General Practice

Status and Prospects of Genetic Disease

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SUMMARY

The current status of our knowledge of genetic diseases is reviewed. The incidence of monogenic, multifactorial and chromosomal disorders, according to the literature to date, is given, and the possibilities of mass screening programmes are discussed. The prospects for antenatal diagnosis of genetic diseases are reviewed, with emphasis on the indications for amniocentesis and the safety of the procedure. Finally, speculations are made regarding the possible effects of medical and social practices on the frequency of genetic disorders in future generations.

Biology has been revolutionized only during the past 20 - 30 years and we still know relatively little about human biology, particularly human genetics. Thus the genetic determinants of normal traits as well as of common diseases and birth defects are largely unknown.

During the past 2 decades the role of genetics in the aetiology of disease has become more and more apparent. It has been estimated that 4 - 5% of liveborn infants suffer from genetic or partly genetic disorders.[1-4] As infectious diseases decline in frequency and environmental conditions improve, genetic disease becomes relatively more important as a cause of mortality and morbidity. Carter[5] has shown that the frequency of congenital abnormalities, as a cause of infant mortality, has increased from about 5% to 20% in the last 70 years. Roberts et al.[6] found that of the total number of deaths of children in hospital, over 40% were genetic or partly genetic in origin. Recent data from paediatric hospitals indicate that 20 - 30% of inpatients have genetic diseases,[6-10] the majority being polygenic disorders with a few single gene or chromosomal anomalies.

INCIDENCE OF GENETIC DISEASES

Monogenic Disorders

A great variety of monogenic conditions exists, most of which are individually rare. Many of them are not obvious at birth, and many are difficult to diagnose. McKusick[11] listed the known dominant, recessive and X-linked phenotypes in man. Table I shows the numerical status of the classification of genetic traits under dominant, recessive and X-linked modes of inheritance. The entries

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in these categories reflect the degree of variability in man and provide a useful guide in the search for the basic defects in genetic disorders.

TABLE I. CLASSIFICATION OF GENETIC TRAITS ACCORDING TO DOMINANT, RECESSIVE AND X-LINKED MODES OF INHERITANCE[11]

Phenotype	Number classified	Total
Autosomal dominant	583 (+635)	1 218
Autosomal recessive	466 (+481)	947
X-linked	93 (+78)	171
Total	1 142 (+1 194)	2 336

In each of the categories in Table I the phenotypic traits are either classified as being quite certain, or included because the suggestions for the particular mode of inheritance are strong enough to warrant inclusion (numbers in parentheses).

The total number of loci identified by these categories is a very small proportion of the total number of genes in man. The number of structural genes — those that determine the amino acid sequence of polypeptide chains of proteins, and which occur in single copies so that mutations behave in a Mendelian manner — may be of the order of 50 000.[12-14] With a total of 1 142 'proven' traits, the categories reveal perhaps about 2% of the total structural genes. Carter[15] recently collated studies of the frequencies of individual monogenic conditions which were carried out by workers with special interests in a particular condition.

Dominant Conditions

The total frequency of the more common dominant conditions in Caucasoid populations is 6/1 000 live-births.[15] One-third of these are caused by monogenic hypercholesterolaemia. The less common dominant conditions are given as 0,3/1 000 live-births. Carter[15] concluded that 7/1 000 would be a reasonable figure for all presently known serious dominant conditions.

Recessive Conditions

Autosomal recessive conditions which appear to have birth frequencies in Britain of about, or greater than, 0,1/1 000 were compiled and the total of about 2,5/1 000 live-births for the presently known recessive conditions is given.[15]

Among the few recessive conditions in which mental retardation is preventable by early diagnosis and treat-

ment, are certain inborn errors of metabolism. It was not possible to estimate the frequency of these disorders in the general population until results of mass screening of newborn infants became available.[16,17] Abnormalities of amino acid metabolism occur in about 1 in 100 newborn infants.[18,19] Most of these are considered to be temporary (and presumably benign) but about 1 in 3 000 result in a permanent defect.[17]

X-Linked Conditions

The total frequency of X-linked conditions compiled by Carter[15] is given as 0,5/1 000 male births, and he concluded that the total of all X-linked conditions presently known might be of the order of 0,8/1 000 live-births.

Total Frequency of Monogenic Conditions

The total birth frequencies of presently known serious and moderately serious monogenic conditions are about 1%.

Multifactorial Diseases

The multifactorial model assumes that there are many genetic loci and many environmental factors involved in the cause of the disease. Most of the more common diseases are polygenic or multifactorial in their inheritance, and the frequency in the population affected by these diseases is of the order of 2 - 3% or more.[2,20]

Chromosome Anomalies

A considerable proportion of heritable diseases in man results from the presence of constitutional chromosome anomalies which fall into broad categories: (i) those where an abnormal number of chromosomes are present; and (ii) those where there is an abnormal chromosome structure.

Estimates from studies on large numbers of consecutive neonates indicate that for disorders arising from chromosome number anomalies, the incidence is about 5/1 000, and those resulting from chromosome structural rearrangements about 2/1 000.[21-23] Of the total number of chromosomal anomalies about half (3/1 000) involve the autosomes and a further 3/1 000 the sex chromosomes — a total of 6 - 7/1 000 live-births. These figures represent information obtained by means of conventional chromosome staining techniques. With the advent of the new banding techniques, more structural anomalies are expected to be found, increasing the frequency in this category. No large survey on a newborn population, utilizing the new techniques, has yet been published. The total frequency of chromosome disorders in the live-born is estimated at 10/1 000 or 1%.[24]

GENETIC SCREENING

Genetic screening is defined as a search in a population for individuals possessing certain genotypes,

Screening for Disease

The object of the search is to find the persons who have specific genetic diseases, or who have the genotypes that in special circumstances may lead to disease, in order to provide treatment or medical management to reverse or prevent the adverse effects of their disorders.

Today 90% of all babies born in the USA are tested for phenylketonuria (PKU). Mass screening for this disease was begun, not for genetic reasons, but as a means of eliminating one form of mental retardation. Experience with PKU has served as a model for the screening of newborn infants for other metabolic disorders. The results of a recent survey,[25] indicate that State support in the USA of mass neonatal screening has rapidly increased during the past 2 years. The number of States engaged in screening for galactosaemia has risen to 17. At least 9 States screen for histidinaemia, 11 for homocystinuria, 12 for maple syrup urine disease and 10 for tyrosinaemia. Twelve States indicated that they screen some neonates (presumably Blacks) for sickle cell anaemia, and 7 of these test some infants for β-thalassaemia.

An example of mass screening of a selected population is the programme which began in the USA in 1971, the object being to discover couples at risk and to reduce the incidence of Tay-Sachs disease by selective abortion.[26] Tay-Sachs disease is a recessive disorder occurring in Ashkenazi Jews with a frequency of 1/3 600. The carrier state is as high as 1 in 30 Jews.

The most effective screening programmes are those used for detecting genetic diseases whose frequency is relatively high in the newborn population. Among the dominant conditions, the frequency at birth of hyperlipidaemia is estimated to be as high as 2/1 000 live-births.[15] Goldstein et al.[27,28] produced evidence of 3 monogenic forms, namely, hypercholesterolaemia, hypertriglyceridaemia, and a third in which serum levels of both metabolites are elevated. With current methods, screening would have to be carried out several times — during infancy, childhood and young adult life. While experimental studies are underway to distinguish the genetic from the non-genetic causes of hyperlipidaemia, and the single gene and multigene types, a practical alternative for physicians would be to study the offspring of individuals manifesting any of these 3 disorders.[29] Dietary regulation for any individual found to have raised lipid levels might then be tried.

Cystic fibrosis is another condition which occurs in 1 in 2 000 newborn infants.[15] In a selected population in South West Africa, it has been reported to occur in 1 out of every 622 newborn babies.[30] Although the treatment of this disease is only supportive, there is no question that the life expectancy has been increased and the burden reduced for patient and family. Strenuous efforts are being made to find a test for detecting affected infants before the onset of symptoms, particularly in the newborn period.[31-33]

Screening for genetic diseases has not yet had much impact on the awareness or the health of the public. PKU screening may be judged to have been successful in the USA in the prevention of mental retardation. Sponsors of screening plans have pointed out that in addi-

tion to the prevention of tragedy in a family, the cost of the screening programme is significantly less than the cost of caring for a single patient with PKU during his lifetime. There are still significant weaknesses in some PKU screening programmes. A good screening effort requires more than a low-cost, high-accuracy method to identify presymptomatic infants. At the very least, provision should be made for guaranteeing access to good medical care, providing reliable counselling to the parents of the affected infants and protecting the confidentiality of the screening records. Many countries lack the required logistic system to reach and follow-up each child. To screen for rare genetic diseases at a time when malnutrition and infectious diseases are the principal problems would be a waste of resources. Perhaps screening could be limited to relatively small populations in which the particular disease occurs at a high frequency.

ANTENATAL DIAGNOSIS OF GENETIC DISEASES

At the present time, analysis of cultivated fetal cells can provide a firm diagnosis for essentially all known chromosomal disorders. The observation by Brock and Sutcliffe[34] that fetal neural tube defects (anencephaly and open spina bifida) are associated with elevated levels of alpha-fetoprotein in amniotic fluid, has widened the scope for prenatal monitoring. Milunsky and Atkins[35] have reported that at present, at least 71 inborn errors of metabolism can be diagnosed prenatally, and in 28 of these, a firm diagnosis has been reported in the literature.

Indications for Amniocentesis

Amniocentesis for early prenatal diagnosis of certain abnormalities is now an established part of clinical genetic practice and antenatal care. Apart from the experience of single units, several collaborative studies from North America and Europe have been reported. Polani and Benson[36] collected the results of over 1 700 amniocenteses from published reports as well as from personal enquiries. The results of about 1 500 antenatal diagnoses from 41 centres in North America were reported by Milunsky.[37] Lindsten et al.[38] reported the results from 6 large centres in Europe, and the latest review published by Galjaard[39] was on 6 121 cases from 46 of the major Western European countries.

From these studies the present indications for diagnostic amniocentesis to detect cytogenetic disorders are: (i) advanced maternal age; (ii) previous child with Down's syndrome; (iii) family history of Down's syndrome; (iv) family history of other chromosome abnormalities; (v) one of the parents carrying a balanced translocation; and (vi) fetal sex determination because of the likelihood of one of the X-linked disorders. The results of these data further indicate that the risk of a fetus having either trisomy 21 or some other chromosome anomaly is about 5% for mothers over the age of 38.[40] If one of the parents is a carrier, the chance of an unbalanced translocation in the fetus is about 7%. For the other cytogenetic indications, the risk is often less than 1,5%, but here the

value of amniocentesis lies in relieving parental anxiety.

Other reasons for amniocentesis are to detect inborn errors of metabolism. Out of the total of 6 121 amniocenteses, 206 were performed for enzyme defects where the risk of the fetus was 1 in 4. The 206 analyses were done for 23 different enzyme defects.[39] Amniocentesis will also detect a neural tube defect such as anencephaly or spina bifida aperta. From a total of 2 708 pregnancies, 81 fetuses with anencephaly or spina bifida were detected by alpha-fetoprotein analysis.

Safety of Amniocentesis

More specific investigations into the technique and safety of amniocentesis have been published by the National Institute of Health in the USA[41] and the Canadian Medical Research Council.[42] The evidence so far suggests that the procedure carried out at about 16 weeks in a major health centre is safe, accurate and reliable when monitored by ultrasound. Under these circumstances, the miscarriage rate seems to be no greater than that in control pregnancies.

Eugenic Effects of Antenatal Diagnosis

Antenatal diagnosis will contribute to the lowering of the frequency of a genetic disease in the current generation. The effect on subsequent generations will be mostly beneficial (or eugenic) although in some situations it may be deleterious (or dysgenic).

The contribution of genotypes to future generations depends on their relative fitness. If their fitness is not zero and their frequency in the population not reduced to zero by antenatal diagnosis, then the frequency of the abnormal allele in the next generation, although reduced, will not be zero. Therefore, the reduction in gene frequency for dominant and X-linked conditions in future generations will be substantial, although smaller for recessive conditions.

Deleterious effects of antenatal diagnosis may arise if families tend to replace fetuses diagnosed as affected with other children — so-called reproductive compensation. For dominant conditions, there should be no dysgenic effects because antenatal diagnosis and compensation for affected genotypes should lead to only normal children being born. In autosomal recessive conditions, two-thirds of children compensating for affected genotypes will be carriers, therefore an increase in the frequency of the abnormal allele may result. Effects of antenatal diagnosis for X-linked disorders will depend on the possible applications of antenatal diagnosis, namely: (i) abortion of affected males and carrier females; (ii) abortion of affected males; and (iii) abortion of all males from carrier mothers. In the first instance, the frequency of abnormal alleles will be reduced to a new equilibrium depending on the mutation rate and the proportion of carrier women ascertained. Abortion of affected males, with full reproductive compensation, will lead to a new equilibrium with the frequency of carrier females being about 1,5 times the original rate. The abortion of all males from carrier mothers with full reproductive compensation is more dysgenic, since carrier mothers will contribute an equal pro-

portion of normal and abnormal genes to their daughters with no elimination of abnormal genes. Mutations will continually add new abnormal genes to the gene pool. The gene frequency will rise linearly with time at a rate equal to the mutation rate, which will lead to doubling of the gene frequency every two generations.

Antenatal diagnosis will contribute to the lowering of the frequency of chromosomal and multifactorial conditions in the current generation. Its effects on the frequency in future generations will be small since the recurrence risks are normally low.

GENETIC COUNSELLING

Genetic counselling is a process of communication, concerning the occurrence and the risks of recurrence of genetic disorders within a family. The aim of counselling is to enable a couple or a person to make rational decisions about whether or not to reproduce.

The first prerequisite in genetic counselling is a firm diagnosis of the disease,[43] and in single gene or multifactorial disorders, a thorough pedigree study. In simple Mendelian disorders, the mode of inheritance is known and recurrence risks can be derived from genetic theory even for complex family histories.[44] The recurrence risks for multifactorial diseases are not the simple Mendelian ratios, and the best available estimates are the empirical risks — the observed frequency of the disease in relatives of affected patients. In practice, however, these risks may vary with the sex, severity and age of onset in affected individuals and with the number of affected members in the family concerned. New methods of estimating recurrence risks for multifactorial conditions have been developed,[45] and these can be used in genetic counselling to supplement empirical risks in complex situations. Computer programmes are also available for calculating recurrence risks for use in genetic counselling.[46,47] Tables of recurrence risks estimated from a multifactorial model of liability to some common congenital malformations have been calculated.[48]

Although some follow-up studies[49-51] have suggested that those who have been counselled grasp the meaning of risk and avoid reproducing if the risk of having affected children is high, some data have indicated that the meaning of genetic risk may not always be well understood.[52-54] Most counsellors put the interest of the patient and his family before the interests of society and the State, and pursue medical rather than eugenic objectives. Untoward effects on society may be pointed out, but most counsellors do not usually attempt to give advice based on the consideration of the gene pool. Genetic counselling has thus traditionally been non-directive. It is usually maintained that every family situation is different and that the meaning of a given risk varies from family to family, so that in some cases, a future pregnancy may be justified even with high recurrence risks.

EFFECTS OF MEDICAL AND SOCIAL PRACTICES ON THE FREQUENCY OF GENETIC DISORDERS

In the past many workers have studied the effects of various

factors on the human gene pool.[55-58] The emphasis has usually been on single factors with dysgenic effects and on long-term changes and the time to reach new equilibria. In recent years, a number of new medical practices such as improved treatment for affected individuals, genetic counselling, population screening and social customs, such as family limitation or selective abortion, have been introduced and are being widely adopted. Not all of these are dysgenic and some have eugenic effects on the gene pool. Because of the very complicated interaction of the strategies and tendencies, it is not easy to make any realistic prediction of their overall long-term effects. The dysgenic effects are usually predicted without consideration of compensatory eugenic effects. From the results of Holloway and Smith,[59] in studies of the effects of a variety of practices used and their overall effect on the gene pool, there generally seems to be little cause for alarm about the deleterious effects of the new medical and social practices being adopted.

The main deleterious effect may be from improved reproductive fitness, for example, by surgical treatment for dominant and X-linked diseases, which can lead to substantial increases in gene frequency and in disease in future generations. If, however, therapy is cheap and effective, the burden of the disease to the individual and to society is slight. If the therapy is expensive or not very effective, families will seek ways to prevent recurrence of the disease. In recessive disorders, a small reduction in the average fitness of carriers detected by population screening and antenatal diagnosis would outweigh any deleterious effects of other practices such as selective abortion and reproductive compensation. The dysgenic effects will occur in a term so long that it exceeds any reasonable projection of the time when the relatively crude methods of prevention and treatment will be replaced by better methods, based perhaps to a greater degree on gametic rather than zygotic selection.[56]

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Xerographic Parenchymal Patterns and Breast Cancer

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SUMMARY

The xerographic mammography records of 3 002 patients with breast disease were reviewed and classified according to the criteria of Wolfe. The parenchymal P2 pattern occurred in 59% of patients with cancer and in only 16,9% patients under the age of 40 without cancer, but the incidence of the DY pattern was much the same in patients with cancer and in those without cancer in almost all the age groups studied. The incidence of the P2 pattern tended to rise slightly in patients without cancer, whereas the incidence of the DY pattern tended to remain the same in all groups. The findings of Wolfe and others have been confirmed by this study, which also supports the suggestion that women under the age of 40 undergo a baseline xerographic examination of the breasts for cancer and that subsequent screening be based on the presence of a P2 pattern. This will involve a selection of 16,9% of the under 40-year-old subjects without cancer who might, on screening, be expected to show 60% of the cancers in each decade after the age of 40. This information coupled with other factors indicating a high risk for the development of breast cancer, such as florid epithelial dysplasia, a previous history of breast cancer or a family history of breast cancer, should increase the yield of early carcinomas at a preclinical stage and reduce costs of a screening programme.

The mortality of breast cancer, which has remained unchanged for a long time, can be lowered by early detection of the malignant lesion, and the most important technique for this is mammography.[1] The application of screening techniques, including mammography, to the total number of women at risk is prohibitively expensive, and doubts have been raised about the possible risk of inducing breast cancer in young women by the frequent use of routine mammography,[2] although a number of authors have indicated that the danger from this type of radiation exposure has been grossly overstated.[3] Experience gained from screening projects in the USA proves that the number of cancers detected in an open screening programme is low.

More effective use can be made of screening techniques by confining these to women at high risk of developing breast cancer. A number of factors are associated with such a high risk. They include the age of the patient, a family history of breast cancer, nulliparity, a first pregnancy late in life, previous cancer in the contralateral breast, marked epithelial hyperplasia on biopsy, an adverse hormone milieu, hypothyroidism, impaired immunological competence, chronic psychological stress and exposure to radiation.

Wolfe has reported yet another high-risk factor, namely

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