Middle Articles

CONTEMPORARY THEMES

Ascertainment and Prevention of Genetic Disease

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Summary: A genetic register system has been developed for the ascertainment and prevention of genetic disease. Its potential value is illustrated with data collected from 478 families with serious genetic disorders which had been seen during the past five years. Of these 249 were referred specifically for genetic counselling, autosomal dominant disorders accounting for the largest group of families with individuals at high risk of becoming affected. Of 717 individuals at high risk of having affected children (or carrier daughters in the case of X-linked recessive disorders), only 101 were referred specifically for counselling. Many were referred only after the birth of an affected child which might otherwise have been prevented. A genetic register system linked to practitioner, hospital, and health department records could be a valuable means of preventing genetic disease.

Introduction

In recent years several investigators have argued the need for some form of genetic disease register (Miller, 1964; Newcombe, 1966; Renwick, 1968; McKusick, 1969; Wertelecki, Lawton, and Gerald, 1969). Most of these reports, however, have been concerned only with identifying affected individuals for either welfare or research purposes. Yet in such families there are likely to be others who are also at risk of becoming affected or of having affected children. Ascertaining and following-up such people are important practical reasons for establishing a genetic disease register.

The potential value of a register system in preventing different types of genetic disease has already been discussed (Smith, 1970). In this department such a register is being developed and is referred to by the acronym "RAPID" (Register for the Ascertainment and Prevention of Inherited Disease). The aim of this report is to illustrate the potential usefulness of a genetic register system in preventing disease by using data on the families of people who have been referred to us during the past five years.

Patients and Methods

All the families studied came from either the Edinburgh or the Manchester regions. Many families were referred specifically for genetic counselling but others were referred for different reasons—for example, research interest, teaching, diagnosis, etc. Some families, mainly with hereditary myopathies, were also traced from hospital and health depart-

ment records. No attempt has been made to ascertain all cases of genetic disease within a region. This is therefore a family rather than a population study.

Only patients with *serious* hereditary disorders have been included. Those referred for chromosome studies because of abnormalities of sexual development or for advice about consanguinity when there was no family history of a serious hereditary disorder have been excluded. The term "multifactorial inheritance" refers to familial diseases which are possibly due to many genes plus the effects of environment; these include idiopathic epilepsy, schizophrenia, and certain congenital malformations (Carter, 1969).

Pedigree data were usually obtained from the first person in a family to be seen, and this provided most of the information on which the following analyses were based. From the pedigree and the known mode of inheritance risks were calculated for all individuals of (a) becoming affected themselves (in late manifesting diseases such as Huntington's chorea) or, if under 40 years of age, of having (b) an affected child or (c) a carrier daughter in the case of X-linked recessive disorders such as haemophilia and Becker type muscular dystrophy. Risks were calculated by Bayesian methods (Murphy, 1968) based on the family history and relevant biochemical tests when these were indicated (Emery and Morton, 1968). The number of cases which might have been prevented by genetic counselling has also been estimated.

"Preventable cases" have been defined as affected children born in the past 10 years to parents who, a priori, were at high risk of having affected offspring. For example, a boy with an X-linked recessive disorder would be included if his maternal grandfather was affected, because in this situation his mother must be a carrier; but the first child in a family to be affected with an autosomal recessive disorder would not be included.

Details on all subjects at high risk (arbitrarily defined as being greater than 1 in 10) were recorded on cards specially designed for computer storage, analysis, and follow up. Full

Individuals at Risk in Families with Serious Genetic Disorders Referred Specifically for Genetic Counselling (C) or for Other Reasons (O). (Number of Families Given in Parentheses)

	Autosomal Dominant (108)		Autosomal Recessive (93)		X-linked Recessive (87)		Multifactorial (81)		Chromosomal (26)	
	C	O	C	O	C	O	C	O	C	O
At risk of becoming affected . . .	7	238	0	0	0	27	0	8	0	0
At risk of having affected children or carrier daughters in X-linked disorders . . .	28	331	35	11	18	269	18	5	2	0
"Preventable cases" (see text) . . .	12	9	12	1	6	14	2	0	0	0

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details of the register, including operational details and the design of the register cards, will be published later.

Results

Data on 478 families have been collected. In 83 families the disorder in question either proved not to be genetic or the cause was unresolved. No individuals were considered to be at risk in these families. The distribution of the various types of genetic disease (see Table) among the remaining families is not representative of the population as a whole, but partly reflects the department's particular interests—for example, in the X-linked muscular dystrophies.

Of the 478 families, 249 were referred specifically for genetic counselling—50 autosomal dominant, 56 autosomal recessive, 33 X-linked recessive, 61 multifactorial, 22 chromosomal, and 27 in which the disorder was either not genetic or the cause was unresolved.

Individuals at risk of becoming affected themselves mainly concerned autosomal dominant disorders—that is, 245 out of a total of 280 subjects were considered to be at risk. This is mainly because many of these disorders were of late onset and occurred in large families—for example, myotonic dystrophy, Huntington's chorea, and polyposis coli.

Of 717 subjects at risk of having an affected child or of having a carrier daughter (X-linked recessive disorders), autosomal dominant and X-linked disorders accounted for 646. In the case of autosomal dominant disorders many were at risk both of becoming affected and of having affected children.

A total of 56 affected children ("preventable cases") were born to parents who, a priori, were at high risk of having affected offspring. There were a further 94 individuals at high risk of becoming affected, but so far they have shown no signs of the disease.

Discussion

Our results indicate that the main scope for preventing genetic disease lies with the simply inherited disorders, because in general the proportion of individuals at high risk is greater than in the case of multifactorial and chromosomal disorders. Even in simply inherited disorders, however, it will be possible to prevent only a proportion of cases, since some will occur in families in which there has been no previous history of the disease.

Only a relatively small proportion of individuals at risk

of having affected children (or carrier daughters in the case of X-linked disorders) were referred specifically for genetic counselling (101 out of a total of 717, or 14%). Many affected children were born to parents who, a priori, were at high risk of having affected children but who had never been counselled and were therefore unaware of the risks. Others were referred for counselling only after the birth of an affected child which might otherwise have been prevented. At present no defined procedure for tracing such individuals exists. Herein lies the value of a genetic register system.

The first step in such a system is the ascertainment of those at risk. This could be achieved through general practitioner, hospital, and health department records linked to a genetic register. The next step is to develop procedures for contacting, through their family doctors, individuals who are found to be at risk. The final step is to provide adequate advice and follow-up for those at risk. The latter could be achieved through a genetic register system. This approach to the prevention of disease could have important implications, both for the individual and for society. Not only would such a register be of value in tracing and following up those at risk of having affected children but it might also be of value in alerting individuals with inherited susceptibilities to drugs and for detecting and eradicating life-threatening complications of genetic disease, such as intestinal malignancy in polyposis (McKusick, 1969). The main function of such a register system, however, would be to prevent genetic disease.

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Assessing Reports of Therapeutic Trials

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Summary: A check list is described which helps the systematic assessment of reports of therapeutic trials, particularly the aspects that need to be considered in assessing their validity. The check list was used to examine 141 reports of therapeutic trials published in four British non-specialist journals in the first six months of 1966 and of 1969. Of these reports 51% were found to be acceptable and a further 16% probably acceptable; 33% were considered unacceptable because they lacked one or more of the features required in a valid report. The check list has been found useful in assessing claims made for drugs and other therapeutic measures on the basis of published reports.

Introduction

Every doctor who reads reports of therapeutic trials has to face the problem of assessing their validity and their relevance to his practice. Though much is now known about what constitutes a satisfactory therapeutic trial, only those who spend their time planning, executing, and studying such trials can efficiently assess reports of trials.

One of the earliest criteria of a satisfactory trial to be

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