Genetics of ischaemic heart disease

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Summary

Coronary heart disease, especially when it affects younger individuals, tends to cluster in families. Known risk factors occur in 50-75% of patients with myocardial infarction. Yet commonly occurring risk factors are not strongly inherited, and the familial aggregation of coronary heart disease may not be attributable to familial resemblance in serum cholesterol and blood pressure levels. Alternatively, such aggregation may be due to unknown familial risk factors. Nevertheless, screening of relatives of individuals with evident risk factors is of importance, and environmental manipulation is likely to be of value in prevention of coronary heart disease.

ALL illnesses have a greater or lesser hereditary component. In regard to coronary heart disease (CHD) knowledge of genetic factors is very limited, except for the less common forms of the disorder; in these they present particularly in kindreds with the familial hyperlipidaemias, where the defect generally involves single genes. There is a great need to detect and treat such individuals. However, there is a great need also to assess the role of familial-genetic factors in the much larger segment of the population which gives rise to the majority of persons with coronary disease. Here, as for common diseases in general, the inheritance tends to be polygenic in a multifactorial situation where the environment plays a decisive role. The emphasis in the present review will be on the population approach, to provide a background for including families in community programmes for the prevention of coronary heart disease.

Aggregation of coronary heart disease in families

In making a case for the importance of familial factors in the aetiology of coronary disease, the first step is to show that the condition clusters in families. This has long been known to occur in hypercholesterolaemia and xanthomatosis. In the last 20 years, several studies have indicated that relatives of

coronary disease index cases show a greater frequency of the disease than do relatives of control subjects. An example is provided by the study of Rose (1964) which shows excess risk especially with regard to mortality. Similar findings were reported by Patterson and Slack (1972), the excess being greatest for younger relatives, especially those with hyperlipoproteinaemia. Evidence that at least a part of this resemblance has a genetic basis comes from the Danish and Swedish twin registers since the proportion of affected co-twins of patients with CHD is greater in monozygotic than dizygotic pairs.

Risk factors in patients with coronary heart disease

What factors in CHD index cases could explain the transmission of susceptibility to their relatives? It is reasonable to assume that at least a part of this resemblance in disease is due to the fact that index cases harbour an excess of risk factors which they share with their family members. For this reason it is important to know the frequency of elevated risk factor levels in patients with CHD since hyperlipidaemia, hypertension and hyperglycaemia are correlated amongst relatives.

Estimates of hyperlipidaemia in survivors from myocardial infarction vary widely. Clearly, the frequency is considerably higher in the Carlson and Wahlberg (1966) study than in the Framingham (Gordon, Sorlie and Kannel, 1971) even though the cutting point in the Framingham study is considerably lower. The same is true of the study by Patterson and Slack (1972). The Seattle data (Goldstein *et al.*, 1973a), on the other hand, are not much different from those from Framingham. The frequencies reported by Nikkilä and Aro (1973) from Finland resemble the Swedish data, as do those by Lewis *et al.* (1974) from London. The most recent data by Carlson and Ericsson (1975) show a higher frequency of hyperlipidaemia than those from the earlier study, owing to a greater prevalence of the combined form.

Taking a bird's eye view of these data, it would seem that between 33% and 50% of the survivors from myocardial infarction have one or the other form of hyperlipidaemia, with serum cholesterol or triglycerides in the upper 5% of the distribution or

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higher. Extrapolating from the Seattle study (Goldstein *et al.*, 1973b), about 50% of these hyperlipidaemias will be familial and monogenic, and the rest polygenic or 'sporadic'.

These are very high frequencies, which underline the importance of the more severe forms of hyperlipidaemia in the genesis of coronary disease. At such high levels, the hereditary factor—whether monogenic or polygenic—must be strong and the need for environmental control from the point of view of prevention very great.

Unfortunately, there are no published data to estimate the frequency of hypertension and diabetes—latent or overt—among the hyperlipidaemic and non-hyperlipidaemic survivors of myocardial infarction. It is said that some 40% of all heart attack patients have hypertension. The data of Wahlberg (1962) would suggest that some 50% of patients with arterial disease, mostly myocardial infarction, have abnormal glucose tolerance; even if only half of these were diabetics clinically, this would still be very high. Thus, making allowance for inter-relationships between hyperlipidaemia, hypertension and hyperglycaemia, at least 66–75% of survivors are likely to harbour one or the other of these three risk factors singly or in combination.

Prospective epidemiological observations, in contrast to the mostly retrospective studies just mentioned, tend to give rather lower estimates for the proportion of coronary disease events which can be accounted for by established risk factors. From the best information available, not more than 50% of the events can be predicted by elevated serum cholesterol or blood pressure levels and smoking but this proportion would be smaller if the cutting point for cholesterol were set at, say, 285 rather than 260 mg/100 ml. Presumably, glucose intolerance and hypertriglyceridaemia, to the extent that either carries independent risk in terms of multifactorial analysis, could explain another 10 or 20%.

Thus, disregarding smoking, which also shows some familial resemblance, at least 50% and more likely 66–75% of the survivors of myocardial infarction will have one or more metabolic risk factors or blood pressure in a range where an excess of elevated risk factor levels can be expected in their close relatives. The next step, therefore, is to assess the frequency of hyperlipidaemia, hyperglycaemia and hypertension in the family members of patients with coronary heart disease and, more generally, in the relatives of persons with elevated risk factor levels.

Familial resemblance in risk factors

There are no data which deal specifically with the frequency of hypertension and hyperglycaemia in the relatives of myocardial infarction patients but

such information is available for the hyperlipidaemias. Patterson and Slack (1972) examined the first-degree relatives of myocardial infarction survivors with types II and IV hyperlipidaemia and found, as expected, an excess of elevated cholesterol or, respectively, triglyceride levels amongst them. Nikkilä and Aro (1973) studied the relatives not only of hyperlipidaemic but *all* survivors from myocardial infarction; in spite of this, the frequency of hyperlipidaemia amongst relatives in their study was higher than that observed by Patterson and Slack—29% as compared with 18%. In the Seattle Study (Goldstein *et al.*, 1973b) reported in the same year, only the relatives of hyperlipidaemic survivors had higher lipid levels.

For the present purpose, only the general magnitude of the proportion of affected family members matters since the exact percentage of relatives showing the same lipid abnormality as the *propositus* depends on many factors of selection, methodology and, especially, on the cutting points used to define 'abnormality'. It is apparent that the observed proportion of hyperlipidaemic family members of index patients falls considerably short of the 50% correspondence seen in families with the fully developed type IIa hyperlipoproteinaemia, being in the region of 25%. Thus, the majority of persons with hyperlipidaemia, whether survivors from myocardial infarction or in the more general population, shows the disorder in the sporadic rather than the familial form.

In the Tecumseh Study (Deutscher, Ostrander and Epstein, 1970) which dealt with an entire population, it was possible to look at this question with regard to several risk factors simultaneously in the same sibships. For serum cholesterol, the proportion of sibs of index subjects in the upper quintile of the distribution who were themselves in the upper quintile is about twice greater than expected, but still only somewhere in the range of 25%. For blood pressure, the resemblance is somewhat lower; for relative weight somewhat higher; and for blood glucose, after a standard load variable, depending on age.

Familial aggregation of coronary heart disease as related to risk factors

In the foregoing discussion, a large proportion of patients with coronary heart disease was shown to harbour one or more risk factors in a range sufficiently high to expect that an appreciable proportion of their close family members would also show an increased frequency of risk factors. In this way, familial clustering of disease could be explained in terms of familial resemblance in risk factors. The degree to which this will be true depends firstly on the shape of the curvilinear relationship between

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risk factor level and risk and secondly on the strength of correlation between risk factor levels amongst relatives.

Concerning risk factor level and risk, the relationship for serum cholesterol is linear up to values of about 300 mg/100 ml as shown in the Framingham data (Gordon *et al.*, 1971). Within the steep rise above such levels, the 16-year risk for Framingham men aged 45–55 is around 40%, which is similar to the findings in three studies of persons with monogenic familial hypercholesterolaemia. The cumulative risk by the age of 40 years is remarkably similar, despite much variation in the material and methods. In men, it tends to be around 20% increasing to around 50% or more by the age of 60, as in the most recent and largest series by Stone *et al.* (1974) from the National Heart and Lung Institute in Bethesda. However, from the population point of view, relatively few events occur at such high levels of serum cholesterol, and at lower levels the familial transmission of the trait is less marked. The same considerations would apply to other risk factors.

The stage is set, therefore, to try to view the situation as it presents in the population at large. Lacking actual prospective data, recourse is taken to a model developed several years ago but still valid. It is based on incidence data from Framingham and data on the familial resemblance in risk factors from Tecumseh which are both representative of the general population. The aim is to calculate whether the degree of familial resemblance in risk factors is sufficient to explain familial clustering of disease. Since elevated serum cholesterol and blood pressure are the most potent known predictors of coronary disease and also show the greatest known degree of familial correlation, they were chosen for this test. A thousand couples were studied. They were divided into those at higher and lower risk, 30% being at higher risk on account of elevated serum cholesterol or blood pressure or both. It can be calculated that of the 1000 couples, ninety are both at higher risk, 490 are both at lower risk and 420 have only one member at higher risk. It can also be calculated how many spouses within each of these three groups of couples will have suffered a 'heart attack'. Next, it is assumed that each couple has a son and, from the Tecumseh family data, it can be calculated how many of these sons show elevated serum cholesterol, blood pressure or both, depending on whether both, one or no parent are in the upper risk range. It may then be estimated how many sons in these two categories have a family history of a 'heart attack' and how many will develop a heart attack themselves in the next 10 years, depending on whether they have a positive or negative family history. Surprisingly, it appears that the predictive power of a positive family

history is hardly greater than that of a negative family history of 'heart attack' (Epstein, 1967).

This unexpected result could mean that familial aggregations of disease are not mediated through familial resemblance in serum cholesterol and blood pressure levels. Not all parents with coronary disease have elevation of these risk factors, those with elevated risk factors do not necessarily have children with the same finding, and children with high risk factors do not necessarily develop coronary disease. All this would reduce any effect of familial risk factor resemblance on familial clustering of disease. The result could also mean that there are as yet undiscovered familial-genetic factors which account for the familial aggregations of disease. There is a need to design prospective studies along the lines of this model, to extend epidemiological observations on individuals to their family members.

Implications for prevention

Irrespective of what causes familial aggregations of disease, detection of elevated risk factor levels in an individual calls for the screening of the family members. This includes school children, even though ranges of risk in that age group have not yet been well defined. The higher the level in the proband, the greater the chance of finding elevated levels in the close relatives. However, as demonstrated above, the degree of familial resemblance is less strong than is often thought, at least if lipids are expressed in terms of lipoprotein types rather than being viewed as continuous variables. Based on the Seattle Study (Goldstein *et al.*, 1973b), there will only be one person with monogenic familial hypercholesterolaemia for every twenty-five people in the uppermost 5% of the serum cholesterol distribution in the population. Similarly, the frequency of hyperlipidaemia is not particularly high in the close relatives of patients with coronary heart disease; but, as stated, occurrence of coronary heart disease calls for risk factor screening of all close relatives.

It would be important to know the yield from screening the relatives of patients with coronary heart disease, and of still pre-clinical high risk individuals, applicable to the population at large, in terms of the several risk factors singly and combined, by age and sex and using several screening levels. While this information is lacking, all the evidence still points forcibly to the need for screening the families of affected or susceptible persons. Families share their habits as well as their genes. Whatever the relative importance of genetic and environmental factors in causing familial resemblance, prevention through taking care of the environment is likely to be of benefit. Contrary to the prevalent and fatalistic view that genes are largely a

matter of destiny, Sir Frederick Gowland Hopkins once wrote that nurture can assist nature.

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