A GENETICIST'S WORLD

Inaugural Lecture of the Professor of Genetics delivered at the College on March 14, 1967

by

J. A. BEARDMORE
B.SC., PH.D. (Sheffield)

UNIVERSITY COLLEGE OF SWANSEA

UNIVERSITY COLLEGE OF SWANSEA

A GENETICIST'S WORLD

Inaugural Lecture of the
Professor of Genetics
delivered at the College
on March 14, 1967

by

J. A. BEARDMORE
B.SC., PH.D. (Sheffield)

A GENETICIST'S WORLD

AN inaugural lecture serves at least two useful functions. In the first place, it permits the members of the University community to examine the individual whom they have chosen to designate Professor of whatever discipline it may be. For the individual himself, however, it presents the type of opportunity which appears rather rarely : that of being able, before a necessarily captive audience of non-specialists, to discuss his subject and its origins, and to bring forward points of view of a more general nature. Some of what I have to say may strike you as mildly philosophical or ideological in nature, but these are also reasons why genetics is an absorbing subject.

As many of you will know, Genetics as a discipline began at the turn of the century when the significance of a paper written by an Augustine monk, later abbott, from Brunn, thirty-five years previously, was recognised for the first time by others. Independently, de Vries in the Netherlands, Correns in Germany, and von Tschermak in Austria wrote in the scientific press of their confirmation of the principles discovered by Gregor Mendel, working with the pea plant.

These principles distinguishing clearly for the first time between the units of inheritance and the outward manifestation of those units, or if you like, between gene and character, laid the foundation of the science of Genetics.

Much has happened since then, and I could have chosen to try to present to you a potted history of subsequent developments. Attractive as this might be to some, it would demand a good deal of technical explanation, and for this reason I have chosen not to attempt to do so, but to try to illustrate some of the highlights, some areas of excitement and controversy, problems for the future, and generally to try to describe why doing Genetics is fun.

The first topic that I would like to discuss is that of the nature of the gene itself. In this we see perhaps most clearly the essential unity of biological processes. In all

organisms which have been investigated, the genetic material, that is, those elements which are inherited by one generation from the previous generation, turns out to consist of either desoxyribonucleic acid (DNA) or, in a few forms, the very closely related ribonucleic acid (RNA). A gene is quite simply a message or piece of information, and the message is written in a code. What precisely the meaning of the message is I shall discuss a little later.

The fact that all organisms use DNA in itself suggests that life had a unitary origin, and may also indicate that life as we know it has a DNA system, *not* because it is the best of all possible systems, but because it was the first to arise. I mention this point because, until less than twenty years ago, most people thought that genes were protein molecules. This was, in a way, quite natural, and one of the reasons why this belief was so common was that characteristically the bodies into which genes are organised—the chromosomes, which are constant in form and number for a given species—consist of a complex of DNA and protein. Biochemical knowledge has advanced a good deal since then, but it seems to me entirely possible that we are still relatively ignorant of other molecular ways in which genetic information could be encoded. It would, for example, be exceedingly dangerous to suppose that life elsewhere in the universe (in my view by no means a remote possibility), must have the same system or a less efficient means of transmitting genetic material. A few years ago, quite a lot of fuss was made, and quite properly, about possible contamination of other planets by organisms brought from Earth by space vehicles. Such is the mass egocentricity of man, that little attention was paid to the far more dangerous possibility that Earth could be infected by organisms wittingly or unwittingly brought back from other worlds, and that these forms of life might be more efficient than those here, perhaps because of a different system of genetic coding.

But to return to the nature of the gene.

In the last fifteen years, a vast amount of work utilising the rapidly breeding, morphologically simple, bacteria, fungi and viruses has enabled the nature of the gene to be determined more precisely. The classical genes of Mendel and his successors were shown, after all, not to be unitary, but to consist of subunits resolvable by genetic recombination. This posed great problems, for it was not at all clear at this point what the limits and size of a gene might be. Quite early on it had been shown that the chromosomes are the material basis of the hereditary material, and that the manner of organisation of genes in chromosomes was a simple linear situation, such that for a given organism, gene X would be located and was always locatable between gene P and gene Z, and further that the relative distances P—X and X—Z would be estimated with some accuracy on a genetic scale, and in some cases on a more absolute scale.

Perhaps I might very briefly indicate to you the nature of the giant molecule of DNA in order better to discuss this point. The structure of the molecule is something like a spiral staircase with two parallel strands running vertically, and between them linking elements which you may like to call steps. The structure of the double strands is that of an alternation of sugar and phosphate molecules, and this alternation is perfectly fixed and regular for the whole length of the strands. The linking units, however, show variation, and each consists of two nitrogen bases. There are four bases which we can call A,B,C and D, and they are always found combined as A—B, or C—D. Thus if we read the base composition along one strand as B C C D A B, we know automatically that on the other strand it must be A D D C B A. This is the famous Watson-Crick model, a landmark in modern biology.

This variation of nitrogen bases from point to point along the DNA does show some parallelism with the linear arrangement of genes along chromosomes which I have already mentioned, but it is at first sight not at all

obvious what the specific relationship is. The clue to the resolution of this point was the realisation that the primary action of a gene is in determining the structure of a protein. These are, of course, the so-called building blocks of life, and all organisms consist to a greater or lesser degree of proteins and, in particular, the enzymes needed for all biochemical conversions are proteins. The form of protein molecules varies greatly, but they all consist of smaller units called amino acids, linked together in a more or less linear way. There are 20 different amino acids used in making proteins, and this figure permits some degree of speculation about the nature of the genetic code. Four genetic elements have to represent 20 character elements ; clearly a one to one relation will not work, using two genetic elements $4 \times 4 = 16$ elements can be coded for and using three elements $4 \times 4 \times 4 = 64$ elements can be coded for. This argument alone suggests that at least a triplet of bases is required to code for an amino acid, and there is good evidence that this really is the case.

By using special agents of mutation, that is chemical or physical factors causing more or less permanent and constant change in the hereditary material, it has been possible to demonstrate the validity of this statement. Use of the substances known as acridines on DNA adds or removes bases, usually singly, from the molecule. By using bacteriophage able to grow on a particular bacterium and treating with an acridine, bacteriophage mutants were obtained which were unable to grow on this host, although they could be kept by being cultured on others. The sites of mutation could then be localised in the genetic map of the bacteriophage by appropriate crosses. A new treatment of each mutant with acridine then followed, and new types were picked up which had mutated back and showed the ability to grow on the original host. By an elegant series of crosses, Crick and others were able to show that two sorts of mutants had been obtained. The first type had 1 base extra (or+),

the second 1 base less (or —) ; in the first case, back-mutants were then + —, and in the second — +. Combinations of 3 +'s and 3 —'s also in general produced the normal growth pattern. This demonstrates that the code must be read in threes, and that a shift in the way the bases are read (the reading frame) is produced when bases are added or removed.

An obvious question is, if you have 64 possible code words, and only 20 words which need to be coded for, what function have the other 44 ? The biochemists and molecular geneticists together have been very busy working out this problem, and it turns out that the code is very highly degenerate, that is, several triplets in the DNA can correspond to a single amino acid in the ultimate protein. Strictly speaking, we should say a section of a protein since where, as in haemoglobin, we have a protein molecule built up of several large polypeptide units, one gene is needed for each of these large units.

Fortunately, not all of the possible triplets correspond to amino acids, for this would mean a situation in which the message would have no beginning and no end. A sensible and useful message requires punctuation, and the genetic code includes at least three triplets which may be concerned with punctuation though precisely how they work is not yet clear.

The account that I have so far given does not explain what it is that enables a particular triplet, say BBC, in a DNA strand in a chromosome to specify the particular amino acid, say lysine, in a given protein, but merely the correspondence. The functional connection is more complex, and I do not want to discuss it in any detail but merely to say that probably only one of the two strands of the DNA is the information strand, that this produces a complementary single stranded RNA, or if you like, a negative of itself, and that this, using a gamut of the cellular machinery is used as a sort of matrix in the assembly of the translated positive protein chain.

The code seems to be universal, that is, that the triplet BBC codes for lysine in bacteria, frogs and mammals, but there are interesting indications that even at this level of molecular mechanism evolutionary divergence has taken place. For instance, three RNA triplets coding for the amino acid serine recently examined by Nirenburg and co-workers show relatively different quantitative effects in three different species when tested in an artificial system. These differences if confirmed in the living system are likely to be of some adaptive significance, and indeed a most promising field of study for the future is that of examining products of evolutionary processes on this molecular level.

It is a pity that the enormous strides made in our genetical knowledge through the use of microbes have led in some quarters to an intellectual arrogance which assumes that microbial genetics is the only really worth while area in the discipline. In my view, this is demonstrably untrue, when we look at the excellent work going on in a whole range of other organisations, but perhaps even more importantly it ignores the fact that a bacterium is in a general sense an abnormal organism. The average organism is morphologically complicated, has a double set of genes compared with the single set of the bacteria, and has an extremely different type of breeding system. Among the great problems which face us for the future is that which has to do with the ways in which genes act during development, what are the molecular switches which determine that here an eye shall develop, and here a limb. Tissue and organ differentiation is one of the great mysteries of biology, and will require to be attacked in diverse ways using many techniques and different organisms.

Not the least interesting results of the microbial work have nothing to do with the nature of the gene, but concern rather the population or species. These are the breeding systems by which genetic variability is, to some extent, maintained. In an organism which is limited to

wholly asexual methods of reproduction, each existing genetic constitution can be reproduced quite faithfully, but no new types can arise through reshuffling of existing types to give recombinations. It used to be thought that the bacteria and many fungi were asexual, and that they would therefore be wholly dependent upon mutation to provide new genetic types. However, whilst mutation is probably adequate for much of the time in these organisms, it is significant that in all groups of microbes which have been really critically examined, evidence of sexual-like processes has been uncovered. These processes include that of transduction, in which a virus transports from one bacterial host cell to another a piece of a bacterial chromosome which, by substitution for a corresponding piece of the new cell, furnishes new genetic potentialities to that call, and, more importantly, to its descendants. Some viruses, too, are able to produce recombinant types in their own genetic endowments by a highly sophisticated kind of pairing and exchange process during the multiplication period within the host cell. This recombination will, however, only occur if two different genetic types are infecting the same cell.

These processes and others, such as conjugation in bacteria where a strain of one mating type may receive a variable fraction of the single chromosome possessed by another mating type, are not strictly sexual. The organisms which possess them, however, benefit in a similar way that sexual organisms do from the effects of these processes in promoting variability in the collective genetic endowment, the gene-pool, of the species and we call them para-sexual.

It has often been said that the human species is unfavourable for genetic work, and in the sense that the controlled matings possible with other organisms are not available, this is true. It is, however, a striking fact that man has provided the best single example of the effect of a single gene worked out at all levels from that of the molecule to that of the population. The blood pigment,

haemoglobin, which transports oxygen round the body is known in a variety of forms. One of these, termed sickle because of the effect produced on the shape of the red blood cells which carry it, is found in quite high frequencies in various parts of the Mediterranean area and Africa. The difference between normal and sickle haemoglobin is very simply genetically determined, being due to a single gene. A double dose of the gene Hb^A ensures that all haemoglobin of the individual concerned is of normal type (A). A double dose of Hb^S ensures that all the haemoglobin is of sickle (S) type, and this produces early death from anaemia. An individual possessing an Hb^A and an Hb^S gene, however, possesses both types of haemoglobin, and suffers from a rather mild anaemic condition. With such a situation, it would be expected that the frequency of the Hb^S gene would be vanishingly small, since Hb^S/Hb^S individuals do not reproduce and the population would be losing Hb^S genes continually.

In some populations, however, as in East Africa, the frequency of the gene is such that up to 35% of the individuals carry it. The explanation for this seeming

Genetic Constitution	*Frequency %*	*Fitness*	*Total Fitness*
Hb^A/Hb^A	64	0.8	51.2
Hb^A/Hb^s	32	1.0	32.0
Hb^s/Hb^s	4	0.0	0.0
			83.2

Total fitness for a population with only Hb^A=80
Difference = 3.2 or 4%

Table 1. The effect on fitness of the gene for sickle haemoglobin in a malarial environment.

paradox is to be found in the fact uncovered by Allison and others, that the heterozygotes carrying the single dose are superior in their young years to either type of homozygote in their resistance to malignant tertian malaria, a disease endemic in this area.

A simple calculation (Table 1) shows that despite the loss of the Hb^S/Hb^S individuals, it is worth while to such populations to possess this gene to secure an increase in overall fitness of about 4% over a population without the gene.

There are two lessons we can learn from this population level consideration. The first is that a load of genes producing deleterious or even lethal effects in double dose, may still be, biologically speaking, worth carrying. Secondly, the notion of the "fittest" is entirely dependent upon the conditions under which the fitness is examined. When the selective factor of malaria is removed, the heterozygote is no longer the most fit, and the Hb^S gene will gradually disappear from the population, as indeed is happening in descendents of these peoples living in the United States, where there is no malaria.

Proceeding towards the molecular level, elegant analyses by Ingram have shown that the only difference in the structure of these two haemoglobin molecules resides in one section, peptide 4 of the β chain, where at one position the amino acid Glutamine is substituted by Valine ; no other changes are observed and the α chains are entirely similar in both haemoglobins. A substitution of about one third of one per cent of the structure of a molecule has, we see, very profound consequences. But this example also tells us more. In haemoglobin, entirely different sites of mutation are found to affect the α and β chains, and this is critical evidence for the view that the synthesis of an enzyme or other protein may depend upon assembling the separate and inactive products of independent genes into one active molecule.

Having looked very briefly at the nature of the gene, we may ask the question : do all genes work all the time, and

if, they do not, what controls them ? The answer to the first question is no. Genes can be seen to have periods of activity correlated with certain developmental stages in, for example, the giant chromosomes of Diptera. As to the controlling functions, very little is known except that it seems likely that there are so-called operator genes, sensitive to messages (at present of unknown quality), and that these genes act by switching on other genes to start their synthetic activity, and by switching them off. Although an elegant theory of gene control has been developed, the evidence is at present insufficient to sustain it on every point, and since there are many complexities, it does not lend itself to discussion before such an audience. I should however say that this is an area in which developmental biologists, cytologists, virologists and students of neoplastic disease should all be vitally interested.

We know nothing about the first genes, and we do not therefore know how the typical genetic constitution of, say, a mouse reached its present form. Some facts are, however clear. Duplications, that is repeated sections of chromosomes, are common. The evidence for this comes from two sources. The giant chromosomes of some flies have a differentiated pattern not possessed by other chromosomes, and duplicate sections, as shown in Figure 1, are common. Amino acid analysis of, for example, the α and β haemoglobin chains of man also shows this. If we accept the deletion postulated at positions 8 and 9 in Fig. 2, eleven of the eighteen bases agree in the two chains, and of the seven which do not, the genetic change involved is only one base in six cases. However, the α chains of man and gorilla are practically identical (no more than two different), as are the β chain (no more than one). This therefore indicates that the presumed α—β duplication antedates the evolutionary bifurcation responsible today for the presence of gorillas and man. Such comparisons in what may be called palaeogenetics are, of course, of great use in deriving

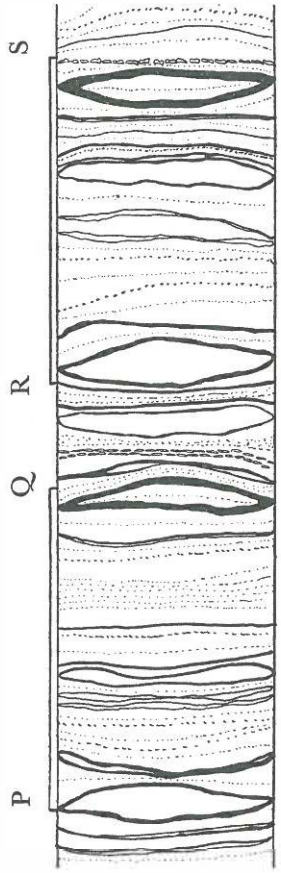

Fig. 1. Duplication of a chromosome segment. The sections P—Q and R—S show very similar patterns of banding indicating duplication of chromosome material at some time in the past.

						8	9											
α chain	Ala	*Ala*	Try	Gly	Lys	Val	*Gly*	Ala	His	*Ala*	*Gly*	Glu	*Tyr*	Gly	*Ala*	Glu	Ala	Leu	*Glu*	Arg
β chain	Ala	*Leu*	Try	Gly	Lys	Val	*Asn*	—	—	*Val*	*Asp*	Glu	*Val*	Gly	*Gly*	Glu	Ala	Leu	*Gly*	Arg

Fig. 2. Amino acid composition of corresponding regions of the α and β chains of human haemoglobin.

evolutionary pathways, but great care must be exercised in discussion as to whether changes of amino acids are of adaptive significance or not. Because the *in vitro* activity of many proteins seems not to be greatly affected by substitutions or deletions in the molecule, some people, particularly amongst the biochemists, are inclined to regard these changes as essentially random rather than directed. I would not agree with this. One must have evidence, of course, but it seems likely to me that since the resolving power of natural selection is extremely great, most changes of this sort *are* adaptive. One way of attacking this problem is to examine the sort of changes which take place on a time scale, which can be tackled in the laboratory, and studies of the proteins of incipient species and recent species could be most rewarding in this connection.

In his inaugural lecture, Professor Oliver quoted in a quite different context the words of Spate, that "environment is not the answer to everything". This statement is highly relevant to the point I would like to bring before you now. The old struggle of nature v. nurture, the question whether inborn qualities or outside influences are the determinants of human personality, and hence achievements, is still being fought. There are those who, for reasons of ideology, believe not only that all men are born equal, but that all men are equally endowed. Of course, the statement that all men are born equal is not in any way scientific ; it represents a political or moral viewpoint not readily subject to scientific analysis. To pretend however, that the real differences between individuals either do not exist, or if they do, are attributed to differences experienced in the environment, is a standpoint which is open to critical comment. The geneticist knows that practically any character, be it the height of pea plants, milk yield, or intelligence in man, will be under some degree of genetic control.

The question which *should* be put is how much of the observed differences between individuals can be ascribed

to genetic causes, and how much to nongenetic. For characters like the blood group substances in man, no effect of environmental factors can be demonstrated, whilst for characters like height and weight, or seed yield in crops, very considerable effects can be present, due, for example, to differences in the level of nutrition.

The definition of Genetics, due to Bateson, is "the study of heredity *and variation*" ; even in 1906, he realised quite clearly that if one did not try to establish what types of variation existed, one stood little chance of progressing further with genetic analysis. It is, of course, particularly in relation to man, and specifically to his personality attributes, that the nature/nurture argument gives so much difficulty. There are, in fact, with characters such as intelligence, so many steps removed from the primary working of the genes, no *a priori* reasons for attributing the major share either to one or the other. Appropriate use of parent/offspring correlations, identical and fraternal twins and so on, will give us an idea (Table 2) of the relative importance of genetics and environmental determinants for a few characters.

I.Q. (man)	70
Egg weight (poultry)	60
Milk yield (cattle)	30
Age at puberty (female rat)	15

Table 2. Percentage of observed variability that can be attributed to genetic differences between individuals. These may be underestimates, but are not likely to be overestimates.)

It is perhaps interesting to note that politically here, as in other connections, the extremes of right and left have a common bond. The mad racism of Nazi Germany, and

the reign of Lysenko for sixteen years (1949-65) in the Soviet Union, both suppressed objective investigation in favour of ideological dogma. The first was crushed ; and the second was toppled from within. In fact, it seems likely that the Lysenko doctrine denying any weight at all to genetic factors came into disfavour not because of a shift in ideological thinking, but because Lysenko could not deliver the harvests he promised. That the crop failures may have been due more to unforeseen climatic extremes than to any unsuitable strains is perhaps an ironic twist fitting to the story. As would be expected, although Genetics is once more a respectable discipline in the USSR, it will be a long time before it regains its former place.

Ideological struggles aside, in quantitive genetics generally, we are faced with problems of trying to decide how great a role the environment may play, and how great that of genetic factors. This is of great consequence in economic terms, since most characters of significance to the farming economy are quantitative. The term "quantitative" implies many factors operating, each of small effect, and we have a convention to speak of polygenes in quantitative inheritance since the number and location of the genetic factors in such cases is usually difficult to specify. Polygenes have always been something of a puzzle to those interested in gene action rather than genetic processes, and it has been a source of dissatisfaction that their working could not be brought easily into the same frame of reference as the genes of large effect, major genes. The way is now appearing more clearly. In the milk yield of Jersey cows, a classical quantitative character, about 10% of the observed variation from cow to cow can be ascribed to the presence of two alleles or variants of the gene controlling a transferrin (blood protein). The transferrin character is qualitative, the milk character quantitive. A milk polygene is a transferrin major gene.

It may be significant that the two forms of the

transferrin molecule are distinguished only by a very slight difference, probably that of a single amino acid. Use of electrophoretic techniques in recent years has demonstrated that most animals and plants possess a very high level of variability of this and other types, a situation which we call polymorphism.

In part, these polymorphisms can be explained on the basis of a superior heterozygote, as in the sickle cell case, for wherever the hybrid A/A_1 is at an advantage, all three genotypes A/A, A/A_1, and A_1/A_1 will continue to be represented indefinitely in the population. This is not the explanation for all polymorphisms, however ; other factors such as negative correlation between fitness and frequency in a population will promote polymorphism. Yet another type is that in which different gene-combinations are favoured in different places or at different times. Working with populations of fruit flies exposed to degrees of variation in temperature, two of my students, Mr. Long and Mr. Veeman, have recently shown that for two classes of genetic variability the differences between populations in uniform and variable environments are quite striking (Table 3).

Type of Environment	*Lethal Gene Frequency*	*Additive Genetic Variance*
Uniform	100	100
Regular diurnal variation	120	117
Regular monthly variation	119	109

Table 3. Relative genetic variability in similar populations maintained in uniform and varying conditions (uniform — 100).

These data demonstrate that even quite simple environmental variation has large effects upon the composition of the gene-pool, and conversely indicate that the more uniform the environment the greater the uniformity of the gene-pool. The long term implications of these data are simply that evolutionary potential is greater in populations which are not living under uniform conditions, for the ability to adapt to future changes is conditioned largely in higher organisms by the genes they possess now.

One consequence of polymorphism is that we shall expect to find natural selection promoting the growth of favourable interactions between the different types of morphs of the polymorphism. This is so because each morph will represent a part of the environment for all other morphs.

I would like to end this part of my discussion by arguing that we can extend the view that there is seldom, if ever, a single best genotype to the social scene. Just as biologically for a population, diversity is desirable, so for man, as I see it, diversity of culture in the broadest sense is good. Even those who see no harm in a uniform society must recognise that only an ecological approach allowing different social niches for different personalities can produce healthy results.

Another field of fascinating study which I would like to mention briefly is that of the genetics of behaviour. This is beset by pitfalls, because there are very large difficulties in measuring behavioural attributes, and partly because the latter, unlike say bodily dimensions, can be influenced by parents, siblings and others, through learning processes. One very curious feature of experiments in behavioural genetics is that in a cross between two inbred lines, genetically uniform but different in the offspring, shows greater variability for the character examined than either parental line. This is in striking contrast to morphological character, where the reverse situation is usually found. This variability cannot be of genetic origin, since although these hybrid (F_1) individuals possess a variety of genes, one

individual is genetically the same as the next. True differences between individuals will be seen in offspring of F_1 individuals mated together, and it is in this F_2 generation that on general principles one might expect the variance to be very large. In the cases I am discussing, however, the differences between individuals in the F_2 generation tends to be, if anything, smaller than that in the F_1. Mr. van Oortmersson working with one behavioural character in the mouse has recently been able to shed some light on what sort of causal basis this phenomenon may have.

The character he used was the fraying of paper strips for nest-building. This is not strictly a behavioural character, but the result of behaviour ; but it is exceedingly convenient to have a record on paper of the degree of biting and fraying of the nesting material. Both parental strains are very inbred, and therefore each strain is highly uniform genetically, though there are large differences between the strains, for example, in coat colour. Observations on the two parental strains and their hybrids showed that the variation in fraying behaviour between animals was significantly greater in the F_1s than in their parents. Further analysis by Mr. van Oortmersson showed, however, that the fraying values obtained in the F_1 cross were dependent upon the age at which the animals were tested. If younger animals were used, values resembling those of the A parent were found, whilst with older animals values more in the direction of the B parent were obtained. (The magnitude of this effect was sufficiently great to account for about half of the observed variance displayed by the F_1 animals).

The implications of these results are thought-provoking; the change in average behaviour with time is unlikely, because of the experimental design, to be due to any kind of learning process. What it appears to represent is a change in gene activity relationships in time, perhaps, though not necessarily, in dominance. If this is true, it suggests that sometimes in behaviour, just as normally in

differentiation, the activity of different genetic loci can vary in time, and that this may happen in such a way as to make it rather difficult to define accurately the form and value of the characters being examined.

Of course, there are many steps involved between genes and a behavioural trait, and in most cases we have no idea what the genes are primarily concerned with. In a few cases, this is possible, in untreated phenylketonuriacs for example, the average I.Q. is, I believe, of the order of 30 or so, and their behaviour is therefore different from the majority of the population. Here the action of the gene is known, a defective version of the enzyme, which converts the amino acid phenylalanine. Quite a lot is known about the toxic action of the phenylalanine and phenylpyruvic acid which accumulates. It is instructive to ask how far other socially important characters may be influenced by genetic variability. For example, criminality has long been thought to have something of a genetic basis, though since crime correlates with broken homes, disturbed youth, overcrowded conditions, and other factors of human ecology, these have perhaps received greater attention.

One way in which cytogenetic research has helped in this connection is the recent work of a group in Edinburgh who have been working on the chromosome constitution of males confined in security institutions. The mechanism of sex determination in man and many other organisms is such that females normally have two X chromosomes, whilst males have one X and one Y chromosome. In the formation of reproductive cells, eggs normally receive one X, sperms either an X or a Y. Subsequent fusion of X egg plus X sperm gives a female zygote, and X plus Y gives a male zygote. Some individuals possess an abnormal number of chromosomes, and amongst these are the individual with one X and two Y's. These individuals appear to be present in prison populations at frequencies of the order of fifty times greater than their frequency in the general population. Clearly, this

particular chromosome abnormality at the very least predisposes to criminality (theft rather than violence, except when resisted). These would be types who turn up as black sheep, rather than being one of several in a family, because of the nature of the process of chromosomal non-disjunction by which they arise.

This finding, which I suspect will be followed by others of a similar sort, bears out very strongly my thesis that for biological reasons alone an ecological approach to social betterment is needed. The measures which will produce a useful citizen in one case, may fail miserably in another, simply because the raw material is biologically of a different quality.

I would like to close by referring to what may be called the new Eugenics. In the nineteen-twenties, there was a great deal of thinking and writing about the need for genetic improvement in the human species. A good deal of this was racist in outlook, and the *Herrenvolk* philosophy tended to discourage interest after World War II. In recent years, however, there has been an upsurge of new literature and discussion.

The reasons for this new activity are multiple, and some have their origin in the spread of automation and changes of social structure. There are, however, important stimuli from biology. The most important are :

1. the improvements in techniques for keeping tissues and cells viable in a deep frozen condition,
2. the knowledge that a nucleus containing one set of genetic information can be transplanted into another cell from which the nucleus has been removed,
3. the possibility of removing a fertilized ovum from one mother and allowing it to develop within the body of another,
4. increasing knowledge of the way in which mutation can be made less a random and more a specific event,
5. advances in the techniques of tissue culture.

All of these suggest ways in which the evolution of man could be directed. Nobel prize winner, H. J. Muller,

until his recent death, was an advocate of the Sperm Bank by which the genetic endowments of outstanding individuals (males naturally), could be preserved with the idea that for those women who so wished, the prospect of bearing an unusually gifted son or daughter would be created. There are at least three significant points of contention in relation to such proposals. The first in the ethical problem, which certainly will be considerable for some. The second problem is, who decides, and upon what criteria whose genes go on deposit in the deep freeze ; and the third and perhaps most serious is that, if the desirable qualities are attributes like intelligence, drive, creative ability and the like, if such a scheme were adopted we might, as I have suggested elsewhere, be tending to promote a caste-system with a genetic basis. The politico-social consequences of this could obviously be very serious. This is, technically speaking, a perfectly feasible operation at the present time—I do not think it should be dismissed as fantastic.

Some of the other possibilities which have been suggested for genetic betterment are dependent upon successful improvement and modification of techniques derived from work with other organisms. The use of chemicals like 5 Bromo-uracil, which can substitute specifically for the base thymine in the DNA, and by subsequent mispairing during replication cause replacement of adenine by the base guanine, offers some, if slight, hopes for being able to correct metabolic errors of genetic origin. Again, however, this seems to me to be beset with problems, the main one being that it seems most unlikely that we shall ever be able to change only one gene and no other in a living organism. A better way out would be to find the appropriate corrective in the environment, such as in the case of the phenylketonuriacs, where a diet free from phenylalanine practically compensates for the genetic defect.

Tests for detecting the carriers or heterozygotes of genes, which in double dose (homozygotes) produce

disease, obviously offer a good deal of scope to the eugenecist. If you wish to remove such a gene from a population, preventing only the homozygotes from breeding is a highly inefficient procedure, as Table 4 shows. The genetic load, that is the presence of concealed deleterious genes, that any population carries is partly a result of chance effects, like mutation, and partly of systematic effects such as natural selection favouring a range of different genetic constitutions. Clearly, if we wish to avoid increasing this load, we must endeavour to limit the use of those agents which increase the frequency of mutation, such as irradiation of various types. The load can never be reduced to zero, and probably we should not try to lower the frequency of many existing genes. Diversity of human germ plasm is just as valuable now as it has ever been, and the concept of a single ideal genotype implies, as I have already tried to suggest, a single type of milieu which is far from what the ecological structure of society is.

		0.996 A	0.004 a
0.996	A	AA	Aa 0.007968 1 in 122
0.004	a	Aa	0.000016 1 in 60,000

250 x more 'a' genes in heterozygotes than homozygotes.

Table 4. Distribution of a rare recessive gene (a) in a population (frequency of 'a' assumed to be 0.04%).

Finally, it is, of course, true that in future advances in medicine will permit more of the genetically handicapped

to survive, where in the past they would have died, and this will have the effect of raising the frequency of the genes responsible in the population. Not indefinitely, but to a higher level than previously. The affected individuals are the expression of the genetic load ; whether the load can be borne or not is not at all a geneticist's problem, but rather that of society as a whole. As I see it, if technological progress gives society the biological engineering required, the expressed load is reduced very considerably, and increasing dependence upon technical aids is, after all, going on all the time. There seems little justification for, say, discouraging sufferers from *diabetes mellitus* from reproducing on the grounds that amongst their genes are two which necessitate factories producing insulin and hypodermic syringes.

In the last fifty minutes or so, I have tried to describe to you something of the elements of genetics, some of the unsolved problems, and some of the manifold connections it has with other subjects. It is difficult to tell how far I may have succeeded in conveying to you something of the nature of my subject, but I hope that this talk may perhaps have helped you look, if briefly, through a window on to a Geneticist's World.

GOMERIAN PRESS, LLANDYSUL