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HUMAN GENETICS AND PUBLIC HEALTH

**Second Report
of the WHO Expert Committee on
Human Genetics**

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HUMAN GENETICS AND PUBLIC HEALTH

Second Report of the WHO Expert Committee on Human Genetics

The WHO Expert Committee on Human Genetics met in Geneva from 10 to 16 December 1963. Dr M.G. Candau, Director-General, opened the meeting and welcomed the participants. He referred to the rapid development of genetics in recent years and the difficulty frequently experienced by non-geneticists in comprehending its present scope, its importance to the practising physician, and the contribution it can make at present to public health thinking and practice. The need for an examination of the present and future significance of human genetics to public health had recently been felt acutely by many public health workers.

Dr Candau added that, with increasing control of infant mortality and infectious diseases, inherited abnormalities are assuming a proportionately greater importance in medical practice. He indicated that human genetics is, however, much more than the study of inborn abnormalities; it is the study of endogenous factors in health and disease. It can be hoped that a fuller comprehension of genetics will lead to greater understanding of the complex interactions that have taken place in the past and that exist at present between man and his changing environment, and also of their implications for the health of future generations.

Dr J. A. Fraser Roberts was elected Chairman and Dr Z. Štich, Vice-Chairman. Dr H. B. Newcombe was elected Rapporteur.

INTRODUCTION

Man's body and his mind, and his physical and mental well-being (or disease) are all products of the interactions between his heredity and the environments he encounters in the course of his life. Neither human heredity nor the environment is constant. Except for identical twins and other identical multiple births, probably no two human beings have identical genes. No two persons are exposed to quite the same sequence of environments. The aim of the medical sciences, stated in broadest terms, is to devise environments in which human genetic endowments will

produce healthy minds in healthy bodies. The achievement of this aim is complicated by the fact that no one environment is optimal for all heredities. For example, an environment that supplies insulin is favourable for carriers of the hereditary endowments that, without insulin treatment, lead to the development of diabetes mellitus and its complications. An external source of insulin is superfluous for carriers of most other genetic endowments. Public health measures must take into account that different environments have to be devised for different heredities. Public health officers, practising physicians, and medical scientists have to face the fact that man is genetically heterogeneous.

In recent years the science of genetics, including human genetics, has been making rapid progress. Increasing realization of the importance of genetics to medicine has led to the establishment of courses of human genetics in many medical schools. Understanding the nature of the inborn genetic diversity of human beings is an essential prerequisite for taking care of their physical and mental health. The idea still lingering in some circles that hereditary diseases are almost by definition incurable is far from justified. At least in principle, curability depends on an understanding of those physiological processes and developmental patterns that are related to the symptoms of a given disease, and on the availability of environmental means, hygienic regimens, drugs or surgical interventions whereby these processes and patterns may be altered. Although one cannot "mend" the gene complement with which an individual starts his life, progress in the medical sciences is making it more and more often possible to control the manifestations of unfavourable genes.

Genes contain the information, encoded in their chemical structure, which is translated into the developmental pattern of the individual in his embryonic, pre-adult and adult life. Biology has laboured for a long time to decipher the code in which the genetic information is packed in the genes. A large measure of success has been achieved in recent years, and this achievement almost certainly deserves a place among the most fundamental discoveries of natural science. Although work on microorganisms played a most important role in the development of biochemical genetics, the study of man, particularly of inborn errors of metabolism, has also made important contributions.

Striking progress has been made in developing techniques for the examination of human chromosomes under the microscope. Some anomalies and diseases, the causes of which were obscure, are now known to be connected with abnormal numbers or shapes of the chromosomes. In a great majority of inherited anomalies and diseases, however, the chromosomes do not show any visible changes. Gene mutations do not in general cause any visible alteration in the chromosomes as seen under the microscope. With many genetic variants, new biological methods have made possible a thorough analysis of the pathways leading from the primary

change in the genetic material to the visible anomaly in the physiological or morphological traits of the organism.

Conspicuous success has also been achieved along quite different lines of analysis. The interplay of forces which determined the incidence of inherited traits in populations is being investigated by population geneticists. The quickly changing environmental conditions under which people live, and the changing breeding structure of human populations, influence profoundly the human gene pool and consequently the frequencies of different genetic constitutions which determine the biological basis of the health of populations.

The new cytological and biochemical methods have found very successful applications but do not, of course, supersede the classical methods and techniques of human genetics. Thus, studies leading to accurate calculation of empirical risks for relatives of patients with disorders of genetic origin remain of great practical importance. Similarly, comparisons of monozygotic and dizygotic twins are necessary to clarify the interplay of the genes and environments in the causation of certain diseases, anomalies, and other human characteristics. The new and the older methods supplement each other, and are suitable in different circumstances and for the investigation of different problems.

The growing practical importance of hereditary anomalies and diseases is largely due to the fact that many exogenous causes of disease have been brought more and more under control. This has led to an increase in the relative frequency of patients who suffer from diseases in which at least some genetic component is involved. Knowledge of hereditary diseases is important not only because they present very serious problems of public welfare, but, to a still greater extent, because in an increasing number of cases an adequate therapy is becoming possible, provided that the anomaly has been diagnosed correctly.

1. BURDEN TO THE COMMUNITY OF GENETIC DISEASE

The burden imposed upon the individual, the family, and society by genetic disease and genetically determined detrimental deviations from normal can be estimated only approximately. This evaluation will vary greatly in different communities according to many factors, for instance, the state of development of the economy and the medical services, and the cultural values involved. Mental retardation provides one of the clearest examples of how relative this evaluation must be: in a fairly primitive pastoral community, a mentally-retarded person may find a niche easily. In some early societies, the simple-minded have been surrounded by a particular reverence, and neither their lot nor their family's has been

an unhappy one. However, in a developed and industrialized economy, the mentally retarded individual represents a burden to the society; how far this burden falls also upon his family will be determined by the availability of suitable medical and educational institutions for his care.

Another obstacle to making a valid evaluation of the burden of genetic disease is the considerable geographical variation in the reported frequency of genetically determined abnormalities. This variation may reflect a true difference in incidence or merely a difference in methods of sampling or surveying; the problem is one that urgently requires clarification.

In the preparation of the following sections, much use has been made of material from the reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).^{1,2}

1.1 Diseases with simple inheritance

1.1.1 Diseases associated with chromosomal anomalies

A number of conditions have, in the past four years, been shown to be associated with abnormality in the number or the structure of the human chromosomes. The following conditions may be mentioned:

(a) Most cases of Down's syndrome (mongolism) are caused by an extra chromosome identical to members of the normal pair known by convention as number 21. The condition is therefore sometimes referred to as chromosome-21 trisomy. Occasional cases of Down's syndrome result from an extra chromosome 21 being attached to a member of the group 13-15, or to chromosome 22 (referred to respectively as 13-15/21 and 22/21 translocations). The differential diagnosis is important because the risk of the mother of a mongol having a second affected child approaches 1 in 3 in the case of translocation, while for the more usual case of trisomy it is only one or two per thousand.

(b) Trisomies of chromosome 18 and of a chromosome in the group 13-15 are known to produce severe multiple malformations incompatible with long survival.

(c) Most cases of Turner's syndrome (ovarian dysgenesis often associated with oligophrenia and somatic malformations) result from lack of one of the sex chromosomes (that is, only one X-chromosome is present).

¹ United Nations (1958) *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation*, U.N. General Assembly Off. Rec. 13th session Suppl. No. 17 (A/3838), New York.

² United Nations (1962) *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation*, U.N. General Assembly Off. Rec. 17th session Suppl. No. 17 (A/3838), New York.

Persons suffering from this syndrome have 45 chromosomes instead of the normal complement of 46.

(d) Klinefelter's syndrome occurs in individuals having two or more X-chromosomes in addition to one Y-chromosome. The patients have non-functional testes.

(e) Females with three or four X-chromosomes (XXX or XXXX) have been found. They are normal except for a lowered intelligence in some instances.

(f) Normal males with an extra Y-chromosome (XYY) have been found.

(g) An abnormal chromosome (Philadelphia chromosome), smaller than the smallest normal ones, has been found in leucocytes of patients with chronic myeloid leukaemia.

(h) Many cases of mosaic constitution (for instance, individuals having normal cells as well as trisomic cells) have been described. Particularly interesting is a case with normal and triploid cells (three chromosomes of each type).

A number of other chromosome abnormalities have been found in rare instances.

The incidence, at birth, of the more common chromosome abnormalities is about 1 in 400 among males for Klinefelter's syndrome, 1 in 500 for Down's syndrome, 1 in 800 among females for the XXX syndrome, and 1 in 2500 among females for Turner's syndrome. If other chromosomal aberrations sufficiently gross to be detected by present techniques are added, it is reasonable to think that about 1% of all live-born infants have some such harmful trait. Moreover, evidence is accumulating that a significant fraction of intra-uterine deaths is caused by a variety of chromosomal aberrations.

Common consequences of gross chromosomal aberrations, for which there is at present no treatment, are mental retardation and sterility.

1.1.2 *Dominant, recessive and sex-linked diseases*

An attempt to estimate the combined incidence in man of diseases and disabilities in this category was made in 1958 by UNSCEAR;¹ it was based on a list of specific traits and their estimated frequencies in the population of Northern Ireland. Individual frequencies will be different in other populations, but this is the most comprehensive survey undertaken to date and, taken in conjunction with data from different parts of

¹ United Nations (1958) *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation*, U.N. General Assembly, Off. Rec. 13th session Suppl. No. 17 (A/3838), New York

Europe, North America and Japan, provides a useful body of data on which to base over-all estimates. These traits are at present estimated to affect seriously about 1% of all live-born individuals at some time in their lives. The majority of the traits are dominant with a high degree of penetrance, but some are autosomal recessive and a few are sex-linked. Their clinical severity varies considerably. The majority of dominant traits are sufficiently mild in their effects to be transmitted through several generations but about a third are severe. In contrast, most of the detrimental recessive traits are severe enough in their effects to prevent reproduction of the affected individuals.

1.1.3 *Diseases maintained in polymorphic balance*

The conditions described in the preceding two sections are believed to be largely maintained by recurrent mutation. This is, of course, of considerable significance to public health authorities since a certain number of agents, such as ionizing radiation, are known to be mutagenic. Their control, and the promotion of research on other agents that might possibly be mutagens, are now recognized as an intrinsic responsibility of public health authorities.

In the case of some other inherited conditions, however, a balance of selective forces is believed to operate to maintain the gene frequency at a relatively high level from generation to generation: such a situation arises when a gene confers reduced reproductive fitness in some circumstances and increased fitness in others; this may result in a situation known as a balanced polymorphic system. Deleterious polymorphic traits so far investigated are prevalent only in particular geographic regions or racial groups.

Of the several balanced polymorphic systems discovered so far, sickle-cell anaemia has been the most carefully investigated. This trait is often fatal in the homozygote. Its distribution is very uneven in different parts of the world and it is exceedingly rare in many populations, yet the frequency of the homozygote is about 4% in some parts of Asia and Africa, and in some places reaches as much as 10%. It has been shown that the heterozygote for this trait benefits from the selective advantage of an increased resistance to malignant tertian malaria.

It seems inevitable that other serious haemoglobinopathies, including thalassaemia, as well as deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD) in red blood cells, must also be maintained by balancing selection. The heterozygous carriers of the gene causing the latter deficiency benefit from relative immunity to malaria. The possession of this sex-linked gene by the male, or in double dose by the female, has not yet been shown to be of any significance, unless fresh fava beans are eaten by such a person, in which case he or she may develop an

anaemia long known as favism. There is, however, one additional risk; the administration of certain drugs such as primaquine and some sulfo-
namides induces a haemolytic anaemia in males who carry this gene and
in homozygous females, making hazardous the indiscriminate use of such
drugs in a population with a high frequency of this gene. In certain low-
land villages in Sardinia, for example, the proportion of persons carrying
the gene is of the order of 25-40%.

1.2 Diseases with more complex inheritance

There are very many developmental malformations and diseases
of later life, the inheritance of which is not simple, mainly because environ-
mental factors are frequently involved. A large part of such conditions
may be regarded as resulting from the action of an unfavourable environ-
ment on a genetically susceptible individual. The relative importance
of the environment on the one hand and of the genotype on the other
may vary widely in different diseases.

The nature of the hereditary component may also differ for various
disorders. The predisposing factor may be a single dominant or recessive
gene which is irregularly expressed or, alternatively, susceptibility may be
determined by an accumulation of genes at a number of loci, of which
the majority have effects that are similar in direction and cumulative
(polygenic systems). Other more complicated genetic mechanisms are
also possible. Although a battery of tests is available to distinguish
these various types of inheritance, their application presents difficulties
in practice which have restricted their use. Detailed knowledge is for this
reason slow in accumulating. Nevertheless, figures for empirical risks
among relatives are very valuable, and are available for many conditions.

1.2.1 *Developmental malformations*

Of the variety of conditions known as congenital malformations,
for which the mode of inheritance is not yet well understood, some few
may perhaps be due to differences in single chromosomes or genes. Evid-
ence is accumulating, however, that with some others the genetic basis may
be multifactorial. Maternal health and intra-uterine environment appear
to play a considerable part in determining the likelihood of occurrence
of these anomalies. There is also some familial concentration, greater
than would occur by chance, but seldom sufficient to satisfy the criteria
for single gene differences.

The frequency of these traits has been estimated to be 1.5% of the
live-born, the figure being higher if stillbirths are included. An additional
1% of affected children can be detected at the age of 5 years.

1.2.2 *Mental diseases and deficiency*

The morbidity risk for schizophrenia, the most common of the psychoses, has been shown to be as high as 2-3% in a study of a highly inbred population in northern Sweden, whereas it is normally estimated as being about 1%. Data from a large number of studies on families and twins yield morbidity risks of 7-16% both for the siblings and for the children of schizophrenics. Estimates of the risks for children with two schizophrenic parents range from 40-60%. Extensive twin studies have shown concordance rates of 76-91% for monozygotic and 10-17% for dizygotic pairs. Whether genetic predisposition is determined by a single gene difference or is multifactorial is still undecided, although the latter view is perhaps favoured at the present time.

Schizophrenics represent a great burden for the community. They make up about 50% of the resident population of mental hospitals, partly because no very successful therapy has been found, but also because of their youth on admission (usually 15-35 years of age) and the long-term hospitalization that is often involved. Patients suffering from manic-depressive psychoses represent a further 3-5% of the resident population in mental hospitals.

Two classes have been distinguished among mental defectives: those of low grade, primarily idiots and imbeciles, and those of high grade, essentially the feeble-minded. Low-grade defectives usually owe their condition to single accidents of development. Known genetic entities such as phenylketonuria, epiloia and amaurotic idiocy, caused by single gene differences, are found among them. It is believed that some proportion of low-grade deficiency of no specially identifiable type is also due to recessive genes. With high-grade deficiency, essentially the lower end of the distribution of intelligence in the general population, the condition seems to be due to multiple causes, the genetic component being large and probably polygenic.

1.2.3 *Other "constitutional", chronic and degenerative disorders*

The so-called constitutional disorders include such conditions as diabetes mellitus, idiopathic epilepsy, pernicious anaemia and some abnormalities of the thyroid gland. They are probably not all true traits in the genetic sense of being the expression of a single genotype. Most of them can probably be determined by more than a single biochemical mechanism and, in so far as has been genetically determined, by a variety of gene combinations. Diabetes has been thought by some to be due to a simple recessive gene, not always expressed, but this is not universally agreed and a polygenic inheritance may well be involved.

These diseases together probably affect at least 1% of all adults, although such estimates must be regarded as far from precise and the

incidence figures differ considerably in different communities and for different age-groups. The frequency of diabetes mellitus, for example, among persons aged 60 and over was given as 20 per thousand for one Danish survey, but was as much as 51 per thousand for a town in New England, USA. Even in severe cases, however, treatment allows the diabetic to lead a more or less normal life. Since the discovery of insulin in 1922, the life expectancy and general health of diabetic persons have improved greatly and the likelihood of their reproducing has increased considerably. This must almost certainly have led to a higher frequency in the present generation of the alleles that determine the predisposition to diabetes.

There are a number of rare tumours that develop on the ground of a precancerous state, which in turn is due to a single gene. Neurofibromatosis, certain cases of retinoblastoma, multiple intestinal polyposis and xeroderma pigmentosum might be mentioned as examples. For most types of malignant growth no simple genetic basis is apparent. Some slight familial associations have been observed, but the question remains open whether and to what degree they are due to genetic differences, or whether they at least partially reflect correlations with certain environmental factors among members of the same family. As comprehensive twin investigations have shown, the concordance rate in monozygotic twins for the common types of cancer is surprisingly low, and does not very much exceed the concordance rate in dizygotic twins. This would seem to show that genetic factors are in most cases of only slight importance in determining whether a person develops one of the common types of cancer or not.

Much information has been collected on the question of the genetic contribution to common cardiovascular disease of complex etiology, although no clear picture has yet emerged.

Evidence for the action of genetic factors in coronary artery disease is provided by family and twin studies, and by studies of body build, lipid metabolism, and ethnic characteristics. The data, however, are limited and observations are susceptible of various interpretations. There is a possibility that genetic differences in clotting propensity may be of significant importance. Granted that a disturbance in lipid metabolism, expressed by elevation of blood lipids, predisposes to atherosclerosis, there is a considerable amount of information on the genetic control of lipid metabolism which can be taken as evidence of the genetic influence in atherosclerosis. Serum cholesterol has been the most frequently employed index of lipid metabolism. Studies in twins, monozygotic and dizygotic, living together and apart, indicate that both genetic and environmental factors are operative in determining the level of serum cholesterol. Genetically-determined differences in the anatomy of the coronary arterial tree might also account for increased vulnerability to atherosclerosis in certain persons.

The level of the arterial pressure exhibits a measure of genetic determination. This is shown by family and twin studies and by comparison of different racial groups living in similar environments; it is also shown by studies on animals. There are two schools of thought about high blood pressure, particularly when it takes the form of benign essential hypertension. One would invoke a dominant, or intermediate, gene in which case genetic determination of hypertension is extremely strong; in fact it may be nearly complete. The other school of thought is that the level of arterial pressure is a graded character, like stature, with benign essential hypertension as the positive tail of the curve. If this idea is correct, the genetic component in causation is considerably less strong but is still substantial.

Significant familial aggregation has also been shown for gout and ankylosing spondylitis. A similar controversy to that on essential hypertension is centred on gout: is the genetic component in the inheritance polygenic or monogenic? Higher uric acid values have been found in the blood of siblings of gout patients than in the blood of controls. However, the distribution is not bimodal but continuous. Hereditary hyperuricaemia is thus regarded as an extreme variation of a normal feature. Environmental factors, however, cannot be ignored, as shown by population studies in which the spouses of hyperuricaemic probands showed an increased incidence of hyperuricaemia. For another condition, ankylosing spondylitis, however, the mode of inheritance is most satisfactorily explained as due to a single autosomal dominant, the penetrance of which varies with sex.

A number of other common chronic diseases appear to have significant genetic components in their etiology, for instance the allergies, and in particular asthma and duodenal ulceration.

1.3 Susceptibility to infection

Infectious diseases result from complex interactions between host and parasite. These interactions have a dynamic character which tends to promote mutual adaptation of the organisms concerned. Selection of genetically more resistant individuals has probably occurred in significant degree whenever a large population has been subjected for a long time to particular diseases. It is only natural, therefore, that human populations should be heterogeneous with respect to the degree of genetic susceptibility to different infectious diseases.

A much greater similarity in the expression of tuberculosis has been noted for identical than for non-identical twins; family and ethnic studies have also tended to confirm that susceptibility to tuberculosis is partly under genetic control. This conclusion has received further support from experiments in which the local reaction of the skin to tuberculin

injection has been investigated in twins, and in different strains of rabbits. However, with tuberculosis as with other infectious diseases, the clinical course shows great individual variation, which may depend partly on the genotype of the patient, but is also affected by the degree of previous immunization, the type of infection, the patient's sex and age, diet and living conditions. The possibility of differences in genetic susceptibility to leprosy is also quite strong, although available data do not permit a clear decision.

Studies have been carried out on possible inherited differences in susceptibility to measles, scarlet fever, diphtheria, mumps and whooping cough. For each disease, the identical twins are more frequently concordant than the non-identical, but the differences, while significant, are not striking and might be accounted for by the greater environmental similarities in the case of identical twins and the greater chances of contagion. A genetic element in the determination of paralytic poliomyelitis seems to be well established.

There is evidence that carriers of various ABO blood groups display different responses to the bacteria and viruses responsible for certain epidemic diseases widespread in the past. The latter association may be a major cause of the geographic variations in A, B and O genes observed to-day.

1.4 The genetic contribution to reproductive wastage

The genetic contribution to reproductive wastage is particularly difficult to assess. A number of quite different genetic mechanisms might conceivably be involved, including chromosomal anomalies and recessive genes. Blood group incompatibility, polygenic determination and dominant genes arising by mutation may also contribute. Probably about 50% of human zygotes of each generation fail to contribute to the next one by reproduction. This includes zygotes that are lost at all stages of pregnancy, those that result in stillbirths and neonatal deaths, and those that develop into malformed or sterile individuals, or persons who never mate. Some half of reproductive wastage is quite likely of genetic origin.

Sterility is a frequent consequence of chromosome aberration. It is also associated with a number of the malformations referred to earlier in this paper, either as a pathological condition, or as a "social" phenomenon resulting for instance from gross deviations from what is accepted as normal appearance, as in achondroplastic dwarfs.

Chromosome abnormalities would seem from preliminary data to be a significant cause of both early embryonic wastage and stillbirth, but there is need for further investigations.

Data from studies in the United Kingdom suggest that live-born children represent perhaps 70% of all zygotes and that, of the 30% who fail

to survive *in utero* at any stage of development, at least half are malformed. No estimate can be given of the relative importance of genetically-determined conditions among these malformations.

2. POSSIBLE GENETIC CONSEQUENCES OF CURRENT HUMAN ACTIVITIES

The hereditary basis of human life is inextricably related, both in historical origin and in its contemporary form, to environmental factors, past and present, which have determined the frequencies of the various alleles in the collective pool of human genes. Environmental factors of a physical, chemical, biological and cultural nature have all been influential in this process. The importance of changes in cultural factors in recent times can hardly be over-emphasized. Modern man is now busily at work further altering his environment, and he is doing this at what appears to be an ever-increasing rate. He is synthesizing new chemical compounds with which life has never before been confronted, using some as drugs, putting others into the atmosphere as wastes, and spreading still others on crops as insecticides. As a result of modern medical and public health practice, not only are vast numbers of people, even whole populations being injected with new chemical and biological preparations, but in addition the lives of individuals who would otherwise have died of genetically determined disabilities are being preserved. Man is migrating and mixing, and he is altering his social, family and marriage patterns. What are the genetic consequences of these changes, particularly in terms of human health and disease ?

2.1 Mutagenic agents in the human environment

We know that certain external influences can increase the mutation rate. These include ionizing radiation and chemical mutagens. To what extent either of these influences is, at present, increasing the mutation rate above the "natural" level is not certain. However, irradiation is known to produce mutations in all organisms so far studied and there is no reason to believe that man is an exception. Studies in mice provide at least a rough picture of the extent to which the mutation rate may be increased by irradiation. There have even been some attempts to estimate the order of magnitude of the additional burden imposed on a population as a result of exposures to various levels of radiation. The topic has already been dealt with elsewhere.¹

¹ See: United Nations (1962) *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation*, U.N. General Assembly Off. Rec. 17th session Suppl. No. 16 (A/5216), New York; and also, *Wld Hlth Org. techn. Rep. Ser.*, 1962, 248

Considerably less is known regarding the genetic effects of chemical mutagens. Two things, however, are certain : mankind is being exposed for various reasons, but particularly in connexion with medical treatment, to an ever-increasing variety of chemicals; and a large number of chemical compounds have genetic effects which may provisionally be classed together under the heading "mutations".

These effects have been demonstrated in different species by means of various genetic and cytogenetic techniques. Special genetic methods have been used, for example, in micro-organisms and in fruitflies, and to a very small extent also in mice, whereas in plants mainly visible chromosome changes have been studied. As a result of differences in the research methods used in individual experiments, only a part of the total genetic change is detected. This makes comparison between the various organisms studied difficult. In particular, it becomes impossible to apply the results of research of this nature directly to human beings, as the organisms employed in the experiments differ greatly from man. This is the essential problem in evaluating the significance of chemical mutagens to human health.

The most potent mutagenic compounds which can be shown to act on all test organisms belong to the alkylating agents, a group that also includes the so-called "radiomimetic" compounds. These agents break chromosomes, cause gene mutations, stop cell division, cause cancer, and depolymerize nucleic acids. Some substances belonging to this group are the ethyleneimines, nitrogen mustards, sulfur mustards, epoxy compounds, and methanesulfonic acid esters. Because of their cytostatic action they are, or have been, used in tumour therapy, particularly for the treatment of leukaemia and allied conditions. That some substances of this group do penetrate mammalian cells and cause genetic damage is apparent from the occurrence of chromosomal aberrations in cells of liver, marrow and other tissues following administration of nitrogen mustard. Recent research seems to indicate that there is direct chemical reaction with the genes themselves.

Apart from these alkylating compounds which have a mutagenic effect on all almost the forms of life tested, there is a series of other substances most of which have so far been tested extensively only on plants and micro-organisms. On the basis of the known or suspected mechanism of their action, this second group may be divided into various sub-groups, of which the anti-metabolites are particularly interesting. These compounds inhibit the course of biological reactions by changing natural metabolic products. Thus, caffeine and theophylline probably act as purine base antagonists, as their chemical structure is similar to that of essential parts of the genetic material. Compounds of this group are used for numerous purposes in medicine. Although the radiomimetics may be assumed to have a mutagenic effect on man, this may not be so with the second group. Some disturbances in proper distribution of chromosomes during cell

division can be brought about in plant cells by a further, still larger, group of substances. The extent to which they represent a danger to human beings is unknown, but probably they are not harmful.

The problem will be considered in more detail in the case of caffeine, since this substance is of particularly great practical importance in view of its large-scale use. Because of its chemical structure, which is very similar to that of adenine and guanine, it might be suspected *a priori* that caffeine could have a disturbing effect on the synthesis of the genetic material in the cell. It has actually been shown by a relatively large number of tests to have a mutagenic effect on plants and micro-organisms. Similar results have also been reported in fruitflies but have not been confirmed. Some pilot investigations on the mouse, using different methods, did not show any significant rise in the mutation rate. Nevertheless, there was a fall in the fertility of male mice. Inhibition of mitosis in human tissue cultures has resulted after the addition of caffeine, but structural changes in chromosomes have not been seen.

As this single example shows, research with micro-organisms or plants is not sufficient to justify a definitive statement that a substance be regarded as harmful for the human genome. Even studies with fruitflies, for example, can supply only preliminary indications. There is no way of evading the study on mammals of suspicious substances and the final, definitive step should be, wherever technically possible, statistical studies on man himself. In the absence of sufficient evidence it is difficult at present even to speculate about the magnitude of the genetic consequences to man of exposure to the many potential mutagens in his present-day environment.

One point that might be mentioned briefly is the question of genetic hazards from irradiated foodstuffs. Some preliminary data in fruitflies seem to suggest a possible increase in mutation rate after feeding with irradiated food. Since extensive research is at present being undertaken on preservation of food by irradiation for human consumption, further work is needed to see whether such food is likely to be a source of mutation in man.

A third possible mutagenic factor occasionally discussed is temperature. That elevated temperature may sometimes increase germinal mutation rates has been shown for certain experimental organisms such as fruitflies,¹ but such effects have not been demonstrated in studies in plants.

2.2 Consanguineous marriage

Marriages of blood relatives give rise to certain increased risks in the offspring. These risks arise both for traits controlled by recessive

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1962, 248

genes and those determined by polygenes. In either case, the result is to expose a proportion of the otherwise largely hidden component in human genetic variability. This proportion is substantial enough to matter.

This is illustrated most simply by the coming together, through mating of blood relatives, of pairs of harmful recessive genes. In random mating, the likelihood of rare identical genes coming together in the child is small indeed and is determined by the frequencies of these genes in the population. The chance is increased when blood relatives marry each other, because a proportion of their genes are necessarily identical, being derived from the same ancestor genes. This proportion is, for example, 1 in 8 for first cousins. The remainder of their genes may be the same or different, with probabilities that are the same as in the marriage of unrelated persons. Clearly the risk of rare recessive defects appearing is increased in consanguineous marriages, but what is important to the individual couple is not the increase in the relative risk, but the amount of the absolute risk. Looked at theoretically, the amount of the increased risk has not seemed very large, or of a size that would be a serious deterrent to sensible people informed of the facts. But, of course, small risks to individuals may give rise to serious consequences to the community as a whole, and from every point of view careful observations on the results of consanguineous marriages are most desirable to provide improved information on this subject.

With traits having polygenic causation, an inbreeding effect may be expected even where there is no recessiveness or dominance. With each polygene locus that is rendered homozygous by inbreeding, fewer units are free to assort themselves independently and to cancel one another out. The effect is much the same as with recessive inheritance, in that more of the hidden genetic variability is thus expressed as phenotypic variation.

In either case, parental consanguinity may have less effect in populations in which it has been practised for some time, and may be more serious in its consequences where outbreeding has been the rule.

The results of recent informative studies show a very considerable measure of general agreement. There is little difference between the outcome of consanguineous and control marriages up to and including birth. That is, the interval from marriage to the first conception is not increased; there are very few more miscarriages, and there is no excess of stillbirths, provided those due to recognizable major deformities are excluded. Thus, the effect of increased homozygosity does not seem to operate by causing early wastage. From birth onwards, however, the findings are different; in a certain Japanese city a death-rate of 116 per 1000 was found during the first 8 years of life amongst the offspring of first cousins, against 55 amongst the controls. The proportion of major congenital abnormalities was rather less than doubled. In a certain American city, with a lower total death-rate, the difference in death-rate between

the offspring of consanguineous and control marriages was naturally greater. Amongst the offspring of consanguineous unions the death-rate by the age of 10 years was 81 per 1000 compared with 24 per 1000 in the controls.

A very striking fact is that only a few of the deaths were due to recognized recessive conditions and the same is true of the congenital malformations not necessarily resulting in death. Multiple congenital defects figure prominently, and these have not hitherto shown any particular indication of being recessively inherited. There is, however, a possible explanation in terms of polygenic inheritance. In any case, the extra risks to the offspring of consanguineous marriage, even if not very great in the case of the individual couple, are not insignificant, as has been seen above, when looked at from the point of view of the community as a whole. The problem is not an urgent one in communities in which the rate of first-cousin marriages has already fallen to a very low figure, not more perhaps than 3 per 1000, and is still falling. In many parts of the world, however, consanguineous marriages represent a rather high proportion of the total marriages. It would be of advantage to the health of the community if these frequencies should diminish. All else being equal — and, of course, social and other considerations are important — an outbreeding human population is a healthier population, and this not only because of a falling off in definite, known, recessively determined defects.

2.3 Economic, cultural and demographic patterns

The problem of over-population is growing increasingly serious in many parts of the world, and various methods of family planning are becoming more and more widely used. Although the problems of population numbers and of population quality are separate ones, it is necessary to inquire what genetic consequences may result from measures taken to limit the population growth.

A reduction in the number of children born as a result of policies encouraging family planning is often accompanied by a reduction of childhood mortality, so that a greater proportion of the children born survive and reach maturity. This does not necessarily result in diminished efficiency of natural selection, since the view adopted by some nineteenth-century biologists that natural selection demands elimination of a majority of the progeny by death is now known to be invalid. In fact, natural selection may be just as efficient in a population in which most of the children survive, provided that the number of the children per family varies depending upon the genetic constitution of the parents. On the other hand, if the variance in family size decreases faster than the mean number of children per family, then the genes adversely affecting fitness may gradually

accumulate in the population. Data bearing on this problem are inadequate. In Japan, the indications are that the variance of the number of children per family has decreased relatively faster than the mean family size.

Another effect of the decreasing mean family size may be a fall in the frequency of consanguineous marriages. With smaller families, a person has fewer relatives, for example fewer cousins, than was the case when the families were larger. Therefore, a general reduction in family size in a society may, even by mere chance, result in a reduction of the frequency of consanguineous marriages. Since consanguineous marriages lead to increased risks of illness and premature death among the offspring, as a result both of homozygosity for recessive detrimental genes carried by common ancestors and of increased expression of polygenic variation, any reduction in the frequency of such marriages should lead to a reduction in the expressed genetic burden in the society, at least for a long period of time.

There are several hereditary diseases that have been observed to occur in rather definite association with parental age or birth order. Down's syndrome, and erythroblastosis due to Rh incompatibility, are by far the best-known examples. The frequency of Down's syndrome has been given as 1.5 per 1000 total births but recent surveys have indicated higher figures, in some cases as high as 2.5 per 1000. There are geographical variations which may be due to differences in maternal age distribution in different populations. The frequency increases with rising maternal age, but is unaffected by the age of the father. The increase with maternal age is, however, rather slow until the mother reaches the age of 35 years, and then it becomes very rapid as the mother approaches the menopause. Compared with the over-all frequency, there is a two-to-fourfold increase for the age group 35-39, a five-to-tenfold increase for the age group 40-44, and after the age of 45, a ten-to-twentyfold increase. When the influence of maternal age is eliminated, any residual effect due to birth order alone is too small to be significant. A contrasting situation obtains for erythroblastosis due to Rh iso-immunization, where the increase in risk of developing the disease is associated with increasing birth order. The incidence of the disease varies from population to population, depending upon the frequencies of the alleles concerned. In Europe and North America, it is about one per 150 births, while in Japan the incidence appears to be as low as one per 5000 births. If family planning were to result in a substantial decrease in the proportion of births to older mothers and to those of high parity, it would lead to a simultaneous reduction in the frequencies of these two diseases.

In countries where population pressure is an urgent problem, overseas emigration is often encouraged. Modern trends towards industrialization have accelerated the tendency of the population to shift, often on a large

scale, from rural to urban areas within a country. With population movements, changes in the distribution of genes will take place, affecting both the area of immigration and the area of emigration, provided that the populations of the two areas are genetically different in some respect. Emigrants are not necessarily a random sample of the general population, and tend in practice to come chiefly from particular groups in a population. Even where selection is not obvious, the emigrants may have some genetically selective attribute; for instance, as compared with non-migrating groups, they may have greater physical and mental resistance to the hardships of the new life. There is no documented evidence for such selective migration between countries, but lack of evidence does not signify the absence of the phenomenon. It has, in fact, been demonstrated within countries.

The breakdown of isolates due to migration tends to equalize the frequencies of those alleles that were formerly different in the separate groups. The number of homozygous individuals in the mixed population is always smaller than the sum of the homozygous individuals in the original sub-groups. Thus, the breakdown of isolates leads to some reduction in the frequency of individuals affected with hereditary diseases due to recessive genes. This reduction is particularly large where there was a large variability in the frequencies of the recessive genes among the original sub-groups. In addition, the intermixing between different sub-groups makes new genic combinations possible.

Family planning practices tend to spread more rapidly in some social strata than in others, and more rapidly among the better educated than among the less educated sections of the population. Correlations with occupation of husband, and with the couple's educational background, are known to occur in some countries, and are in all probability reflected in fertility differences. The possible genetic consequences of these differences are not known.

2.4 Public health measures and medical care services

Many public health measures and medical-care services, like many socio-economic measures, can alter the genetic endowments of the populations to which they are applied, and ultimately the genetic endowment of mankind as a whole. In the long run, and under certain conditions, some of these alterations may be undesirable or harmful. It is one of the basic tasks of human genetics to discover what these alterations are likely to be, and how the unwanted ones could be avoided.

Since the sacredness of human life is a fundamental ethical tenet, it is the duty of the medical practitioner to save the life, and if possible restore the health, of his patients. Some of those whose lives are saved and whose health is restored are, however, carriers of genetically condi-

tioned defects and constitutional weaknesses of various kinds. These individuals are often enabled to produce offspring, and thus to pass on their genes to the following generations. The result may be that, by helping to save carriers of detrimental genes, we may increase the number of individuals who will need to be similarly helped in the generations to come. This has led some scientists, and especially some popularizers of science, to prophecy that medicine will harm people in the long run by helping them in the short run. The problem here involved is one of extraordinary complexity; many pertinent facts are inadequately understood and stand in need of further research.

The process of mutation gives rise to numerous genetic variants which are more or less harmful to their carriers. Natural selection tends to eliminate these deleterious variants from the gene pool of the population by diminishing the probability that their carriers will leave surviving offspring. Some considerable number of generations may, however, intervene between the production of a harmful variant by mutation and its elimination by natural selection. Human populations, like populations of other living species, carry accumulated stores of deleterious genetic variants. These stores of deleterious variants are sometimes referred to as "genetic loads" or "genetic burdens". How large will be the genetic burden carried by a population will be determined by the mutation and selection rates. Any increases in the mutation rates, and any decreases in the selection rates, make the genetic burden larger, and *vice versa*. Public health measures which enable carriers of hereditary diseases, malformations and constitutional weaknesses to survive and to pass their genes to their progeny thus decrease the selection rates and increase the genetic burden.

For example, the lives of individuals with genetically-conditioned retinoblastoma may be saved by timely surgery. These persons may then become parents and transmit their genetic defect to about half their children. The genetic burden on the population is thereby increased. The same fact may, however, be viewed in a different perspective. The rate of natural selection is a function of the environment. The mutant gene which causes retinoblastoma was lethal in environments which did not include modern surgery, but is not always so now that such medical care is available. An increase in the frequency of this gene in populations is nevertheless obviously undesirable. Since the medical profession cannot refuse to save lives of persons afflicted with retinoblastoma, the only alternative to accepting some increase in the gene frequency is to compensate for the reduced natural selection by such measures as are considered below in sections 3.3 and 3.4.

The effects of some genetic variants on the fitness of their carriers may be altered radically by environmental changes associated with the introduction of certain medical-care services. The result may be either

an increase or decrease in fitness. An increase in fitness has been brought about by surgical means for the genetically rather complex, but highly heritable, condition known as pyloric stenosis. Prior to the introduction of Ramstedt's operation, mortality was high; now it is very low. The condition maintained itself at a relatively high frequency even when mortality was high; now its frequency must be increasing.

A form of porphyria due to a single dominant gene is very common in South Africa, and has been traced back to a couple who married in 1688. In the past, the effect on survival and fertility was slight. Affected persons are, however, extremely sensitive to the effects of barbiturates, and above all of barbiturate anaesthetics, and so the gene now carries a serious selective disadvantage when medical intervention is required. These persons may be paralyzed and die if given some medical treatments beneficial to non-porphyrics. This provides an example of a decrease in fitness due to modern medicine.

Some genes are held in populations in a state of balanced polymorphism (see section 1.1.3). The heterozygote has a fitness higher than either corresponding homozygote, and natural selection maintains the homozygous and the heterozygous genotypes in the population indefinitely. There is a good deal of evidence to support the theory that the high frequency of the gene responsible for the sickle-cell trait associated with the abnormal haemoglobin S in several populations of the tropical areas of the world, has been a consequence of the protection it affords against mortality from malaria in infancy to the carriers of this gene in a single dose (heterozygotes). The high frequency of the trait declines gradually when such populations find themselves in a non-malarious environment. Such a decline has been well-documented in the populations of African origin who have lived in the USA for several generations. The carriers of this gene in a double dose (homozygotes) are affected with sickle-cell anaemia, which is often fatal. Effective treatment has not been available in the past and in its absence the only preventive measure would be to discourage marriages where both individuals are heterozygotes. It is known that, on the average, a quarter of the children of such marriages are affected with sickle-cell anaemia, another quarter are normal, and the remaining half are heterozygotes, like their parents.

The decline in the frequency of this deleterious gene in a non-malarious environment is due to the loss of genes in the fatal cases of sickle-cell anaemia, and to somewhat increased mortality in the heterozygotes as compared to normal individuals. Complete avoidance of marriages between individuals who are both heterozygotes would eliminate the occurrence of sickle-cell anaemia in the succeeding generation. The long-term effect of such a prevention on the frequency of this deleterious gene in the population is unpredictable from our current state of knowledge. If the gene frequency declines, it would decline at a slower rate than if

such marriages were not prevented. Eradication of malaria from areas with a high level of the sickle-cell gene will be of double benefit to the population, since it will abolish a serious endemic disease and, at the same time, will tend to decrease the incidence of sickle-cell anaemia.

Mankind is living in environments that are strongly influenced by his over-all culture, and these environments include medical care. This situation is here to stay. The genetic endowment of mankind will have to be continuously fitted to such new cultural environments, not to the environments of the past, even though these are sometimes referred to as "natural" ones. Some genes are either biologically or socially undesirable in all cultural environments, and their incidence should be kept as low as possible. Other genes are compatible with satisfactory fitness if their carriers are placed in special environments devised by medicine or technology (e.g., provision of insulin for the diabetic, eyeglasses for the myopic). Such genes need not be considered undesirable, at least provided that the special environments that they require can be supplied readily in practice. Probably a majority of the existing genetic endowments enable their carriers to become reasonably well adjusted and effective members of their societies and cultures.

3. POSSIBLE PREVENTIVE AND REMEDIAL MEASURES FOR THE CONTROL OF HUMAN DISABILITIES IN THE LIGHT OF GENETICS

A variety of measures are possible that will serve to reduce the amount of genetically caused ill health, now and in the future. Exposure to mutagenic agents can be minimized, parents of genetically handicapped children can seek and receive advice concerning the risk of recurrence in subsequent offspring, eugenic considerations may influence various kinds of private and public decisions and, of greatest immediate importance, many genetic conditions can be alleviated, cured or even avoided in affected or potentially affected individuals. In all such instances, genetic well-being must be considered in the context of other factors that contribute to human welfare, and sometimes short-term objectives must be balanced against long-term objectives.

3.1 Control of mutagenic agents

It is important for every country to achieve the best possible control of mutagenic agents, whether physical, such as X-rays and other ionizing radiations, or chemical. The organization and equipment of health services and the training of medical personnel should be adequate and

appropriate for these tasks. The responsibilities and authority of health services should be such as to ensure the development and application of scientifically sound principles and recommendations with regard to mutagens in public health practice.

In the field of radiation protection, recommendations have been made elsewhere. Public health action has been dealt with in the Report of the WHO Expert Committee on Public Health Responsibilities in Radiation Protection¹ and detailed recommendations on radiation protection have been made by the International Commission on Radiological Protection.² The elimination of unnecessary exposure of the gonads to radiation is a task that calls for the collaboration of everyone concerned with public health. In some cases, effective measures are simple and practical. For instance, thoracic X-ray surveys carried out on a large scale in some countries for the detection of tuberculosis may in some cases submit large fractions of the population to abdominal and gonadal irradiation which could be avoided by installation of simple devices on the X-ray machines employed.

Radiomimetic chemical agents are sometimes used in therapy, particularly in the treatment of malignant disease. These agents tend to be strongly mutagenic, and the question therefore sometimes arises of the advisability of treated patients having children. If future experiments with mammals confirm that it is generally the post-meiotic stages of maturing sex cells that are most sensitive to mutagenesis, as now seems to be the case for certain mutagens, then in many practical instances avoidance of conception for a few weeks or months during and after treatment would serve to reduce transmission of genetic damage. Furthermore, the proportion of the population treated with cytostatics is relatively small, so that at present there is no additional genetic burden of any significance to the whole population resulting from the use of these substances.

Of much greater practical importance is the heterogeneous group of chemical substances that have been identified as weak mutagens, to an extent which varies with the experimental organism employed. Such substances are widely used as drugs, as food additives and preservatives, or are otherwise ingested. The following recommendations may be made in regard to them:

(a) Adequate scientific study of the mutagenicity of these substances is necessary, a primary aim being to work out practical test procedures for the detection of mutagenicity, particularly in mammals.

(b) When suitable test procedures are available, the drug legislation of the various countries would prescribe tests for mutagenic properties,

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1963, 254.

² e.g., International Commission on Radiological Protection (1964) *Recommendations*. . . (Amended 1959, revised 1962), Oxford, Pergamon Press (ICRP Publication 6)

particularly in the case of newly-introduced drugs. In many cases it may be necessary to authorize the use of drugs known to be mutagenic, as for example in cancer therapy. In such cases, however, it might be required that special reference or warning be made as to the mutagenic properties of the product.

(c) Research on the relationship between mutagenic action in mammals and chemical constitution of various substances would be of potential practical value in the recognition of mutagenic activity in new substances prior to their introduction for general use.

Certain substances such as caffeine and nitrites, which are in widespread use, and which have been shown to be weakly mutagenic in some lower organisms but not in others, pose a rather special problem from the practical point of view. Because of their widespread use, further tests for mutagenicity would seem to be important. However, unless positive evidence emerges there seems to be no justification on genetic grounds for recommending any changes in current habits.

3.2 Genetic counselling

Genetic counselling is the most immediate and practical service that genetics can render in medicine and surgery. The proportion of the population which really needs genetic advice is not large, but neither is it negligible. Those who do need genetic advice, however, need it badly, and it is a service to patients which should be available.

Experience shows that in some communities the great majority of inquiries come from couples who have had a deformed or defective child and who want to know what the chances of recurrence may be should they have another. With recessive defects — and these bulk quite largely at a genetic clinic — the usual finding is a negative family history on both sides; the danger is revealed only by the birth of an affected child. Then, with some commoner congenital malformations, the empirical risk of recurrence tends to be rather low. The birth to a relative, even a close one, of a child with, say, spina bifida does not indicate an appreciable risk, but naturally the couples who have had such a child themselves will often be concerned about the risk of repetition. Dominant abnormalities and also sex-linked abnormalities are distinctly rare in comparison, so that queries from people contemplating marriage, or from couples who have not yet had a child, are proportionately not very numerous. It must be mentioned, however, that in some communities, for example those in which cousin marriage is common, a higher proportion of queries comes from those contemplating marriage.

With common diseases which have some genetic element in their causation the increased risk to relatives is usually quite low. Moreover,

one or other of these diseases is almost certain to occur in the family history, so that couples may just as well go ahead without worrying. Routine premarital genetic counselling is to be discouraged, except perhaps in some areas with special problems, for example sickle-cell anaemia; it would be very time-consuming and would tend to encourage neurotic tendencies.

One general exception must be made, however. This is psychotic illness. Here there are often traditional fears which transcend the fears of ordinary physical illness. A level of risk that might be accepted for, say, diabetes could well be considered altogether too large for schizophrenia. Hence, with mental diseases inquiries will come more often from those not yet married.

Ideally advice should be given by the family doctor, and as genetic teaching improves at the medical schools the proportion of cases that can be adequately dealt with in this way will undoubtedly grow. Attention is directed to the first report of the WHO Expert Committee on Human Genetics regarding the teaching of genetics in medical schools.¹ But at present many family doctors will be unsure and will need a further opinion. Sometimes this can be given by the appropriate specialist, for conditions which raise genetic queries are often of the kind that will in any case be referred for specialist opinion. There is no doubt, however, that in present circumstances there is a need for genetic clinics. The most convenient method of reference is to the appropriate specialist in the first instance; should a further opinion be desired, reference can then be made to the clinic. Not infrequently, however, the family doctor may refer a patient direct to the clinic.

At a genetic clinic much can be done apart from the mere assessment of risks. Patients can receive psychological support. They can very often be shown that they are not different from other people, merely unlucky. One can hope to go some way in dispelling feelings of guilt. Reassurance can often be properly given to normal relatives, especially the normal siblings of affected children, concerning marriage and parenthood.

The factors underlying the giving of genetic advice are: diagnosis, the individual family history, and the background of the literature. It is the first of these factors that makes preliminary examination by the appropriate specialist so desirable. Sometimes there are fine points in the nature and course of the condition which affect the genetic outlook, as for example when very similar entities may be differently inherited. The compiling of a systematic family history is not difficult; usually close relatives are much the most important; but in the present state of knowledge, family histories are often taken imperfectly. It is the necessity for a

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1962, 238

knowledge of the literature, however, which raises the biggest difficulties. Inherited conditions, or those in whose causation inheritance plays a part, are very numerous and the literature is scattered. Moreover, it is often necessary to assess the quality of the various surveys. This is the chief reason why special genetic clinics are likely to be needed for a considerable time to come.

The task of giving genetic advice is facilitated by the fact that bad risks are usually associated with simple inheritance. With more complex inheritance, the genetics becomes progressively more obscure and the empirical chances of recurrence correspondingly diminish. Fortunately, when the genetics is very obscure, it is often known that whatever the type of inheritance may be the empirical risk is low. Another advantage is that risks tend to cluster round two points, one high and the other considerably lower.

At the worst, and this should not happen often, if the case is really difficult and no reliable estimate of the risk can be made, at least the patient goes away with the knowledge that no one else knows either, and he is then spared the baleful influence of unhelpful comments from friends and relatives and the old wives' tales with which the subject bristles.

The majority of inquirers at a genetic clinic can be told that the outlook is good and that the risk of recurrence is small, very small, or perhaps negligible. Only a minority have to be told that the risk is serious. For every couple in the population who have had a second abnormal child but who would have refrained from having more children after the first abnormal child had they known what the risks really were, there are probably several couples who have limited their families unnecessarily. In this connexion, it must be remembered that in any pregnancy the chance that the child will be born with some severe malformation or will manifest some serious error of development in early life is at least 1 in 40. A special genetic risk not very much greater than this does not look very serious to most couples when the facts are explained to them.

A word is needed about genetic counselling in psychiatric cases. As already mentioned, where psychiatric problems are involved, inquiries are likely to be more frequent from those contemplating marriage. The most important point, however, is that psychiatric appraisal is needed, both of the inquirers themselves and of the histories they give. The psychiatric reports that may be called for must also be carefully assessed. In addition, more general factors may be important, the background of the home, the attitude of the prospective parents to children or further children, indeed a number of considerations which are far from genetic. For these reasons it seems highly desirable that genetic counselling in psychiatric cases, excluding mental deficiency, should be undertaken only by those with psychiatric knowledge, or in collaboration with a psychiatrist.

3.3 Eugenic considerations

While genetic counselling is mainly directed to the benefit of the individual family, eugenic measures are concerned primarily with the population as a whole. The main purpose of these measures at present is to keep the overall burden of hereditary disease and disability as low as possible (negative eugenics) though in the future it may also be possible to devise measures to improve genetic health (positive eugenics).

Eugenic measures will never cause hereditary diseases or disabilities to disappear completely. Spontaneous mutations, the coming together of heterozygous carriers of recessive conditions, and other factors will always bring about new cases. It may be hoped, however, that should eugenic measures be applied, hereditary disease would become less frequent or that the frequency would increase more slowly than without eugenic measures. It might be possible to modify natural trends in directions which, there is reason to believe, would be positive, even though it is not at present possible to analyse the complicated interplay between mutations on the one hand and the very complex and rapidly changing conditions of natural selection on the other.

In regard to positive eugenics, an important consideration is that the observed differences among people can be considered as reflecting their genetically conditioned differences only in those societies that provide something approaching equality of opportunity for all their members. Some reasonable approach to equality of opportunity is therefore a necessary prerequisite for effectiveness, especially of positive eugenic measures. In addition, although circumstances vary widely in different countries, each country may wish to give thought to the removal of those social obstacles to reasonably early reproduction that bear unfairly upon certain sectors of the community. More specifically, it is desirable that reasonably early founding of a family should not be denied to any groups entering into the various activities necessary for the cultural, social and economic well-being of the community.

Among the numerous aims of negative eugenics, two might be mentioned here: (a) diminishing the frequency of hereditary diseases, and (b) diminishing the frequency of high-grade mental retardation. It is appropriate to separate these two groups as the practical measures required are quite different.

(a) *Methods of diminishing hereditary diseases*

In general, it would be desirable if persons suffering from serious hereditary diseases carrying high (theoretical or empirical) risks of transmission were to be encouraged to refrain from having children. This may be achieved by education and counselling, but may never be en-

forced. In this connexion, the founding of genetic counselling services is strongly to be recommended. The very provision of these facilities cannot but have eugenic consequences.

Family planning is practised on a very large scale in a number of countries. It is possible to make eugenic use of this, especially if the public health authorities take account of the eugenic point of view in their counselling practice. This may be possible, for example, in countries where family planning is already encouraged by the state on a large scale in order to slow down the population increase. Where the size of population is regarded by a country to be the most urgent problem, thought may be given at the same time to reducing the incidence of hereditary diseases. In addition, it is known that, even without medical advice, many parents in whose families hereditary diseases are present voluntarily restrict the numbers of their children.

While the present situation varies greatly in different countries, there are cases in which for one reason or another the usual methods of family planning have not been regarded as sufficient, and procedures such as surgical ligature have sometimes been permitted. Proper safeguards and careful avoidance of some of the abuses of the past are, however, widely emphasized at the present time.

The manner and extent to which any of these measures is applied will naturally depend upon the religious and social patterns within the different countries.

(b) *The problem of a possible increase in the frequency of high-grade mental retardation*

It is to be anticipated that the above-mentioned methods will be largely ineffective in the eugenic problem of high-grade mental retardation. On the other hand, this problem is of special practical importance as the condition is so frequent.

It has been suggested that a compensatory mechanism is acting which tends to balance fertility differences at opposite ends of the intelligence scale. Though possible theoretically, it has never been demonstrated that a balancing mechanism of this type does in fact suffice to counteract the expected relative increase of high-grade mental retardation.

On the other hand the empirical risk figures for relatives, the concordance rates for monozygotic and dizygotic twins, and the high average number of children in families containing high-grade mentally retarded individuals, coupled with the decline in child mortality in such families, present a strong *prima facie* case for considering seriously whether appropriate eugenic measures, short of compulsion, might not help in reducing this part of the genetic burden.

3.4 Other genetic preventive measures

One of the most important aims of genetic preventive measures consists in avoiding unfavourable combinations of harmful genes rather than lessening the incidence of these genes in the population. This applies particularly to recessive (or intermediate) defects. If marriages of heterozygotes for any such defect can be reduced, the incidence of the harmful condition (in homozygotes) will fall; if all such marriages could be prevented the condition would disappear. Already one such application is being made. This is in Italy, where in some areas the thalassaemia gene is very common. Those who receive the gene from both parents suffer from thalassaemia major (Cooley's anaemia) and die, usually at an early age. In the areas of high incidence, tests for detecting the carriers, i.e., those who suffer from thalassaemia minor, are freely available, and are applied especially to schoolchildren. The population is made aware by public propaganda of the danger involved should the carriers marry each other. The same measure could be readily applied to sickling and sickle-cell anaemia, and, if accepted by a high proportion of the population, could lead to a dramatic fall in sickle-cell anaemia in a single generation.

It is possible that in the not too distant future the same kind of prevention might be applied to a number of recessive conditions that are considerably rarer. This possibility arises because it is being increasingly found that carriers of some recessive genes can be distinguished by newly discovered laboratory tests, at least in a high proportion of instances. For example, in some countries fibrocystic disease of the pancreas appears to have an incidence of about one in 1500 or 2000 births; this means that about one person in 20 carries the gene, and if a test for detecting carriers could be devised (there is none at present) it might then be worth making testing facilities available to the public and informing them of the danger should carriers marry each other.

A lowering of the rates of consanguineous marriages would also have the general effect of lessening the incidence of recessive defects; this subject has already been considered in section 2.2.

Reduction in the number of consanguineous and heterozygote marriages would, of course, have the effect of hiding the unfavourable genes; as a result, these would, if all else remains constant, gradually become more common in the population. The rise in gene frequency, however, would be very slow because heterozygotes are so much more common than homozygotes. Thus, with a condition having an incidence of 1 in 10 000, there will be one carrier in 50 people; so even the avoidance of all marriages of heterozygotes could only add to the gene frequency, at most, 0.5% in a generation. With such a small increase the problem could safely be left to our descendants who will doubtless possess far more genetic knowledge.

3.5 Preventive and curative treatment and rehabilitation

It is a not uncommon misconception that inherited conditions, or conditions in whose causation heredity plays a large part, are virtually untreatable. This is true of a number of them, but is far from being true generally. Sometimes the development of the disease may be prevented. Thus, in untreated galactosaemia early death is common, and even if this does not occur there is crippling disability. If a diagnosis can be made sufficiently early, withholding lactose from the diet usually ensures normal physical and mental development. In nephrogenic diabetes insipidus, diagnosis is not easy, early death is common, and severe mental deficiency is usual. But if an early diagnosis is made, the maintenance of a proper fluid and electrolyte balance will usually result in reasonably normal development. With this condition there is a further advantage. The gene is sex-linked and the female carriers can always, or nearly always, be detected by their failure to produce normally concentrated urine. Female relatives of affected boys can therefore be tested to find which of them are heterozygotes and have a one-in-two chance that any male child of theirs will be affected.

An example of successful treatment is provided by the recessive condition acrodermatitis enteropathica. If untreated, early death is almost inevitable. The drug di-iodohydroxyquinoline, however, effects a complete cure and, remarkably enough, treatment is fully effective even if started at a late stage. Another example of completely successful treatment is provided by Ramstedt's operation for congenital pyloric stenosis (see page 24).

Sometimes palliative treatment may be almost completely successful, as in many cases of harelip and cleft palate. Many genetic or partly genetic orthopaedic conditions can be treated with complete or partial success, for example congenital dislocation of the hip, club foot or polydactyly.

With fibrocystic disease of the pancreas, the respiratory complications, which are commonly a cause of death, are kept successfully at bay in many instances by the use of antibiotics. Some children treated in this way have now reached the late teens and it remains to be seen whether they will be able to enjoy a relatively normal life.

A special aspect of prevention is seen in drug-induced disease when there is abnormal susceptibility having a genetic basis. The example of porphyria in South Africa involving a special susceptibility to barbiturates has already been mentioned (see page 24). Another example is the deficiency or abnormality of the enzyme pseudocholinesterase, which seems to have no harmful effect unless the person concerned is given suxamethonium as a muscle relaxant during anaesthesia. Then a severe, even fatal, apnoea may occur. One or other of two recessive genes is concerned, and, remarkably enough, persons with one gene of each

kind are also suxamethonium sensitive. It is probable that the frequency of sensitive persons is as high as 1 in 1000.

A sex-linked gene which determines a deficiency of the enzyme glucose-6-phosphate dehydrogenase is extremely common in some populations. Favism may occur in individuals with the deficiency as the result of eating fava beans, but otherwise there seems to be no disability unless certain drugs, for example the sulphonamides, are given. Then there may be a severe haemolytic anaemia (see page 10).

It is likely that the list of genetically determined drug sensitivities will grow rapidly and become a subject of much practical importance. Discovery of these sensitivities may be difficult, but once they have been recognized public health measures aimed at control could be applied with relative ease.

Finally, a word should be said about rehabilitation. With many genetic or partly genetic conditions causing physical or mental disability, much can be done for the patient and for his family in helping him to lead a better and more useful life.

4. INFORMATION NEEDED FOR PUBLIC HEALTH POLICIES AND RESEARCH

Genetic considerations bear on public health policies, on the planning of health services, and on practical preventive, curative and rehabilitation measures. At the same time, vital and health records available in public health practice can often be utilized for research in genetics. Sometimes additional surveys and records are needed, as in the case of schemes for the early reporting of congenital malformations.

4.1 Particular kinds of information

(a) Detailed knowledge of the incidence of genetic and partly genetic disorders is a basic requirement. It is useful as a starting point for research, for the detection of possible increases in special types of malformation and for the planning of public health and rehabilitation services. Had systematic collection of such data been more common in the past, the effects of thalidomide would have been detected earlier.

(b) In the collection of such information, an improved and internationally agreed classification of congenital anomalies and hereditary diseases would be very valuable.

(c) It is important to know how much of the total burden of disease is genetic in origin. Such information will be derived mainly from stu-

dies of families in which the various diseases occur, and from measurements of the empirical risks among relatives of the affected individuals.

(d) It is also important to know how much of the genetic component of disease owes its presence to repeated new mutations (and might therefore increase with any increase in mutation rate) and how much is maintained by subtle differences in fertility and mortality which serve to perpetuate existing genes and gene combinations. The sort of information that bears on this problem relates to differences in survival and fertility among individuals and families in whom the various diseases occur. Data currently available tend to be crude and refinement is needed.

(e) In certain countries, there are large sections of populations in which the practice of consanguineous marriage is quite common. The available data on the genetic effects in the offspring of such marriages cover only limited aspects and are fragmentary. They are in need of being made more extensive and precise. These data are, in addition, of great theoretical interest.

(f) Studies of the hereditary effects of chemical mutagens are needed along the lines developed for assessment of radiation effects. Particularly important are experiments carried out in mammals. Wherever possible, observations on man should be collected.

4.2 Utilization of vital and health records for research and public health measures

An important aid to certain types of research on the factors that determine the prevalence of genetic conditions in human populations is provided by the various records associated with public health practice. These include the so-called vital registrations of marriages, live births, stillbirths and deaths, the various hospital records and, for many regions, a variety of registers of special diseases, congenital malformations, and handicapped children and adults.

Although the records vary widely in the specificity and quality of the medical information they contain, they have in the past been used in a considerable number of research studies, not only as a means of ascertaining disease incidence but also as sources of other information, such as social particulars and family relationships, e.g., relating to the frequencies and inheritance of such diseases as pyloric stenosis, cystic fibrosis and diabetes, and the consequences of inbreeding. To a considerable extent, such use has in the past been limited by the sheer size of the files and the labour of interrelating facts about the same individual or family that are recorded separately in two or more independently derived records.

Such records will almost certainly increase in quantity and quality in the future, and the labour of extracting information from them in usable

form should be greatly reduced as the technology of data processing advances and is more widely applied. Experimentation with the use of such labour-saving methods for population genetic studies is at present in an early stage. This subject was discussed at the UN/WHO Seminar on the Use of Vital and Health Statistics for Genetic and Radiation Studies.¹ In the future, much greater use of the vast quantities of potentially relevant information that is recorded routinely should become possible, and it is to be hoped that some adaptation of the records to facilitate research studies will occur in appropriate instances.

5. CONCLUSIONS

The Committee wishes to point out that genetic considerations add a new dimension to public health work: a concern not only for the health and well-being of persons now living, but also for the genetic endowment of generations yet to come. In this perspective, attention should be given to the possible genetic consequences to man, in terms of health and disease, of contemporary social and population trends and technological developments, including public health and medical actions that are altering man's relationships to himself and to his rapidly changing environment.

Many public health measures and medical-care services, like many socio-economic measures, can alter the genetic endowments of the population to which they are applied, and ultimately the genetic endowment of mankind as a whole. Some of these alterations may be genetically beneficial, while others may, under certain conditions or in the long run, have some undesirable or harmful aspects. It is one of the basic tasks of human genetics and public health together to discover what these alterations are likely to be and how the unwanted ones may be avoided.

A variety of measures are possible that will serve to reduce the amount of genetically caused ill health, now and in the future. Exposure to mutagenic agents can be minimized, parents of genetically handicapped children can seek and receive advice concerning the risk of recurrence in subsequent offspring, eugenic considerations may influence various kinds of private and public decisions and, of greatest immediate importance, many genetic conditions can be alleviated, cured or even avoided in affected or potentially affected individuals.

In all such instances genetic well-being must be considered in the context of other factors that contribute to human welfare, and sometimes short-term objectives must be balanced against long-term objectives.

¹ United Nations (1962) *Proceedings of the Seminar sponsored by the United Nations and the World Health Organization on the Use of Vital Statistics for Genetic and Radiation Studies*, New York.

As a result of modern technology, a vast array of new chemical substances with which life has never before been confronted are being synthesized and used in many ways. Some are employed as drugs, some are spread on agricultural crops or used in food processing or in cosmetics; others accumulate in the atmosphere or elsewhere in the environment as wastes. Some of these compounds are known to be mutagenic; most have not even been tested. Present knowledge concerning the effects of these substances on the genetic structure and health of human populations is almost non-existent. It is urgently necessary that research be carried out on the mutagenicity in mammals of such substances, and that appropriate measures be taken to control harmful substances in the human environment.

Genetic counselling is the most immediate and practical service that genetics can render to the medical care of individuals and families. Because of the importance of genetic advice to those who need it, and because of its favourable effect on the control of genetic disease, such counselling should be an integral part of medical care services. Popular education on genetic matters of public health importance to the population concerned might also often be of benefit in lightening the burden of genetically determined disability.

Annex

GLOSSARY

- Alleles* : Alternative forms of a gene
- Chromosomes* : Components of the cell nucleus that comprise linearly arranged groups of genes; they are passed from one generation to the next and are the conveyors of genetic information. Man normally has 46 chromosomes : 22 pairs of *autosomes* and 2 *sex chromosomes* (XY in men; XX in women)
- Genes* : The elementary units of heredity
- Dominant alleles* : those that manifest their effects both in the heterozygous and the homozygous state
- Recessive alleles* : those that manifest their effects only in the homozygous state
- Sex-linked alleles* : those that are carried on the sex-chromosomes
- Genotype (genome)* : The genetic constitution of an individual (the sum of the genes)
- Heterozygous* : An individual with a different allele on each member of the chromosome pair is said to be heterozygous for this gene (or locus)
- Homozygous* : An individual with the same allele on each member of the chromosome pair is said to be homozygous for this gene (or locus)
- Locus* : The particular place in a chromosome occupied by a gene
- Multifactorial* : Dependent on several genes at different loci, without the restrictions applied to the term "polygenic"
- Mutation* : A change in the genetic material of an organism which results in a new inherited variation
- Phenotype* : The manifest or detectable constitution of an individual (which results from the interaction of his genotype with the environment he has experienced)
- Polygenic* : Dependent on numerous genes at different loci on the chromosomes, whose individual effects are small and cumulative.

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