ABSTRACT

GENETIC VARIATION IN MAN: SOCIAL ASSET OR SOCIAL LIABILITY

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Man is a very variable animal: the expression of this variability is due to both differences in genetic constitution and to the physical and psycho-social environment to which each of us is exposed. During recent years knowledge of the genetic component in human variation has been increasing at a rapid rate, so that now we can identify the chromosomal defect or single-gene basis for a large number of diseases. We know also a great deal about inherited variation in normal individuals and about the frequency of the genes controlling these variations in different human populations.

Much inherited variation is deleterious, and the social cost of these defects will become an increasing burden on the community. However, other parts of the genetic variability provide a reservoir which acts as a buffer for individuals in the complex ecological situations of human societies. In assessing the nature of man's genetic endowment we must therefore learn to understand more of the interaction between his genes and the environment to exploit this variability to the full.

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Man is a highly variable animal. This is a statement which is so obvious that many would consider it unnecessary to elaborate on it. However, in order to explore the social consequences of this variability we must delve more deeply into the nature of the differences which differentiates not only one person from another, but also one population from another.

The human species is both polytypic and polymorphic. Members of populations in different parts of the world share characteristics in common which differentiates them from members of other populations. These are polytypic or racial differences. Racial types clearly depend on a number of traits which are inherited. Within any one racial group, however, there are differences between individuals resulting from the interaction between man's individual genetic endowment and his environment. Some of these differences which are too frequent to be maintained by mutation we refer to as polymorphic.

The existence of polytypic, or racial, differences is one of the greatest social liabilities stemming from the diversity of man. It has given rise to innumerable theories on the moral, intellectual or physical superiority of one race versus another. Always such theories reflect a basic attitude of man to justify the life pattern of his own group by attempting to denigrate the habits of members of neighbouring groups.

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Such attempts are obviously made more easy when physical attributes such as skin colour, allows one to assign persons to one group or another without examining other attributes in detail. Thus the whole basis of the justification of the superiority of Aryans from the time of Count Gobineau onwards was related to an idealised concept of the physical type of the Aryan race. Such feelings for the superiority of the Aryan, or of the Anglo-Saxon, or other groups which have played such an important part in the recent history of Europe, are not confined however to Europeans and many examples could be cited of similar beliefs held by members of non-Caucasian races. Perhaps one of the most salutory examples of this other point of view is contained in a letter from the Chines Emperor Ch'ien Lung to George III in 1793. In response to a request from the British king for the establishment of a trading centre in Peking the Emperor wrote
"If you assert that your reverence for Our Celestial dynasty fills you with a desire to acquire our civilisation, our ceremonies and code of laws differ so completely from you own that, even if your Envoy were able to acquire the rudiments of our civilisation, you could not possibly transplant our manners and customs to your alien soil".

Let us turn our attention in more detail, however, to the biological basis of racial differences.

We have no precise knowledge of how the genetic characteristics which typify the major races of man arose. We may suppose that when two human populations have been separated for several hundred generations they will have evolved along slightly different pathways due to the operation of selective forces peculiar to their respective environments. Among these factors cliamte and infectious disease may have been two of the most important, leading to marked differences in

the frequencies of genes in the two populations. For some characters during the course of human evolution certain genes have become fixed, whilst others may have been completely eliminated. But the final result, whether by loss or fixation or by establishing new equilibria of genes, is to make typical members of such populations quite different in genetic constitution from typical members of other populations.

Races, then, were born in the isolation of groups of man from one another. Though this isolation was never complete (even palaeolithic man must have sometime wandered far afield), the last few hundred years has seen an ever increasing tempo in the movement of people from one part of the world to another so that today the races of man stand confronted and we must find answers to the social and biological problems involved.

Though the physical differences between races, such as skin colour or hair forms, are frequently the points on which attention is focussed, they only complicate the predominantly psychological basis of inter-group hostility. However, there are many other questions related to the biological difference between races which require further study, if only to clarify claims by some who believe that race-crossing may be harmful, or by others that race-crossing may be beneficial.

We can answer such questions with varying levels of precision. In the first case, where it is know that populations differ with respect to a trait controlled by a gene present in one population, but absent in the other, we can give an exact answer to what happens during the course of mixture between the two populations, with respect to that particular trait. For example, in the White Australian population the rh-Ve gene has a frequency of about 13 per cent, and about 10 per cent of marriages will be between women who are Rh-Ve and men who are Rh+Ve.

Such unions are potentially capable of producing children with haemolytic disease of the newborn, sometimes leading to stillbirth, or if the liveborn child is untreated, to severe mental impairment. New methods of treatment being developed at present suggest that we can prevent this serious disease in new born infants by injecting Rh-Ve mothers with a special gammaglobulin preparation after the birth of their first and subsequent Rh+Ve children.

Many populations in the world, Aborigines in Australia, New Guineans, Chinese and Japanese do not possess the Rh-Ve gene, so that crosses between such populations and Europeans will reduce the incidence of this gene in the European population in proportion to the extent of the race mixing which takes place and consequently there would be also a reduction in the incidence of haemolytic disease of the newborn. In this instance, whether race-crossing is beneficial or harmful depends on which side of the fence one is standing to view the problem. On the European side the effect will be beneficial, a lowering in incidence of disease and a reduction in expensive medical procedures necessary to treat or combat it. On the other side, however, Aboriginal, Chinese, New Guinean for example, the effects of introducing European genes into their population will result in introducing a new specific disease among children which will require a sophisticated medical approach for its diagnosis and treatment.

At a second level of precision we can inquire into the effects of race-crossing as measured by reasonably objective standards of general biological fitness among the offspring, for instance weight at birth, frequency of congenital malformations, incidence of morbidity and mortality, etc., of the children born to racially different parents.

Such information is often difficult to obtain on a

scale sufficiently large to permit adequate statistical analysis or under conditions where due allowance can be made for the effect of environmental variables. For example, a recent study by Propert, Edmonds and Parsons has shown that in birth weight and growth during the first two years of life, half-caste children in Western Australia are midway between values for European babies and those for full-blood Aborigines. We do not know, however, to what extent this intermediate pattern of growth is due to genetic causes or to the social factors affecting half-caste babies. Such evidence as we have at present suggests that social factors are probably very important.

One of the most careful studies of this kind was carried out a few years ago by Morton and his colleagues in Hawaii. The population of Hawaii has several parental populations; Caucasian, Negro, Filipino, Japanese as well as Hawaiian itself. Moreover, considerable crossing between these groups has occurred under conditions where good records and observations are possible.

Morton's study highlighted several minor results of great interest. For instance, the frequency of dizygotic or fraternal twinning, is less for Pacific populations than for Caucasians, and in crosses between them a high rate of fraternal twinning behaves as a partially recessive maternal factor, independent of the paternal race. Equally interesting is that the high male sex ratio characteristic of Koreans, appears to persist in Hawaiians as a character passed on from male to male. Other specific differences concern certain congenital malformations, particularly spina bifida, harelip, clubfoot and polydactyly and these differences may be partly genetic in origin. Spina bifida it may be noted, is more common among Japanese in Hawaii than it is in Japan itself.

The major result of Morton's study may be summarized as follows: "First generation hybrids between races in man are

intermediate in size, mortality and morbidity between the parental groups." and Morton concludes "At the present time human populations do not represent co-adapted genetic combinations which are disrupted by outcrossing." In other words, the study was unable to reveal any overall harmful biological effects from race-crossing in Hawaii.

The third level of precision concerns the effects of race-crossing on physical appearance. We may quantify particular traits, as our Chairman has done for skin colour, and attempt to predict the amount of segregation of this trait in future generations. But we can go very little beyond this except to state that for many body measurements and non-metrical traits, hybrids will have characteristics intermediate between that of the parent populations. But for many traits we do not have sufficient information on their mode of inheritance to predict the behaviour in future generations. Even the study of skin colour inheritance in crosses between white and black Australians is not adequate to enable us to say how similar the situation is to such crosses between Europeans and black Africans. However, let me hasten to add that in our assessment of the social acceptability of such crosses we depend on a highly mutable sense of aesthetics which is much more susceptible to change than are the biological aspects of the traits themselves.

Let us consider now in detail another aspect of human variability, i.e., the difference between individuals within a single population. Some of these differences are obvious, such as hair form and colour, stature, anatomical deviations, etc., but others are cryptic and can be detected only by laboratory investigation. Among the latter differences are an increasing number of traits such as blood groups, serum protein and enzyme groups, all of which are inherited in a simple manner and to which I shall return in a moment.

Some of the detectable variation in man, both of the readily observable and cryptic kind, is due to environmental modification of the genotypic potential of the individual during the developmental period. Thus stature is controlled by one's genotype, and by a complex of environmental factors including the quantity and quality of food and exposure to infection. Mean height varies with social class, position and number of children in the family, decade of birth and whether born in a rural or urban environment as well as on genetic endowment. Similarly, mental attributes such as I.Q. also are affected by complex social environmental interactions and we still have no precise estimate of the range of variation in either stature or I.Q. which is determined by one's genes.

However, much of the genetic variation in man is little affected by the environment. It is due to genes which either in single or double dose produce specific alterations in form or function in the person concerned and I wish now to give some attention to the social implications of this type of specific genetic variability.

In a recent catalogue of man's genes, Victor McKusick has listed more than 1500 genetically determined variations. Most of the variations listed are associated with deviations from normal funtion, placing them in the category of diseases. Many of them are rare, but others are sufficiently common to add up to a sizeable cost in terms of human suffering. If we added together the total cost to the community of its severe genetic deviants, e.g. those with diseases such as muscular dystrophy, Huntington's chorea, or Leber's optic atrophy, Down's syndrome, cystic fibrosis, phenyl pyruvic amentia, haemophilia or Klinefelter's syndrome and that component of low grade mental deficiency, congenital malformations or congenital deafness which is due to genetic factors, the figure would be high

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enough to make even the most budget-wary government wonder whether it was adequately supporting research in the field of human genetics.

Some of the disorders mentioned above, namely Down's syndrome and Klinefelter's syndrome, are due to aberrations in the distribution of chromosomes during the formation of the male or female germ cells. Recent studies have indicated clearly that such aberrations are far more common than previously thought, affecting about 3 per cent of all pregnancies. Fortunately perhaps the vast majority of such chromosomal changes result in spontaneous abortion, but it is well to remember that part of the variability in the population at birth is due to improved social and medical conditions which permits pregnancies to continue to term which formerly would have resulted in early abortion.

There is another group of disorders, relatively common in our society, which raise interesting though at present unsolved problems in relation to their genetic basis, and the significance of their contribution to human variability. Diabetes is an example in this category. This is a common, extremely important disease which for many years was thought to have a simple genetic basis, but which now appears to be the result of a complex interaction between environmental and multifactorial genetics factors giving rise to a spectrum of susceptibility to the disease. It is possible that in the early stages of diabetes it is not just a deficiency of insulin production but in fact is an excess of insulin production which gives rise to the production of insulin antagonists, or alternatively the disease is due to abnormalities of small blood vessels, an abnormal insulin molecule or an endocrine imbalance involving the pituary and adrenal glands. Eventually we may have clarification of what combination of these and or other defects render the individual susceptible to diabetes. However, as Neel and Schull have pointed out recently, even if

genes at three or four loci are involved in determining susceptibility to diabetes, for a disease as common as diabetes the genes concerned must individually have frequencies which cannot be maintained by recurrent mutation. In other words they are polymorphic, and this raises the question which I wish now to discuss in more detail.

During the last few years we have witnessed an explosive increase in our knowledge of genetic polymorphism in man. In an unbiased sample of human enzyme systems a recent study in England has shown that 30 per cent of these systems in normal persons are polymorphic, the variations being controlled in a simple genetic manner independent of any environmental factors. This estimate of the extent of polymorphic variation, because of the manner in which the tests were performed, is clearly an underestimate. It seems likely that something of the order of at least 50 per cent of the body proteins show polymorphic variation, and this includes not only enzymes but antigenic characters on cell surfaces as well as transport proteins such as transferrin and haptoglobin. The random combination of these polymorphs assures that each one of us is not only different in appearance and in the idiosyncracies of speech, gait and personality, but also biochemically.

What is the significance of all this variability, which though it had its origin in mutation, is too frequent to be maintained by mutation pressure. This is a fundamental biological problem, for it concerns not only man, but other animal species as well to probably about the same extent.

Theoretically, various possibilities can be suggested for the existence in a population of any one of these polymorphic systems. The best known model, which has preoccupied our thinking for many years until recently, is that the person who is heterozygous for the two types of gene in the population

enjoys some selective advantage in comparison with persons who are homozygous for one gene or the other. The best example, indeed the only one for which we have sufficient evidence at the moment, concerns populations living in highly malarious regions in Africa. Here, persons born with the heterozygous combination of the haemoglobin S gene with the Hb A gene have a significantly greater chance of surviving to adulthood than do the homozygous individuals, and also a significantly reduced chance, as adult, of dying from the most severe form of the disease. The study of other biochemical polymorphic systems in man, however, has so far failed to yield convincing evidence of a similar kind. Indeed, our Chairman and his colleagues have pointed out recently the extreme difficulty of obtaining such evidence in human populations except in those cases where the selection effect is very striking.

Other possibilities may also be entertained. Some of the polymorphisms in man may be due to the fact that a mutant gene is slowly replacing an older one because of some slight selective advantage conferred on persons carrying the mutant form either in single or double dose, when compared with persons without it. Such selective advantage need not be very great to effect a significant change in gene frequency of a population over the time interval of human evolution. It is unlikely that such effects can be measured directly in living populations, but some polymorphisms show distributions which suggest that they may be due to gene replacement of this kind, and I have shown recently that some polymorphic systems in man can be used to estimate the time at which racial groups diverged from one another.

Other mechanisms are theoretically possible. Gene combinations which now appear to be selectively neutral, may not have been neutral under either different environmental

conditions or under different gene frequencies.

However, the obverse to this argument must also be considered. There may well be combinations of genes which had attained stable equilibria under conditions suitable for primitive man but which are now at a selective advantage or disadvantage in our increasingly population-dense, urban environment.

Finally, we must also examine the possibility of interaction between various polymorphic systems. The existence of a polymorphism at one loci, maintained by a complex set of variables in the environment may well have an effect on the responses of the organism with respect to another locus. For example, we know that foetal loss may occur because of a mother carrying a foetus which is incompatible with her ABO blood groups. Similarly, she may also become immunised by a foetus which is of a different Rhesus blood group to her own, and such a foetus may be stillborn, or if liveborn but untreated, may be severely mentally retarded. The severe effects of this latter response however, are reduced by incompatibility in the ABO blood group system. Indeed, Rh-Ve women married to an Rh+Ve husband will almost never become immunised against the Rh system if her ABO blood groups are incompatible with those of her children. More complex interactions probably exist and intensive study during the next few years may begin to uncover some of these.

At this stage, let me summarize what I have discussed so far about the variability of man and then examine its social implications.

Man is polytypic, the result of evolutionary processes operating in disperse populations over long time intervals. Within single populations, however, Man is also very diversified as a result of a highly variable genetic constitution ~~interacting~~

interacting with variable environments. Man's genetic constitution can be categorised into two main components - one component due to rare mutant genes, some of which impair the function of individuals carrying them so as to produce diseased states. The other component dependent on the presence of a large number of genetically polymorphic systems, asserting themselves so that each one of us is biochemically unique. Some combinations of polymorphs, however, are much more common than others and it may well be that certain of these combinations are more advantageous than others in certain environmental situations, whereas other combinations are more advantageous in different environments.

Let us pause for a moment now to consider the problem of the human environment. When we talk of the evolution of human races as a response to living in different environmental situations most of us have been conditioned to think of fairly broad uncomplicated situations, of palaeolithic man living in the savannahs, the steppes or the tropical rainforest or in the caves of Europe during the interglacial and postglacial periods: as primitive hunting and food gatherers, as shifting agriculturalists or settled neolithic farming communities. The situation must always have been more complex than this, and although certain dominant environmental factors, such as intense sunlight or arctic cold, may have operated to evolve certain gene combinations which became fixed within populations living in these environmental limits, there must in all situations have been sufficient environmental variability to have permitted genetic diversity to persist as well. This becomes more obvious when we look at the contemporary scene.

Man, more than any other species, through the development of language and culture has created an environmental diversity which today is unparalleled in its complexity and in its feedback on the genetic mechanism. For in eating, loving, working and

playing our society can accommodate as well as generate a remarkable range of physical and mental variation. Physical conditions alone vary from undernutrition to gross overnutrition; from overcrowded slums to extreme isolation; from sub-arctic cold to tropical heat. The psycho-social environment is even more complex. The megalopolis offers the greatest range of such environments, but even the rural town and village has a number of environmental niches differing in the demands which are made on persons in them. Finally, the family itself is a complex structure demanding different capacities in the fulfillment of the roles played by its members. The wife needs qualities differing from the husband; an only child may well need mechanisms for socialisation different from one born into a large sibship.

Bearing this complexity of the environment in mind, we realise there is no simple answer to our initial question whether the genetic diversity of man is a social asset or social liability.

The majority of the clear-cut gene differences for which we have information produce disease states in either single or double dose, the social costs of which are relatively easy to compute, at least in financial terms. Polymorphic variation in healthy persons, however, is more difficult to evaluate. At present, as I have stressed already, we have no inkling of the mechanisms which maintain such polymorphisms in the population and only intensified study can lead us to even a tentative solution. It has been a common concept in recent years that the genetic diversity of man is a biological safeguard which enables man to adapt to the wide range of environmental situations of the kind enumerated above. The argument generally adds that it would be folly to attempt to make man genetically uniform, for in his diversity lies protection against unforseen challenges from the environment in the future.

The argument is attractive, but is intuitive only and

can be supported by no real evidence. Our most urgent need at the moment, therefore, is a vastly greater knowledge of the genetics of man than we now have, and I would suggest that the real liability of man's genetic diversity is the need to understand it more fully.

At the level of simple genetic defects medical research must be stepped up to exploit promising leads in controlling the basic biochemical defects where these are known, as in phenylketonuria, or to discover those biochemical defects where they still elude us. We must explore further the possibility of precisely correcting the defects in the DNA of the germ cells, or preventing the conditions which lead to chromosomal abnormality. Remote though this may seem at present, it is perhaps no more fanciful than the idea of reaching for the stars seemed two decades ago; it may indeed cost far less.

In a world in which environmental situations are likely to change rapidly it is important to be able to identify more accurately than we can do now, genotypic combinations which are likely to be at risk in any given situation. This applies not only to the obvious utility of being able to identify those genotypes for example, which are likely to respond unfavourably to high cholesterol content or high carbohydrate content in the diet, but also to identify those genotypes which are likely to respond unfavourably to psychological stress factors in certain environmental situations. Moreover, as we learn not to take for granted the limits of human adaptability set by the range of man's genetic endowment we may move forward to more meaningful attempts to engineer not only our physical but also our psychological environment.

In the past we have been content to allow man to find his own level of adjustment. The evidence indicates that this policy has resulted in a high cost to society as a whole, for

the failure rate has not been insignificant. Now we need a concentrated, urgent study of the biology of man, his genetic endowment, its response in relation to the environment, and its possibility of control. Such studies have begun already but need to be developed and supported so that in the remaining decades of this century we will be able not only to exploit the fundamental knowledge we have now about the structure of the gene, but to add to it for the full benefit of man in modern society.