



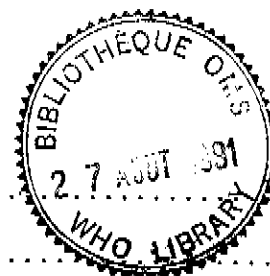
HEREDITARY DISEASES PROGRAMME
DIVISION OF NONCOMMUNICABLE DISEASES AND HEALTH TECHNOLOGY

Geneva, 20-22 November 1989

REPORT OF A WHO MEETING ON
ADVANCES IN DIAGNOSIS, TREATMENT AND PREVENTION
OF HEREDITARY DISEASES

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1. INTRODUCTION

An advisory group meeting in 1985¹ noted that a set of "community genetics services" based on population screening now exist, with important implications for the role of the clinical geneticist. Classically, clinical geneticists provide differential diagnosis, prediction of recurrence risk, and family counselling for people referred to them with suspected genetic problems. However, the growing role of prenatal diagnosis and the possibility of community control of genetic disorders require geneticists to forge close links with obstetricians, neonatologists, paediatric pathologists and epidemiologists, and preventive services based on screening require the development of an outreach approach to the entire population. The group also concluded that genetic disease is important in developing as well as developed countries, and identified issues of particular relevance in different regions. Basic methods for evaluating the need for services (service indicators) were proposed. There has been rapid progress in many aspects of medical genetics since the 1985 meeting of the Advisory Group, and indications for introducing genetic technology and services into developing countries are increasing.

The Regional Offices of the World Health Organization play a key role in promoting the community approach to genetic disease: the Regional Office for Europe in Copenhagen (Division of Maternal and Child Health) has commissioned a study of community genetics services in the region², and the Pan American Health Organization (PAHO) in Washington has produced recommendations on development of medical genetics in Latin America and the Caribbean area³. Similar involvement of the remaining WHO regional offices is necessary.

2. THE CONCEPT OF COMMUNITY GENETICS

A reduction of the mortality, disability and morbidity caused by communicable diseases and malnutrition has resulted in change in the disease spectrum of industrialized countries. On the one hand, about three quarters of people die from diseases such as cardiovascular disease and cancer, which have an important genetic component. On the other hand, congenital diseases have achieved a real public health importance. Depending on the recording system, from 1.5 to 6.5% of newborns have a congenital anomaly of some kind, but the birth prevalence of infants with lethal and severe congenital anomalies is about 2-3% in all countries with well established registration¹⁻³. In industrialized countries, severe congenital anomalies account for more than 20% of infant mortality and cause the largest number of years of life lost and the highest impaired life years of all disease categories⁴.

At present aetiological analysis indicates five main groups of congenital anomalies: major gene or Mendelian entities (about 6% of the total); chromosomal abnormalities (about 5%); multifactorial origin (about 50%); environmental, including both teratogenic and maternal factors (about 5%); unknown aetiology (about 34%). As congenital anomalies vary in their cause and natural history, there is no single prevention strategy. Priorities in preventive health programmes are determined by the magnitude of the problem and availability and effectiveness of methods for prevention. It is estimated that, in theory, about two thirds of all congenital anomalies are preventable or treatable: it is realistic to propose that their incidence might be reduced by about 25% in practice. However, to achieve this decrease will require a major effort to develop optimal preventive programmes. In particular, it is necessary to organize relevant education for policy-makers, health workers, the public, schools, families of affected persons, etc., in order to promote a healthy life-style and to stimulate prevention.

Medical care or the preventive approach is different for severe genetic diseases and for common diseases with a genetic predisposition. Genetic diseases tend to be uncommon, usually start early in life and possibilities for treatment are limited. Birth control methods such as limitation of family size, prenatal diagnosis with selective abortion, and artificial insemination by donor are acceptable to many couples at high risk of having children with severe genetic disorders. Existing "community genetics services" based on screening aim to avoid the birth of affected children or the onset of disease. They include prenatal screening for congenital malformations and chromosomal abnormalities, newborn screening for phenylketonuria (PKU), hypothyroidism, congenital dislocation of the hip, sickle cell disease (SCD), and population screening for carriers of inherited diseases such as the haemoglobin disorders and Tay Sachs disease¹.

By contrast, common disorders with genetic predisposition start late in life and early diagnosis, life-style modification and early treatment are indicated. Early diagnosis is helped by family history and screening. Appropriate life-style modification may include avoidance of triggering environmental factors, and the promotion of protective activities. Ultimately, increased understanding of the genetic component of common diseases is likely to lead to introduction of screening for genetic risk factors into general medical practice.

The time of family planning seems particularly appropriate for pre-reproductive counselling, as young couples are motivated to do their best for their future children. They are also emotionally receptive to other forms of health education, particularly if coronary heart disease (CHD), stroke, cancer etc., have occurred in their parents or grandparents. They are also of an appropriate age to initiate protective changes in life-style.

In practice, there are considerable problems in delivering genetics services equitably to populations. This is especially true in developing countries, where health services are overburdened managing environmental conditions such as infections, diseases and malnutrition. The insertion of genetics services in these countries will require a lot of education to health authorities and health professionals, as well as measures to increase the efficiency and funding for health services in general. Improved delivery will require specialists trained in both genetics and public health², who would be responsible for:

- (a) Coordinating services on a regional basis, and integrating them with existing specialist genetics services;
- (b) Collecting epidemiological data;
- (c) Monitoring and evaluating service delivery;
- (d) Developing information for the public;
- (e) Education of health professionals on genetics, and provision of updating courses for current practitioners.

International collaboration could be very helpful in improving genetic health education at all levels.

3. NEW DEVELOPMENTS IN DNA TECHNOLOGY

Present progress in DNA technology allows diagnosis of a rapidly increasing number of monogenic disorders, including definitive diagnosis of carriers and prenatal diagnosis. An early application of DNA technology was for diagnosis of genetic disease in the first trimester of pregnancy by chorionic villus sampling

(CVS): the majority of high risk genetic prenatal diagnoses are now done at this stage. DNA methods are also being developed for predictive diagnosis of an increasing number of genetic diseases of late onset; in the future it may be possible to identify individuals at high risk for common diseases of middle life that can be prevented or ameliorated by diet, drugs, or more healthy lifestyles.

The commonest monogenic diseases for which DNA diagnosis is already useful are the haemoglobin disorders (sickle cell disease and the thalassaemias), haemophilia, neurofibromatosis and cystic fibrosis (CF). In the near future it may help in the diagnosis of fragile X mental retardation. The multifactorial diseases for which genetically-oriented test systems are likely to be useful include coronary heart disease, diabetes, allergies and auto-immune diseases, and possibly the common psychiatric disorders (schizophrenia and manic depressive disorders).

Rapid advances in gene mapping make it almost certain that all monogenic diseases will be traced to a specific chromosomal location within the next few years. In many cases, this knowledge will help to develop treatment and prevention. The introduction of the polymerase chain reaction (PCR) has allowed development of greatly simplified methods for diagnosis of known mutations, often without the need to use radioactivity, so DNA technology is becoming appropriate for use in developing countries.

DNA diagnostic methods often allow definitive discrimination between carriers and non-carriers in families known to be at risk, so relieving those found not to be carriers of the fear of having children with a genetic disease. The value of diagnosing dominantly-inherited disorders depends on whether treatment is available for the condition: in Huntington's chorea for instance, nothing can yet be done to postpone onset of disease or to ameliorate its severity, and testing has been taken up very cautiously. Psychological effects on the family are being carefully monitored⁵.

Genetic technology may soon be applicable for identifying people with genetic risk factors for the common diseases that now cause 60% of morbidity and mortality in adults, but many problems may arise when this becomes possible⁶, and it is necessary to learn more about the social implications of this form of genetic screening. Previous reports have emphasized the distinction between offering testing to members of families where a disease is already known to exist (retrospective diagnosis), and offering screening to the whole population in order to identify individuals at risk (prospective diagnosis)⁷. In general, once a new genetic test is developed, it is recommended to offer it first to affected families, whose members are already familiar with the disorder and aware of risk. This allows the diagnostic acceptability and usefulness of the test to be evaluated in a group of people already aware of the problem. If testing proves acceptable and useful to family members, it might then be extended to the wider community. The recommendation of a step-wise approach to screening applies both for genetic reproductive risks, and for risk factors for common diseases such as CHD. International collaboration will be required to help developing countries to develop and apply DNA technology for the diagnosis and counselling of the most common disorders.

4. IDENTIFICATION OF THE GENE FOR CYSTIC FIBROSIS (CF)

It is increasingly clear that CF is a common genetic disorder with world-wide occurrence⁸. In developed countries, it is being transformed from a fatal childhood disease to a chronic disorder persisting into adult life: but the final outcome is

still fatal, and CF is among the most serious chronic life-threatening inherited conditions.

The situation in CF changed dramatically with the identification of the CF gene in 1989⁹. The commonest mutation affects 50-70% of CF chromosomes depending on the population concerned; identification of other mutations is progressing rapidly. Using PCR, it is now possible to detect the major CF mutations using minute quantities of cells. The prospect of isolating the corresponding protein opens up the possibility of effective pharmacological treatment in the future. Immediate benefits are, availability of prenatal diagnosis with a theoretical accuracy near 100%, and the possibility of prospective carrier identification for relatives of CF patients and their partners. It is also possible to confirm the clinical diagnosis of CF in doubtful cases. In the future, prospective population screening for CF heterozygotes carrying the commonest mutations will become possible¹⁰ and may lead to a major reduction in the birth incidence of CF. Neonatal screening for homozygotes and heterozygotes will also be feasible using the blood on a Guthrie card.

Control programmes for CF including treatment and prevention, based on the model of the haemoglobin disorders¹¹, should be defined for both developed and developing countries, with the aim of incorporating screening, counselling and treatment into primary health care. A WHO workshop on CF⁸ concluded that there is a need for training programmes in clinical aspects of and genetic approaches to CF. Educational materials should be prepared with the help of national and international CF Associations and the WHO Division of Health Education. Attitude surveys to prenatal diagnosis and carrier screening among CF parents and the general population are needed in a range of different countries and communities. It was recommended to set up a Task Force involving representation from a wide variety of professional and non-professional groups drawn from most WHO Regions. In particular, a regional WHO initiative in Europe would help to ensure appropriate standards of care and collaborative applications of genetic advances.

As it is highly likely that it will be necessary to offer screening for CF to populations of most developed countries in the future, there is an increased indication to develop community genetics services, and to introduce the concepts of genetic screening and counselling into primary health care. CF is known to be prevalent also in a number of developing countries. Although it is not predictable if and when CF screening and counselling will become available in some of these nations, it is important to stress that quality control of both testing and counselling is essential and that probably the programme should be governmentally controlled or regulated.

5. COMMON DISORDERS

Progress in understanding the etiology and pathogenesis of a number of common diseases of later life, such as atherosclerosis, coronary heart disease, hypertension, diabetes mellitus, some rheumatic, oncological and mental illnesses, has illustrated that genetic factors and genetic predisposition are also important in their appearance and manifestation. More and more countries have begun to express awareness and concern regarding these problems. As far as widespread environmental influences interact and unmask these inborn susceptibilities, the first approach toward the control would be environmental improvement including daily living habits, the physical and biological environment, and concomitant social changes. The strategy of prevention of these diseases at the community level often requires environmental changes for the entire population. Those genetically susceptible need

more intensive alterations in their environment than can or should be instituted for the population at large. Thus, there exists a great need to develop genetic tests to identify persons and families preferentially susceptible to specific diseases. Optimal approaches to the prevention and control of the common diseases demand more knowledge of the genetic-environmental interactions involved.

The main purpose of identifying persons with a genetic predisposition to common disorders is either to prevent disease (e.g., arteriosclerosis) or to secure early diagnosis and treatment (e.g., cancer): such testing could be a most important contribution to health promotion. The evidence for a significant effect of genes in the aetiology of common disorders, particularly CHD, continue to grow, and most of the genes contributing to risk of arteriosclerosis will probably be identified in the foreseeable future. At present, genetic risk for premature CHD may be identified by taking a careful family history, conducting a thorough clinical examination, and measuring the serum levels of total cholesterol, high density lipoprotein cholesterol, and Lp(A). Analyses of these parameters should be available to members of the families of persons with premature CHD on a voluntary basis and to others who want a risk factor assessment. There are several reports of associations between DNA variants and risk factor levels or overt CHD, but there are also some discrepancies between studies. The possibility of preventing or delaying the onset of arteriosclerotic disease is particularly important, because preventive measures are available and can be started early in life¹².

The following steps are necessary to develop realistic approaches for preventing common disorders with major genetic determinants:

- (a) Examination of family members of patients with certain diseases, such as premature CHD, for genetic markers: such examinations should also be available to others, on a voluntary basis, and with full data protection.
- (b) Implementation of studies such as that proposed in the WHO report on CHD (1987)¹².
- (c) Stimulation of other studies that may elucidate the usefulness of new genetic markers for common diseases, for disease prediction and prevention.
- (d) Continuous monitoring of progress in this rapidly developing area, making available advice on the usefulness of individual markers as risk indicators.
- (e) Maintaining a central data-base for genetics of common disorders.
- (f) Developing methods to ensure confidentiality of genetic records.
- (g) Developing educational materials on predictive genetic testing.

6. FETAL MEDICINE

The rapid development of modern technology requires that obstetricians responsible for prenatal diagnosis develop and maintain varied skills, and use them in a flexible way. The result has been the emergence of the obstetric sub-specialty of "fetal medicine" which of its nature is intimately related to the practice of medical genetics. New initiatives in fetal medicine include the development of transabdominal CVS and of amniocentesis in the first trimester of pregnancy, evaluation of safety and efficacy of CVS, the possibility of abortion in the first trimester of pregnancy by nonsurgical means following a positive genetic diagnosis, and research on techniques for preimplantation genetic diagnosis. There are also interesting developments in obtaining fetal cells from the maternal circulation for genetic diagnosis, and steps towards intrauterine therapy of inherited blood disease.

First trimester genetic diagnosis

The earlier a prenatal diagnosis is made the higher the social benefit, because earlier diagnosis reduces both the risk to the mother and the emotional impact of genetic abortion. First trimester prenatal diagnosis has represented a major advance, and the number of cases carried out per year continues to increase rapidly. In well-trained hands success for obtaining diagnostic material by CVS is virtually 100%, and chorionic tissue specimens are highly suitable for efficient and rapid diagnostic methods (e.g., direct karyotyping, biochemical assay, DNA amplification and diagnosis). Psychological studies shows that earlier diagnosis is highly acceptable to women, providing that the risks to the pregnancy are not significantly higher than traditional techniques such as amniocentesis and fetal blood sampling.

Though some studies are still in progress, published large clinical follow-up studies of prenatal diagnosis between 8 and 12 weeks of pregnancy suggest a fetal loss rate of 2-5%, and no measurable effect on fetal development and condition at birth has as yet been reported¹³. No major differences in safety and efficacy were found in a randomized trial of transabdominal needling versus transcervical aspiration¹⁴. A current follow-up study of infants 3 years old or more from the CVS series in Milan shows no specific difference between the study population and controls. There is no doubt that, at least for high-risk pregnancies, CVS is the prenatal diagnosis method of choice: preferably both transabdominal and transcervical CVS should be available at diagnostic centres.

It is now possible to carry out CVS at 6-7 weeks' gestation, using high-resolution ultrasound and transabdominal fine needle sampling. Together with rapid diagnostic methods this allows diagnosis before 56 days of amenorrhea (8 weeks from the LMP), with the possibility of "biochemical" termination of pregnancy using RU486 and prostaglandins. Evaluation of risk, and of the effect on psychological and reproductive health is recommended.

Pre-implantation genetic diagnosis

It has now been demonstrated that pre-implantation diagnosis of X-linked genetic disease is possible, using traditional in-vitro fertilization techniques, amplification of DNA by PCR, and fetal sexing using Y-specific probes¹⁵. Efforts have also been made to diagnose specific genetic disease by examining the polar body, in order to exclude the presence of the abnormal gene in the ovum¹⁶.

The objective of pre-implantation diagnosis is to save families at high genetic risk from the possibility of repeated abortions that is associated with classical prenatal diagnosis. It is not expected that the technique will ever be applied for large numbers of pregnancies at lower risk. At present, the main problems lie in the obstetric technique, which requires intensive intervention in the process of conception, and a relatively low chance of conception at each attempt. Though these problems may be overcome many couples, especially those at relatively low genetic risk, will prefer to conceive in the normal way and undergo traditional prenatal diagnosis. Evaluation of the method by comparison with other methods of prenatal diagnosis is necessary from the outset.

Although in most developing countries abortion for fetal reasons is not permitted, prenatal diagnosis followed by interruption of abnormal pregnancies is being performed, mostly in the high socioeconomic classes by private physicians with poor quality control. Efforts should be made to make this service accessible to the population in need irrespective of economic status and to develop methods of quality control.

7. CONSANGUINEOUS MARRIAGE

There is a cultural tradition of consanguineous marriage in many parts of the world: globally over 20% of births occur in such societies¹⁷. Though our present knowledge of the genetic and social implications of this marriage custom is scanty, misguided efforts are increasingly being made to discourage consanguineous marriages on genetic grounds¹⁷. It has therefore become important to develop and publicize a consensus opinion on the genetic and social implications of consanguineous marriage.

8. RECOMMENDATIONS

WHO Regional Offices should be encouraged to identify existing genetics services and resources in the Region, and to support meetings focussing on genetic problems of greatest local significance. Examples are the haemoglobin disorders in south-east Asia, genetic and social implications of consanguineous marriage in the eastern Mediterranean, sickle cell disease in Africa, and common genetic disorders in the Americas.

Experts in genetics and health education from different regions of the world should meet to develop educational materials for the public on the commonest genetic disorders, such as haemoglobin disorders, cystic fibrosis, Down's syndrome, phenylketonuria, hypothyroidism, and disorders with a significant genetic predisposition such as coronary heart disease and hypertension.

Training courses are needed for health workers, focussing on modern techniques in diagnosis of genetic disease, genetic counselling, and delivery of genetics services at the community level.

Developing countries, where a particularly high frequency of genetic disorders occurs, should be encouraged to set up training centres for clinical and laboratory diagnosis, and management of genetic disorders. These centres should be integrated with the general health services and although based in tertiary centres, they should be linked to the primary care level in a regionalized system. Health officials must be educated in the role of genetics in public health. Medical schools should be encouraged to introduce the teaching of medical genetics to it's students.

Guidelines should be developed summarizing the principles of diagnosis and management of the common genetic diseases, and requirements for an effective control programme.

Centralized laboratories should be encouraged to provide standards for quality control for laboratories setting up genetic methodology, including DNA methodology.

Genetically-orientated pilot programmes for diagnosis and prevention of common multifactorial diseases should be encouraged.

Congenital malformation surveillance programmes should be extended to include monitoring the effects of genetic prevention programmes.

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