The relationship of diabetes to cardiovascular disease has been known for over half a century and has been the subject of a number of reviews. The topic was discussed by the author and two colleagues in 1975, and the present paper concentrates on information published since that time.

Although it is well known that diabetic patients commonly die from cardiovascular disease and that cardiovascular disease is particularly common in diabetes, a number of questions remain unanswered. It is now clear that diabetes mellitus consists of at least two distinct disorders that differ both genetically and in their metabolic abnormalities. The majority of diabetics have Type II, or noninsulin-dependent, diabetes mellitus (NIDDM), characterized by mild to moderate glucose intolerance, a high frequency of obesity, absence of a tendency to ketoacidosis, and response to treatment with diet or oral antidiabetic drugs. A minority (20%) of diabetics have Type I, or insulin-dependent, diabetes mellitus (IDDM), characterized by marked hyperglycemia, weight loss, and a requirement for insulin therapy to prevent the development of ketoacidosis. The old terms of “juvenile diabetes” for IDDM and “maturity-onset diabetes” for NIDDM are no longer used, as either type of diabetes can occur at any age. The possibility that the two major types of diabetes have different relationships to atherosclerosis remains to be explored. The criteria for the diagnosis of diabetes are clearly arbitrary, although they correlate with clinical and epidemiological data. Assessment of the severity of diabetes is even more arbitrary, while the duration of diabetes can only be measured as the time since diagnosis.

While classical myocardial infarction with characteristic clinical features accompanied by electrocardiographic (ECG) and other abnormalities can be ascribed to atherosclerosis with some confidence, the pathological processes responsible for congestive cardiac failure, sudden death, and cardiovascular death may not always be primarily atherosclerotic. Many clinical and epidemiological studies have used the latter endpoints in investigating the relationship of diabetes to atherosclerosis; the validity of these assumptions must be questioned. Other questions concern the relationship of atherosclerosis to the severity and duration of diabetes and to its mode of treatment; the role of blood glucose elevations in atherosclerosis in nondiabetics; the relationship of cardiac disease in diabetics to other risk factors for atherosclerosis; and whether diabetics have a specific heart muscle abnormality independent of disorders of the coronary arteries. Each of these topics will be considered in this review.
Atherosclerosis and Diabetes

Autopsy Evidence

Many of the autopsy studies of diabetics published in the past are unsatisfactory by modern standards. In particular, the control groups were not always appropriate, and often there were only limited examinations of the heart and coronary arteries. However, in the largest study in which arteries were examined by standardized techniques, the coronary arteries and aortas of diabetics showed more atherosclerosis than those of nondiabetics regardless of sex, age, race, or geographic location.3

Three recent studies have applied modern techniques to the study of atherosclerosis in diabetes. In a reexamination of the hearts of diabetics in the Mayo Clinic, the degree of cross-sectional area narrowed by atherosclerotic plaques in each of the four major epicardial arteries was measured.4 The patients had all attended a diabetes clinic; in addition, diabetes was defined by standard criteria and included both IDDM and NIDDM. The control group consisted of age- and sex-matched subjects who had had fatal coronary events but not diabetes. The nondiabetic controls were patients who had not attended the diabetes clinic. There was no mention that blood glucose measurements had been made on these patients. Overall, the study disclosed similar degrees of severe narrowing of the main coronary arteries by atherosclerotic plaques in both diabetic patients with or without clinical evidence of coronary heart disease and in nondiabetics with fatal coronary heart disease.

No significant differences were observed in the degree of severe narrowing by atherosclerotic plaques between the proximal and distal halves of the three coronary arteries in either the diabetic group or in the controls. The degree of coronary artery narrowing was not related to the age of onset and the duration of diabetes, nor to the treatment or to the random blood sugar levels. Acute myocardial infarction was the most frequent fatal coronary event in the diabetics studied, with "sudden coronary death" second, and chronic congestive cardiac failure third. The frequency of these three types of fatal coronary event was not altered by the patient's age at onset of diabetes or by the duration of the diabetes. However, a significantly higher frequency of severe narrowing of the left main coronary artery occurred in the patients with diabetes mellitus. Healed transmural ventricular scars were found at autopsy more frequently in the diabetics than in the nondiabetic controls, but a similar frequency of cardiac rupture occurred in the patients with and without diabetes. The results of this study are somewhat difficult to interpret, and it is unfortunate that the study did not include a fourth control group made up of nondiabetic patients who had died from causes other than coronary disease.

In an autopsy study from Baltimore published at the same time, the hearts of 185 patients who had clinically established adult-onset diabetes mellitus of mixed type were examined by a standardized coronary arteriography technique.5 The clinical severity of diabetes was assessed by a review of the medical records. There was no significant association between the overall degree of coronary artery atherosclerosis and either the duration or severity of diabetes. Similarly, there was no significant correlation between the severity of diabetes and systemic, pulmonary, or cerebral atherosclerosis. The type of treatment of diabetes (by diet, oral hypoglycaemic drugs, or insulin) was not related to the degree of coronary atherosclerosis. However, when the diabetic group was compared with an age- and sex-matched control group, the diabetics had significantly more coronary atherosclerosis. The number of myocardial infarctions, the number of diseased coronary arteries, the diffuseness of coronary atherosclerosis, and the presence of coronary arterial collateral channels were all significantly greater in the diabetics than in the nondiabetics. These results suggest that diabetics have more extensive atherosclerosis than nondiabetics. However, the findings also suggest that the progress of coronary atherosclerosis in diabetes of adult onset is independent of the progress of the diabetes itself.

In a rare autopsy study of young, juvenile-onset insulin-treated diabetics, nine patients (average age, 29 years; average age at onset, 9 years) had significantly more extramural coronary narrowing by atherosclerotic plaques than did nine age-matched control subjects.6 Both the degree of narrowing and the extent of coronary arterial involvement were greater in the diabetics. In the diabetics, 47% of the entire length of the coronary arteries was narrowed more than 50%, compared with only 1% in the nondiabetic controls. There was no evidence of a significant abnormality in the small intramural coronary arteries. Although this study demonstrated accelerated coronary atherosclerosis in diabetics, the presence of early-onset diabetes was not always accompanied by severe coronary heart disease 20 or more years later. In two diabetics, little coronary artery narrowing was found, and it has been suggested that this was related to the infrequent occurrence of ketoacidosis in these subjects. A clinical, retrospective case study of coronary angiograms in diabetics and controls also found no evidence of significant disease of the small coronary vessels.7

These studies indicate that coronary atherosclerosis is more severe at all ages and occurs at a younger age in insulin-dependent diabetics.
However, coronary atherosclerosis is not an inevitable accompaniment of diabetes, and all coronary arteries are not equally involved. Atherosclerosis in diabetes is not related to the duration of diabetes, age of onset of the disease, blood glucose levels or type of treatment. No evidence of disease of the small intramural arteries was found.

**Epidemiological Evidence—The Framingham Study**

The Framingham study, a large prospective study of 5209 men and women, has addressed the question of the relationship of diabetes to atherosclerosis. Diabetes was diagnosed when the subject was having treatment for diabetes, had a positive oral glucose tolerance test, or had two or more blood glucose levels higher than 160 mg/dl. By the 16th year of the study, diabetic men and women had developed more cerebral vascular accidents, coronary heart disease, and peripheral arterial disease than age- and sex-matched nondiabetics. The mortality rate from cardiovascular disease in the diabetics was almost three times that of the general population. However, there seemed to be a greater impact on women than on men, since the risk of cardiovascular mortality in diabetic women was 4½ times greater than in nondiabetic women, while the risk ratio in men was 2:1. However, this high risk was confined to women treated with insulin. Although coronary disease was the commonest cause of death in diabetics, the impact of diabetes seemed to be greatest on intermittent claudication. Although the diabetics had higher beta lipoproteins, higher blood pressures, and greater relative weight than the nondiabetics, the differences did not appear to be of sufficient magnitude to account entirely for the excess of coronary heart disease (CHD) incidence in diabetics. Multivariate analysis of the various risk factors suggested some unique effect of diabetes, especially in women, which could not be explained by associated risk factors. The results of later examinations of the Framingham cohort have confirmed the findings of the 16th year examination. In particular, the increased risk of cardiovascular disease in women has been emphasized. Nevertheless, diabetes is not a highly prevalent condition and, thus, in the whole spectrum of atherosclerosis, diabetes carries a relatively low risk. Factors such as elevated blood pressure and serum cholesterol have the same relationship to cardiovascular disease in diabetics as in nondiabetics, and there was no evidence that diabetics cope less well with risk factors than nondiabetics. Even when the protective effect of high density lipoprotein cholesterol (HDL) and the lower HDL values in diabetics were taken into consideration, the impact of diabetes on cardiovascular disease could not be entirely explained by the associated risk factors.

**Blood Glucose and Arterial Disease**

The relationship of mild abnormalities in blood glucose to cardiovascular disease has been the subject of recent studies. The largest investigation has been the Whitehall study, a prospective study of 18,403 London civil servants. Capillary blood glucose was measured 2 hours after administration of a 50 g oral dose of glucose following an overnight fast. The measurement was related to the age-adjusted coronary heart disease (CHD) mortality after 7½ years. Subjects with 2-hour blood glucose levels of 200 mg/dl (11.2 mmoles/liter) or more were designated new diabetics and had the highest mortality. Previously diagnosed diabetics also had high mortality rates as well as the highest age-adjusted ECG measurements. The rates were the same in diabetics treated with insulin and in those receiving other treatment. In nondiabetics with 2-hour blood glucose levels of less than 200 mg/dl, the 2-hour blood glucose level was not linearly related to the age-adjusted CHD mortality, nor was there a linear correlation in the increase in ECG abnormalities with increasing blood glucose. However, there was a sharp doubling of CHD mortality at the 95th percentile (2-hour blood glucose, 96 mg/dl; 5.4 mmoles/liter) with no variation of mortality rate with blood glucose below that point. It was notable that the increased risk of CHD mortality and ECG abnormalities was found at blood glucose levels considerably lower than those recently suggested as indicative of impaired glucose tolerance. These findings contrast with those reported for microvascular disease in diabetes as manifested by retinopathy and proteinuria. In a group of Pima Indians of Arizona, a community with the highest recorded incidence of diabetes, the development of retinopathy in a 3-year period was very rare in those with a fasting blood glucose level of less than 140 mg/dl (7.8 mmoles/liter) and did not occur if the 2-hour blood glucose level was less than 200 mg/dl (11.2 mmoles/liter). Proteinuria was less frequent than retinopathy, but had a similar relation to blood glucose levels.

The Whitehall findings must be judged in the context of the International Collaborative Project, a combined report of 11 different studies of blood glucose levels and coronary heart disease. This project was not planned in advance, and standardized methods of measuring blood glucose levels or assessing cardiac mortality were not used. In addition to the Whitehall study, four other investigations found higher cardiovascular mortality in subjects with the
highest blood glucose levels, although in all of these studies multivariate analysis did not confirm an independent relationship of blood glucose with cardiovascular mortality. 16-19 The other studies showed no relationship between the blood glucose level and the subsequent mortality from coronary heart disease. The relationship between blood glucose and the prevalence of ECG abnormalities was variable. The group of authors found no evidence for an association between blood glucose levels and coronary heart disease in nondiabetics. They did not find sufficient evidence for a threshold relationship, that is to say, a consistently positive relation between the highest levels of blood glucose and the incidence of CHD. It was suggested that hyperglycemia should not be designated an independent risk factor for CHD on present evidence.

There are a number of problems with the International Collaborative Project. 20 Studies were included in the project that differed in a number of respects, including methods of measuring blood glucose, times at which samples were taken for the measurement of glucose, certain exclusion criteria for patients with preexisting diabetes, and differences among populations. The studies that did show an excessive CHD mortality in subjects with the highest blood glucose levels were the only studies in which a significant number of coronary deaths occurred in subjects with the highest blood glucose levels. Indeed, only four of the studies had more than one CHD death in the upper blood glucose quintile, and of these, three showed at least a doubling of mortality in this blood glucose range. The results of the Whitehall study cannot be ignored, since it is by far the largest study and one of only two studies in which glucose was measured in capillary blood. If this study is correct, it would suggest a threshold of impaired glucose tolerance above which the risk of CHD is increased. It is not surprising that multivariate analysis did not reveal glucose as an independent risk factor with a linear relationship to CHD mortality. Furthermore, the small number of people with the highest blood glucose levels suggest that only the largest studies would be likely to identify such a threshold effect.

A new analysis of the Tecumseh study has emphasized the complex relationship between blood glucose and atherosclerosis. 21 Although persons in the upper quartile of blood glucose distribution had twice the risk of CHD compared to those in the lowest quartile, even when those with diagnosed diabetes had been excluded, there was no significant independent linear relationship between blood glucose and the risk of CHD in nondiabetics. These results are consistent with the threshold effect of blood glucose on atherosclerosis found in the Whitehall study. An important, but unanswered, question is whether such a threshold effect results from the metabolic consequences of a critical level of blood glucose, or whether it identifies a group of people who are genetically predisposed to both diabetes and atherosclerosis.

Risk Factors for Atherosclerosis in Diabetes

The question of whether atherosclerosis in diabetes is due to an increased frequency of major risk factors for atherosclerosis in the general population has been studied in a number of ways. Restudy of the Tecumseh cohort21 showed that age, systolic blood pressure, blood glucose, blood cholesterol, and cigarette smoking were all significantly higher in the subjects with CHD than in the rest of the subject group. However, when all the variables were included in a multiple logistic functions analysis, blood glucose was a lesser factor and not significant after exclusion of diagnosed diabetics. It has been suggested that the interaction of risk factors may be more important than any single factor in predicting CHD. In the Whitehall study, the association of age, systolic blood pressure, and ECG abnormalities with CHD mortality was stronger in the group with impaired glucose tolerance than in the subjects with normal blood glucose levels.

In a group of 485 diabetics, the prevalence of atherosclerosis obliterans (ASO) was determined by noninvasive methods. 22 Overall, lipoprotein levels in the diabetics were higher than in an age- and sex-matched nondiabetic group. However, the patterns differed in the different types of diabetes. In noninsulin-dependent diabetics (NIDDM), the prevalence of ASO was most dependent on age, and no independent effect of duration of diabetes was found. In contrast, in the diabetics treated with insulin, there was a significant correlation with both age and duration of diabetes. This difference may be due to the fact that the onset of diabetes is difficult to identify in NIDDM. In diabetics treated with diet alone, low HDL cholesterol was the most significant risk indicator, while in those treated with sulphonylureas, age was the only significant risk indicator. In the NIDDM subjects treated with insulin, all lipoproteins were significantly associated with ASO, but only VLDL triglyceride had a highly significant association. In the IDDM group all indicators except HDL cholesterol were highly significantly related to the prevalence of atherosclerosis. The study did not take into account body weight, blood pressure, or cigarette smoking. The overall prevalence of ASO was 24% in the IDDM subjects and 38% in the NIDDM subjects; the ASO prevalence was 38% in men and 29% in women. However, the sex
Nonatherosclerotic Heart Disease in Diabetes

There is accumulating clinical and experimental evidence that disorders of heart muscle, independent of atherosclerosis of the coronary arteries, may occur in diabetes. These findings may explain the high incidence of congestive cardiac failure that occurs in diabetics and also the fact that diabetics have a higher mortality rate from acute myocardial infarction than nondiabetics.

The Framingham study found that diabetic men aged 45–74 years have more than twice the expected frequency of congestive cardiac failure, and that diabetic women have a fivefold increase in risk. The excess risks were still present when the history of CHD, rheumatic heart disease, blood pressure, weight, and cholesterol were taken into consideration. It appeared that factors other than atherosclerosis and CHD were involved in the development of the cardiac failure.

It is difficult or impossible to distinguish the cause of congestive cardiac failure without carrying out special and often invasive investigations. One study has used these methods. Coronary angiography and left ventricular function studies were performed in a group of 17 adult-onset diabetics who had a family history of diabetes but no hypertension or obesity. Twelve of the group had no significant occlusive coronary disease and no evidence of ischemic heart disease on the basis of coronary sinus lactate levels after pacing-induced tachycardia. However, eight of these who had no cardiac failure did have abnormalities in left ventricular function. Four persons with a history of cardiac failure had similar but more extensive abnormalities. Left ventricular biopsy in two diabetics showed interstitial collagen deposition with relatively normal muscle cells. Postmortem studies in 11 persons with uncomplicated diabetes, many of whom had no coronary occlusive disease, showed accumulation of collagen in the interstitial spaces, fibrosis, and triglyceride and cholesterol in the myocardium. Noninvasive methods such as echocardiography, vectorcardiography, and measurement of systolic time intervals have shown abnormal left ventricular function in young diabetics with no evidence of ischemic heart disease. In one study, young diabetics had no significant abnormality of left ventricular function at rest, but myocardial performance was depressed by doses of alcohol too small to affect cardiac function in normal subjects. Thus, the diabetic heart may respond abnormally to stress. There is only one report of the effect of treatment of diabetes on myocardial function. A group of newly diagnosed diabetics with abnormalities in myocardial function were divided into three groups. In one group, myocardial function returned to normal after treatment of diabetes, suggesting a reversible metabolic abnormality in the heart muscle. In the other two groups, myocardial function did not return to normal after treatment. In one group, there were abnormalities similar to those found in nondiabetics with ischemic heart disease; in the other group, microvascular disease may have been present.

The effect of diabetes on cardiac performance has also been studied by a number of different experimental techniques. The hearts of streptozotocin diabetic rats were shown to have abnormalities in left ventricular contraction and relaxation, in relaxation of isolated papillary muscle, and in the contraction and response to catecholamines of isolated atria. Alloxan diabetic dogs were shown to have impaired cardiac function and an accumulation of cholesterol and triglyceride in the myocardium. Evidence for decreased response to stress in the diabetic heart has come from studies of the effect of increasing ischemia on the development of cardiac failure in alloxan diabetic rats. In all the experimental studies, causes of depressed myocardial function other than diabetes have been excluded.

The clinical and experimental evidence suggests the existence of a disorder of heart muscle in diabetes. This appears to be related to the diabetic state itself and, at least in experimental animals, is not caused by small vessel disease. The existence of a diabetic cardiomyopathy, with its possibly fatal complication of congestive cardiac failure, must cause a reappraisal of some of the clinical and epidemiologic studies of heart disease in diabetes. It is clearly no longer justifiable to ascribe cardiac death or cardiac failure in diabetics to the effects of atherosclerosis. It is possible that low associations of cardiac death with risk factors for atherosclerosis may be explained by the fact that a mixture of cardiac diseases has been studied.
Other Factors Associated with Atherosclerosis and Diabetes

Insulin and Atherosclerosis

A number of clinical studies have reported elevated insulin responses to oral glucose in subjects with atherosclerosis of the coronary, cerebral, or peripheral arteries. Now, three prospective studies have identified a predictive role of circulating insulin levels in the development of cardiovascular disease (table 1). The investigations differed in the populations studied, the glucose load administered, and the cardiovascular endpoints. The Busselton, Australia study was the only one of the three that included women in its population, and was also the only one in which insulin was not measured in the fasting state. It was found that in men aged 60 years and over, insulin levels 1 hour after 50 g of oral glucose were significantly related to the 6-year incidence and 12-year mortality from cardiovascular disease. No relationship was found in other age groups or in women. In the Helsinki policemen study of men aged 30-59 years, the insulin levels taken in the fasting state 1 and 2 hours after oral glucose (75 or 90 g, according to size) as well as the sum of the insulin levels were all significantly related to the development of myocardial infarction and CHD death 5 years later. In the Paris civil servant study of men aged 43-54 years, insulin levels taken in the fasting state and 2 hours after 75 g oral glucose were related to the development of myocardial infarction and death from CHD approximately 5 years later. However, the closest association was found between the serum insulin:glucose ratio and cardiovascular disease. In all three studies, the other cardiovascular risk factors measured included plasma lipids, blood pressure, and blood sugar, while body mass index was also measured in the Helsinki and Paris studies. Multivariate analysis revealed that the relationship of insulin to cardiovascular disease was independent of these measurements.

These investigations have shown that raised serum insulin levels have a predictive role in the development of cardiovascular disease, at least in men. The Busselton results differ from the other two in that the insulin-heart disease relationship was found only in men who were older than those studied in Helsinki and Paris. Busselton was also the only study to include women. The results are of interest in view of insulin's effect on the arterial wall, stimulating smooth muscle cell proliferation and lipid synthesis. Similar studies need to be performed in other populations, including all ages and both sexes. In particular, prospective studies of insulin levels in relation to cardiovascular disease in the main types of diabetes are required.

Chlorpropamide-Alcohol Flushing and Vascular Disease in Noninsulin-Dependent Diabetes

Some patients with noninsulin-dependent diabetes (NIDDM) treated with chlorpropamide show facial flushing after taking a small amount of alcohol. This phenomenon has a dominant inheritance and is particularly common in diabetic patients who also have a first degree family history of diabetes ('Mason'-type diabetes). A frequency of chlorpropamide-alcohol flushing (CPAF) of about 90% in Mason-type diabetes and about 65% in unselected noninsulin dependent diabetics has been reported. It has

<table>
<thead>
<tr>
<th>Study</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Oral glucose load (g)</th>
<th>Hours between glucose dose and blood sample</th>
<th>Duration of study (yrs)</th>
<th>Cardiovascular endpoint</th>
<th>Other risk factors measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busselton, Australia</td>
<td>M,F</td>
<td>21-70+</td>
<td>50</td>
<td>1</td>
<td>6</td>
<td>CHD incidence, CHD death</td>
<td>Blood pressure, blood glucose, cholesterol, uric acid</td>
</tr>
<tr>
<td>Helsinki, Finland</td>
<td>M</td>
<td>30-59</td>
<td>75 or 90</td>
<td>fasting, 1 and 2</td>
<td>5</td>
<td>MI, CHD death, Other CHD</td>
<td>Blood pressure, blood glucose, body mass index, cholesterol, smoking, triglyceride</td>
</tr>
<tr>
<td>Paris, France</td>
<td>M</td>
<td>43-54</td>
<td>75</td>
<td>fasting, 2</td>
<td>5/4</td>
<td>MI, CHD death</td>
<td>Blood pressure, blood glucose, body mass index, cholesterol, smoking, triglyceride</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease; MI = myocardial infarction.
been suggested that CPAF may be due to sensitivity to enkephalin and that enkephalin might have a role in the pathogenesis of this type of diabetes.

In a study of large vessel disease in noninsulin-dependent diabetics, 41% of CPAF-negative diabetics had evidence of macrovascular disease, compared with 24% of a matched CPAF-positive group. The main differences were found in patients whose duration of diabetes was less than 15 years; the differences remained when the presence of severe diabetic retinopathy was excluded. A similar negative relationship between CPAF and diabetic retinopathy has been found. The authors suggest that flushing is related to the pathogenesis not only of large vessel disease but also of small vessel disease. These results are rather unusual in that large vessel disease is often considered to be quite different from small vessel disease in diabetics. CPAF can be blocked by prior administration of indomethacin; those whose CPAF can be blocked with indomethacin are free of both small vessel and large vessel disease. It was suggested that, since indomethacin is a prostaglandin synthesis inhibitor, prostaglandins might be involved in the pathogenesis of the vascular complications of diabetes. Studies in twins suggest that indomethacin blocking of CPAF may, like CPAF itself, be an inherited phenomenon. These findings are difficult to reconcile with the previous reports by the same authors of an association of CPAF negativity with the vascular complications of diabetes.

The frequency of CPAF in noninsulin-dependent diabetics has been challenged by the report of a prevalence of only 4% true CPAF in a group of 50 diet-treated diabetics. In a group of 21 nondiabetics, two also showed the CPAF phenomenon. Thus, CPAF may not be nearly as common in noninsulin-dependent diabetics as was previously suggested and may be only closely related with the small subgroup of dominantly inherited Mason-type diabetes.

It is impossible at present to assign a definitive place to CPAF in the pathogenesis of vascular diseases in diabetes. However, the findings suggest that genetic factors may be involved in diabetic vascular disease.

Conclusions

Recent autopsy and clinical evidence confirms that atherosclerosis is both more common and more extensive in diabetics than nondiabetics. However, the frequency and extent of atherosclerosis is related neither to the severity nor the duration of the diabetes. Although cardiovascular disease has an increased frequency in persons with elevated blood glucose levels, it does not show a linear relationship to blood glucose, but possibly there is a threshold effect. Risk factors for atherosclerosis, including hypertension and abnormal plasma lipoprotein levels, are common in diabetics and have the same relationship to the development of atherosclerosis as in nondiabetics. However, the increased frequency of atherosclerosis in diabetics cannot be entirely explained by an increased prevalence of, or an increased sensitivity to, the effects of risk factors. Diabetes is also associated with abnormalities of cardiac function that are not caused by myocardial ischemia secondary to coronary atherosclerosis, and are probably not entirely due to small vessel disease in the myocardium. These abnormalities contribute to the high mortality from congestive cardiac failure and acute myocardial infarction that occurs in diabetics. Two new associations with heart disease and blood glucose regulation have recently emerged: 1) a relationship of cardiovascular disease with elevated fasting and postglucose serum insulin levels in general populations; and 2) a negative association with chlorpropamide-alcohol flushing in noninsulin-dependent diabetics. The available information suggests that diabetes has a trigger mechanism in the pathogenesis of atherosclerosis, initiating a process that then progresses under the influence of other factors. The trigger may be related to the blood glucose itself, or to some underlying cellular abnormality, perhaps genetically determined. The other factors involved in the pathogenesis of atherosclerosis in diabetes include well-established risk factors for atherosclerosis such as hypertension and hyperlipidemia, and perhaps also abnormal serum insulin levels. It is likely, although still hypothetical, that attention to these factors will reduce, although not eliminate, the high incidence of atherosclerosis in diabetes.

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