present controls of genetic research are partly based on these fears. I can only make one or two comments on this subject today.

First, genetic engineering as a true technology in the sense that we can design an organism and implement that design does not exist. Nor will it exist until we know much more about the biology of cells and organisms than we know now. All we can do is a little 'tinkering', but that, as François Jacob (1977) has pointed out, is nature's way and not ours.

The second point is that much of human activity depends not on our biology but on our culture, and it is much cheaper and easier to change people by talking to them than by altering their genes. In one sense, 'Brave New World'

has been with us now for a million years, based on cultural changes rather than on changes in genetic polymorphisms. This area of human biology—the old argument about nature versus nurture—particularly where it touches on human behaviour, is controversial. We shall no doubt hear views on this controversy at this meeting. These are difficult and fascinating questions but they do not match the fascination and challenge of discovering how a fertilized egg with 10^9 nucleotide pairs of DNA can make a human being.

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Cultural change and its relevance for human genetics

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Abstract The first part of this paper summarizes conclusions drawn from theoretical analysis of cultural change, as appeared in various papers (published and unpublished) by the author in collaboration with Marc Feldman. Among conclusions emphasized are the tendency to homogeneity of cultural traits with most mechanisms of cultural transmission, the great variation in rates of change and conditions determining them, and the major factors responsible for change. The possibility of genetic variation in learning ability adds considerable complications and determines joint biological and cultural evolution.

In the second part of the paper, one very specific example of biological and cultural coevolution is outlined. Archaeological information shows that agriculture spread slowly from a Near East area of origin of domestication of plants and animals. The spread towards Europe is particularly well mapped. There are good reasons why the spread of agriculture may have been accompanied by a spread of farmers from the area of origin. It turns out that synthetic gene maps of Europe showing such a spread of farmers would be an excellent explanation for the geographic distribution of genes in Europe.

About ten years ago I became interested in the variation in, and evolution of, cultural traits. To a biologist like myself, one reason for excitement was the discovery that much of the conceptual framework which has been developed for biological evolution could also be usefully applied in the context of cultural change. In other words, the evolutionary factors which we identify with respect to genes, such as mutation, selection, drift and migration, translate into cultural equivalents when, instead of the evolution of genes, we consider the evolution of customs, languages, technology or any other aspect of culture.

Somewhat surprisingly, however, the literature of cultural evolution is very sparse. How is it possible that linguists, anthropologists and so on have had so little interest in the evolutionary aspects of culture? Certainly there were

attempts to study these aspects, but most of them aborted, some so badly that they generated widespread taboos. Thus there is a tendency among some scholars to avoid even the use of the expression 'cultural evolution'; others limit the term to very specific problems of sociopolitical change. Most of the treatments in existence are typically macroevolutionary. The micro-evolutionary approach, which was so fruitful in biology in providing opportunities for the verification and extension of theory, is almost absent.

What seems to have been neglected beyond belief is the study of cultural transmission. It is true that in biology it was possible to understand, before specific knowledge of biological transmission was available, how adaptation could evolve under natural selection. The full understanding and verification of Mendelian principles, which are at the basis of biological transmission, developed later. But it was only with the help of knowledge of transmission that it became possible to fill the evolutionary picture with the other factors: mutation, migration and drift. In fact evolution can be viewed as the sum of exceptions to a perfect transmission so that an understanding of transmission rules is a necessary complement to the study of evolution.

One cannot fail to be struck by the enormous difference between biological and cultural transmission. Even if almost no scientific work is available on the latter, everyday experience provides some insight. By contrast, biological transmission has been the object of innumerable and often very sophisticated studies and we know that, with few exceptions, it takes place exclusively from parent to offspring. According to the well-known Mendelian probabilities, with one gene and two alleles (three genotypes) there are nine possible matings, each of which gives rise to the three genotypes with fixed probabilities (for instance 1,0,0 for genotypes AA, Aa, aa in mating AA $\times$ AA, 1/2:1/2:0 in matings Aa $\times$ AA or AA $\times$ Aa, etc.).

In lieu of this set of probabilities, a cultural trait existing in three types could have any set of values leading to potentially very complex rules of transmission. In practice there will be eighteen parameters to specify parent–offspring transmission. In addition there is no guarantee that these parameters will be constant from generation to generation. Even more important, there will be transmission not only from parent to offspring but also between sibs, other types of relatives, friends, especially age peers, and from chiefs, teachers and through public media, etc. (Cavalli-Sforza 1971; Cavalli-Sforza & Feldman 1973*a,b*, 1976 and unpublished; Feldman & Cavalli-Sforza 1975, 1977 and unpublished).

The task of formalizing this protean set of rules may seem absolutely hopeless. But there are bound to be obvious simplifications. My Stanford collegue, Marc Feldman, and I have done the spadework and have started

considering the generalizations which emerge. It is of interest to contrast these generalizations with the expectations in biological evolution. In the latter, transmission is such that in the absence of evolutionary factors such as mutation etc., there is no change in populations. This static condition (otherwise known as neutral, or indifferent, equilibrium) is rarely to be expected for a cultural trait. Transmission rules for determining neutral equilibria may exist, but only exceptionally; more often, unlike the biological counterpart, transmission of a cultural trait is likely to change the frequency of the trait. This does not deny the possibility of stable equilibria; cultural transmission rules will indeed lead to stable equilibrium frequencies for a trait, but these will often be frequencies of zero or one. However, internal stable equilibria may exist, especially if parent–offspring transmission is also involved. In sum, even in the absence of the classical evolutionary factors, such as mutation etc., a great variety of types of evolution may be generated through transmission. For instance, a cultural trait (which can exist in three phenotypes) may take Hardy-Weinberg proportions at every generation (M. Feldman & L. L. Cavalli-Sforza, unpublished work), but the frequency of the trait will be unstable and change all the time until it hits a stable equilibrium. Rather subtle changes in the transmission rules may make proportions widely different from Hardy-Weinberg. Superficial imitation of Mendelian transmission and even of sex linkage is possible, and has in fact been observed in the case of kuru, an infectious transmission determined by cultural customs.

There is one important correlate of the fact that stable cultural equilibria are very frequently found at the boundaries, for trait frequencies of zero or one. Extinction or fixation of a cultural trait means one thing: *cultural homogeneity*. The trend towards homogeneity is even clearer if we study a continuous rather than a discrete trait. In the latter, in fact, homogeneity involves the rather extreme conditions of fixation or extinction, but in the former one can estimate the variance of the trait at every generation.

The interest of these conclusions is strengthened if one considers that stabilization of the variance of a trait to a sufficiently low value, that is a high degree of cultural homogeneity, is a prerequisite for the existence of culture and society. Homogeneity of the language spoken by all individuals belonging to the same linguistic group, for example, must be very high for effective communication to be possible. One conception of culture is that of biological adaptation making it possible for an individual to learn from the experience of others in ways that will increase the fitness of the individuals. For this aim, some kind of communication is essential; language is only one way, but a very efficient one. It is not, however, the only part of culture which requires a high degree of homogeneity for full effectiveness. Clearly,