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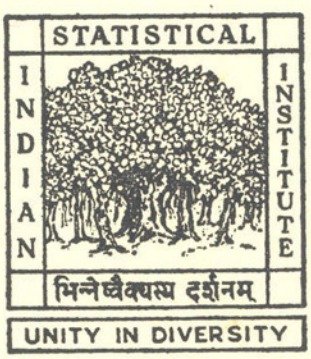

CONVOCATION ADDRESS

HUMAN GENETICS AND THE BIOLOGICAL FUTURE OF MAN

BY

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Professor S.N. Bose, Professor Mahalanobis, Dr. Rao,
Ladies and Gentlemen,

It is a fine tradition to have a Convocation address once a year on the Convocation day and to ask a foreign guest to deliver this address. Personally, I appreciate very much the high honour of being selected this year. I wish to address especially you, the young scientists, on whose behalf this Convocation is being held. You have completed successfully an important part of your scientific and professional training, and today, you will be awarded academic degrees.

I shall try to show you the central problems of my science, human genetics, as well as the practical impact of these problems not only for ourselves, but also, and still more, for the generations to follow us. These problems, I am hoping, should be of interest to you not only as thinking human beings, in general, but also as statisticians, as human genetics is a vast playing ground for statistical methods and reasoning.

Man develops from the impregnated zygote by intimate cooperation of the genes, which he has got from his parents, with manifold environmental factors. The genes contained in the zygotes of one generation might be looked at as a sample from the gene pool of the preceding generation. However, as this preceding generation consists of genetically different individuals, the sampling procedure would be at random only if all persons of the preceding generation would have exactly the same number of children, which is apparently not the case.

The sample of zygotes also changes its composition up to the time, when development of mature individuals has been completed. Some zygotes will already come to abortion during early pregnancy, for example, because they contain too many or too few chromosomes. Some others will contain a dominant mutation which causes early

death of a malformed child during the first years of life. Other genetic changes which do not interfere with life directly, might detract so much from vitality and performance of their bearers that they will rarely or never have children. An additional number of individuals will die during childhood or early adult life from infectious diseases, and another group, though perfectly healthy, will simply not marry or have no children for one reason or the other.

In the cases mentioned first, genetic factors are obviously responsible for the elimination of zygotes. In the last-mentioned examples, one would be inclined to suspect that elimination of zygotes is at random with respect to genetic factors. However, it was shown that even here genetic factors do have a certain importance in combination with the environment.

Wherever genetic factors have an influence on whether a zygote develops to a mature individual, and how many zygotes it will contribute to the next generation - one big power is at work which has directed human evolution up to now, and which will also determine our biological future: this is natural selection.

However, natural selection could not be efficient over a long time, if some other force would not continuously add to the rough material from which the fittest can be selected. This means: in order to maintain efficiency of selection, new genetic variability must constantly be created. Indeed, this variability is created due to sudden genetical changes which are called mutations. The mutation process is the second big power of evolution.

Investigation of these two powers, selection and mutation, is the main topic of human genetics and especially of human population genetics.

Now, my thesis, which I shall explain more in detail later on, is the following: the process of evolution, the results of which

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are the human beings we are facing at present, has not been finished. On the contrary, it is being in full progress, and due to the basic changes in almost all conditions of life brought to us by modern civilisation during the recent one hundred or two hundred years, genetic changes are expected to go on very rapidly. Due to this speeding up of evolution, not only beneficial possibilities but also serious dangers have to be faced.

At the same time, however, and for the first time in history, it occurred, as Huxley has put it, that 'the vast process of evolution, in the small person of inquiring man, has become conscious of itself.' This means that we are now able to investigate the evolution process empirically. Maybe that sometimes in the future, it will be possible to influence special aspects of it in order to promote positive tendencies or to prevent negative ones. However, as we are used to in medicine, a very careful and painstaking diagnosis has to precede any therapy. For this diagnosis, all information available has to be collected. Wild fantasies, such as have occasionally been uttered during recent years even by very famous geneticists, can only detract from the real problems, create uneasiness in the general public, and make the scientists untrustworthy.

I have said that human evolution has speeded up recently. What are the facts justifying this thesis? In order to find the answer, we all have to analyse the two main powers of evolution in man.

First, mutation frequency has changed, and there can be no doubt that under the conditions of modern civilisation, more mutations will occur than in earlier times.

Secondly, natural selection has also changed, but these changes cannot be brought to a common denominator.

What do we know in man about the mutation process and its changes? I shall sum up very briefly.

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Generally, genom and chromosome mutations, which means visible alterations in number or shape of chromosomes, are separated from gene or point mutations. The single mutational event is a chance event which cannot be predicted. If one observes larger number, however, a statistical rule emerges. Under the same internal and external conditions, spontaneous mutations have a constant probability which is called the mutation rate. In genom mutations resulting in anomalies of chromosome numbers, the rate will generally increase very steeply with the age of the mother, whereas gene mutations are more or less related to the age of the father. In most cases, gene mutation will only affect one single base in the DNA chain of the genetic material. Recently, we even have come to know that a base is very frequently, though not in all cases, replaced by a similar base, for example, a purine by another purine or a pyrimidine by another pyrimidine. But, of course, replacements of a purine by a pyrimidine and vice versa do occur, too.

Now, two important exogenous factors are known to increase the spontaneous, natural mutation rate: Ionizing radiation and chemical mutagens. The genetic danger due to ionizing radiation has been discussed very frequently during recent decades, and many experiments in animals, especially mice, as well as statistical surveys in human populations have been carried out in order to get an idea of the order of magnitude of this danger. While not all differences in opinion have been settled so far, we are able today to conclude this with some confidence: the additional load due to radiation, as observed today even in highly industrialised countries will increase the natural mutation rate by no more than a small percentage. This increase does not imply any <u>acute</u> danger for the future of man, but we have to realise, on the other hand, that we have to pay in the long run for our technical and especially for our medical progress with a certain increase of human ailment and suffering.

Much more complicated and almost completely unexplored as regards man is the problem of mutation rate increase due to chemical

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mutagens. As a part of the general industrial progress, man is synthesising continuously new chemical compounds. Many of them are being applied to human beings, either voluntarily, for example, as drugs or stimulants, or involuntarily, for example, food contaminated with insecticides. A good number of these compounds have become known as mutagenic by experimental research. For example, cytostatic drugs, widely used in tumour therapy, but at an increasing rate also in other branches of medicine, are strongly mutagenic in all organisms examined, and there is no reason, why they should not act as mutagens in man too. Many other drugs become known as mutagens in one organism or the other, including even caffeine, which is widely used as stimulant and is mutagenic at least in some micro-organisms and plants.

In order to find out which chemical substances are dangerous for man from a genetic point of view and, furthermore, which are the special conditions of this danger, and how it could be avoided; a carefully and comprehensively planned research programme is required. Experiments in mammals using genetic as well as cytogenetic methods have to be combined with statistical surveys in man. My institute in Heidelberg is presently trying to contribute to this problem.

To sum up, the spontaneous mutation rate has been increased due to ionizing radiation as well as due to chemical influences. This effect is disadvantageous, as it leads to an increase of genetically determined ailment and malformations. Especially because of our ignorance as to chemical mutagenesis in man, we have not yet been able to estimate the extent of this disadvantage.

Now, let us face the second big power of evolution, natural selection, which changes have to be noticed here? Reading in some older books, or asking some other geneticists, you will get a very clearcut answer to this question. The answer will be: mortality before and during reproductive age has decreased very

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strongly. This has led to a very definite relaxation of selection. Weaklings and unfit persons, who had been eliminated earlier, will now live and reproduce. This must lead to quick deterioration, unless energetic measures are taken very soon to prevent this. What about this argument? Is it correct? To say my opinion in advance: I believe that it is partially correct. Taken as a whole, however, it is a very big oversimplification. Reality is much more complex.

Sure, mortality in younger age has decreased considerably. In my country, Germany, only two hundred years ago, more than 50% of all newborn children died before having reached the age of 20. This figure is taken from a very interesting book published by Sussmilch in the middle of the 18th century, which is one of the classics of demography. At present, however, a newborn has a chance of more than 95% to reach the age of 20. Also in India, recent years have witnessed a decrease of mortality during the first year of life from about 25% down to about 7% , mainly due to malaria eradication, if my information is correct.

Is it true, indeed, that this decrease of mortality has mainly favoured the weaklings? In order to find an answer, the question has to be put more specifically. We shall try to do so by clearly separating some different situations. Things are relatively simple, when hereditary diseases with a clearcut Mendelian mode of inheritance are concerned, which have caused early death in former times, whereas now, phenotypically successful therapy has become possible, and the patients will reproduce. Obviously, an increase in population incidence has to be expected, which corresponds to the increased reproduction of the patients. We know of many such examples. Hence, as to these cases, a pessimistic view seems to be justified. Fortunately, however, these hereditary diseases are rare. There are, on the other hand, many more anomalies and malformations, which are mainly genetically determined or contain an important genetic component, and in which a successful

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therapy will lead to an increase in frequency. Many examples, in which this assumption has much to favour it, could easily be enumerated.

But even these anomalies did not very frequently cause early death. The big majority of children did not die from these hereditary anomalies and malformations, but from infectious diseases and malnutrition. What about natural selection in these cases? Will the genetic consequences also be disadvantageous, when these causes of death will be eliminated?

Some geneticists have doubted this very much since a long time. The great geneticist Haldane, who was personally known to many of you, had quite a different opinion. According to his views, the strong selection due to infectious diseases could very easily have led to certain compromises in the sense that for a specific genetic advantage, for example, better resistance to certain infections, other genetic disadvantages had to be taken into account. As soon as the infection was eliminated, this specific genetic advantage would automatically disappear, and in the course of time, changed selection pattern would lead to an automatic elimination of the disadvantage. In this case, the genetic effect of selection relaxation would be advantageous.

Meanwhile, we have come to know of empirically confirmed models for this effect in man. The best known example is the relative resistance of heterozygotes for the sickle cell gene against falciparun malaria which led to a high gene frequency in certain parts of the world in spite of the fact that the homozygotes suffer from a severe haemolytic anaemia, from which they died very early in former times. You see the compromise: the advantage, malaria resistance, has to be paid for by a disadvantage, severe hereditary anaemia.

A much more complicated pattern of natural selection in man emerges, once we are looking to the A-B-O blood groups, which are known to all of you. However, evidence is accumulating that at

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least some important aspects of selection in this system can also be seen in this context. In areas of the world, in which infections do not play any important role any more, almost the only significance of these blood groups will be that the physician must not carry out blood transfusions with incompatible blood. However, evidence has been brought forward that the A-B-O blood groups seem to influence susceptibility to, as well as severity and outcome of different infectious diseases. It is well known that the A-B-O gene frequencies are very much different in different parts of the world population, and these gene frequencies could - besides other factors - have been influenced by the infections prevalent in earlier times in different parts of the world.

Smallpox is a very interesting example. You know better than I do, that this disease has been prevalent especially in this part of the world population, in India, since many centuries. Some years ago already, we had reasons to assume that persons with blood groups A and AB would suffer more severely and die more frequently from small pox than persons with blood-groups B and O. As you will know, group A is relatively rare here, whereas group B is relatively frequent. Soon after we had realised that there could be some interaction with the blood groups, we tried to investigate small pox patients. Preliminary, and very limited results, seemed to support our assumption. A definite confirmation is now available resulting from a cooperative study between the Indian Statistical Institute and the Institute of Human Genetics, University of Heidelberg. Under very difficult field conditions, Dr. M.R. Chakravartti of the Indian Statistical Institute investigated, during last summer, according to a plan suggested by me, 200 suffering patients of Burdwan district in West Bengal together with 200 carefully-matched controls. At the same time, he could examine 405 surviving patients of the 1964 epidemic together with controls. You may ask, why he did not simply go to the infectious diseases hospitals. The answer is that there, the sample of patients is biased, and prognosis is much better than in the villages. In order to get an idea of natural selection in earlier times, the disease had to be studied under natural and primitive conditions.

The result was very clearcut. Incidence of smallpox is indeed higher in groups A and AB as compared with B and O. Furthermore, groups A and AB contain much more severe cases, and - most important for population genetics - mortality is much higher. This year, I have joined the field work as guest of your Institute, and we hope to clarify some additional aspects of this relationship.

There are also other infections, which seem to be influenced by the A-B-O blood groups, such as infant diarrhoea, leprosy, hepatitis, the paralytical type of poliomyelitis, some other virus diseases, and possibly plague.

Taking these influences into account, it is really tempting to speculate whether the A-B-O polymorphism might be an adaptation to the manifold and changing threats due to various infections, - an adaptation, which contributed to the survival of a part of the population.

Now there is also a disadvantage of the A-B-O polymorphism: it leads to a loss of zygotes due to serological incompatibility between mother and unborn child. Consequences are abortions or erythroblastosis. Once the selection due to infections is eliminated, and provided that no other important selective factors are being at work - it can be shown that also the A-B-O polymorphism will disappear in the course of time. Probably, group O will become very much prevalent. Of course, A-B-O incompatibility will also become rarer, and will finally disappear. The effect will again be an advantage due to selection relaxation.

Now, please, do not understand me this way, as if selection relaxation must in all cases be a benefit. We already saw that the opposite is possible and might very well be more frequent. I only wish to show you that advantages are also possible.

In this context, however, I wish to stress a different, practical aspect: It was only possible to work out the relationships between smallpox and blood groups here, in India, and only in

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cooperation with Indian scientists. The reason is very simple. This disease does not occur any more in the industrialised countries of the West. But the same is true for many aspects of natural selection, the study of which is of utmost importance for our understanding of human evolution in past, present, and future. They can only be studied in countries and populations, which have not taken part fully in the modern refashioning of almost all aspects of human life. Even in these countries, these possibilities will disappear very quickly, and no time must be lost to make use of them.

There are a good number of frequent diseases, which are partially due to genetic factors, and where we simply do not know whether selection relaxation will primarily be disadvantageous or advantageous. I only mention diabetes mellitus or coronary heart disease. Besides genetic influences, overnutrition in the industrialised countries is here an important factor. Comparisons between populations living under conditions of overnutrition, populations living in undernutrition, and especially populations which are shifting from under-to overnutrition can be of high value to clarify the genetic basis and the selective factors involved. Here, too, we depend on countries like India.

You are fully justified, and everybody will share your feelings, if you regard poverty, undernutrition and infectious diseases in a major part of our population as a very severe social and human problem which has to be overcome as soon as possible. But I would ask you to recognise one thing. As long as all these evils do exist, there are also chances to solve problems of human biology, which will never come back again.

Let me finish. I am repeating: the evolution of man is being in full and rapid progress. A certain increase of mutation rates is expected

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/ have a limited disadvantageous effect. Selection relaxation will have partially disadvantageous, and also partially advantageous effects. Nobody can say, which of them will predominate in the long run. It is our big chance that we have come to know the problems in principle, and will be able to investigate their special aspects. We can hope that, sometime in the future, we shall find the remedies to prevent the bad and to promote the good.

Calcutta
12 April, 1966

F. Vogel