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SYMPOSIUM ON 'NUTRITION AND DIABETES'

Atherosclerosis, diabetes and obesity

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Many post-mortem studies have reported a higher level of atherosclerosis in diabetics. The two most convincing are the International Atherosclerosis Project (Robertson & Strong, 1968) and the Five Towns Study (Ždanov & Vihert, 1976). In the first of these, the influence of many factors, including diabetes, was assessed on the nature and degree of atherosclerosis in more than 34 000 autopsies from thirteen national centres, using standardized techniques of preparation and measurement. Diabetics had significantly more fatty streaks in the coronary arteries, though not in the aorta. However, raised lesions were more frequent both in the coronary arteries and the aorta of diabetics. This was true even when cases with other associated conditions, like hypertension, were excluded from the analysis. Diabetics also had more fibrous plaques, more complicated lesions, more calcification and more coronary stenoses than non-diabetics. There was, nevertheless, considerable geographical variation in the prevalence of atherosclerotic lesions in the diabetics, broadly reflecting the prevalence in the populations from which the diabetics were derived.

The Five Towns Study was similarly standardized. The extent and severity of atherosclerosis was greater in diabetics than matched non-diabetics, especially in the coronary arteries. Diabetes was also particularly associated with calcified lesions, both in the aorta and in coronary arteries. The combination of diabetes and hypertension was associated with the greatest degree and severity of atherosclerotic lesions.

There are many reports in the literature concerning increased mortality and morbidity from arterial disease in diabetics (see Jarrett & Keen, 1975). In the Framingham prospective community study (Garcia *et al.* 1974) there was increased mortality amongst diabetics from sudden death, cardiac infarction and cerebral vascular disease. There was also an increase in non-fatal events due to coronary, cerebral and peripheral vascular disease amongst the diabetics. Particularly striking was the increased incidence of coronary deaths among female

diabetics, who appeared to have lost the usual 'protection' from coronary disease experienced by female non-diabetics. This is the usual experience in other studies, with the sole reported exception of Warsaw (Krolewski *et al.* 1977) where diabetic women had an increased risk similar to that of male diabetics.

Some of the increased mortality amongst diabetics may be due, in addition to a greater frequency of cardiac infarction, to a greater risk of dying in the acute stage of an infarct. Reports before (Jarrett, 1961; Honey & Truelove, 1957) and since (Soler *et al.* 1974; Harrower & Clarke, 1976) the advent of coronary care units have demonstrated a greater hospital mortality in diabetics. Some of this may be attributed to the precipitation of ketoacidosis by the infarct (Bradley & Bryfogle, 1956). Other possibly deleterious factors include pre-existing disease of the fine divisions of the coronary arteries (Ledet, 1976) and depletion of cardiac nor-adrenaline stores in the hearts of long-standing diabetics (Christensen, 1979).

The term 'diabetic cardiopathy' has been introduced to embrace diverse cardiac abnormalities in the diabetic not attributable to atherosclerosis or valvular disease. A number of histopathological abnormalities have been described in autopsy studies and in vivo measurements, using echocardiography and other techniques, have demonstrated subclinical myocardial dysfunction in diabetics. Some of the abnormalities are reversible by improved blood glucose control (Sykes *et al.* 1977). There is, as yet, insufficient information to allow an estimate of the contribution made by 'diabetic cardiopathy' to cardiac mortality and morbidity in diabetics. However, in the Framingham study the occurrence of congestive cardiac failure was more frequent in insulin requiring diabetics and this could not be explained by co-existing, overt coronary heart disease.

The increased arterial disease risk for diabetics is most obvious in countries where atherosclerosis is common in the general population. In countries, such as Japan, where atherosclerosis is relatively uncommon and mortality from coronary heart disease is low (Keys (editor), 1970), mortality is also relatively low in diabetics. Nevertheless, in a large autopsy study, myocardial infarction was found twice as frequently in Japanese diabetics compared with non-diabetics (Goto, 1978). The low rate of coronary heart disease in Japan is not due to ethnic factors, for Japanese migrants to Hawaii and California have rates of CHD similar to North Americans in general (Kawate *et al.* 1978) and CHD is increasing in Japan itself (Sasaki *et al.* 1978). Apart from the Japanese, there are other ethnic groups reported to have low or very low rates of CHD, both amongst diabetics and non-diabetics (see Jarrett & Keen, 1975). My interpretation of the epidemiological observations is that atherosclerotic disease in the diabetic responds to the same environmental determinants as that in the non-diabetics, albeit with some 'amplification'. What the amplifying factors are remains a subject for debate.

Risk indices for coronary heart disease in diabetics

There is some controversy over the relative prevalence in diabetic and non-diabetic populations of such well known indicators of risk as hypertension, lipoprotein cholesterol levels and cigarette smoking (see Jarrett & Keen, 1975).

Different studies have given different answers and it is not known how much of these differences is real or how much is due to bias in sampling, both of diabetics and non-diabetics. A further problem in analysis is a general failure in most studies to differentiate between insulin dependent and non-insulin dependent diabetics, who differ in many respects, though not in their propensity to atherosclerosis.

In the Framingham Study (Garcia *et al.* 1974; Gordon *et al.* 1977) multivariate analysis was used to examine the predictive power of several conventional risk indices for CHD (mortality plus morbidity) in the diabetics of that population. While the usual risk indices gave some degree of prediction, they were insufficient to account for the excess arterial disease rates in the diabetics. Similarly, in the Whitehall Study, a prospective study of male Civil Servants (Reid *et al.* 1974), known and newly found diabetics had similar CHD death rates 7.5 years after initial observation, which were twice those of the non-diabetics studied, although mean values of blood pressure, serum cholesterol and cigarette consumption, were almost identical in all three groups (R. J. Jarrett, unpublished results).

Obesity

There can be no doubt that obesity is the major environmental factor in determining the prevalence of non-insulin dependent diabetes in a population. A great many studies support this. On an international scale, the epidemiological studies of West & Kalbfleisch (1971) in ten populations yielded a high degree of correlation between diabetes prevalence (above the age of 35 years) and 'average fatness'. A more dramatic illustration of the association is the relatively recent appearance of diabetics in almost epidemic proportions in several populations, the two most notable being the Pima Indians in Arizona (Hamman *et al.* 1978) and the population of the Pacific Island of Nauru (Zimmet & Taft, 1978).

Any link between obesity in diabetics and atherosclerosis, however, is much less obvious. Firstly, obesity is not a notable feature amongst insulin-dependent diabetics, who, nevertheless, are at greater risk of arterial disease. Secondly, prospective studies have failed to show any predictive power for obesity when other factors linked to obesity, such as levels of blood pressure and serum lipids, are allowed for in the multivariate statistical analysis (Gordon *et al.* 1977; R. J. Jarrett, unpublished results). In the frequently quoted UGDP Study (University Group Diabetes Program, 1970) mortality rates from cardiovascular disease were actually less in recruits to the trial with the higher relative body-weights.

Several other prospective studies have also failed to show any specific effect of obesity upon cardiovascular mortality rates in diabetics. These include the actuarial study in Birmingham, England (Hayward & Lucena, 1965) and the study of diabetics working for the Dupont Corporation in the USA (Pell & D'Alonzo, 1970).

Thus, while obesity pre-disposes to the development of non-insulin dependent diabetes and while this and insulin-dependent diabetes pre-dispose to atherosclerosis and clinical arterial disease, there is little to suggest that obesity can explain the enhanced risk of arterial disease. Nor, despite the theoretical

benefits of reduced blood pressure and serum cholesterol level achieved by substantial weight loss, can we point to demonstrable evidence of a reduction in arterial disease, morbidity or mortality in successful diabetic slimmers.

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