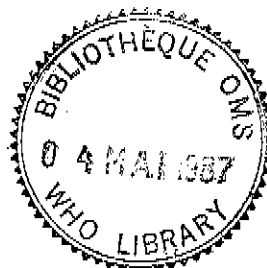




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HEREDITARY DISEASES PROGRAMME
 DIVISION OF NONCOMMUNICABLE DISEASES



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COMMUNITY APPROACHES TO THE CONTROL OF HEREDITARY DISEASES - p+c

Report of a WHO Advisory Group

genetic counselling

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1. INTRODUCTION

Recent progress in understanding human hereditary diseases and in developing approaches that can be applied at the community level, has led to the differentiation of a group of community genetics services, relevant to many aspects of Primary Health Care. However, a residual concept of clinical genetics as a speciality appropriate only for the most developed parts of the world obscures its real relevance for public health in both developing and developed countries. During the past three years a series of WHO activities has been undertaken, to collect and quantify information on the application of genetic knowledge at the community level and to initiate some programmes, in order to develop approaches suitable for incorporation into health services. The emphasis has been on conditions that are common globally, being relevant also in developing countries.

Examples of general importance are the haemoglobinopathies (1,2), Glucose-6-phosphate dehydrogenase (G6PD) deficiency (3), fetal diagnosis in the first and second trimester of pregnancy (4,5), cystic fibrosis (6), lactose maldigestion (7), common diseases including coronary heart disease (8), mutational diseases (9), and birth defects monitoring (10).

This report is concerned with the community aspects of genetics services. It seeks to illustrate their relevance for health care by addressing some quantifiable examples of the control of hereditary diseases; important new technical developments; approaches that may be incorporated into primary health care; evaluation of community-based services; gaps in the existing medical structure that need to be corrected in order to deliver these services; the importance of genetic information in health education; the ethical problems associated with genetics services; and research needs and opportunities.

2. EXPERIENCE IN THE CONTROL OF HEREDITARY DISEASES

One of the most important objectives of community genetics services is to reduce the frequency and clinical manifestations of the severe congenital disorders, i.e. those disorders that arise at the time of conception or during intra-uterine development. Not all congenital disorders are of genetic origin (Fig.1), but as the clinical geneticist is inevitably involved in their differential diagnosis, treatment and prevention, they are usually considered in the context of hereditary disease.

The birth incidence of infants with congenital disorders, including those that are trivial or relatively easily corrected, is generally estimated to be about 25-60/1000. The incidence of severe congenital disorders that can cause early death or life-long chronic disease ranges from about 15/1000 in most of the more developed countries, up to about 45/1000 in some less developed parts of the world (Table 1). Most infants with a severe congenital disorder (such as a haemoglobinopathy, Down syndrome, congenital heart disease, malformation of the urinary tract, or cystic fibrosis) are particularly susceptible to infections, and in many parts of the world affected children simply disappear into the general infant and childhood mortality without attracting special notice. However, the infant mortality can fall below the local birth-rate of severe congenital disorders only if these vulnerable children are diagnosed and treated, or if their birth-rate is reduced; i.e. through a genetics service. The by now substantial experience of the effects of such services, both at the individual and the community level, is summarised here.

2.1. Monogenic disorders

From 3-8% of married couples in different countries are at high and recurrent risk of producing offspring with a severe disorder that is inherited in a Mendelian fashion. Prediction of recurrence risk, treatment and prevention depend on sound epidemiology and accurate diagnosis, and these are the scientific responsibility of the clinical geneticist.

However, genetic counselling (with or without fetal diagnosis) for couples at risk, significantly affects the birth-rate of affected children only when it is delivered prospectively, i.e. before the couples have borne their first affected child. Prospective counselling is technically possible at present only for conditions where heterozygotes can be

accurately identified, i.e. the haemoglobinopathies and Tay-Sachs disease. Carriers of some sex-linked conditions such as haemophilia and Duchenne Muscular Dystrophy can be identified with rather less certainty by conventional methods, and one of the most important benefits of DNA methods is improved accuracy of carrier diagnosis for these conditions. Prospective heterozygote detection also depends on community education, so that healthy individuals are sufficiently alerted to a genetic risk to ask for testing and counselling. The birth-rate of affected children will fall only if these couples are identified prospectively, and also use the genetic information by refraining from reproducing, or seeking fetal diagnosis and selective abortion. Therefore a fall in the annual birth-rate of affected infants is the simplest single criterion for measuring the prevention component of a genetic control programme, starting with education and ending with the reproductive behaviour of at-risk couples.

The haemoglobinopathies (the thalassaemias and sickle-cell disease) are the commonest of the lethal monogenic disorders. They can be managed with reasonable success, and prevented by heterozygote diagnosis and counselling, with the offer of fetal diagnosis and selective abortion of affected pregnancies. This has had a particularly important effect in reducing the birth-rate of thalassaemia major, and several studies have shown that a similar approach would be equally acceptable for other severe disorders such as cystic fibrosis, if it became available (11). The existing haemoglobinopathy control programmes therefore provide a model for the general possibilities and limitations of control programmes for severe Mendelian disorders.

The global distribution and health burden of the haemoglobinopathies is summarised in Fig.2. Nearly 200 million people (about 4% of the world population) carry a potentially pathological haemoglobinopathy gene. Though more than half are thalassaemia genes, about 75% of the 250,000 children born every year with a major haemoglobinopathy have sickle-cell disease, and 65% of all affected children are born in Africa, because such a high proportion of Africans carry a sickle-cell trait (2). Migration has brought the haemoglobinopathies to many previously non-endemic areas, so that, for example, more children with a major haemoglobinopathy are now born in North than in Southern Europe, and their birth-rate now exceeds that of cystic fibrosis in most industrial areas of North-West Europe (12).

Comprehensive thalassaemia control programmes that combine optimal treatment with a community-based approach to prevention are now established in many Mediterranean countries, and are beginning to extend into Asia (Fig.2). Fig.3 shows that as a result, the thalassaemia major birth-rate has fallen to zero in the Ferrara district of northern Italy, to about 6% of expectation in Cyprus, and 50% of expectation in Greece (and most of mainland Italy). In Sardinia it had fallen to 35% of the expectation by 1982, then rose again because of failure of finance for a planned health education campaign (2), and is now falling once more.

Clearly, though such services ultimately depend on fairly advanced laboratory and obstetric techniques, they can be delivered effectively to the community only if information and screening are integrated into primary health care. One important aspect of monitoring these programmes is to interview the parents of affected children born after the establishment of the programme. Fig.4 shows that most residual births have been due to ignorance of the risk and of the existence of the prevention programme on the part of the families or their doctors, rather than to rejection of fetal testing (13). In addition, it proves to be more difficult to establish such services in large than in small communities, mainly because of the difficulty of involving the large number of health-care workers concerned. This need for improved medical and community education is a recurring theme in medical genetics.

Second trimester fetal diagnosis can lead to undesirably late termination of pregnancy. This is particularly distressing for mothers at high genetic risk, who may have to terminate more than one affected pregnancy, and is unacceptable among some ethnic groups in Europe, and in several Middle-Eastern and Asian countries. First-trimester fetal diagnosis by chorionic villus sampling (CVS) combined with gene-mapping allows selective abortion of affected pregnancies before 12 weeks of gestation. It has therefore increased the general acceptability of prevention, and has put it within reach for many couples who could not previously accept second-trimester diagnosis (14).

Up to 80% of fetal diagnoses for the haemoglobinopathies are now done by CVS and gene-mapping at several European centres. Besides being of great psychological benefit for the families, this provides experience of the advantages and limitations of the large-scale application of the DNA methods. First-trimester diagnosis is already applied in China for both α - and β -thalassaemia, and is presently being established in Thailand.

The introduction of effective prevention has generally been accompanied by an increased commitment to the care of the existing patients, through focussing public attention and medical expertise on the problem. The fact that a prevention programme "contains" the number of affected children may even make it possible for less prosperous communities to provide them with optimal treatment, when this would not have been possible before. A simple criterion for measuring the success of treatment is to monitor the patients' survival. Fig.5 shows the number and age-distribution of thalassaemic patients in Cyprus. Very few are now born, and most existing ones seem to be surviving in good health (though not without problems), so they form a limited cohort programmed to pass steadily through the medical system in the coming years. This is only one example of a more general situation, since the management of previously fatal diseases of childhood is continuously improving and more patients who need comprehensive support are surviving to adult age. However, the system-oriented training of adult physicians does not usually prepare them for managing such patients' complex physical, social and psychological problems, so some way must be found either to retain these patients in the care of the group that has looked after them from infancy, or else to prepare selected adult physicians to take over their comprehensive care. The scale of the future service need for treating the adolescent and young adult "survivors of chronic disease of childhood" can be predicted by collecting data as shown in Fig.5:

There has been less progress in controlling sickle-cell disease, despite the fact that it is more common than thalassaemia, and probably equally lethal in many of the societies where it is found. One reason may be its relatively lower "medical visibility", since it often causes such rapid death from infection in infancy that the underlying genetic condition remains unsuspected. In most of Africa the vast majority of homozygous children die in this way in their very early years, but it is still not known what proportion die undiagnosed in infancy in Western Europe and South America.

Sickle-cell disease (and trait) can be detected relatively simply and cheaply in the newborn period using cord-blood, or haemoglobin eluted from the (fresh) Guthrie blood spot. There is now positive evidence that neonatal diagnosis followed by family counselling, with simple protective measures, regular monitoring and the appropriate use of antibiotics, can reduce the early mortality and morbidity of the sickling syndromes (15). Nevertheless, sickle-cell control programmes based on neonatal screening have been implemented only in parts of North America, a few of the Caribbean islands, and a few small districts in Europe.

Fetal diagnosis of sickle-cell disease is technically simpler but socially more complicated than that of thalassaemia. When only mid-trimester diagnosis is available, most couples at risk for infants with sickling syndromes have requested neonatal diagnosis rather than fetal diagnosis, largely because of the uncertain severity and prognosis of the condition.

However, diagnosis of sickle-cell disease by gene-mapping is one of the most straightforward applications of DNA technology, and can be done in the first trimester of pregnancy. Comprehensive sickle-cell programmes combining neonatal diagnosis, heterozygote screening and counselling, and the offer of fetal diagnosis by CVS and gene-mapping are being established in Cuba, Martinique and Guadeloupe. This approach is likely to spread further in the future.

Tay-Sachs disease was the first monogenic disorder to be prevented by prospective heterozygote screening and counselling combined with fetal diagnosis (16), and so has a particularly important place in the history of genetic disease control. It can be detected reliably in the heterozygote, and between 3 and 5% of Ashkenazi Jewish populations and perhaps 1% of non-Jewish populations are carriers of the gene. Though the numbers involved are relatively small and the families are scattered, there is evidence of a 70-90% fall in affected births in the United States between 1970 and 1980 (5).

Phenylketonuria provides the classic example of the control of a rare, severe and easily-treated inherited disease. It occurs in European populations with a frequency of 1 in 13,000 to 20,000, and is detected between 5 and 10 days of life in most developed countries by assaying the phenylalanine level in blood-spots dried onto filter-paper and posted to the screening laboratory. Dietary treatment preserves normal intelligence. Fetal diagnosis by gene-mapping is now available for many families, but its uptake has so far been rather limited.

The establishment of neonatal screening for phenylketonuria as an integral part of primary health care created a public health structure through which nearly every member of the population is provided with genetic testing at a critical point of their life. It shows that once such a structure has been established for one purpose, it can also be used for the control of other conditions. The same approach is now used for the neonatal diagnosis (and so effective treatment) of congenital hypothyroidism, sickle-cell disease, galactosaemia, and some amino-acid disorders, in different populations. They also provide a basis for genetic epidemiological research on the birth-incidence of other inherited diseases such as amino-acidopathies and cystic fibrosis.

Cystic Fibrosis (CF) is the commonest lethal recessively-inherited disease among Caucasians, about 5% of whom are heterozygous. A study is under way to extend knowledge of its geographical distribution, which may be wider than was believed hitherto (6). There is good evidence that survival and quality of life are improved by early diagnosis, regular physiotherapy, and treatment with prophylactic antibiotics. Surveys have shown a lively interest among the families in prevention. Recently there has been important progress towards fetal diagnosis by assay of alkaline phosphatase in amniotic fluid at about 19 weeks gestation, but there appears to be about a 10% misdiagnosis rate, with both false positives and false negatives (17). The recent identification of several restriction fragment length polymorphisms flanking the locus of the CF gene has improved the situation, because first-trimester diagnosis by gene-mapping now appears possible for about 80% of families with an affected child (18).

Of course, the localisation of the CF gene engenders hope that the abnormal gene-product will soon be identified, and that this knowledge will make it possible to provide more effective treatment for the patients, and reliable prospective heterozygote testing for the population. However, it proves to be very difficult to locate a gene in a relatively large section of DNA when the gene-product is unknown, so this outcome may depend on a combination of progress in conventional and DNA approaches.

Haemophilia, an X-linked disease that occurs in about 1 in 10,000 males, provides a remarkable example of progress in treatment and prevention of an inherited disease. Fig.6 shows that treatment with Factor 8 or cryoprecipitate can return life-expectancy, and quality of life nearly to normal in the whole group of patients, though complications due to exposure to hepatitis or AIDS virus in the preparations are now causing anxiety to many families. Until recently fetal diagnosis was done by a 2-step procedure in the second trimester of pregnancy: amniocentesis to determine the sex of the fetus was followed, in the case of a male, by fetal blood sampling to reach a definitive diagnosis. However, both fetal sexing and diagnosis by gene-mapping can now be done in many cases by a single procedure in the first trimester (19).

Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency), the commonest enzyme disorder of the human red cell, is also inherited as an X-linked recessive, and like the haemoglobinopathies confers protection against falciparum malaria. This is most marked in the female heterozygote, possibly because the existence of two populations of red cells, one normal and one G6PD deficient impedes adaptation on the part of the parasite (20). The distribution of G6PD deficiency therefore coincides with that of the haemoglobinopathies (Fig.7). About 12% of the world population carry the gene, and about 4% of all newborns are male hemizygotes or female homozygotes. In these susceptible individuals G6PD deficiency can cause neonatal jaundice with the risk of kernicterus, leading to death or chronic athetoid cerebral palsy. It may also lead to episodes of acute haemolytic anaemia in childhood or adult life, when susceptible individuals are exposed to certain drugs or foodstuffs. "Favism" describes the acute haemolysis that can occur in some susceptible individuals following the ingestion of broad (fava) beans.

The predominant form of G6PD deficiency varies in different parts of the world, the common African form being rather milder than the common Mediterranean and Asian forms. The global number of infants at risk is extremely large, including from 3 to 15% of all newborns in many parts of the world. It is not known what proportion of those at risk actually develop complications in different settings. Historical data from Singapore (3) suggest that about 7% of infants at risk died in the past, and it is to be expected that a similar proportion sustained some lasting damage. It is therefore not surprising that neonatal jaundice is recognised as an important but neglected cause of perinatal mortality and morbidity in many developing countries (21).

The complications of G6PD deficiency can be controlled by simple and inexpensive measures, such as newborn screening for susceptible infants, exposure of jaundiced babies to light, and educating the population not to dress babies in clothes that have been stored in mothballs, and not to feed broad beans to children. The incidence of kernicterus can be brought to nearly zero and the need for exchange-transfusion reduced to a very low level by these approaches, in populations where G6PD deficiency is common (3).

X-linked mental retardation associated with a fragile X chromosome is another common genetic disorder that can be detected in the fetus by karyotyping, in principle. However, fetal diagnosis is still unreliable technically, and female fetuses with one fragile X chromosome present a problem because of the variability of the associated clinical picture. Improved DNA technology may assist with some of these limitations, though it is unlikely to resolve the problem of variable manifestations in the female.

Finally, Huntington's Chorea is the best-known example of a dominantly-inherited condition that is lethal in middle life. Heterozygotes inevitably develop the disease unless they die early of something else. Their surprisingly high frequency, about 0.5/1000 in European populations, may be due to the fact that in the past affected individuals apparently had more children than the population average (22).

Until recently, the only possible application of knowledge about the disease following diagnosis of the propositus, was genetic counselling of the relatives and psychological and social support for the family. Counselling relatives of affected individuals usually curtail their reproduction for fear of transmitting the disease to their offspring (Fig.8), and this behaviour, if continued over several generations, would lead to the virtual disappearance of the disease. Though this restraint relieves some of the anxiety of those at risk, it is at best only a partial solution. Recently, definitive diagnosis of carriers has become possible by gene-mapping for a significant number of families (23). However, in the absence of realistic hope of improved treatment this involves formidable psychological problems for the families and their doctors. As with cystic fibrosis, there is now increased hope of identifying the basic defect, and so discovering if therapeutic intervention will become possible. If so, much of the anxiety associated with heterozygote diagnosis would be allayed.

2.2. Chromosomal disorders

Down syndrome accounts for one quarter to one third of all cases of mental retardation in developed countries and a slightly smaller proportion in developing countries. Since women over 35 have an increased risk of bearing a fetus with Down syndrome or another chromosomal non-disjunction (Fig.8), in many developed countries they are offered the possibility of amniocentesis and selective abortion. The cut-off point of maternal age for the offer of amniocentesis varies from one region to another, according to the availability of resources. The "uptake" rate also differs remarkably in different areas, depending on whether and how the pregnant women are informed (5).

During the last 20 years there has been a general fall in the crude birth-rate by about 35% in many developed countries. This fall has been particularly great among older mothers, in large part due to terminations of pregnancy on grounds of maternal age (Table 2). There has consequently been a decrease in the incidence of Down syndrome from about 1.7 to as low as 1 per thousand live-births in some countries (Fig.10). As far as can be ascertained, the age-specific risks for trisomy 21 have not changed (24). Consequently though amniocentesis offered

only to older mothers is of great value to individual women, it loses much of its impact in preventing Down syndrome at the population level. Amniocentesis offered to all mothers over 35 might have reduced the birth incidence of Down syndrome by about 50%, if fully used before 1970; but now its maximum effect could be a 10% reduction. However, in most of Europe, no more than 30% of mothers in the designated age-group actually receive an amniocentesis, so this activity can have reduced the birth-rate of infants with Down syndrome by at most 3%, compared with about 25% due to therapeutic abortion on grounds of maternal age (25). It is necessary to improve the delivery of this service by ensuring counselling of mothers at risk; and also to find new ways of identifying at-risk pregnancies. For instance, a correlation exists between a low level of maternal serum alpha-fetoprotein (AFP) and the presence of aneuploidy in the fetus in the second, and possibly also in the first trimester of pregnancy (26). Retrospective studies show that a group of younger mothers at high risk (more than 1 in 200) can be identified by integrating the maternal serum AFP level with maternal age (27). The offer of amniocentesis to these mothers would increase the proportion of Down syndrome cases detectable to about 40%, while only about doubling the present number of amniocenteses.

In many developing countries the birth-rate of infants with Down syndrome remains above 2 per thousand because most women continue reproducing to the end of their fertile life. Education about the elevated risk of older women, combined with family planning programmes would be a useful and inexpensive strategy, and is a simple example of the general need for increased education about genetic diseases.

2.3. Congenital malformations

Malformations such as congenital heart defects, neural tube defects cleft palate etc are thought to result from the interaction of unknown exogenous and genetic factors. They generally show a familial tendency, the recurrence risk being of the order of 1-6% depending on the number of affected relatives, the severity of malformation, and the prevalence among the general population.

Routine ultrasound monitoring in pregnancy is at present the only way to detect many fetal malformations. In a recent study, 2.5 out of 2.9/1000 major congenital malformations (excluding congenital heart disease) were directly detected by scanning at 16 weeks' gestation at an expert centre (28), and it is also possible to detect major congenital heart disease at 16 weeks of pregnancy (29). Ultrasound scanning later in pregnancy sometimes provides the opportunity for intra-uterine corrective surgery (though this has as yet had limited success); more often it permits prediction of the need for early neonatal surgery.

The newborn incidence of neural tube defects varies from around 1-2 per thousand in most parts of the world, to as much as 4-8 per thousand in the UK, Egypt, Northern India and parts of China (5). Exogenous factors certainly play an important part, since the background incidence has fallen by about a half (for unknown reasons) in Northern Ireland and most of the UK in the past 7 years (30). There is also evidence that periconceptional vitamin supplementation for mothers who have already had an affected child can greatly reduce the recurrence-rate, at least in high-incidence areas (31). Nutritional supplementation around the time of conception may reduce the general incidence of these severe malformations where they are common, but it is unlikely to abolish them altogether.

The neural tube defects were the first group of serious congenital malformations to be diagnosed in significant numbers in the fetus, because in most cases both the amniotic fluid AFP and the maternal serum AFP are raised. The development of a simple screening test, with further diagnostic refinements to exclude false positives, has allowed maternal serum AFP screening on a mass scale in some countries, with a reduction of from 60-70% in the incidence of anencephaly and spina bifida in both high and low-incidence areas (Fig.11).

2.4. Maternal-fetal interactions

Numerous genetically-determined or genetically-influenced maternal-fetal interactions may have serious consequences for either the mother or the fetus.

Rhesus haemolytic disease of the newborn is an important complication of pregnancy that can be prevented simply, effectively and cheaply. The frequency of the Rhesus-negative (d) gene in a population (32) determines both the incidence of homozygous Rh-negative females (dd) and their risk of mating with a homozygous or heterozygous Rh-positive male (DD or Dd). The frequency of maternal immunisation depends on the incidence of ABO blood-group incompatibility between the parents, the number of previous pregnancies (including abortions) some aspects of delivery that may affect the number of fetal red cells entering the maternal circulation, and the characteristics of the mother's immune response; so the incidence and the complication-rate of Rh incompatibility differs in different parts of the world. In Northern Europe, about 15% of matings and 10% of pregnancies are at risk. In the past, maternal immunisation led to stillbirth or neonatal death in about 0.7/1000 births, and to long-lasting neurological damage from hyperbilirubinaemia in a significant percentage of survivors. Treatment of the affected fetus by intra-uterine transfusion and early delivery, and of the newborn by phototherapy and exchange-transfusion are now integral parts of obstetric and paediatric practice in many countries, while prevention of maternal induction by routine injection of anti-D globulin after delivery or abortion, has been integrated into basic health care. Stillbirths and neonatal deaths due to Rh-haemolytic disease have been reduced by over 95% in most developed countries since 1950 (33).

The low incidence of Rh negativity often leads to the neglect of rhesus incompatibility in many parts of Asia and Africa. However, as the frequency of the d gene falls, the chance that a dd homozygote will mate with a homozygous (DD) partner rises, so the reproductive risk of a Rh-negative woman in Africa, Asia or China may be three times that of her European sister. Rh-negative individuals in these areas are also at increased risk of being unable to obtain blood if they need a transfusion, while transfusion without rhesus testing has a high risk of imposing life-long incapacity to bear living children. It is cheap and easy to detect Rh negativity, and (within limits) the less common it is, the stronger the genetic indication for detecting it, providing advice, and taking appropriate precautions.

Maternal phenylketonuria, though rare, can cause a severe maternal-fetal interaction. Phenylketonurics usually relax their strict diet once they have passed adolescence, but a high phenylalanine level in maternal blood can cause microcephaly and severe mental retardation in the fetus, ironically reversing the maternal compensation that allowed the phenylketonuric mother herself to reach birth undamaged. To avoid these problems, it is essential for the mother to return to a strict diet prior to conception, and to maintain it throughout the pregnancy.

Diabetes mellitus, one of the most common genetically-influenced disorders, causes an increased frequency of congenital malformations, as well as complications at delivery and in the neonatal period. These problems can be reduced by early diagnosis and strict control of maternal diabetes, and by ultrasound monitoring during pregnancy to detect major congenital malformations. The increasing frequency of diabetes as a disease of affluence among even young women, in some large population-groups that are genetically pre-disposed (e.g. Asian Indians and South American Indians), is likely to lead to an increase in the birth-rate of infants with congenital malformations.

Maternal infections can have serious consequences for the fetus. Rubella was the first common teratogenic agent to be defined, and termination of pregnancy in the first trimester when the mother is known to have been infected by the virus has been accepted as legitimate medical practice in most countries for many years. In most developed countries girls are encouraged to be immunised against Rubella, and pregnant women are screened for antibodies to this and other infective agents such as toxoplasmosis and cytomegalovirus. It is now becoming possible to make a definitive diagnosis of infection of the fetus by estimation of IgM in fetal blood, but diagnosis by this method can be done only after 22 weeks of pregnancy, since it is necessary to wait for the maturation of the fetal immune system. However, it may now be possible, using DNA methods, to identify the presence of virus in samples of chorionic villus material obtained in the first trimester of pregnancy (34).

Genetic disease in the fetus may also constitute a risk to the mother. For instance, hydrops fetalis due to homozygous α zero thalassaemia, in which the fetus has no chance of surviving, may complicate up to 4/1000 pregnancies in some South-East Asian populations. It may cause pre-eclampsia and eclampsia, obstructed labour and post-partum haemorrhage. Fetal diagnosis by gene-mapping in the first trimester of pregnancy, and selective abortion of hydropic fetuses is now being developed in Asia.

Diagnostic intervention in pregnancy may in itself cause fetal abnormality. There is evidence that amniocentesis, at least as it was practised some years ago, led to spontaneous abortion in about 1% of pregnancies, and could cause some correctable pressure-deformities of the limbs and disturbances of lung development in a small proportion of cases (35). These effects may have been due to occult persistent leakage of amniotic fluid. The technique has since been improved by increased use of ultrasound and disposable needles of a smaller external gauge, and it seems that these risks have decreased. However, fetal diagnosis by ultrasound, amniocentesis and CVS is used on such a large and increasing scale, that it is of the utmost importance to monitor any potential pathological effects. The risk associated with amniocentesis continues to be studied (36). A WHO-sponsored international registry (37) shows that CVS been associated with subsequent abortion in about 4% of cases worldwide, and with about 2% of cases at very large, experienced centres (38). The background rate of spontaneous abortion at this stage of pregnancy of viable, chromosomally-normal fetuses is thought to be about 1.5%, so the additional loss provoked by CVS seems to range from about 0.5-2% at different centres. In order to study the short and long-term risks more accurately, internationally-co-ordinated randomised controlled studies have been generally accepted (39).

3. GENETIC APPROACHES FOR HEALTH PROMOTION

The objective of health promotion is to encourage a healthy life-style, through education and other means. Certain identifiable individuals or groups run a particularly high genetic risk of some common diseases (such as coronary heart disease, diabetes, or some forms of malignancy), or may be vulnerable to specific environmental or dietary hazards. It is useful to identify people with such genetic predispositions, if they can then protect themselves by adjusting their lifestyle or behaviour; but before such recommendations can be made on a mass scale, there must be very clear evidence for the reality of risk and the effectiveness of the avoiding action. To achieve the maximum good and avoid harm, it is advisable to take the normal range of human variation into account, because recommendations valuable for particular groups could actually be harmful for others. It is also necessary to provide easily-accessible, clear and balanced educational aids for the general public in order to convey information without creating unnecessary anxiety.

For coronary heart disease, where the familial tendency is fairly strong, it is important to advise relatives of their increased risk, and of the value of investigation: appropriate changes in lifestyle involve diet, exercise and avoiding smoking (8). In populations where diabetes is increasing in frequency it is particularly important to try to prevent the development of obesity by promoting a balanced diet.

There is considerable evidence of genetically-determined differences between population groups in the ability to tolerate specific foodstuffs in their diet. Information on the geographical distribution, frequency and significance of such characteristics is useful for appropriate nutritional and public health strategies. The genetic basis for the tendencies indicated in Fig.12 is clearer for some conditions than for others. For instance, lactose non-digestion, a recessively-inherited disorder of the enzyme neutral lactase, is especially prevalent in developing countries, among populations without a tradition of using milk and dairy products (Fig.13). In such societies milk is usually converted to yoghurt or cheese, or handled in some other way that reduces the lactose content. The condition is relevant because dried milk is so often used for food supplementation in famine and disaster-relief programmes. Fortunately most children possess the necessary level of the enzyme at least up to the age of 6 years, and are not intolerant of lactose, but questions remain about how to use milk supplements in severely malnourished children or children recovering from diarrhoea, and for older children and adults (7).

Certain drugs can cause acute haemolytic reactions in individuals with G6PD deficiency. The very high frequency of G6PD deficiency in people originating from the tropics and subtropics makes it important for health-workers to be aware of which drugs may be hazardous - and also of those that are not, in case useful drugs are needlessly withheld (3). This is particularly important in view of the recent resurgence of falciparum malaria, because G6PD deficiency limits the range of anti-malarial drugs that can safely be used by affected individuals. New drugs should be tested for their ability to cause haemolysis in G6PD deficiency before being introduced into relevant countries.

Iron-supplementation of basic foodstuffs is desirable in many countries. However, in parts of Asia 3-4/1000 of the population may have haemoglobin-E/B-thalassaemia, a severe iron-loading anaemia. Unless diagnosed and advised, they would be put at increased risk by dietary iron supplementation.

1-4.5% of those Caucasian populations that have been studied are carriers of α -1 antitrypsin deficiency. Homozygotes have an increased risk of developing emphysema in a polluted atmosphere, and there is evidence that heterozygotes are specially at risk for the pulmonary complications of smoking: but the usefulness of identifying and advising them is still uncertain.

At present, few genetic variants are known to constitute real occupational hazards. The best example is the need to exclude red-green colour blindness in pilots and train drivers. Various other tests have been suggested, but most lack any adequate basis for curtailing choice of employment.

Social and economic development in itself brings about a reduction in the infant mortality and the birth-rate. When families are small, it is increasingly important to the parents for each child to be free from congenital disease. Balanced information is important to help potential mothers to minimise avoidable risks, and to reduce fears of unknowingly causing damage to the fetus. They need to know that single most important precaution is to have a balanced diet before, during and after pregnancy: that in theory, the best age for childbearing is between 18 and 30 (though social conditions sometimes tend to delay childbearing to the mid- or late thirties): that they should avoid drugs and habits such as smoking and alcohol intake that have been shown to be potentially harmful to the fetus (but that risks refer to excessive exposure, rather than to moderate drinking or smoking that may have occurred incidentally around the time of conception): to be immunised against rubella infection: and to seek testing for any detectable genetic condition common in their community, prior to embarking on a pregnancy.

Social development also increases the possibilities of accidental exposure to mutagens such as ionising radiation or chemicals. Public concern over the possible genetic consequences is being expressed globally. At present, knowledge is gravely limited by ignorance of the basic mechanisms of mutagenesis. There is evidence from studies on the mouse that about 3% of naturally-occurring mutations may be due to background radiation. However, apart from the obvious inference that a small addition to the background level of radiation will necessarily lead to a small increase in the mutation rate, it is difficult to make any firm statement about the genetic effects of exposure to radiation in man. There is no well-characterised background level of exposure to use as a baseline for mutagens other than radiation. It is nevertheless important to provide the public with a balanced view of the present state of knowledge, related to the natural background of radiation and other hazards (9).

Studies on populations exposed to radiation have been conducted on children born to parents surviving the atomic bombings of Hiroshima and Nagasaki, and on populations living in areas with relatively high background radiation levels. In Hiroshima and Nagasaki the findings were in the direction of a genetic effect of the exposure, but in no instance was there a significant difference between the children of parents who received essentially no excess radiation, and those who received doses up to the maximum compatible with survival. However, difficulties in estimating the actual dose of radiation received impeded the calculation of the "doubling dose" (for mutation) of acute radiation exposure. Previous estimates are now being revised. The incidence of cancers has been investigated in parts of India and China with a high natural background radiation, but so far no correlation with exposure has been documented.

Efforts to evaluate whether new industrial developments have resulted in an increase in mutation rates have been compromised by the inadequacies of present methods of evaluation.

Therefore reliable studies are necessary to meet public concern; for the regulation of exposures to real hazards; and for reassurance about imaginary or trivial risks. It is also important to analyse the costs and benefits of efforts to prevent mutational disease, taking into account the risks that society accepts in other contexts.

To facilitate well-planned studies of the potential problem of increased mutation rate, it is advisable to identify and study groups at unusual risk of mutation. (These might include pregnant women and children in groups accidentally exposed to mutational hazards such as radiation, or exposed to chemical hazards such as smoking). The studies should be conducted with suitable populations available for comparison. Since the number of children born to parents with unusual mutagenic exposures will generally be small, special emphasis needs to be placed on the development of methods to extract maximum information from each subject.

Better procedures are needed, and promising developments involve the examination of protein and DNA by modern methods. Repositories of cell-lines from children at risk and their parents and suitable controls, should be established when possible to allow future studies by better techniques when these become available. Co-ordinated international effort in the study of avoidable mutational diseases is necessary to facilitate technical developments and exploit collaborative arrangements.

Better promotion depends above all on education. The possibilities for preventing some common recessively-inherited diseases, together with present knowledge of genetic predispositions to common diseases, indicate a need for effective, broadly-based programmes in health education that should involve all sections of the population, particularly in communities that seem to have a specific genetic predisposition. These must persuade the young, who perceive no imminence in health-risk, to seek relevant heterozygote testing or to alter their life-styles, and the middle-aged and elderly must be dissuaded from cultural norms encouraging obesity, unwise culinary practices and the like. The women of the community are particularly important as they bear and care for the children and are the chief preparers of food. No simple, one-dimensional approach will succeed in genetic, or in other forms of health-education. A clear and flexible strategy, patience, persistence and reiteration are needed to achieve a successful outcome.

There is a shortage of the necessary educational resources, such as books pitched at the appropriate level, both for primary health care workers and for the community, and their production should be encouraged. Since health education for genetic risks is still a research area, it is desirable to collect and monitor existing programmes, in order to develop an effective model.

4. THE GENETIC COMPONENT OF HEALTH SERVICES

Since they have been relatively recently developed from a research basis, clinical genetics services are at present available only in the most developed countries. This explains the common view that a genetics service is an inappropriate luxury where malnutrition and infection are still important problems. However, inherited and other chronic diseases are more common, and their burden falls much more heavily on the family, in developing than in developed countries. As control becomes more feasible, it is necessary to reconsider when and how to introduce community genetics services into developing health systems.

As recent initiatives in primary health care reduce the infant mortality, congenital disorders are inevitably beginning to be recognised in developing countries. For instance, child nutrition programmes promoted by the WHO involve weighing children regularly so that those who are not thriving can be given dietary supplements; those who do not respond are referred for medical advice. This approach, directed to a common basic problem, incidentally functions as a filter for detecting children with congenital disorders presenting as failure to thrive. Similarly, much effort is devoted to developing effective malaria control. Once this is realised in Africa, where most infants with sickle-cell disease die of infections including malaria, there will be improved survival of a large number of children with severe chronic disease.

Inherited disease may have a particularly severe effect on families in developing countries. In the absence of genetic advice couples usually realise that a disease is inherited only by having more than one affected child; if a diagnosis is made and they would like to avoid further pregnancies they may have limited access to contraception and therapeutic abortion; and medications prescribed for affected children may be either unobtainable (PKU diet) or impossibly expensive (haemophilia, thalassaemia). Consequently the family is often rapidly impoverished, and this puts the lives of the remaining healthy children at unusually high risk when there is a high prevalence of malnutrition and infection. For example, the average infant and childhood mortality in families with thalassaemic children in Pakistan approaches 50%, compared with 22% for the general population (Fig.14).

In West Africa, about 2% of newborns have sickle-cell disease, and most die from infections in their very early years; so this single inherited disease contributes about 14% of the general infant mortality (which is about 140/1000). It also ensures a very uneven distribution of the infant mortality: for the 8% of couples that are both carriers of sickle-cell trait it is at least 390/1000, compared with about 120/1000 for the 92% of couples that are not at risk (see Fig.15c). There are good reasons for introducing an appropriate service for a genetic disease that is so common, and has such severe effects on a large minority of the population.

Knowledge, being cheap, spreads faster than technology, which is expensive, and this creates a general problem for developing countries, illustrated by the fact that the ability to diagnose genetic disease is spreading ahead of the ability to provide whatever treatment is possible. Once a common and severe congenital disorder that can be treated or prevented is diagnosed, it is very difficult to ignore it; the fact of diagnosis and the knowledge that goes with it, without the ability to treat it properly can make the families' situation worse in many ways, while the need for tertiary level medical care can tend to increase existing distortions in the health system. Therefore it is reasonable to evaluate the potential burden of congenital disorders in every country, whatever the stage of development, with a view to introducing preventive measures at the appropriate time.

4.1. Indicators for introducing genetics services

The following simple indicators (which may be particularly helpful in developing countries) can be used in evaluating the local importance of hereditary diseases, and the need for control programmes.

The general level of development is indicated by the infant mortality and the birth-rate. "Best estimates" of these parameters for 1980 for every country in the world (40) give a "global development curve" (Fig.15a) that shows a direct relationship between infant mortality and crude birth-rate, until the latter reaches a maximum of about 50/1000. As the development curve is dynamic, and most countries are moving steadily to the left as the infant mortality falls, the curve can be used to follow a country's rate of development.

In theory, one might think that the need for a comprehensive genetics service could be predicted from the local incidence of severe congenital disorders and the projected date when the infant mortality will approach this figure. However, there are many other genetic disorders presenting later in life, and the approach is also inadequate because the infant mortality represents the whole society only in developed countries (at the bottom left-hand corner of the curve). In most developing countries there is a very wide range of birth-rate and infant mortality, both being low among the urban middle-classes (at the bottom left) and rising to a maximum among the rural poor (stretching away to the right). In these countries, the need for a genetics service will be felt first in the more developed section of the curve, the urgency of the demand being related to the local frequency of genetic problems.

The epidemiology of severe congenital disorders can be approached by using some simple general principles.

Congenital malformations involving major external alterations of body form are relatively simple to document: the neural tube defects are among the commonest and most obvious, and as information on their frequency can be gathered in any large obstetric service, it is already known to vary very much world-wide. Since the frequency of congenital malformations is related to variables such as Rubella infection, maternal diabetes and the frequency of consanguineous marriage, it is important to collect "baseline" data on their incidence in large maternity services, in communities where the frequency of these factors is changing. Since many malformations are internal, good paediatric pathology is required to obtain reliable figures.

The main variable in the frequency of chromosomal non-disjunctions is maternal age, the proportion of mothers over 35 varying from 4% to 22% in different countries (Fig.16). The age specific birth-incidence of trisomy 21 is well-known (4), and there is no evidence for differences between societies, so the birth frequency of chromosomal non-disjunctions can be calculated from basic demographic information on maternal age distribution. It seems that the birth-rate of infants with Down syndrome may be as high as 2.5/1000 live births in parts of Africa, South America and Asia, compared with 1-1.5/1000 in Japan and most Western countries.

The best ways of describing the frequency of Mendelian conditions are: a. as the percentage of the population that are carriers (when this can be measured or calculated), and b. as births per thousand of affected infants. The average global background frequency of births of infants with major single gene defects is thought to be about 3.5/1000, but the commonest disorders like G6PD deficiency, the haemoglobinopathies and cystic fibrosis differ greatly in frequency between populations. Newborns can be screened to establish the incidence of G6PD deficiency (3) and cystic fibrosis (6): and as the haemoglobinopathies can be diagnosed simply and reliably in heterozygotes, a good approximation of the birth-rate of homozygotes can be calculated from survey data, even when a high infant mortality makes direct studies of birth incidence impossible (2).

About 14% of the world's population and 19% of all births are located in areas where consanguineous marriages occur by choice rather than by accident (Table 3 and Fig.17). A careful study in Japan (42) showed a modest effect of such inbreeding on mortality and morbidity, but the scanty data available also indicates that the birth incidence of infants with recessively-inherited conditions is increased in populations where consanguinity is combined with monogamy, the extent of the effect being inversely proportional to the historical age of the tradition. Consanguineous marriages are also common in areas where mobility is restricted, so in many parts of the world, small pockets of high frequency of different genetic disorders are often found, due to founder effects combined with isolation. The proportion of different populations involved could be documented. There is evidence from Japan and Finland that as the frequency of consanguineous marriage has fallen with increased mobility of the population (Fig.18), the incidence of recessively-inherited diseases has also fallen.

Figure 19 shows that the effect of consanguineous marriage on the birth incidence of lethal recessive diseases is more marked for rare than for common conditions. These curves can be used to estimate the statistical effect of a given proportion of cousin marriages at any heterozygote frequency: for example, both the 17% of first cousin marriages in Turkey (B-thalassaemia trait 2%) and 50% of first cousin marriages among British Pakistanis (B-thalassaemia trait 6.5%) doubles the expected birth incidence of homozygotes, from .1 to .2 per thousand in the first instance, and from 1 to 2 per thousand in the second. Therefore, data on the frequency of consanguineous marriage is highly relevant to the need for genetics services.

Traditional cousin marriage has important social functions, and any attempt to discourage it on genetic grounds would certainly do more harm than good. A better approach is to offer genetic advice to the extended family whenever an individual with a genetic disease is diagnosed, and to promote counselling for young related couples prior to marriage or reproduction (43).

Final family size has an important influence on the possible effect that retrospective genetic counselling (i.e. after the birth of the first affected child) can have in limiting the number of new births of children with inherited diseases (Table 4)(44). When most couples have only 1-3 children the effect can be small or negligible, but in countries where the average couple has 6 or 7 children, genetic counselling with access to family planning could, in

theory, reduce the birth incidence of severe inherited disorders by up to 50%. Therefore, a family planning service could be the first step towards a genetics service in many developing countries. However, in such societies voluntary childlessness is an even less acceptable solution for the problems of genetic disease than it is in more developed countries, so pressure will inevitably arise for the introduction of methods that allow couples to achieve a healthy family.

It is also important to monitor common conditions that are related both to lifestyle and to genotype, such as obesity, diabetes, coronary heart disease and some malignancies, as this information is also relevant to the need for genetics services.

4.2. Community Genetics Services

It has been found that genetics services are most effectively delivered on a regional basis, and most conveniently-sized units can provide all types of service for a population of 2-3 million persons(45). Their community responsibilities include (either directly, or indirectly through co-ordinating the relevant elements in the existing medical and community services): fetal diagnosis of cytogenetic and biochemical disorders, and of congenital malformations including neural tube defects; appropriate neonatal and heterozygote screening of the general population, including defining the social strategy and arranging the laboratory service; continuing assessment of all aspects of genetics services, based on knowledge of local genetic epidemiology; centralisation of information about common genetic conditions, such as Down syndrome, metabolic diseases, cystic fibrosis and the haemoglobinopathies, that are normally treated by general paediatricians; and provision of the professional training and community educational aids that are needed to ensure the adequate delivery of the service to the population. It is also important to provide detailed clear and accurate information for individuals who carry, or suffer from, specific hereditary diseases.

The scale of the new developments in prevention of congenital disorders during pregnancy through obstetric techniques such as ultrasound, amniocentesis, CVS and intrauterine treatment has led to the emergence of fetal medicine as a new component of obstetrics. It is so closely related to the work of the geneticist that both services benefit greatly from close physical proximity, when this can be arranged.

There is also a particular need to develop community-based genetic counselling. Counselling at the specialist level needs to be done by an expert clinical geneticist, but counselling for the narrower range of simple common conditions that are the targets of the community genetics services has to be provided through the primary health care system. At present, this approach is very under-developed, so there is a need for education of primary health care workers, particularly midwives, nurses and others concerned with maternal and child health, in common genetic problems and appropriate actions.

4.3 Evaluating genetics programmes

Evaluation is an important component of genetics services, as it both defines the target and monitors progress towards it. Some aspects of a genetics service can be measured relatively simply, such as the changes in birth-incidence or lethality of the conditions mentioned in the first part of this report. However, the possibility of monitoring using simple statistical parameters as shown in the figures that summarise the impact of various services, depends on the geneticist having access to information about the birth, diagnosis and death of patients with congenital disorders in the region. At present, conditions diagnosed at birth are usually reported, but many genetic disorders such as cystic fibrosis, haemophilia and the haemoglobinopathies present later, and are not systematically registered in most countries. Agreement on registration of patients, at least those with preventable congenital disorders, should be encouraged to assist in programme evaluation.

However, one of the most valuable functions of a genetic consultation is to relieve people of anxiety about a possible genetic risk, or of guilt about their possible responsibility for their own or their child's illness. It may be difficult to evaluate some such aspects of the service, but approaches to measuring effects on the psychological quality of life need to be considered. It is as necessary to avoid the assumption that only what can be measured is worthwhile, as to avoid the idea that the effect of services cannot or should not be measured.

Cost-benefit analysis is a form of evaluation that is increasingly practised in countries with a social commitment to comprehensive medical care. In the field of fetal diagnosis, the analysis has usually been conducted by balancing the cost of the medical care of affected children for society, against the cost of preventing their births through a genetics programme. It is easy to show that restraint of reproduction by at-risk couples and selective abortion of fetuses with chronic disease saves money even in the short term, and such arguments show that there is no excuse for not setting up these services, even when money is short. However, this approach requires considerable further development. There have so far been very few good studies of the real cost to the family and society of the birth of a severely-handicapped individual; and the limited approach described above encourages an implied assumption that genetics services should cost society less than the amount of money they can save - a criterion that is not applied to any other form of medical practice.

A more realistic approach is to try to measure the amount of health that can be bought for a given amount of money: for example a fetal diagnosis service could be evaluated by observing how many families use it to attain their reproductive goals. Many couples at high genetic risk do not dare to reproduce unless fetal diagnosis is available, so up to three wanted healthy children may be born for every affected fetus aborted; and for the cost of the fetal diagnosis, parents at genetic risk may either obtain a healthy child or avoid the problems associated with the birth of a sick one. Elaborating this sort of approach further depends on defining quantitative criteria for the many kinds of benefits provided by a genetics service, including more subtle ones such as relief of anxiety.

5. ETHICAL ISSUES

Ethical questions in connection with genetics services should be viewed in the light of their general objective, which is to help people with a genetic disadvantage to live and reproduce as normally and as responsibly as possible.

It is important to recognise that these issues involve the majority of the human race. For example, at some time in their reproductive life up to half of the women in the world conceive a fetus with a severe congenital disorder, but most such pregnancies miscarry. Infants born with clinical birth defects represent only the small proportion of affected fetuses that survive the pregnancy.

The ethical issues connected with medical genetics services are very broad. They can be approached here only in a selective manner, with emphasis on a few outstanding topics. For practical purposes, the ethical questions that are most commonly raised may be divided into the speculative and the real. For example, the question of abortion (because of an unacceptable risk of bearing a severely affected child) is often brought into the discussion: but the abortion issue is in fact extraneous to debate about medical genetics. The acceptability of abortion under specific circumstances is decided on general social and medical, rather than on genetic grounds, and a fetal diagnosis service can operate only within the framework of such general decisions. In most countries abortion because of a severely affected fetus is accepted as a legitimate medical procedure; and clearly in those countries where abortion is legal when the pregnancy is unwanted, it must also be legal if the pregnancy is unwanted because the child is severely ill or malformed.

Concern has been voiced that selective abortion for severe genetic disorders may alter attitudes toward the rights of handicapped people, but there is no evidence to support this notion: no country where fetal diagnosis has become established has reduced its efforts to care for the handicapped. There are intrinsic reasons why the existence of prevention makes it more important, and more feasible, to provide optimal care for the handicapped (46), and in many countries there are now firmer recommendations than ever that individuals with congenital disorders should be given optimal treatment. In reality, heterozygote diagnosis, fetal diagnosis and patient care are complementary, not competing, approaches to helping people with a genetic disadvantage.

Progress in understanding the mechanisms of inheritance, performing genetic diagnosis and controlling genetic disability often evokes fears of a "brave new world", including coercive control of peoples' reproductive behaviour for political ends. However, the geneticist's principle of the autonomy of the individual (see below) excludes such activities even if they were possible.

The fact that such speculative issues occupy the foreground of public debate obscures the really important ethical issues of medical genetics, and impedes the development of necessary services by creating the false impression that this area of medicine is beset with insoluble moral problems.

The guiding principles of clinical geneticists, that are included in professional teaching and adhered to in practice, have been studied empirically and summarised in a set of "guidelines" for genetic counselling, fetal diagnosis and screening. Core principles are the autonomy of the individual or the couple, their right to adequate and complete information, and the maintenance of the highest standards of confidentiality (47). It follows that the choices that are to be made should be made by the individual or the couple and that genetic counselling should be provided in a non-directive manner. Non-directive counselling does not mean simply giving people the facts and letting them make up their own mind. It is a special skill requiring an appropriate personality and training, and involves accompanying "counselees" in decision-making by helping them take account of their unique medical, social and moral situation.

The principle of confidentiality should also be used not only to protect the privacy, but also to serve the true interests of the people involved, and other members of their kindreds. Thus, the establishment of useful and confidential genetic registers should be considered.

The broadest of the real ethical issues is the limited availability of genetics services. The care of the handicapped and support for their families is universally deficient, and at the same time the services that can now be provided for responsible family planning are not effectively delivered, and are unequally distributed even in developed countries. The poor delivery of amniocentesis to older mothers in Northern Europe is only one example. As a result, women unnecessarily bear seriously affected children, and the realisation that the problem could have been avoided then makes the situation worse. The limited delivery of these services is partly due to inadequate resources, especially for counselling; and partly due to inadequate provision of health education for the community, and technical information for health professionals.

Application of the new genetic technology can create real new ethical problems. For instance, whenever a new DNA probe or technique is developed, it is an important medical responsibility to make it available for research, so as to expedite the developments so urgently needed by patients with chronic disease, or at high genetic risk: but at present this is sometimes impeded by non-scientific considerations. In view of the serious consequences of predictive tests for severe monogenic disorders, they need to be highly reliable; for instance tests based on genetic variation at a linked locus (RFLPs) should be widely used only if the linkage is very tight, or if loci on both sides of the gene in question can be used, so that recombination can be excluded for practical purposes.

Other difficulties are illustrated by the possibility of predictive tests at the DNA level for the Huntington's disease gene. When such a test becomes reliable it will in principle be possible for people belonging to Huntington disease kindreds to avoid passing the gene on to future generations; however, the price for many people will be the definite knowledge that they carry the gene for this severe disease, and there is justified worry that this could lead to tragic consequences such as suicide. There is, however, no easy way out. Not making the test available means that more people, namely the spouses and offspring of the patients, will be involved in these anxieties. It seems reasonable that spouses of people at high risk for such diseases should share their partner's knowledge, but the responsibility for this decision should rest with the individual at risk.

There is a possibility that DNA technology will ultimately permit the identification of many normal as well as pathological inherited characteristics, in the fetus as well as in the adult, and there is need for some guidance on the usefulness of offering fetal diagnosis for conditions associated with clinical consequences of variable severity, such as α -1 antitrypsin deficiency. As the final responsibility for the decision rests with the counselled couple, the best way to find out how to use new diagnostic tests is to discuss them with the affected families and record their reactions. The most objective approach is to make fetal diagnosis available, and to observe how families at risk make use of it.

There is increasing awareness that genes at the ends of the normal range of genetic variation, such as α -1 antitrypsin deficiency, may confer a predisposition or resistance to common disorders. The genes themselves do not cause disease, and in fact most of their bearers may be completely healthy. Every measure should be taken to ensure that individuals can have tests for such characteristics conducted, without fear that the results could be used to their disadvantage, for instance in limiting choice of employment or in weighting life insurance. Such application of this information would be unfair, since testing is available for only a few of the risks that actually exist; it is essentially random by which tests are available at a given time and place; and individuals with positive results are likely themselves to take appropriate avoiding action. As knowledge of such normal genes grows, it is increasingly important to establish rules governing confidentiality, and this could require new laws in some countries.

Fetal sexing provides an important example of non-pathological genetic diagnosis. Termination of pregnancy in the mid-trimester on grounds of fetal sex is generally not accepted, but the possibility of sex selection in the first trimester, at a stage when termination of pregnancy on social grounds is widely available, is a new issue. There seems no contra-indication to providing information on fetal sex within the context of genetic diagnosis. On the other hand, sex selection as a primary indication for fetal diagnosis is generally viewed as an undesirable expression of inequality of the sexes, and there can be little doubt that its practice by geneticists in developed countries would endanger the genetics services by producing a negative reaction. It follows that it should not be offered in the framework of a genetics service.

Inevitably the social and ethical aspects of genetics services differ between developing and developed countries, because economic factors are so critical and genetic disease may be so destructive, when there is no social support system. Consequently, an important element in genetic counselling in developing countries is information on the economic consequences for the family, of the birth of an affected child.

6. FURTHER RESEARCH NEEDS

Clinical genetics services have important fundamental research implications, and need to be conducted in contact with expert research centres, but useful research need not always be highly technical.

Knowledge of the nature and geographical distribution of genetic characteristics relevant for health is essential and forms an important part of the background for many aspects of health care. Since each human population is genetically unique, genetic epidemiological information is needed from every country, and is in itself a contribution to the science of human genetics.

To deliver community genetics services effectively, it is necessary to have cheap and simple technology that can be used on a mass scale. The availability of ultrasound and karyotyping is still limited to some extent even in developed countries by expense. Simplified techniques are needed so that these useful approaches can be applied more widely. The development of cheap portable high quality ultrasound machines, and simpler DNA-based screening methods to estimate chromosome dosage, would overcome some of the most important limitations in our ability to offer fetal testing to all who need it.

However, even those genetics services that are available are not yet being delivered effectively, partly because basic genetic counselling is not yet integrated into primary health care, and partly because of the difficulty of alerting the healthy population to the reality of genetic risk. Therefore studies of genetic health-education strategies and of methods for delivering community-based genetics services should be encouraged.

Research on the genetic background of common diseases such as coronary heart disease and diabetes may be particularly indicated in parts of the world where populations of different ethnic origins share a similar environment and diet, and where these diseases of affluence are also on the increase. In the cancer field it is clear that some people are at higher risk than others of developing a malignancy, and comparison of regional differences may cast light on the genetic factors involved.

Atypical drug reactions and reactions to environmental agents often have a genetic basis and should be investigated more systematically to broaden our knowledge of human variation, relevant to health-promotion.

There are particularly interesting opportunities for genetic epidemiological research in countries where consanguineous marriage is a longstanding tradition. Since most specific inherited disorders are caused by a variety of different mutations, and most patients with a recessively-inherited condition who are offspring of a consanguineous marriage are homozygous for the same mutation, they provide unique opportunities for studying the relationship between genotype and phenotype. Comparison of the relative incidence of consanguineous and non-consanguineous marriages among parents of children with a given recessively-inherited condition provides a simple way to assess the frequency of the mutant gene in question in the population. When the mutant gene is rare, practically all affected children will be the offspring of consanguineous couples, but when a gene is more common, the proportion of non-consanguineous couples among the parents of affected children is higher. Thus, once biochemical genetic diagnosis is available, a "genetic profile" can be mapped more easily than in most other populations. Differences in the proportion of children with different congenital malformations in the offspring of consanguineous and non-consanguineous marriages may also cast light on the contribution of inheritance to congenital malformations, while the frequency of homozygotes for more than one kind of recessive disease in extended inbreeding families may clarify the question of the number of recessively-inherited lethal traits carried per person.

7. CONCLUSIONS

The general objective of genetics services is to help people with a hereditary disadvantage to live and reproduce as normally and as responsibly as possible. Activities include diagnosis, counselling, and technical interventions, which range from treatment of affected individuals, and prevention by alteration in lifestyle, to selective abortion of fetuses found to have a severe disorder.

The central ethical principles of genetic practice are respect for the autonomy of individuals, their right to adequate and complete information, and preservation of the highest level of confidentiality.

Genetic information promotes individual autonomy by increasing people's ability to control their own health and that of their family. Genetic misinformation is the main complication of inexpert approaches. As the range of possible options and the proportion of the population involved is extending steadily, it is necessary to encourage wider understanding of genetic issues by offering simple and realistic information to the community. This should help people to use genetic information when it is relevant, and to avoid unnecessary anxieties related to knowledge of genetic risk, or to possible hazards such as radiation and toxic substances in the environment.

Genetic factors are an important element in human health. Depending on the country, from 1.5 to 4.5% of newborns suffer from a congenital disorder that will lead to death or lifelong problems. Genetic factors are also important in resistance to infection, and in diseases such as atherosclerosis, diabetes, cancer and hypertension, while due to the wide range of human variation, inherited predispositions are highly relevant for health promotion. Some genetically-determined pathology can now be prevented by programmes delivered at the community level, which may be defined as community genetics services.

An important problem, especially where prevention is concerned, is that though collectively they are numerically significant, genetic disorders include a very large number of different conditions, many of which are relatively rare. Community genetics services therefore depend on setting up simple mass-scale screening programmes, which will contact almost everyone in the population at a relevant point in their life.

Much of the progress in developing these approaches in the past 15 years has been achieved through collaboration between the geneticist and the obstetrician. Examples are: newborn screening using the Guthrie blood spot for phenylketonuria, congenital hypothyroidism and sickle-cell disease; screening of pregnant women for Rhesus blood group, maternal serum

alphafetoprotein (AFP) level and haemoglobinopathy traits, as well as for exposure to relevant infections; ultra-sound scanning; and the offer of amniocentesis to older mothers. Once such testing systems have become part of basic health care, a foundation exists for other approaches to be introduced; while integration may improve the resolving power of screening tests, for example, the possible application of a low maternal serum AFP for detecting fetuses with Down syndrome.

The ability to offer help to at-risk individuals identified in screening programmes depends largely on obstetric techniques such as ultrasound scanning in pregnancy, and obtaining samples of fetal material for genetic diagnosis by amniocentesis, fetal blood sampling or chorionic villus sampling. Association between clinical genetics and the new obstetric discipline of fetal medicine greatly strengthens genetics practice and is promoted by locating these two disciplines physically together, at least in some centres.

The increasing need to inform the population about the possibilities for preventing congenital disorders, means that it is now necessary to promote basic genetic screening and advice in Primary Health Care.

Community genetics services are relatively inexpensive and highly cost-effective, in view of the great social and financial burden of the chronic disease avoided. They require to be co-ordinated by specialist geneticists, usually based on research institutions with relevant expertise, and closely associated with obstetric colleagues. In addition to solving specialised genetic problems, the clinical geneticist's responsibilities now extend to developing and organising community genetics programmes and integrating them into the health system, educating the relevant health-workers, ensuring quality control, and monitoring the services to promote high quality and continuing progress.

A review of available experience on the control of avoidable conditions in more developed countries shows that: changes in social factors such as the distribution of maternal age has greatly reduced the background frequency of births of children with Down syndrome; hereditary disease control programmes have brought about major reductions in the births of infants with neural tube defects, thalassaemia, Tay-Sachs disease and some other inherited diseases, and more moderate reductions in births of children with Down syndrome; neonatal jaundice with kernicterus leading to death or chronic disability, due to Rhesus haemolytic disease of the newborn or G6PD deficiency, has been almost eradicated from many areas where it was common; early diagnosis and treatment have improved the survival and quality of life of patients with phenylketonuria and other amino-acid disorders, congenital hypothyroidism, and sickle-cell disease; and the prognosis of some common conditions such as haemophilia, thalassaemia and cystic fibrosis has been greatly improved by careful attention to management. The benefits of the community approach to genetically-determined disorders are now clear, and extensive experience of organising effective programmes is available for guidance, in extending them to more of the world's population.

The burden of genetic disease is, in general, heaviest in developing countries. The haemoglobinopathies and G6PD deficiency are common in areas with a previous history of malaria; a high proportion of older mothers leads to a high birth-rate of infants with Down syndrome; and where consanguineous marriage is common, the birth-rate of infants with recessively-inherited diseases may be considerably increased. Furthermore, because of the lack of a social support system, the heavy burden of chronic disease for the individual and the family places added emphasis on the desirability of prevention. A set of indicators is proposed to assist in evaluating the need for genetics services in developing countries. They include basic statistical data on infant mortality and birth-rate, maternal age distribution, the frequency of avoidable genetic conditions such as the haemoglobinopathies, and the incidence of consanguineous marriages.

Even in developed countries the delivery of existing genetics services is very uneven. Some, such as newborn screening are provided to over 95% of many populations, but others such as amniocentesis for the prevention of Down syndrome, or carrier screening for the haemoglobinopathies, are provided to only a fraction of those who really need them. It appears that one of the main problems in delivering genetics services is the difficulty of informing the profession and the community of the real significance of genetic problems. There is therefore a need for international collaboration in improving genetic health-education at all levels, particularly through the development of appropriate educational aids.

At the level of health-promotion, the present most important need is for further development of genetic approaches for identifying groups of people at increased risk from coronary heart disease, so that they can be offered further testing and useful advice. The development of similar approaches for reducing the incidence of other common diseases such as diabetes and cancers is a priority area for genetic research.

Finally, the relevance of the normal range of human variation, illustrated by local differences in ability to digest lactose, to eat broad beans or to take certain antimalarial drugs with safety underlines the importance of further mapping of common hereditary traits relevant to health, in order to assist appropriate development of social and health policies.

8. PARTICIPANTS

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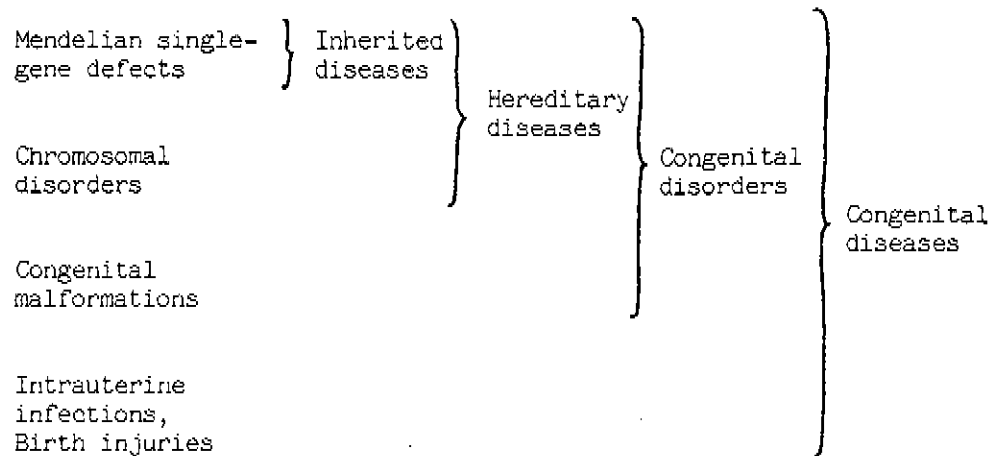


Fig.1 Categories of Congenital Diseases.
("Common diseases" are not included)

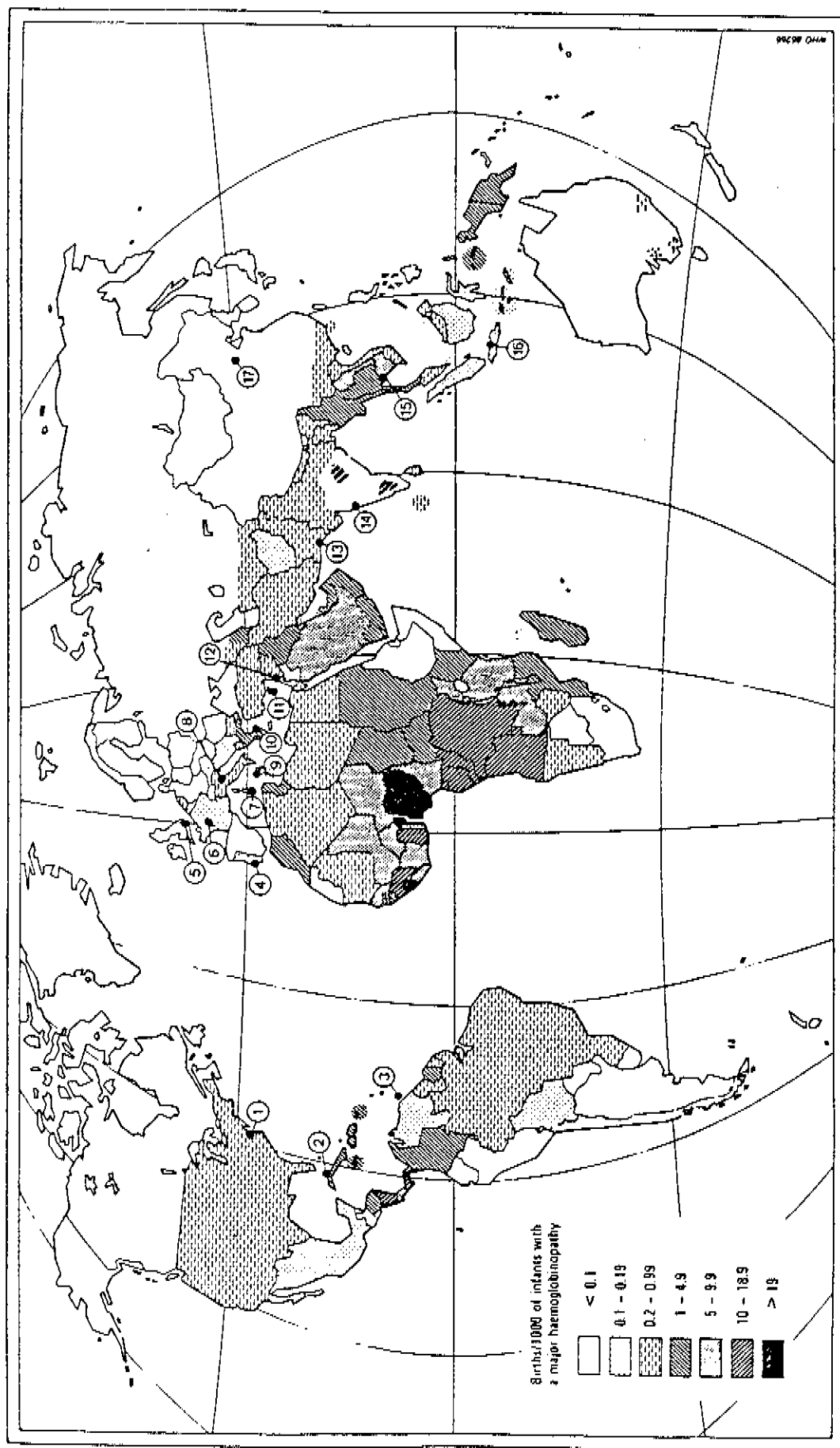


Fig.2 World distribution of the haemoglobinopathies (sickle-cell disease and thalassaemias), expressed in terms of births of homozygotes per thousand. The numbered rings indicate centres associated with the WHO Working Group for the Community Control of the Haemoglobinopathies. (Data from ref. 2).

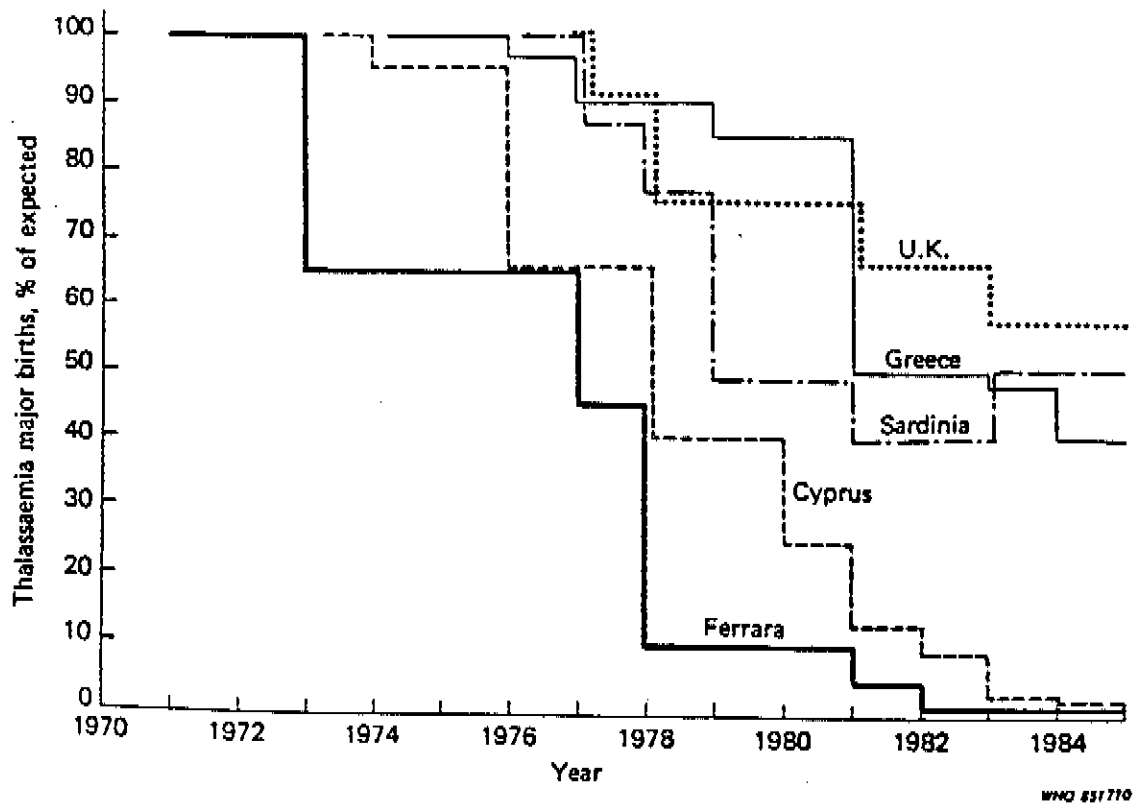


Fig.3 Fall in the birth-rate of infants with thalassaemia major associated with several thalassaemia control programmes. (Data from ref. 2).

CAUSES FOR THE BIRTHS OF 193 THALASSAEMIC CHILDREN
IN 3 REGIONS WITH THALASSAEMIA CONTROL PROGRAMMES

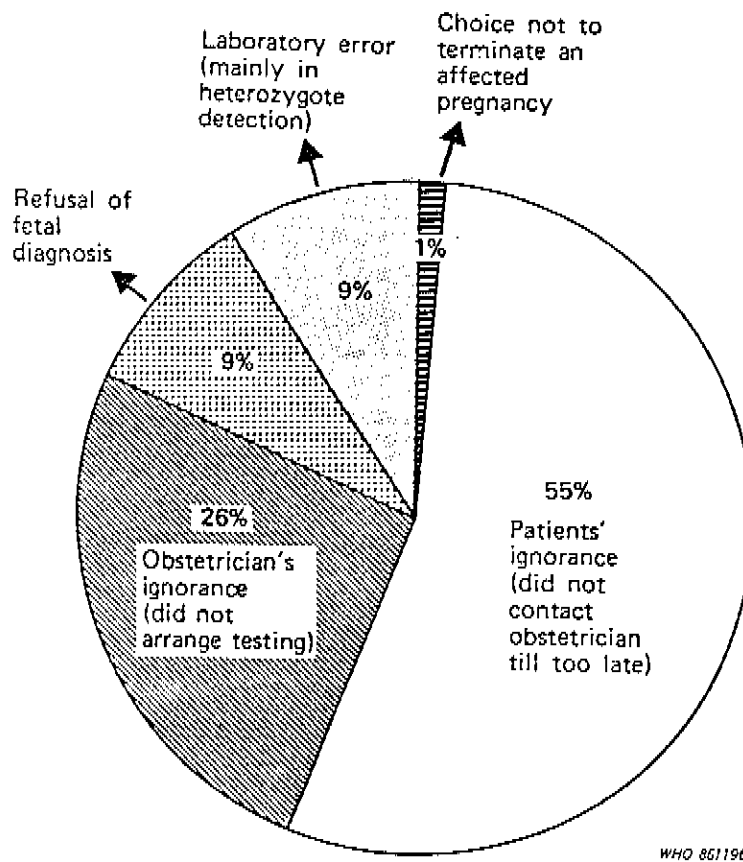


Fig.4

Pie chart summarizing the results of interviewing the parents of thalassaemic children born since the start of the control programme. Only a minority of these births were the result of the parents' informed choice not to request fetal testing, or not to abort a pregnancy where the fetus had been shown to be affected with thalassaemia major. Most were born because either the parents or the obstetrician or both, were unaware of the reality of risk, and the possibility of prevention. It is also noteworthy that as the number of affected births falls, the proportion that are due to an error of diagnosis rises - emphasizing the very high level of responsibility associated with heterozygote screening. (Collected data from Sardinia, Athens and Cyprus; from reference 13).

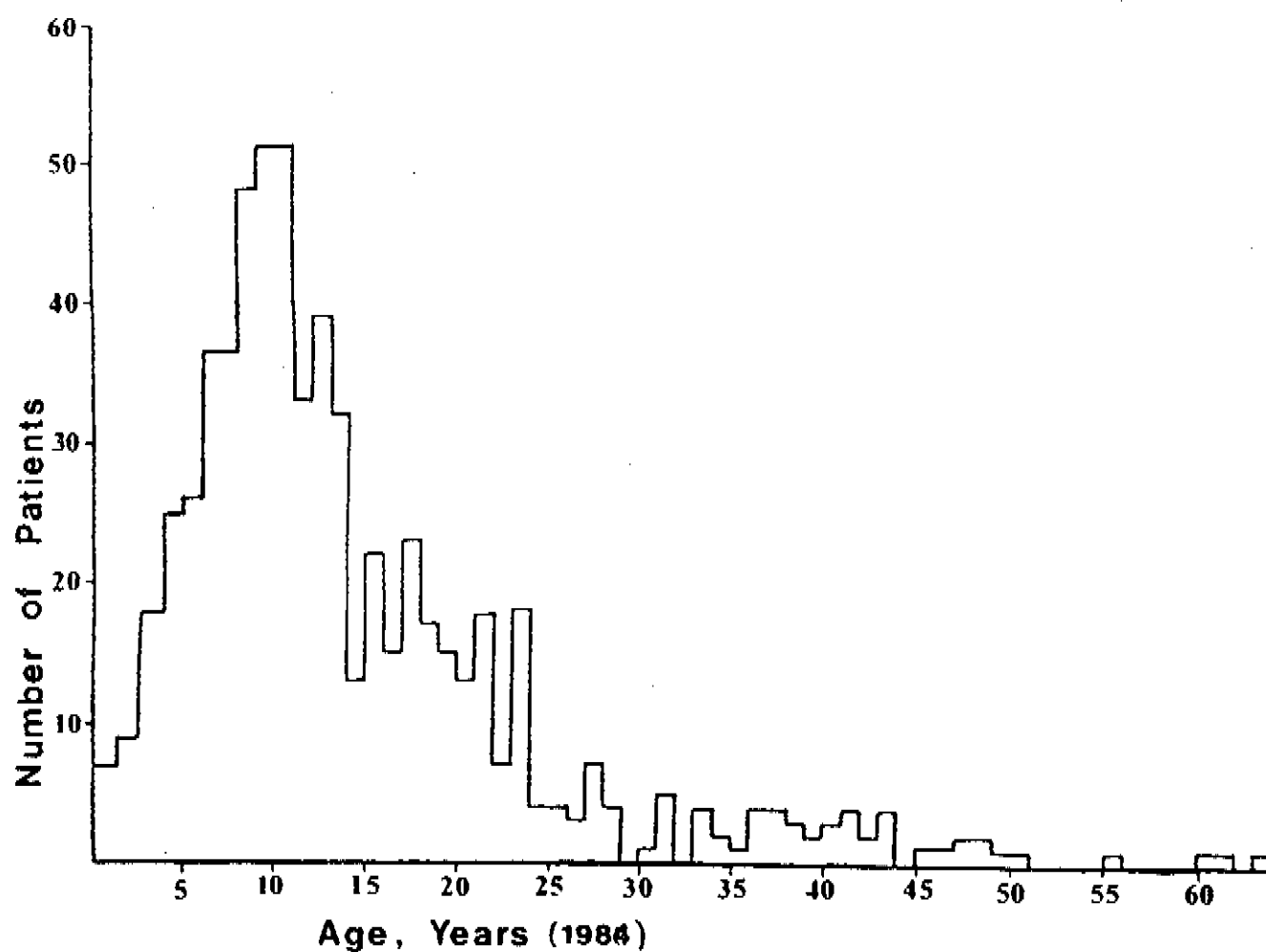


Fig.5 Age-distribution of patients with homozygous B-thalassaemia in Cyprus in 1984. The leading (right) edge of the curve can be used to monitor the patients' survival - i.e. the effectiveness of treatment. The trailing edge measures the effectiveness of prevention. In Cyprus, the thalassaemia problem has now been "contained" by an energetic programme combining treatment and prevention. (Data from ref. 13).

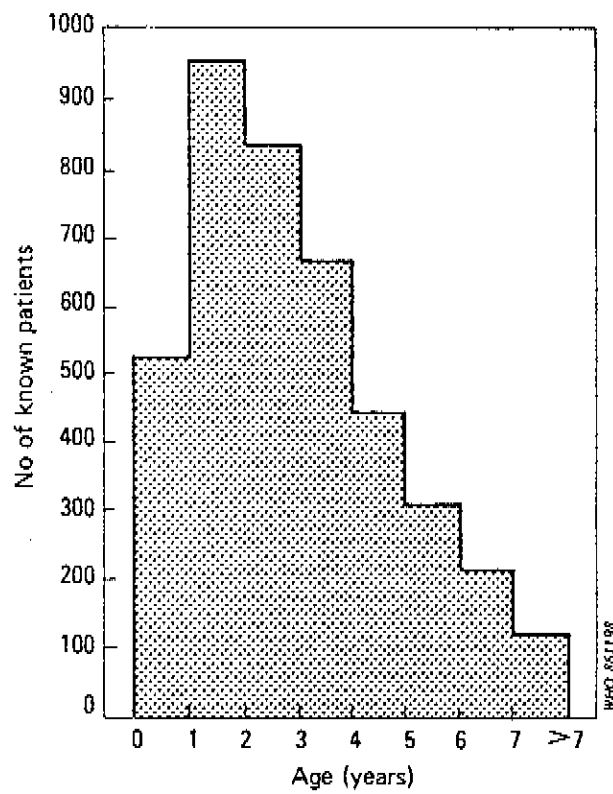


Fig.6

Age-distribution of known patients with haemophilia A in the UK, in 1980. Number of patients shown = 4089. A further 232 whose age was not known are not included. The leading (right) edge of the curve measures the increasing effectiveness of treatment with time. Data on recent deaths collected in 1980 showed that the life-expectancy in haemophilia resembled the normal at that time. (Data from reference 48).

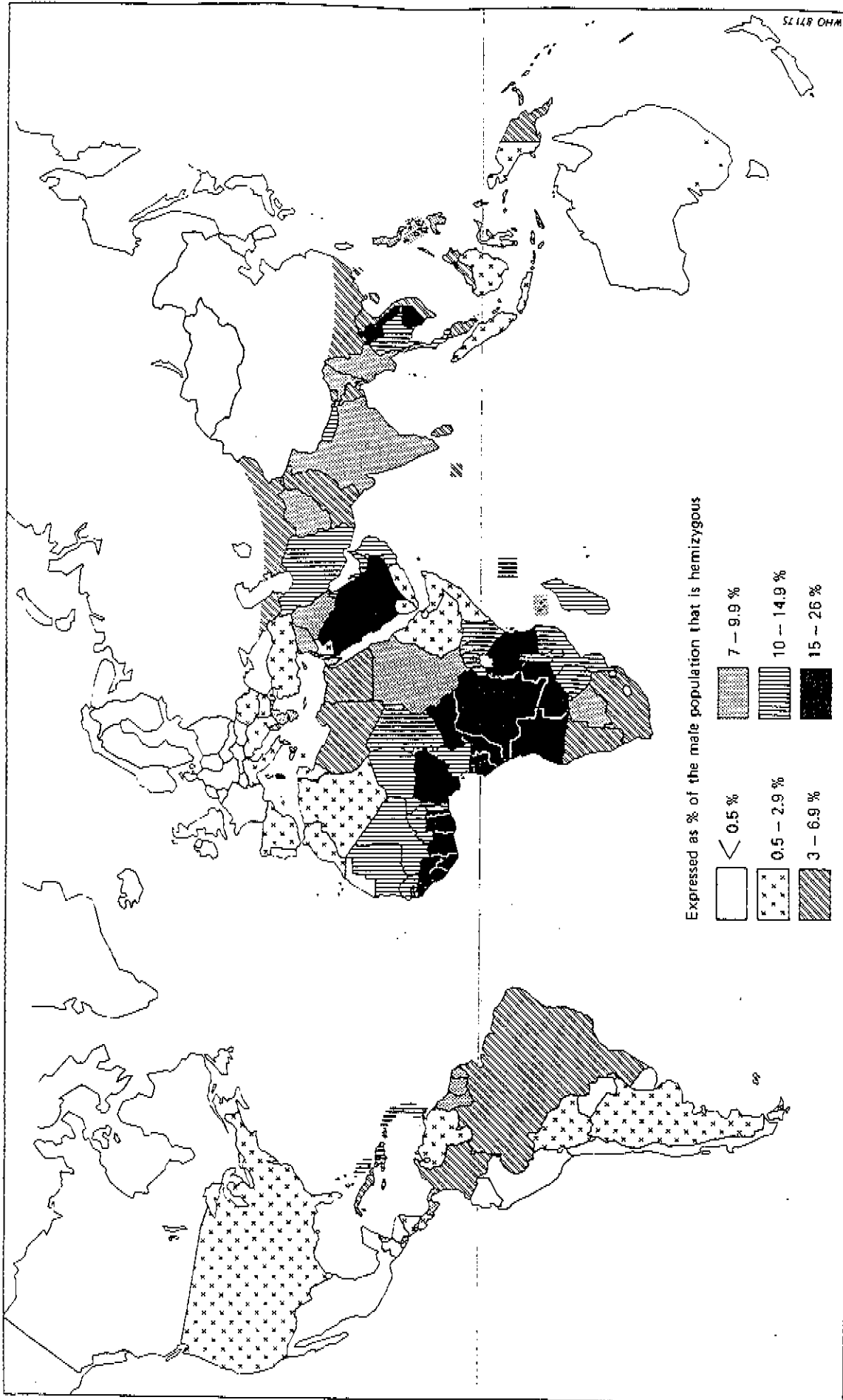
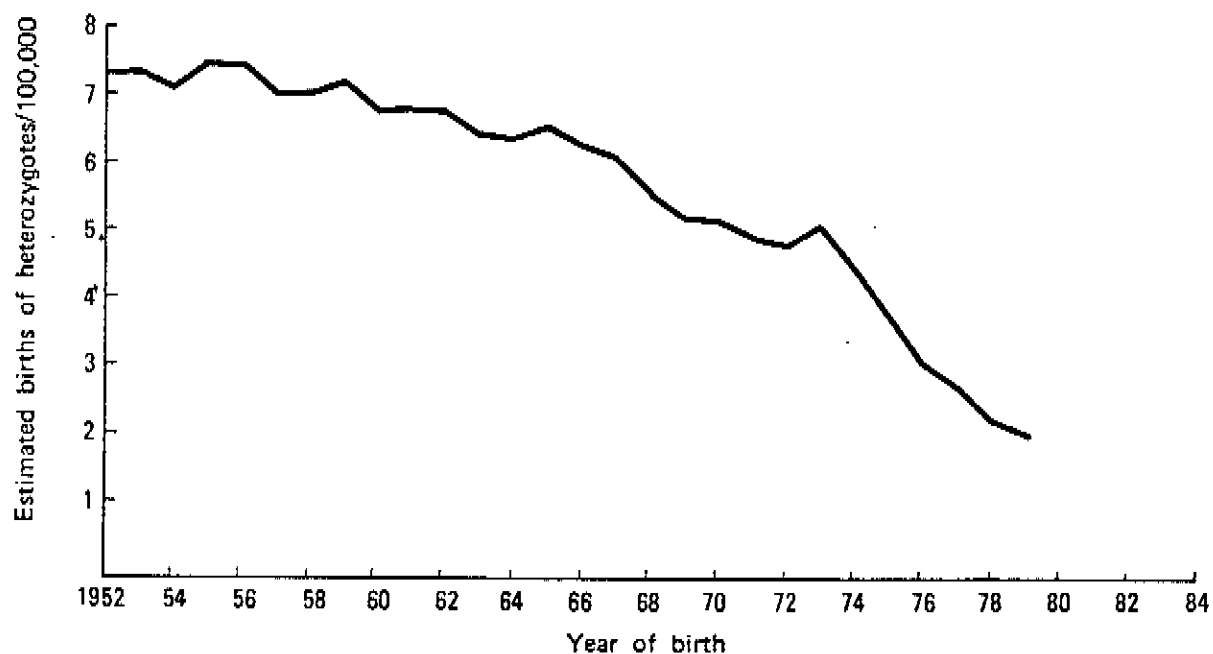


Fig.7 World distribution of G6PD deficiency, expressed as a percentage of the male population that are hemizygous (i.e. carry the gene on their single X-chromosome). The incidence of female heterozygotes is approximately twice that of male hemizygotes. (Data from reference 3).



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Fig.8 Decrease in the number of births of individuals at risk for developing Huntington's chorea in South Wales. As a result of genetic counselling and family support, many members of kindreds transmitting Huntington's chorea decide not to reproduce, in order to avoid handing on the gene. (Data from ref. 23).

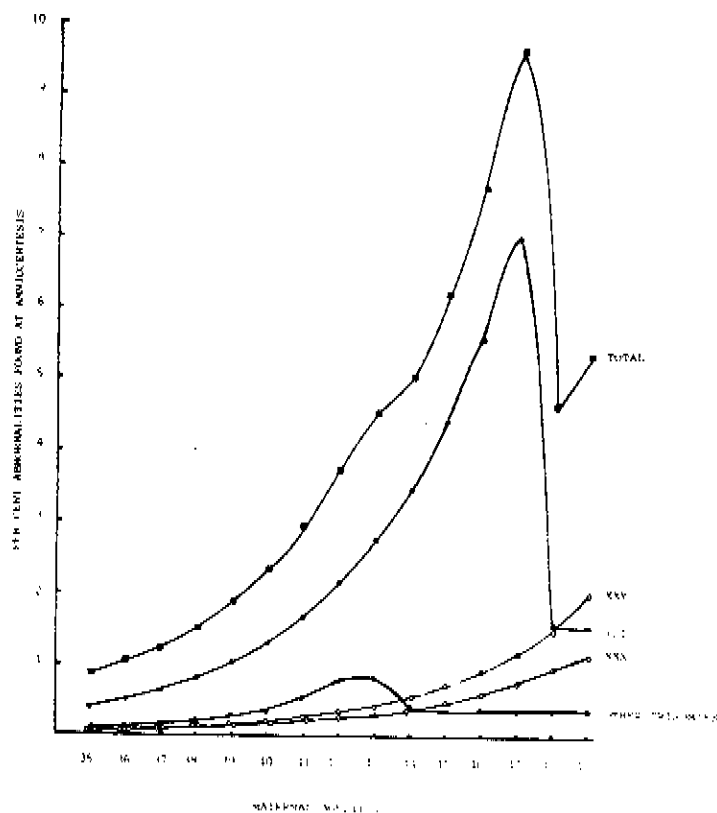


Fig.9 Increasing risk of carrying an aneuploid fetus with increasing maternal age. The data are for findings at amniocentesis; since about one-third of chromosomally-abnormal fetuses abort spontaneously between 16 weeks and term, the risk of delivering a live-born chromosomally-abnormal child is about one third less than that shown. The relationship with maternal age is complicated by the fact that the early spontaneous abortion rate of fetuses with trisomies other than trisomy 21 increases after the age of 40, so that though more are conceived, fewer survive long enough to be diagnosed at amniocentesis. The sudden drop in the number of fetuses with Down syndrome diagnosed after 47 years of age may be an artefact due to the small numbers of mothers in this age-group studied, or the result of increased tendency to spontaneous abortion of the chromosomally-abnormal fetus in these much older mothers. (Data from ref.49).

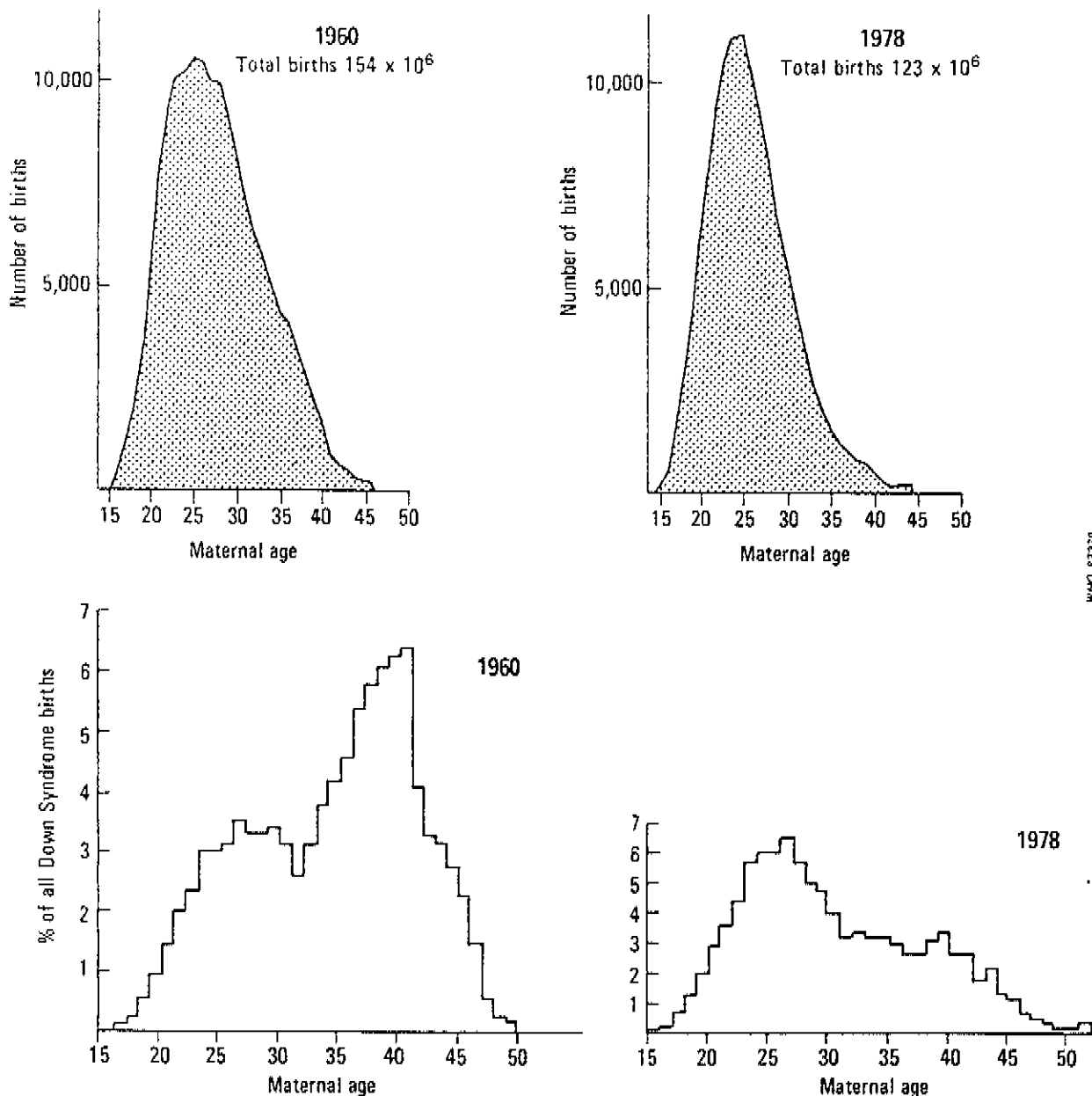


Fig. 10 Changes in the distribution of maternal age, and in the number and age-distribution of infants with Down syndrome, in Belgium between 1960 and 1978. The upper part of the figure shows that in these 18 years there was a 20% fall in the number of births, and that half of this fall has been due to a reduction in births to mothers over 35 years of age. The incidence of Down syndrome births has fallen by about 34%, (from 1.6-1.7/1000, to 1.0-1.1/1000), and the annual number of Down syndrome births has fallen by 47%. The lower part of the figure shows that of these, the percentage born to mothers over 35 has fallen from 53% to 28%: i.e., the maternal age distribution of mothers of infants with Down syndrome has been almost perfectly "reversed". The scale of the graph representing Down syndrome births for 1978 has been reduced to half that of the corresponding graph for 1960, in order to indicate the absolute fall in the number of affected infants born every year, as well as the maternal age distribution.

FALL IN THE INCIDENCE OF NEURAL TUBE DEFECTS IN SCOTLAND

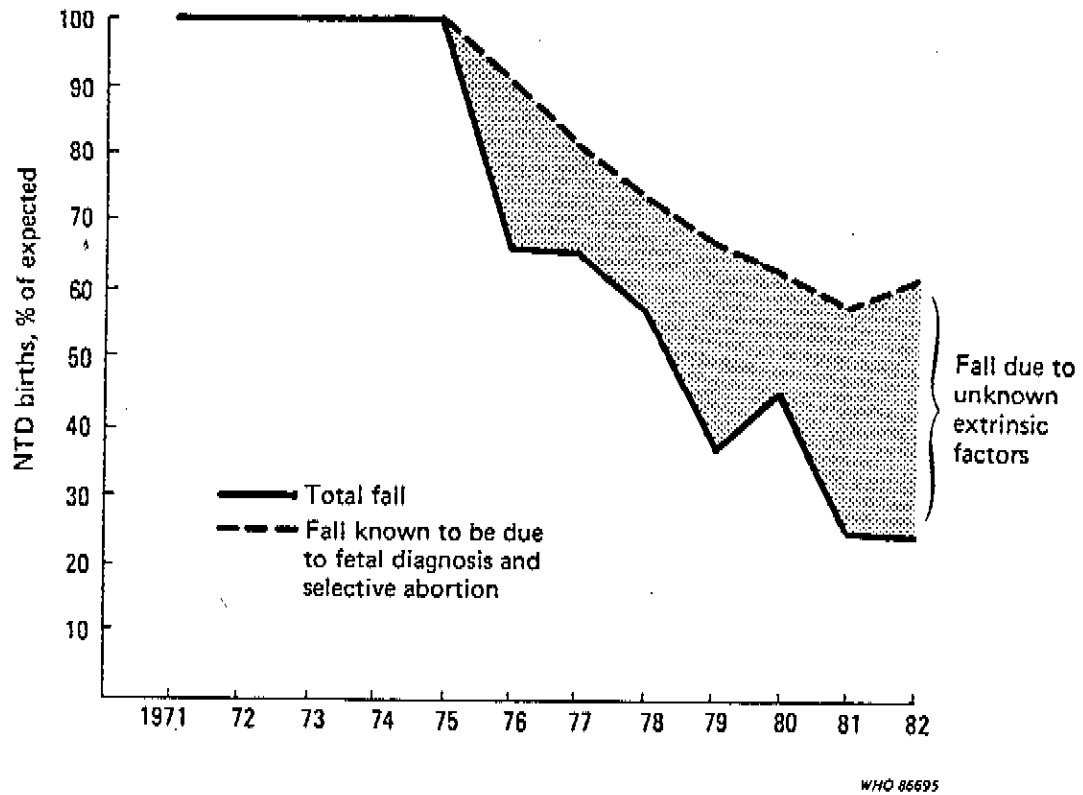


Fig.11 The incidence of neural tube defects has fallen in Scotland by almost 60% since maternal serum AFP screening was introduced. However, records of abortions because of the diagnosis of an affected fetus suggest that only half of the fall has been due to fetal diagnosis, the remainder being due to a fall in the background incidence of neural tube defects in the UK. This fall, which started at the same time as the screening programme, may be due to a change in dietary habits. This coincidence underlines the importance of accurate monitoring. (Data from ref. 30).

Ethnic group mainly involved	Genetic trait	Causative agent	Result
Caucasians (specially Celts)	unknown	bread (gluten from wheat & rye)	Coeliac disease
Asians, Blacks (except Japanese, Bantu)	lactase non-persistence	lactose	maldigestion
	G6PD deficiency	broad beans	acute haemolysis
Blacks	unknown	salt	hypertension
Amerindians	unknown	alcohol	impaired catabolism

Fig.12 Common dietary problems associated with genetic variability.

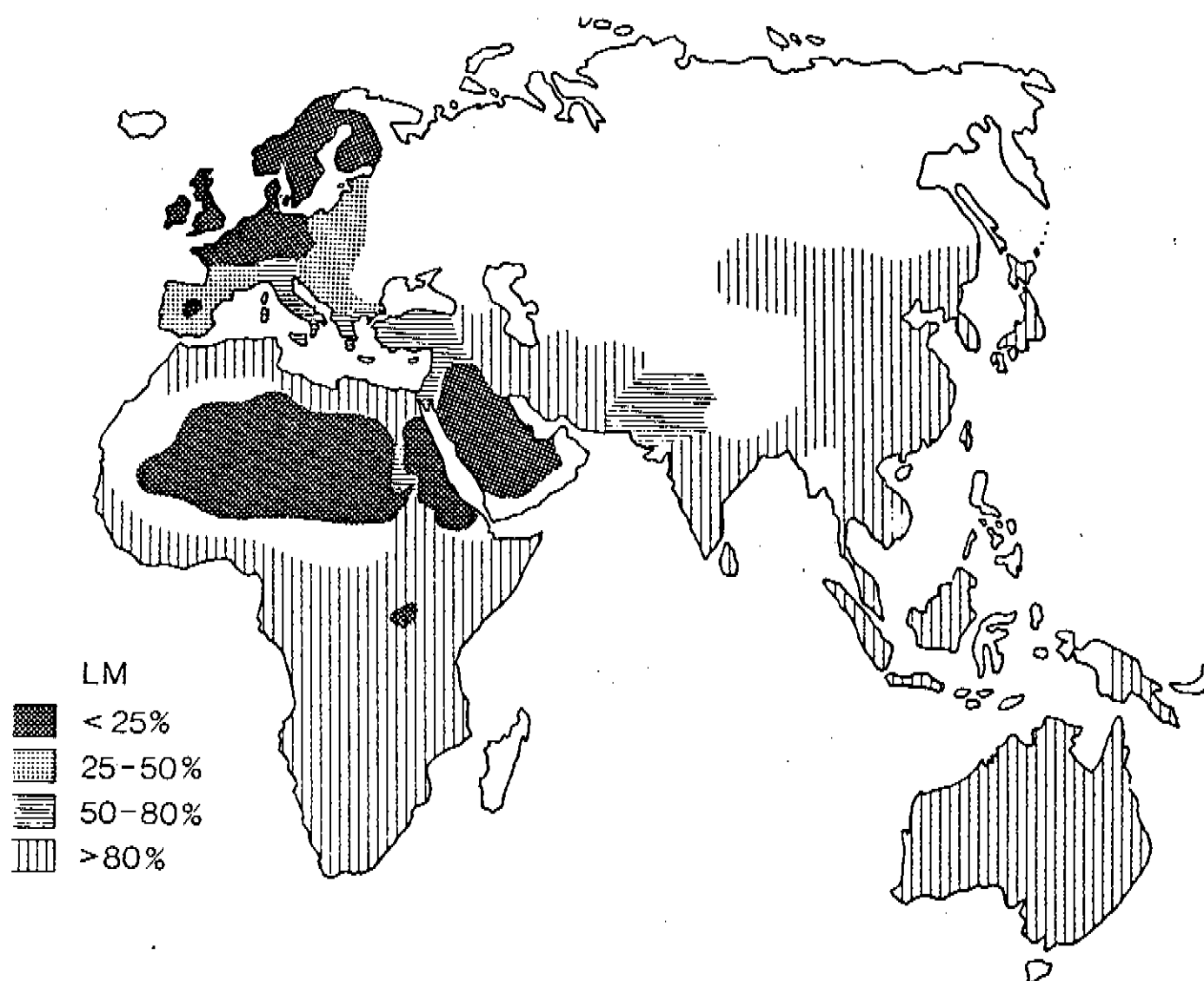


Fig.13 Distribution of the adult lactase phenotypes, lactose digester and lactose non-digester, in the Old World. No, or insufficient data is available for the areas left blank. (Data from ref.7).

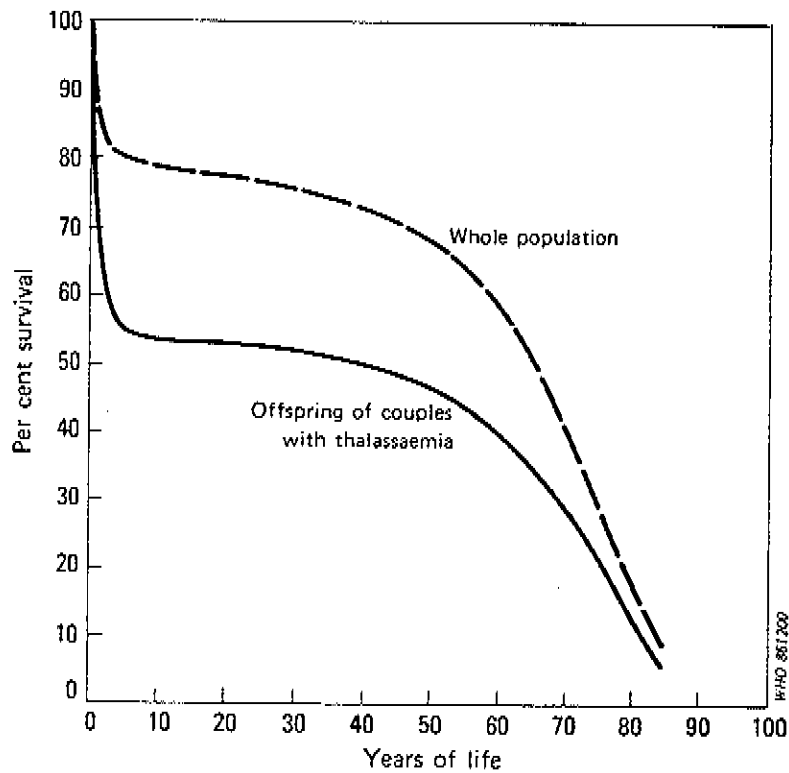


Fig.14

The contrast in the life-table for the general population of Pakistan, and the life-table for the offspring of families with thalassaemia major (or any other lethal recessively-inherited disease) provides an example of the impact of inherited disease on the family, in developing countries. When the general infant and childhood mortality amounts to 20%, the additional losses of children due to inherited disease increases the figure to at least 45%. (Data on the general life-table for Pakistan from reference 50: on the childhood mortality in families with thalassaemia, personal communication from Dr Ziaur Rehman).

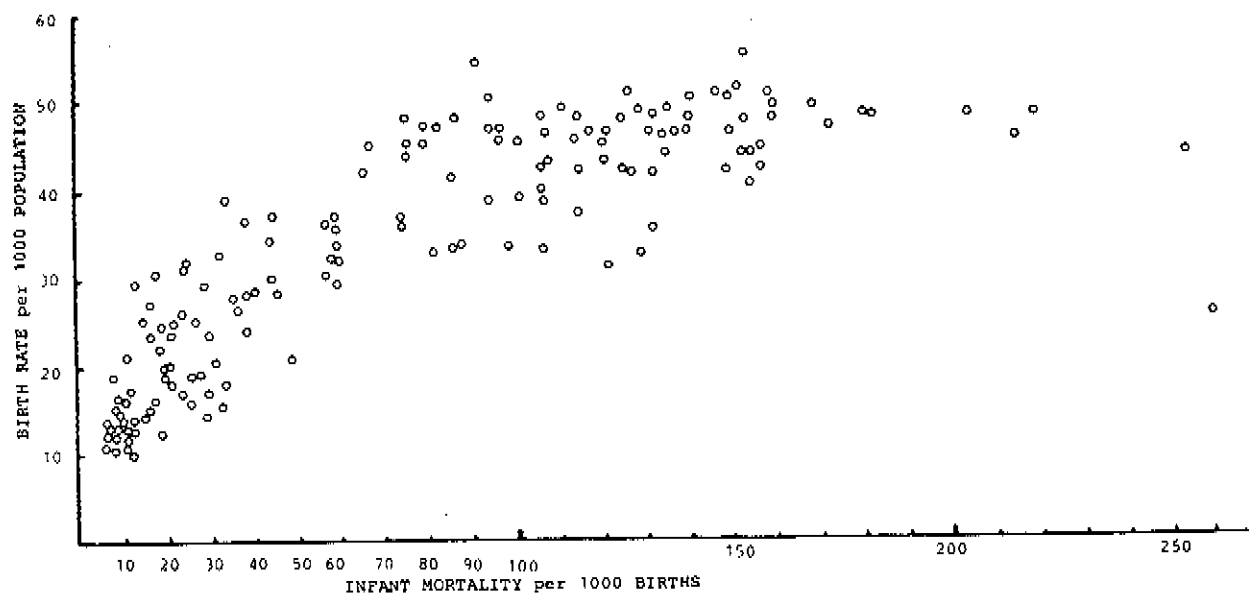


Fig.15a The relationship between the infant mortality and the birth-rate for the countries of the world, forms a "global development curve". Each country is represented by one point. The countries of Europe and North America and Japan are at the bottom left-hand corner; those of South America and Asia are scattered along the curve, while most African countries are on the plateau and to the right. The figures for the left-hand end of the curve are reliable, but those for the right-hand end are "best estimates" based on surveys, and could include considerable inaccuracies. (Data from ref. 40).

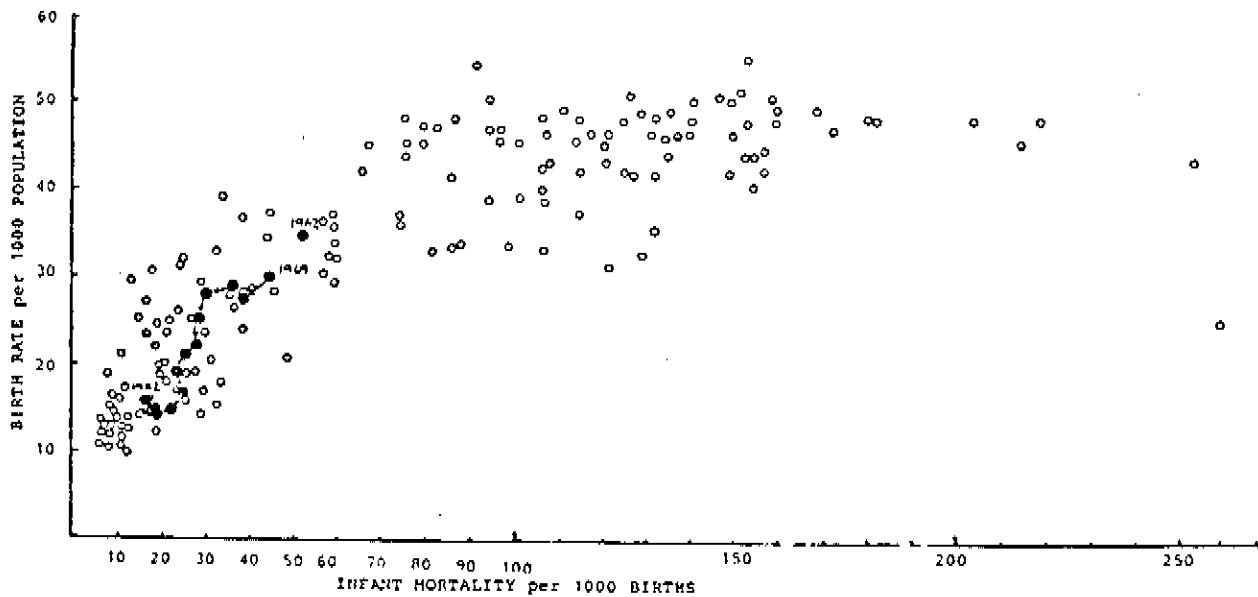


Fig.15b. The global development curve is dynamic and can be used to demonstrate the evolution of some aspects of development in individual countries. This example shows the change from 1962-1982 in a single country.

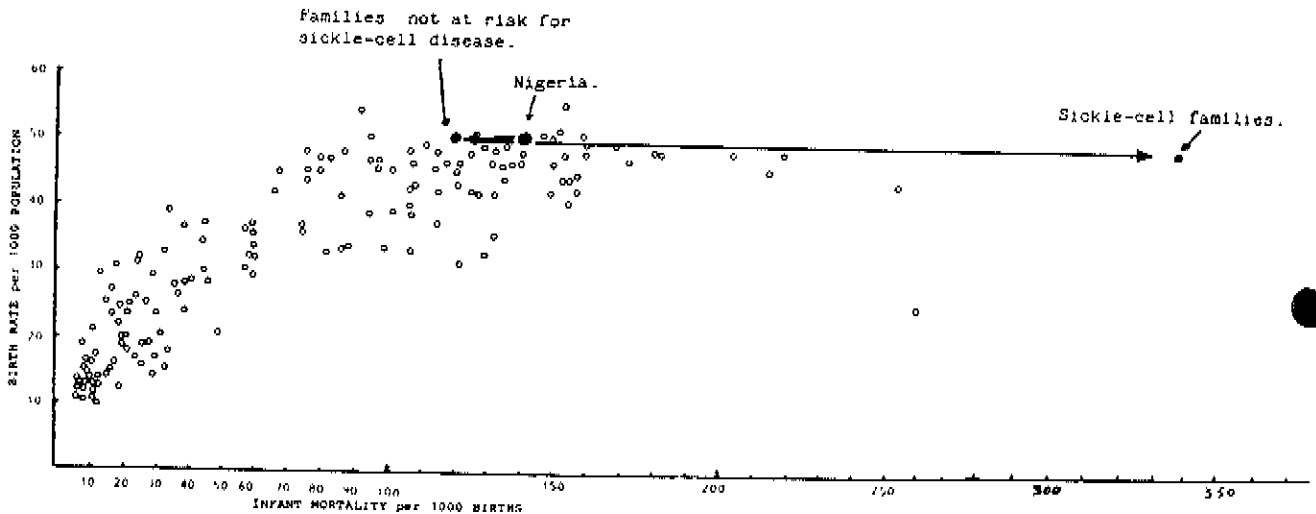


Fig.15c. The curve can also be used to demonstrate the contribution of particular conditions to infant mortality. In much of Sub-Saharan Africa, about 8% of couples are at risk for having children with sickle-cell disease, which usually leads to death in early childhood; so the average infant mortality of about 140/1000 in this part of the world (e.g. for Nigeria) can be divided into two components: about 340/1000 for the group of families at risk for sickle-cell disease, and 120/1000 for the families not so at risk. It is difficult to ignore a disorder that affects such a large minority of the population so severely.

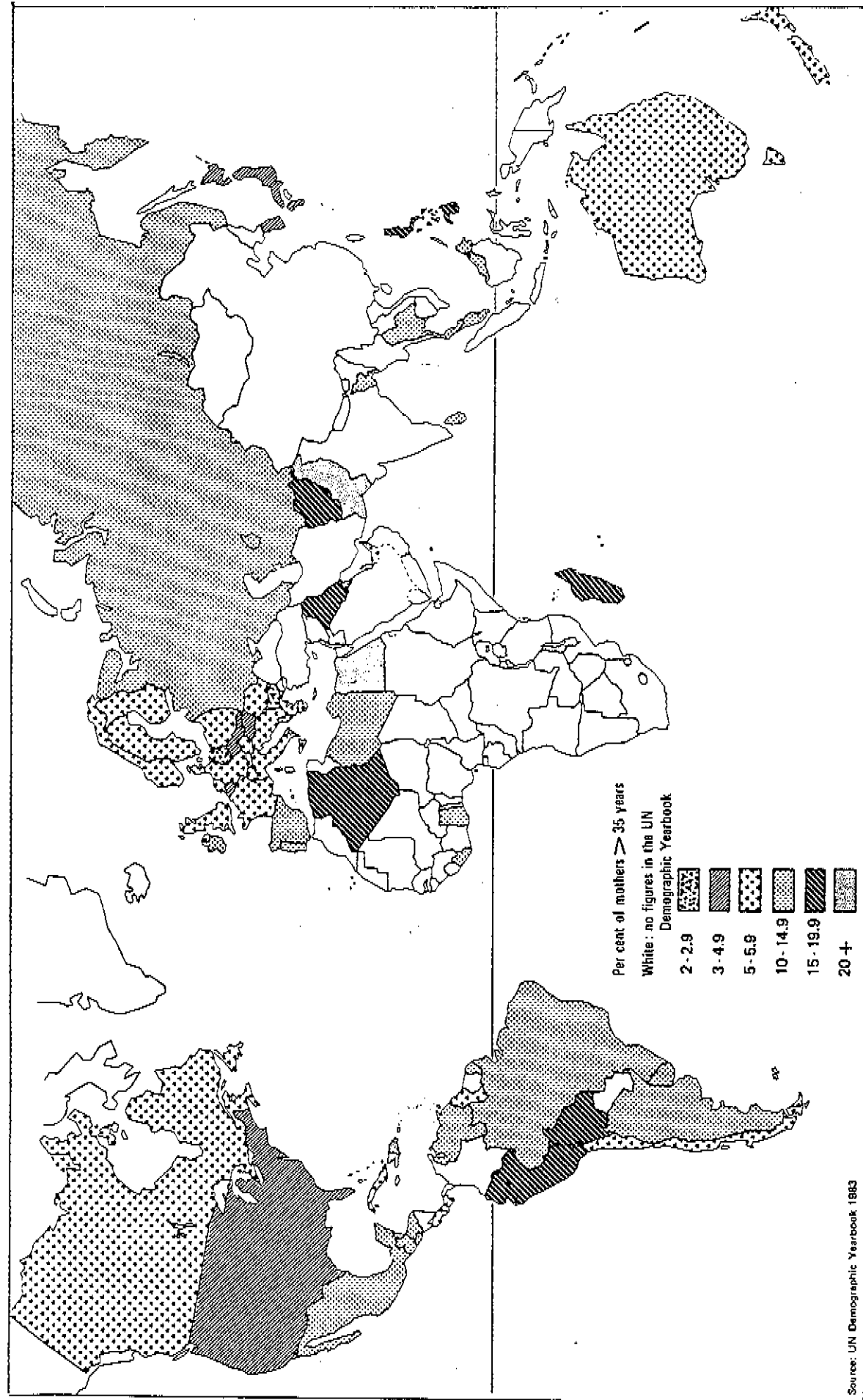
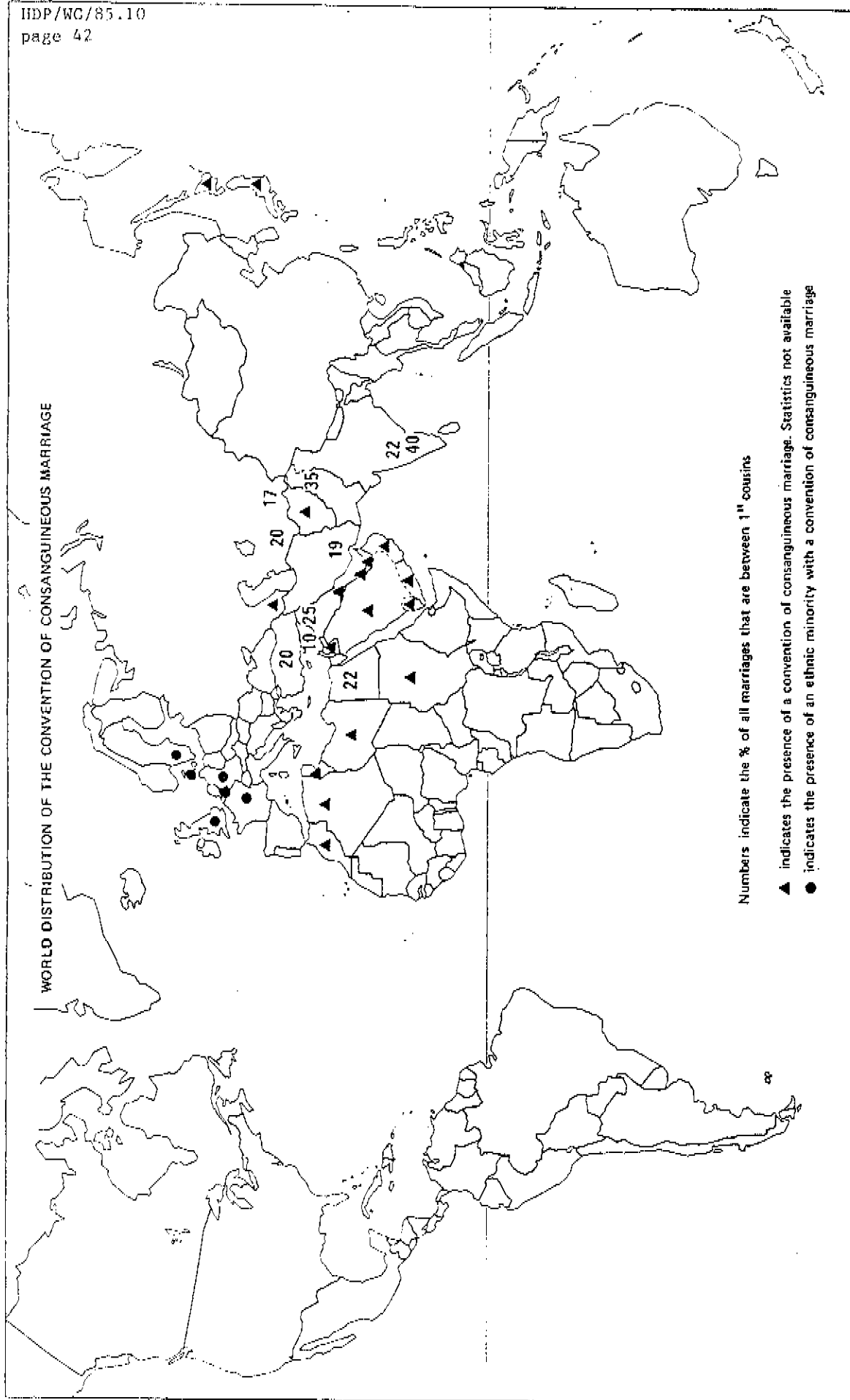


Fig. 16 The proportion of mothers more than 35 years old varies globally from as low as 2% to over 20%. The estimated incidence of Down syndrome births therefore also varies from a minimum of 1/1000, to a maximum of about 2.8/1000. (Data from the UN Demographic Yearbook for 1983).



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Fig.17 Cousin marriage is positively favoured, for social reasons, throughout North Africa, and the Middle East including Pakistan. In South India close consanguineous marriage, including uncle-niece marriage, has been traditional for thousands of years. In Japan, it was also customary until very recently, though officially disapproved. In most European countries, there are ethnic minorities originating from areas where consanguineous marriage is traditional: and they tend to preserve the tradition.

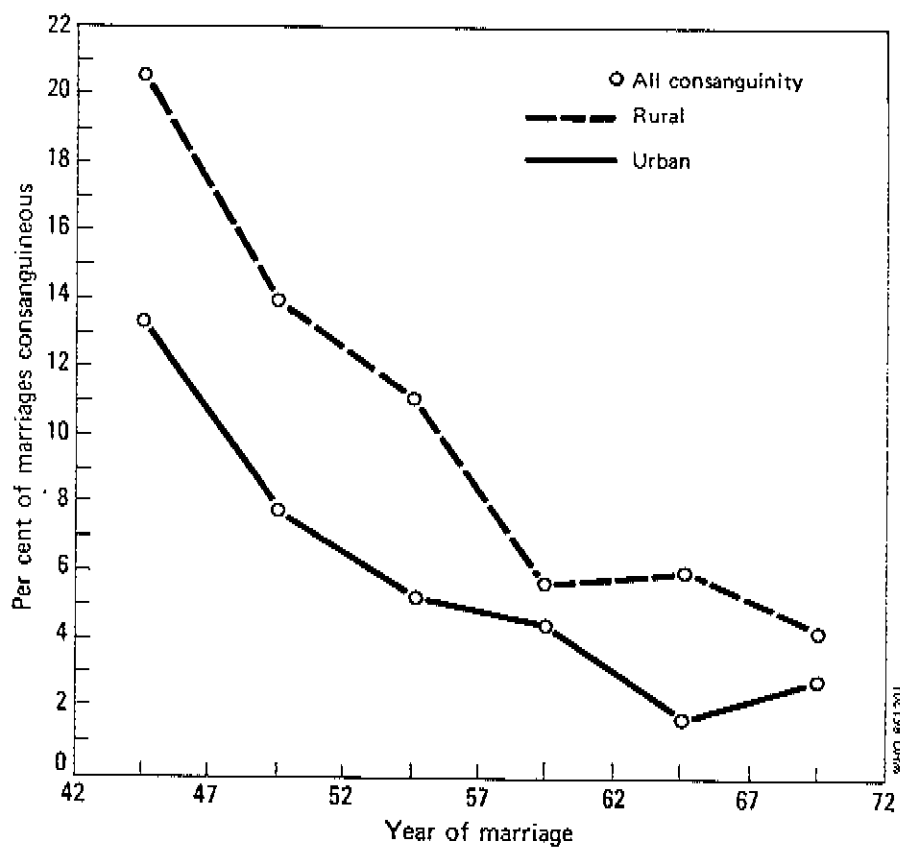


Fig.18

In Japan, there has been a very rapid decrease in the frequency of consanguineous marriages in the last 40 years, coinciding with rapid industrial development and increased mobility of the population. (Data from reference 51).

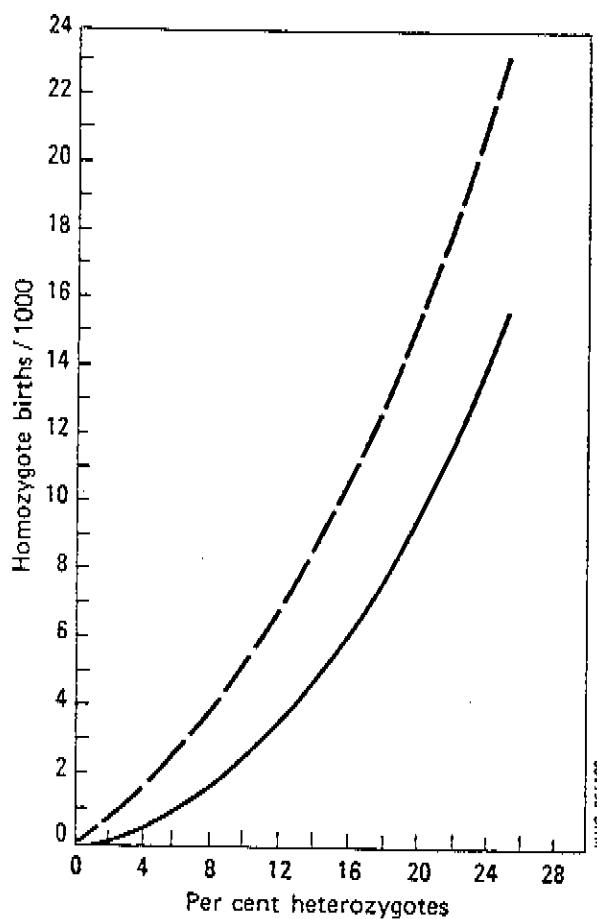


Fig.19

Relationship between the incidence of heterozygotes, and the birth-rate of homozygotes, for conditions inherited as Mendelian recessives. The lower curve shows the relationship under conditions of random mating, the upper curve shows the relationship with first cousin marriage. Consanguinity increases the birth incidence of rare disorders much more than that of common ones. For instance, when the heterozygote frequency is 10%, 100% first cousin marriage would only double the birth incidence of homozygotes; when the heterozygote frequency is 4% it quadruples it, and when it is 1%, it multiplies it twelve times. The effect of a given proportion of first cousin marriage (n%) in a population can be calculated by adding n% of the birth-rate for first cousin marriage, to 100-n% of the birth-rate for random mating.

Table 1
ESTIMATED FREQUENCY OF CONGENITAL DISORDERS

Type of disorder	All disorders, incidence per 1,000 births	Severe disorders, estimated incidence per 1,000 births
Congenital malformations	17-30	8-15
Chromosomal aberrations	4-9	2-5
Mendelian disorders	4-7	4-7
Haemoglobino- pathies	0-16	0-16
Total	25-62	14-43

(Data from ref. 5)

Table 2

CHANGES IN REPRODUCTIVE BEHAVIOUR OF OLDER MOTHERS
AND THEIR EFFECT ON THE NUMBER OF BIRTHS OF CHILDREN
WITH DOWN SYNDROME, IN THE USA 1960-1977

Maternal age group	% fall in birth rate 1960-77	% of recognized pregnancies aborted, 1977	Calculated fall in Down syndrome births 1960-77	
			Total	Due to abortion
<35	34	24) 50%	22%
35-39	66	30		
40+	73	42		

(Data from ref. 25)

Table 3

POPULATION NUMBERS IN REGIONS WITH A
CONVENTION OF CONSANGUINEOUS MARRIAGE

Region	Population (millions)	Annual births (millions)
North Africa	98.1	4.951
West and North Asia	161.5	6.649
India (one third)	237.3	7.899
Pakistan	87.1	4.200
USSR (part)	37.7	1.278
Total	621.7	24.98
Global figures	4,577.0	129.6
Proportion of world population involved	13.6%	19.3%

Table 4

THE PROPORTION OF BIRTHS OF INFANTS
WITH RECESSIVELY-INHERITED DISEASES THAT CAN BE PREVENTED,
IF PARENTS REFRAIN FROM FURTHER REPRODUCTION
FOLLOWING GENETIC COUNSELLING,
DEPENDS ON THE FINAL FAMILY SIZE

Average final family size (number of offspring)	Maximum % reduction in birth incidence through avoiding recurrence in the same family
1	0
2	13
3	23
4	32
5	39
6	45
7	50
8	55

(Data from ref. 44)

= = =