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GENETIC COUNSELLING

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

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WHO EXPERT COMMITTEE ON HUMAN GENETICS

Geneva, 24-30 September 1968

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GENETIC COUNSELLING

Third Report of the WHO Expert Committee on Human Genetics

The WHO Expert Committee on Human Genetics met in Geneva from 24 to 30 September 1968. Dr P. Dorolle, Deputy Director-General, welcomed the participants on behalf of the Director-General. In his opening remarks, he referred to the second report of the Expert Committee, which had stated: "Genetic counselling is the most immediate and practical service that genetics can render in medicine and surgery."¹ In the last five years, there had been considerable advances in the understanding of human genetics, and public health authorities were becoming increasingly aware of their responsibilities in matters of genetic counselling. The present Committee had therefore been convened to advise on the aims and functions of genetic counselling, and on the best way of setting up counselling services.

Dr J. A. Böök was elected Chairman, and Dr D. Klein Vice-Chairman. Dr A. E. Boyo and Dr E. Goldschmidt were appointed Rapporteurs.

INTRODUCTION

In the present state of medical knowledge the proportion of people in the population who might profit from genetic advice is not large, but by no means negligible. It is probable that, in all countries, not less than 4% of live-born individuals suffer from some genetic or partly genetic condition and might benefit from genetic counsel. At least 1% of all infants, for example, have a major chromosome abnormality. In some areas of the world the proportion of persons suffering from a genetic disorder is much higher. Moreover, the severity of these conditions and their repercussions on the family are so great that the availability of genetic advice is essential. A further important point is that genetic counselling may facilitate early diagnosis, and this may be a major factor in instituting successful treatment.

Experience at specialized clinics shows that at present about 90% of inquiries come from couples who have had a child suffering from some disorder, and fear that there may be a considerable risk of recur-

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1964, No. 282.

rence if they have another child. The bulk of the remaining inquiries concern people with some abnormality that they fear they might pass on, and people who are anxious that something in their family history may imply special risks for their children. There are other important reasons for inquiry, but these are less frequently encountered. It should be emphasized, however, that this situation may well change in the future as scientific knowledge increases, and as the awareness of the medical profession and the public is heightened. Furthermore, in certain parts of the world there are special problems due either to the prevalence of common inherited conditions, such as sickle-cell disease and thalassaemia, or to a high frequency of consanguineous marriage.

The possibility of giving useful genetic advice has steadily increased over recent years and this trend will undoubtedly continue. This is partly because more and more inherited disease entities are being recognized, defined and subdivided, and because many of the inevitable complications are being identified. In this progress, biochemical and other technical advances have played an extremely important part. In addition, there are many conditions, notably amongst the commoner congenital malformations, that are not due to simple genetic mechanisms, even though they are significantly more frequent amongst the close relatives of affected persons than in the general population. In the absence of a simple genetic pattern, the large-scale surveys that are being carried out in increasing numbers enable empirical risk figures to be established, so that the family can be given suitable advice.

The great advances in human cytogenetics in the last 15 years have made it possible to give efficient counsel in this new field. Cytogenetics is not only of scientific interest in its own right, but has stimulated medical and lay interest in the whole subject of genetic counselling.

Nowadays it is becoming increasingly possible to distinguish the outwardly normal carriers of harmful genes. To quote a single example, a few years ago the sister of a boy suffering from muscular dystrophy of the Duchenne type could only be told that there was a chance of 1 in 2 that she was a carrier, so the risk of any son of hers being affected was 1 in 4. Estimation of the level of creatine phosphokinase in the blood now makes it possible to tell about 80% of such women either that they carry the gene and that the risk is therefore 1 in 2, or that they do not carry it, so that the risk is negligible.

It should be pointed out that although risk figures are frequently high and may well deter couples from parenthood, even more often the risk is little greater than that inevitably present in any pregnancy, and the inquirers can be reassured that they are unlikely to transmit genetic defects to their children. Moreover, all risk figures have to be considered in the light of the particular condition concerned and its impacts — medical, social, psychological, etc. — on a particular family. The

availability or otherwise of efficient therapy or prophylaxis must be taken into account. Even high risk figures can be faced with reasonable assurance when it is understood that an affected child may, if corrective measures are taken, be able to lead a more or less normal life.

1. RECENT DEVELOPMENTS

1.1 Genetic counselling services

Genetic counselling services are unevenly distributed throughout the world; and their present level and scope in a given area does not necessarily reflect the public health importance of the area's prevailing genetic problems. In tropical Africa, for instance, there are certain areas where the sickle-cell gene is carried by 25% or more of the population, but genetic advice is rarely, if ever, available. Some governments, however, have reacted to a high prevalence of genetic disorders by setting up special counselling services. The Italian network for thalassaemia detection, for instance, comprises an institute in Rome and sixteen provincial centres that provide facilities for the systematic detection of thalassaemia and for premarital counselling.

In the USA, states are beginning to organize genetic counselling programmes under the aegis of maternal and child health services. Already fifteen states have a genetics programme, and most of these have been introduced within the last five years. More frequently, however, both in the USA and elsewhere, genetic counselling services have developed as organic units within hospitals or medical faculties. In many instances, the initiative has come from members of science faculties.

An *ad hoc* survey carried out by the WHO Secretariat showed that the reasons for seeking genetic advice vary considerably from one clinic to another. This may have reflected the country's legal framework (e.g., the accessibility or otherwise of termination of pregnancy or sterilization), or the widely known expertise of the director of the clinic. Consultation was chiefly sought in connexion with congenital malformations, mental retardation, psychiatric illness and inborn errors of metabolism. The principal reasons for seeking advice were the birth of a child with some abnormality and the risk of recurrence in subsequent children, or the existence of some defect in one of the spouses themselves or in a relative. However, in several clinics, a considerable proportion of queries concerned consanguineous marriages. Counsellors were also requested to interpret the cause of a disease, to give a prognosis for an affected child, and to advise on paternity disputes and adoption.

In the experience of most counselling centres only a minority of couples sought premarital advice, and the clinic was usually approached

only after the birth of the first affected child. Counselling in most clinics was conducted by medically qualified persons, and the number of families seen annually varied from 10 to 600.

1.2 Technical advances relevant to human genetics

Recent technical advances have greatly increased the number of diagnostic tools available to the genetic counsellor.

1.2.1 *Human cytogenetics*

Technical developments in mammalian cell culture *in vitro* and in cytological methods have made it possible, since 1956, to define and examine the human karyotype more precisely. Following the exact determination of the chromosome number of man, associations were soon discovered between deviations from the normal chromosome number and well-known clinical syndromes of obscure etiology. Down's syndrome, for instance, was found to be associated with a chromosome number of 47 due to the presence in triple dose (trisomy) of autosome 21. The mere fact that patients with trisomy 21 usually constitute 10–20% of mentally retarded individuals in institutions hinted, at an early stage, that cytogenetics was to make an important contribution to human pathology.

Most deviant karyotypes in man are the result of recent random events, although a number of factors are known or suspected to affect the frequency of such deviations, e.g., ionizing radiations, various chemicals, infectious agents, and parental age. As a consequence, in most situations with which the geneticist is faced in counselling the risk of repeat within the same sibship is low. Moreover, most deviant karyotypes are associated with profound malformations or severe mental retardation, and are therefore unlikely to be transmitted to the next generation, or with anomalies of sexual development that lead to permanent sterility.

However, it is important to note the exceptions to this general pattern. Karyotypes that include structural chromosome changes in a balanced form, e.g., translocation heterozygosis, can be associated with normal development and function. Individuals with such karyotypes may have children who carry the translocations in an unbalanced form. In families where this occurs, as in families where mosaic gonads are present, the risk of a repeat may exceed 30%.

While routine karyotyping is generally performed on mitotic (somatic) chromosomes, technical improvements have permitted examination of the chromosomes of meiotic divisions in man as well. In males, they can be analysed in preparations from small testicular biopsies, but examination of the meiotic chromosomes in females is still at the

research level. Perfection of these techniques is of great importance, since the interpretation of certain karyotypes will remain controversial as long as their analysis is restricted to mitotic chromosomes, and the pairing of homologous chromosomes at meiosis will provide the final key.

Chromosome analysis during meiosis is of great value in cases of clinical sterility of unknown origin, particularly for the detection of disturbances due to translocations and inversions. A complete clinical fertility investigation, therefore, should include examination of the mitotic chromosomes of both partners and the meiotic chromosomes of the male partner.

It can be concluded that cytogenetic examinations are a valuable aid to the genetic counsellor, and the very rapid new developments in this field make it likely that they will become increasingly important. Because of the work and expense involved in karyotyping, however, the referral of a patient for cytogenetic analysis must have good clinical justification.

1.2.2 *Human biochemical genetics*

Advances in techniques such as electrophoresis, gel filtration, chromatography, and enzymatic analysis, have now made it possible to identify the basic abnormalities underlying a number of molecular diseases and inborn errors of metabolism. It has been shown that many of these conditions are due to genetic abnormalities that may affect the metabolism of certain substances or the structure and rate of synthesis of some enzymes and haemoglobins. This discovery may have practical implications for treatment and prevention. Phenylketonuria, for example, a condition characterized by extremely serious mental and behavioural disturbances, is caused by a lack of phenylalanine hydroxylase. This leads to accumulation of phenylalanine in the blood and to the excretion through the kidneys of an excessive amount of certain metabolites, of which phenylpyruvic acid is the most important. In galactosaemia, the galactose of milk cannot be properly metabolized because of the lack of a galactotransferase. This causes serious digestive trouble, complicated later by cirrhosis of the liver and ultimately by varying degrees of cataract and of mental retardation. The appearance of clinical manifestations of phenylketonuria and galactosaemia can be prevented by prescribing diets free of phenylalanine and galactose respectively, over a long period.

Other disorders affecting the metabolism of leucine, isoleucine, and valine (e.g., leucinosi, also known as maple syrup urine disease) result in still more serious neurological complications that represent an immediate danger to life.

These genetic diseases are particularly interesting because they are amenable to treatment, and systematic screening of newborn infants

is therefore important. This task is within the scope of a suitably equipped biochemical genetics unit, and techniques at present being developed will make it possible to carry out simultaneous screening for several inborn errors of metabolism at relatively low cost.

Most of these metabolic disturbances are caused by the presence in double dose of an autosomal recessive gene, and in the case of certain traits a high proportion of carriers can be detected. With phenylketonuria, for example, this can be done by means of a phenylalanine loading test, and galactosaemia carriers can be detected by direct measurement of the enzyme activity of the red cells. In the case of severe recessive sex-linked disease it is particularly important to detect the female carrier (see p. 6).

In Hurler's disease,¹ the accumulation of mucopolysaccharides in the tissues produces marked skeletal changes and serious mental retardation. Two varieties of this disease are known at present; one is transmitted as an autosomal recessive character, the other as a sex-linked recessive character. In the autosomal form, mucopolysaccharide deposits can be detected in fibroblasts cultured from biopsy specimens from both parents, but in the sex-linked form deposits are found only in cells originating from the mother. The distinction between the two forms of the disease is of essential importance, for it greatly affects the probability that the child of a patient's sister will suffer from the same complaint.

This technique can be applied to fibroblasts derived from the umbilical cord and could probably be adapted to amniotic cell culture.² At present, however, amniocentesis involves a serious risk to the further development of the foetus and is still at an experimental stage. Future improvements in technique may well render this operation harmless, and then it could also be applied, when indicated, to detect chromosomal aberrations at an early stage of intra-uterine life. In the case of harmful, sex-linked, recessive traits, examination of cells in the amniotic fluid for the presence of Barr bodies might indicate the sex of the foetus, and enable the counsellor to give appropriate advice. It must be stressed, however, that this hazardous technique should not be used to discover the sex of the unborn merely for the sake of curiosity.

1.2.3 *Modification of germ plasm*

Evidence is accumulating that the germ plasm of mammals can deliberately be modified by external action, although at present only a few micro-organisms can be treated in this way. A simple instance is the Shope virus, which causes tumours in rabbits. It may also infect

¹ Lamy, M., et al. (1968) *Les maladies héréditaires du métabolisme chez l'enfant*, 2nd ed., Paris, Masson.

² *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 401, p. 41.

man, with no harmful consequences, but infected persons produce a new form of the enzyme arginase that is typical of the virus but is not normally synthesized in man. The explanation has been given that the virus is silent in the human genome, except for the production of its arginase, which may be used by the host cell. Looking into the future, one may speculate that research along such lines could result in the modification of human germ plasm with a view to effecting the permanent cure, in individual cases at least, of some inherited defects.

2. TYPES OF CASE REQUIRING GENETIC COUNSEL

From the genetic point of view, the conditions that lead people to seek advice fall into a few groups, although these groups overlap to some extent.

2.1 Conditions due, or probably due, to single genes

When a condition is known or presumed to be due to a single gene, the outlook for the inquirer is usually bad. But although inheritance is simple, a number of complications make expert advice necessary in many instances. These complications include :

(a) The immense number of simply or fairly simply inherited conditions. Nearly all of them are rare, but their aggregate importance is considerable.¹

(b) Mimic genes : the very numerous conditions, with similar manifestations, that may be due to any one of several quite different genes (see dwarfism, section 3.3). Here such factors as an assessment of the individual's family history and a knowledge of the relative frequencies of the different kinds of gene are very important in counselling.

(c) Phenocopies : the numerous conditions, apparently identical, that may be due either to genes or to non-genetic influences. Deaf-mutism is a notable example.

(d) Genetic conditions in which the abnormal gene can be identified but which only become symptomatic in a specific environment, e.g., acute intermittent porphyria.

(e) Failing penetrance, i.e., genes that are sometimes expressed and sometimes not. There may also be wide differences in the degree of abnormality, i.e., variable expressivity.

¹ About 1500 such traits are listed in McKusick, V. A. (1968) *Mendelian inheritance in man*, Baltimore, Johns Hopkins.

(*f*) Particularly in the case of some dominant genes, the condition is of relatively late onset. Some knowledge of the distribution of ages of onset is needed if reasonable risk figures are to be calculated.

2.2 Conditions partly of genetic origin

These conditions are usually polygenic; other factors, environmental or unknown, are also involved, frequently to a greater extent. For such conditions, the most notable examples of which are many of the commoner congenital malformations, there are no precise theoretical genetic ratios. Instead, empirical risk figures for the chance of recurrence in close relatives have to be estimated on the basis of large-scale surveys. Expert advice may be desirable in assessing the results of such surveys. In general the outlook for the inquirers is good, or relatively good.

2.3 Conditions of variable origin

With some conditions the majority of cases are partly of genetic origin, and the risk of recurrence is low, but occasionally a single gene is responsible. For instance, most cases of low-grade mental retardation that do not fall within any recognizable entity or syndrome carry a low risk of recurrence. Some cases, however, are due to single genes, usually recessive, and careful assessment of the family history is needed. The influence of a recessive gene is strongly indicated if two similarly affected children are born to the same parents, or if the parents of an affected child are first cousins. No precise etiology can be ascribed to the majority of instances of isolated central cleft palate, but a minority may reasonably be attributed to a dominant gene of reduced penetrance. Again, the family history must be carefully assessed.

2.4 Chromosome abnormalities

Chromosome analysis is recommended in all cases of : (*a*) suspected Down's syndrome; (*b*) juvenile oligophrenia; (*c*) repeated spontaneous abortions, stillbirths, and multiple malformations; (*d*) sex-chromatin findings not consistent with phenotypic sex; (*e*) exposure to mutagenic agents; and (*f*) infertility in males with normal phenotype.

The Committee realized that few, if any, laboratories could at present undertake this large and costly programme. It was of the opinion, however, that under ideal conditions all such cases should be karyotyped.

3. GENETIC COUNSELLING SERVICES

3.1 Aims and functions

Genetic counselling, like any other medical service, should be devoted to the welfare of the individual or family seeking advice. The counsellor should not pursue any genetic programme designed to benefit future generations if this programme conflicts with the immediate interests of his patients.

The person seeking advice should receive a clear estimate of the risk about which he inquires. Counsellors should be as neutral as possible when stating the risk estimate, although when pressed to say what they would decide in a similar situation some counsellors will offer more explicit advice. If possible, the risk estimate should be given through the referring physician.

The risk should be explained in a manner appropriate to the inquirer's educational level. He should be provided with the basic facts, without any attempt to relieve him of the responsibility for making his own decision. It may be advisable, for example, to tell him that there is a 75% chance of a favourable outcome of a given pregnancy and not merely that there is a 25% risk of an unfavourable outcome. In many cases it may be possible to relieve the inquirer's anxiety by assuring him that the condition is not genetically determined and a recurrence is therefore most unlikely. In other cases, persons in whom genetic diseases may develop can be detected early and can be given either prophylactic treatment or proper advice on occupations that will be open to them in spite of their affliction.

Some centres provide information on treatment and refer patients to institutions responsible for the education, medical supervision or hospitalization of afflicted individuals. In other centres it is customary to refer applicants to clinics that give advice on safe contraceptive measures.

Although in several countries a high genetic risk to a future child is recognized as a legal ground for voluntary termination of pregnancy or voluntary sterilization, in many other countries this risk is not recognized as legal justification for either of these operations.

In many cases the geneticist can help the general practitioner to improve or refine the diagnosis of a patient. This diagnostic advice may be based (a) on the pedigree evidence; (b) on laboratory facilities at the disposal of the genetics centre (karyotyping, biochemistry, haematology, dermatoglyphics); and (c) on the counsellor's knowledge of the medical literature on genetics.

In this way genetic counselling may help in the recognition and definition of specific inherited anomalies that had not previously been identified. Information relevant to such research will usually emerge from the summaries of cases of certain types dealt with in the centre over a number of years.

The research interest of cases referred to a counselling centre often leads other departments and laboratories in the hospital or in the same city to co-operate. The appeal of advances in genetics to the general practitioner may also be instrumental in increasing the number of referrals to counselling centres. Research, however, can never be considered the main object of the consultant, whose primary concern is the counselling of physicians and their patients.

3.2 Referral

The majority of patients seen at counselling centres are referred by general physicians or medical specialists. In the case of referral by specialists, the genetic counsellor is provided with at least a preliminary diagnosis of the condition for which he has to estimate the recurrence risk. Further examinations by specialists may be required, however, before a final diagnosis is reached.

In some cases people approach the counselling centre on their own initiative, by telephone or by correspondence. Many counselling centres will accept these inquirers and grant them an interview without the mediation of a general practitioner, particularly if the case requires no pathological diagnosis, as in the instance of premarital counsel to close relatives with no recorded recessive disease in the family, or if the centre has diagnostic facilities at its disposal (cytogenetics laboratory, dermatoglyphic equipment, or facilities for the detection of haemoglobinopathies).

The Committee felt that direct application to the centre should not be encouraged, and that referral by a physician is preferable. In some countries referral is required by established hospital practice, and in others by the social insurance system.

The ideal system of referral is a three-tier service. The patient would go in the first instance to his family doctor; he could then be referred to an appropriate specialist, who could, if necessary, arrange for him to be seen at a genetic counselling clinic. The general practitioner may be able to give the necessary advice himself, although it is doubtful whether this will happen in more than a small minority of instances for a long time to come.

Many of the cases on which advice is sought will in any event be referred to appropriate specialists for other reasons. These specialists may provide genetic advice, but many are reluctant to do so in a large proportion of cases. The vast number of inherited conditions makes

it difficult for them to keep abreast of the developments in genetics, even in their own field. This is why it is so important to set up genetic counselling centres, where the staff have a thorough knowledge of the literature and possess the experience required to balance alternatives and probabilities. One centre can cover a large population, for referrals are at present relatively few in number per unit of population, and are unlikely to increase substantially for some time to come.

3.3 The counsellor's qualifications and approach

Genetic counselling should be governed by a relationship of the doctor-patient type. Presumably the counsellor will have a medical degree, and he should also have extensive training in basic genetics and medical genetics.

In complicated counselling cases, it is customary for a team approach to be made by experts in karyotyping, biochemical tests, or other laboratory examinations, and geneticists familiar with the calculation of risk estimates. The results are communicated to the patient by the family physician or some other person qualified for the task. It is essential that someone with extensive training in human genetics should participate in every counselling case.

Since the diagnosis is the basis for determination of the genetic mechanism and for an estimate of the risk, the counsellor must take particular care to ensure that it is of the highest scientific quality. The necessity for checking the original diagnosis is illustrated by dwarfism, of which there are at least six genetically distinct types. Diastrophic dwarfism is characterized by club-foot, cauliflower ear, distal hyperextensibility of the thumb (hitch-hiker's thumb), and other anomalies. It behaves as an autosomal recessive and is therefore completely different, from the point of view of genetic counselling, from classical achondroplastic dwarfism, an autosomal dominant.

Once the diagnosis has been firmly established, other qualities of the counsellor become important. He must be willing to listen patiently to his client, to establish some degree of rapport, and to win his client's confidence. To ensure that he can give correct advice, he must be willing to give generously of his time in helping the inquirer to obtain records and other necessary documentation from relatives and others.

Once scientific information on the client's case becomes available, it should be imparted with the tact and psychological skills that all counsellors should possess. The counsellor should always be aware of the emotional and social problems his client faces, as for instance in cases of threatened blindness or severe neurological affection. Loss of sight or any physical or mental impairment often leads to feelings of

deep frustration in the patient, and sometimes in other members of the family as well, that may trigger unrealistic reflex actions such as suicide.

3.4 Screening

An important service can be performed by screening programmes for specific diseases. For example, if a child with phenylketonuria is detected in the course of a screening programme for biochemical defects, the parents will automatically be told that they carry the disease, and the risk involved in the conception of further offspring will be made clear to them.

In developing regions the importance of genetic counselling will grow as the problems of undernourishment and the high morbidity and mortality due to infectious disease decrease. There are certain areas, however, where deleterious genes, in particular those responsible for defects of the red blood cell such as sickle-cell disease or thalassaemia, are so common that adequate screening programmes for the active detection of carriers should be encouraged at an early stage in the development of the country's public health system.

These programmes should be directed by trained medical haematologists. The training of haematological teams for countries where the haemoglobinopathies are common should be encouraged.

Screening of populations for metabolic or cytological (e.g., sex chromatin) abnormalities is highly desirable, but will usually be outside the scope of the genetic counselling clinic. However, such screening would be practicable in countries where the public health service is prepared to organize a nationwide screening system in conjunction with a comprehensive network of genetic counselling centres.

It is also noted that some countries are setting up community centres for family hygiene and genetic counselling, staffed by physicians, geneticists, trained laboratory technicians, nurses, midwives, and social workers.

3.5 Follow-up

Follow-up investigations at regular intervals are to be encouraged as a valuable complement to counselling. They will make it possible (a) to estimate the general reliability of the advice given, (b) to determine how far the advice has been followed, and in what manner, and (c) to maintain contact with the families seen at the clinic and complete the data on them. Data collected by counselling services, however, are not to be used indiscriminately as a basis for estimating empirical risk figures or other parameters related to the population served by the clinic, since

the number of cases of any one specific anomaly is often relatively small and there is a danger that the families followed up may give a biased sample.

The follow-up procedure adopted is dependent upon the location of each centre and the funds available. In a large city, for instance, it is desirable for families to be interviewed personally, possibly by specially trained social workers, but in areas where the population is scattered questionnaires may be sent by mail. If the proportion of unanswered questionnaires is large, however, this may introduce a bias into the calculations. Direct contact with the families wherever possible therefore seems the best procedure for follow-up.

3.6 Facilities

Diagnostic facilities available to the genetic counselling centre should ideally be as comprehensive as possible. Preferably the clinic should be affiliated to a large hospital, such as a university hospital, so that for refinement of diagnosis it has access to certain laboratories and services, such as a blood grouping laboratory, haematological laboratory, and facilities for audiometry, retinoscopy, electroretinography, and psychological testing, including IQ and personality tests. Under optimum conditions, the main investigations relevant to the diagnosis will be carried out before the inquirer arrives at the genetic counselling clinic.

Laboratory techniques that human geneticists have particularly helped to develop are karyotyping and analysis of dermatoglyphics. These techniques should be available to all large counselling centres.

For more specialized procedures, such as the identification of unusual abnormal haemoglobins, variants of glucose-6-phosphate dehydrogenase or other rare genetic markers, specimens may be referred to the WHO reference laboratories and reference centres listed in the Annex.

The storage, preservation and retrieval of all data relevant to the cases dealt with in counselling centres are of the utmost importance. These data include the results of laboratory tests, dermatoglyphic prints, photomicrographs of chromosomal anomalies, photographs of patients with visible malformations, and pedigree data collected for a given family.

The case histories collected by a large genetics centre in the course of several decades may form the nucleus of a comprehensive register of the pedigrees of most families in the area that are affected with certain categories of inherited anomalies. Obviously, such projects will only be justified in areas where the population is relatively settled. The establishment of an international register of human chromosomal anomalies, including those that do not appear to impair the health of their carriers, seems desirable.

The importance of complete documentation, including illustrations of all rare and controversial anomalies that require refinement of diagnostic criteria, should also be stressed. This applies to many major and minor malformations, and in particular to novel karyotype anomalies.

4. ROLE OF GENERAL PRACTITIONERS

It is doubtful whether it is safe to encourage general practitioners to give advice on genetic matters unless they have a good deal of genetic knowledge, or are dealing with some condition that is genetically particularly straightforward or for which empirical risks of recurrence are well established and widely known. In other cases their attempts might on balance do more harm than good.

Even if the general practitioner can deal directly with only a few relatively simple problems, however, his importance in a counselling service must on no account be underestimated. He has a vital part to play in the three-tier service outlined in section 3.2. The specialist may see a subject on only a few occasions, and parents may be seen only once at a genetic clinic, although a second interview is desirable. The family doctor, on the other hand, is in constant touch with the family and its problems. He can give continuing support, and repeat and explain any advice that has been given. Moreover, he can often give helpful guidance that takes into account many personal and social factors in addition to purely genetic considerations. At the same time, he should be alert to the genetic problems that may be troubling his patients, even if they themselves are only dimly aware of them.

As was emphasized in the Committee's first report,¹ the education of the general practitioner in medical genetics is most important. Teaching should be given at both the preclinical and clinical levels of medical education. It is equally important, however, that medical genetics be dealt with in postgraduate education and in refresher courses.

5. EDUCATION OF THE PUBLIC

As a result of the rapid expansion of the science of genetics and of its application to man, human geneticists are often called upon to help instruct physicians or the general public in the principles of modern genetics, with special emphasis on the inheritance of normal and abnormal traits in the human family and in human populations, including the consequences of consanguineous marriage.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1962, No. 238.

The media that may be used for adult education in genetics range from talks and demonstrations in lecture theatres, on the radio or on television to semi-popular articles in magazines or the daily press.

In spite of the great appeal these educational activities may have for the general public, their impact on the adult listener or reader may be limited. An adult audience often shows wide variations in educational level and in capacity to absorb new information. Nevertheless, in some cases public lectures have stimulated the referral of many new cases for counselling.

The secondary school would seem to be the right stage for disseminating knowledge of genetics. It appears that most modern biology curricula allot sufficient time to the teaching of genetics and that examples used to demonstrate the principles of genetics are to a large extent drawn from man. The emphasis on human genetics in biology teaching appears desirable, provided that the teachers are sufficiently conversant with the material and can keep their knowledge up-to-date.

The Biological Science Curriculum Study programme initiated in the USA has stimulated a reform in biology teaching in many countries, and the instruction manuals for teachers and pupils are being translated into many languages. This teaching programme usually begins with a series of refresher courses, in which the secondary school teachers become acquainted with recent advances in biology and with methods for the class and laboratory teaching of genetics in particular.

Educational programmes in human genetics are certainly desirable, but their success depends on the tact exercised by the teachers. Every instructor should bear in mind that the science of genetics has been abused in the past to furnish a pretext for ethnic discrimination. The heterogeneous distribution of deleterious genes among different population groups can be explained without arousing feelings of fear or guilt among any members of the audience.

6. CONSEQUENCES OF GENETIC COUNSELLING

It is useful to distinguish between the short-term and the possible long-term effects of genetic counselling. Although it may prevent illness and suffering in individual families, genetic counselling is unlikely, at the present time, to lead to significant changes in the frequencies of deleterious genes.

Presumably, genetic counsel will eventually be given to the majority of families who are in need of it, and then it might well alter gene frequencies. It is difficult to predict the consequences on the frequencies of the individual genes without postulating (a) specific mating patterns, and (b) specific

mechanisms for the maintenance of the gene in the population before counselling affected the mating pattern. Since the conclusions reached will depend on the mating patterns and the mechanisms of maintenance postulated, such studies are for the moment a theoretical exercise for the population geneticist. It is advisable to carry out research on mathematical models.

However, the impact of genetic counselling in cases of dominant and sex-linked genes may be immediate, and in consequence the gene frequency may drop very substantially, and eventually reach a level not greatly in excess of the mutation rate, which is the irreducible minimum.

In the interests of the individual it is often necessary to give advice that, if accepted, may not reduce the frequency of the harmful gene in the population. For instance, if two heterozygotes for betathalassaemia or for the sickle-cell gene seek premarital advice, they may refrain from founding a family together and choose other, unaffected partners. Each of them will then pass on the defective gene to future generations, whereas a marriage between them would have promoted selection against that gene by producing the lethal or sublethal homozygote. Very similar considerations apply to premarital advice to close relatives. If, on the other hand, a couple to whom a child homozygous for a deleterious gene has already been born asks for genetic counsel, and decides in consequence to limit its family, this could help to reduce the frequency of that gene.

The establishment of efficient counselling services should be proceeded with, despite the conflict that may arise on some occasions between the interests of the individual and those of future generations. In the present elementary state of our knowledge of population genetics, the possible long-range dysgenic effects of premarital counselling must be disregarded. These dysgenic effects are probably negligible compared with those of modern therapy.

7. RECOMMENDATIONS

Genetic counselling centres should be established in sufficient numbers in regions where infectious disease and nutritional disorders are being brought under control and the relative importance of hereditary disorders is increasing, and in areas where genetic disorders have always constituted a serious public health problem. In some parts of the world the high frequency of certain lethal or sublethal genes, such as those responsible for sickle cell and thalassaemia, will require a special genetic counselling service for carriers, as well as suitable medical facilities for the care of afflicted individuals.

Since genetic counselling centres and the specialized medical and laboratory services they require are an integral part of medical care, they should be covered by health and social insurance schemes.

It will not be possible to implement these recommendations unless trained personnel are available. In this connexion, attention is directed to the first report of the Expert Committee on Human Genetics, which recommended minimum requirements for instruction in genetics at both preclinical and clinical levels of medical education and in postgraduate training.¹

In addition, facilities should be provided for specialized training in medical genetics. Courses should be available in basic human genetics, human cytogenetics, haematological genetics, human biochemical genetics, and other subjects essential for competent genetic counselling. The Committee has noted the work carried out under the WHO Fellowship and Training Grant Programme to promote such training, and recommends that these activities continue.

As human genetics is a relatively new discipline, it was not included in the formal education of most physicians and public health administrators, and the organization of continuing education (refresher) courses in medical genetics is recommended. It would also be helpful if pamphlets dealing with genetic problems of particular importance in an individual country could be made available for distribution to general practitioners or, in certain instances, to the general public.

The Committee recommends that ministries of health should provide their health personnel with a descriptive list of the staff and facilities available for genetic counselling.

In order to encourage consultation between centres and facilitate referral for highly specialized advice, it is recommended that WHO consider requesting the above information from each country and preparing an international directory of genetic counselling services, indicating the facilities and specialized skills available at each centre.

All pedigree data and documentation, including microscopic and macroscopic photographs and dermatoglyphic prints, on cases dealt with in genetic counselling centres, should be preserved and filed for easy access. This applies in particular to the results and records of cytogenetic analysis.

The Committee recommends the establishment of an international register of human chromosome anomalies, as was proposed in 1966 by the Chicago Cytogenetics Conference.² The material described in the previous paragraph would be particularly useful in this project.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1962, No. 238.

² [Proceedings of the] Chicago Conference : *Standardization in human cytogenetics*. In : *Birth Defects Original Articles Series*, New York, National Foundation — March of Dimes, Vol. II, No. 2 (1966).

Annex**WHO REFERENCE CENTRES**

As part of its research programme in human genetics and immunology, WHO has established a network of international and regional reference centres. At the discretion of their directors, these centres advise on technical procedures and the testing of sera, undertake the identification of rare variants, and provide training facilities. Where necessary, they also maintain sets of standardized reagents, or reference panels of all available variants, and whenever possible they will supply samples to qualified investigators. They are also concerned with the development of methodology, including techniques for the transport and storage of biological material.

The centres concerned with human genetics or immunology are as follows :

WHO International Blood Group Reference Laboratory

Medical Research Council's Blood Group Reference Laboratory,
Lister Institute of Preventive Medicine, London, England

WHO International Reference Centre for Abnormal Haemoglobins

Medical Research Council's Abnormal Haemoglobin Research Unit,
Department of Biochemistry, University of Cambridge, England

WHO International Reference Centre for Immunoglobulins

Institut de Biochimie, Lausanne University, Switzerland

WHO Regional Reference Centre for Immunoglobulins

National Cancer Institute, National Institutes of Health, Bethesda,
Md., USA

WHO International Reference Centre for Genetic Factors of Human Immunoglobulins

Centre départemental de Transfusion sanguine et de Génétique
humaine, Bois-Guillaume, France

WHO Regional Reference Centres for Genetic Factors of Human Immunoglobulins

Department of Medical Microbiology, University of Lund, Sweden
Department of Biology, Western Reserve University, Cleveland,
Ohio, USA

WHO International Reference Centre for Serum Protein Groups

Zoology Department, University of Texas, Austin, Texas, USA

WHO International Reference Centre for Glucose-6-Phosphate Dehydrogenase

Department of Medicine — Medical Genetics, University of Washington, Seattle, Wash., USA

WHO Regional Reference Centres for Glucose-6-Phosphate Dehydrogenase

Department of Haematology, Tel-Hashomer Government Hospital, Israel

Sub-department of Haematology, University College Hospital, Ibadan, Nigeria

WHO International Reference Centre for the Serology of Auto-immune Disorders

Department of Immunology, Middlesex Hospital Medical School, London, England

WHO Regional Reference Centres for the Serology of Auto-immune Disorders

Department of Bacteriology and Immunology, State University of New York at Buffalo, Buffalo, N.Y., USA

Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Melbourne, Australia

WHO International Reference Centre for Tumour-Specific Antigens

Division of Immunology and Oncology, Gamaleja Institute of Epidemiology and Microbiology, Moscow, USSR

WHO International Reference Centre for the Use of Immunoglobulin Anti-D in the Prevention of Rh Sensitization

MRC Experimental Haematology Research Unit, St Mary's Hospital Medical School, London, England

WHO International Reference Centre for Testing of Natural Resistance Factors

Department of Immunology, Institute of Epidemiology and Microbiology, Prague, Czechoslovakia

WHO International Reference Centre for Processing of Human Genetics Data

University of Hawaii, Honolulu, Hawaii, USA

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