Many clinical studies have shown an increased insulin response to oral glucose in patients with ischemia of the heart, lower limbs, or brain. Hyperinsulinemia also occurs in patients with angiographically proved atherosclerosis without ischemia and thus appears to be related to arterial disease and not to be a nonspecific response to tissue injury. Fasting insulin levels and insulin responses to intravenous stimuli, including glucose, tolbutamide, and arginine, are normal, suggesting a gastrointestinal factor may be involved in the increased insulin response to oral glucose. In patients with atherosclerosis, insulin sensitivity appears to be normal or enhanced with respect to both glucose and lipid metabolism. Five population studies have shown that insulin responses to glucose are higher in populations at greater risk of cardiovascular disease. Many of the hyperinsulinemic populations also had upper-body obesity, hypertriglyceridemia, lower high-density lipoprotein (HDL) levels, and hypertension. These prospective studies support an independent association between hyperinsulinemia and ischemic heart disease, although their results differ in detail. Hyperinsulinemia is associated with raised triglyceride and decreased HDL cholesterol levels. Total and low-density lipoprotein (LDL) cholesterol is less closely related to hyperinsulinemia. Upper-body adiposity is associated (in separate studies) with coronary heart disease, diabetes, hyperinsulinemia, and hypertriglyceridemia. Insulin and blood pressure are closely related in both normotensive and hypertensive people. Although obesity and diabetes are often found in hypertensive people, hyperinsulinemia also occurs in nonobese nondiabetic hypertensive people. Thus, hyperinsulinemia is closely associated with a cluster of cardiovascular risk factors, i.e., hypertriglyceridemia, low HDL levels, hypertension, hyperglycemia, and upper-body obesity. There is a possibility that insulin may play a role in the sex differences in ischemic heart disease incidence and their absence in diabetes, but additional work is required for its clarification. Long-term treatment with insulin results in lipid-containing lesions and thickening of the arterial wall in experimental animals. Insulin also inhibits regression of diet-induced experimental atherosclerosis, and insulin deficiency inhibits the development of arterial lesions. Insulin stimulates lipid synthesis in arterial tissue; the effect of insulin is influenced by hemodynamic factors and may be localized to certain parts of the artery. In physiological concentrations, insulin stimulates proliferation and migration of cultured arterial smooth muscle cells but has no effect on endothelial cells cultured from large vessels. Insulin also stimulates cholesterol synthesis and LDL binding in both arterial smooth muscle cells and monocyte macrophages. The multiple effects of insulin provide evidence of a potential direct role for this hormone in the development of atherosclerosis. The combination of clinical, epidemiological, and experimental evidence favors a direct role of insulin in the development of atherosclerosis. Insulin may also promote atherogenesis by its effects on lipids and blood pressure. If hyperinsulinemia has a role in atherogenesis, regular physical exercise and avoidance of obesity should be effective in preventing atherosclerosis. Diabetes Care 13:631–54, 1990
have continued to accumulate, most of it supporting the hypothesis, although some of the details have had to be modified (2-6). This article reviews the evidence in a historical perspective but concentrates on recent developments, particularly new ideas on the interrelationships between hyperinsulinemia and other cardiovascular risk factors. Clinical and epidemiological data are first reviewed, followed by experimental evidence.

HYPERINSULINEMIA IN CARDIOVASCULAR DISEASE

CLINICAL STUDIES

Ischemic heart disease. The knowledge that diabetes is associated with an increased frequency of cardiovascular disease and that abnormal glucose tolerance tests are found in patients with ischemic heart disease led to measurements of insulin levels in patients with these diseases. The first studies were published in 1965, soon after methods for measuring insulin by radioimmunoassay became available. Seven patients who had had myocardial infarctions >6 mo before were subjected to oral glucose tolerance tests (OGTTs). There was little difference in the glucose levels between the patients and a healthy control group, but the patients had significantly higher insulin concentrations while fasting and 30, 60, and 150 min after glucose was taken (7). A study of 47 patients with ischemic heart disease, 55% of whom had abnormally high insulin levels after oral glucose, was reported in the same year, although there was no difference in the fasting levels between those with and without ischemic heart disease. The insulin responses to intravenous glucose and intravenous tolbutamide were the same in the patients and the control subjects (8).

Other studies of insulin responses to oral or intravenous glucose have been published and are summarized in Table 1 (7-36). In general, insulin responses to oral glucose are exaggerated, but the findings for fasting insulin and the insulin response to intravenous glucose

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref.</th>
<th>Glucose load</th>
<th>Abnormal glucose tolerance test</th>
<th>Increased insulin in ischemic heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters and Hales, 1965</td>
<td>7</td>
<td>50 g</td>
<td>±</td>
<td>/</td>
</tr>
<tr>
<td>Nikkila et al., 1965</td>
<td>8</td>
<td>1 g/kg</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Tzagournis et al., 1967</td>
<td>9</td>
<td>75 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Tzagournis et al., 1968</td>
<td>10</td>
<td>75 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Kashyap et al., 1970</td>
<td>29</td>
<td>100 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Malherbe et al., 1971</td>
<td>27</td>
<td>100 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Getter et al., 1972</td>
<td>30</td>
<td>75 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Berchtold et al., 1972</td>
<td>13</td>
<td>100 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Inoue et al., 1975</td>
<td>12</td>
<td>100 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Sorge et al., 1976</td>
<td>31</td>
<td>100 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Bergstrand et al., 1979</td>
<td>22</td>
<td>100 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Larsen et al., 1981</td>
<td>18</td>
<td>50 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Sewdarsen et al., 1984</td>
<td>15</td>
<td>75 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Hamsten et al., 1987</td>
<td>16</td>
<td>1.75 g/kg</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Oral glucose tolerance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Devlin and Stevenson, 1968</td>
<td>-</td>
<td>-</td>
<td>/</td>
<td>-</td>
</tr>
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<td>Mookherjee et al., 1984</td>
<td>-</td>
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<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Intravenous glucose tolerance</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nikkila et al., 1965</td>
<td>8</td>
<td>20 g</td>
<td>±</td>
<td>-</td>
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<tr>
<td>Christiansen et al., 1968</td>
<td>33</td>
<td>25 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Malherbe et al., 1971</td>
<td>27</td>
<td>0.33 g/kg</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Enger and Ritland, 1973</td>
<td>11</td>
<td>0.5 g/kg</td>
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<td>Enger and Hamlens, 1979</td>
<td>34</td>
<td>25 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Adamson and De Faire, 1982</td>
<td>35</td>
<td>1</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Fendic et al., 1984</td>
<td>36</td>
<td>500 mg/kg</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Hamsten et al., 1987</td>
<td>16</td>
<td>25 g</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Tolbutamide tolerance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nikkila et al., 1965</td>
<td>8</td>
<td>-</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>Kashyap et al., 1970</td>
<td>29</td>
<td>-</td>
<td>/</td>
<td>-</td>
</tr>
<tr>
<td>Arginine infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eaton et al., 1977</td>
<td>14</td>
<td>-</td>
<td>/</td>
<td>-</td>
</tr>
</tbody>
</table>

/?, Present; -, absent; ?, unknown; |, decreased.
arginine. Studies that demonstrate special features will be described in more detail.

A study of OGTTs in 25 patients in Ohio showed normal glucose responses and fasting insulin levels but higher insulin responses to oral glucose 1 and 2 h after 75 g of glucose. Total insulin output was also significantly higher in the patients with heart disease. The free-fatty acid response to oral glucose was identical in the patients and the control subjects, suggesting normal insulin activity on lipid metabolism (9). A further study by the same authors, this time with 50 patients, confirmed these results and was significant in that the patients not only had had myocardial infarctions, but some had angiographic evidence of coronary atherosclerosis or ECG evidence of ischemic disease without a myocardial infarction (10). This suggests that hyperinsulinemia is related to disease of the artery wall rather than being a nonspecific response to tissue injury.

A different approach to studying insulin in ischemic heart disease was used in 57 men who had had their first myocardial infarction >2 yr before. An infusion of 25% glucose was used, and it was found that fasting levels of insulin and the levels from 20 to 120 min after the glucose infusion were significantly higher among the patients than in the control subjects (11).

Obesity is among the factors that may be associated with hyperinsulinemia. Although many studies have excluded obese patients, the criteria have not always been rigorous. A Japanese study found increased insulin responses to oral glucose in patients with coronary heart disease only if they were also obese. Those who were not obese had insulin levels that did not differ from the nondiabetic control subjects (12). Another study suggested that increased insulin secretion might be associated with enlargement of adipose tissue cells (13).

Insulin responses to intravenous glucose and arginine are not increased, suggesting a gastrointestinal stimulus mediated the exaggerated response to oral glucose (8,14).

Hyperinsulinemia in ischemic heart disease has been found in several ethnic groups. Nonobese nondiabetic Indian males living in South Africa had a 75-g OGTT and were compared with weight-matched healthy control subjects (15). Coronary artery disease was diagnosed on the basis of coronary angiography. Both fasting and postglucose levels were higher in the patients with myocardial infarction than in the control subjects. There was no difference in the fasting and 30-min insulin levels, but those at 60 and 120 min and the insulin areas under the glucose tolerance curves were higher in the myocardial infarction patients.

A large and detailed study with intravenous glucose tolerance tests and OGTTs was carried out in 104 nondiabetic survivors of myocardial infarction <45 yr old in Stockholm (16). Reduced oral glucose tolerance and hyperinsulinemnic responses to oral glucose and a glucose infusion were found in many of the patients with ischemic heart disease. Elevation of plasma insulin concentrations among the patients was present in both the early and late phases of the glucose-infusion test and was not related to differences in body weight. The hyperinsulinemic responses were found with all combinations of normal and abnormal oral and intravenous glucose tolerance. On the other hand, the correlation between the magnitude of the early insulin response and the degree of coronary atherosclerosis was negative. Thus, although hyperinsulinemia was found in patients with atherosclerosis, it may not be related to the later progression of the disease.

By far the largest cross-sectional study of insulin and cardiovascular disease was the Caerphilly, Wales, Heart Disease study of 2512 men aged 45–59 yr that showed an association between fasting plasma insulin levels and prevalent ischemic heart disease independent of body mass index (BMI), age, systolic blood pressure, and triglyceride levels (17). There was an inverse correlation between insulin and both testosterone and high-density lipoprotein cholesterol (HDL-chol) levels and positive associations between insulin and systolic blood pressure, BMI, and triglyceride levels. Of the lipids measured, triglycerides had the strongest association with ischemic heart disease.

A study of 10 male patients who had recovered from acute myocardial infarction and 10 control subjects with a 50-g OGTT found normal glucose tolerance but increased fasting and total insulin responses to oral glucose (18). Gastric inhibitory polypeptide (GIP) levels, both fasting and in response to oral glucose, did not differ between patients and control subjects.

There have been several studies on the relationship of insulin to atherosclerosis that have produced apparently negative results. A study of 117 non-insulin-dependent diabetes mellitus (NIDDM) patients found that vascular complications were more common in those with low insulin responses to oral glucose. However, all vascular complications of diabetes were grouped together, including retinopathy, neuropathy, and the presence or absence of peripheral pulses, and it is likely that it was primarily microangiopathy that was studied in this population (19). Similarly, a study of what was called small-vessel disease (ischemic lesions of the toes or feet in the presence of foot pulses) found low insulin responses to glucose tolerance tests (20).

In patients with established coronary artery disease, the 3-h glucose tolerance test was not related to 5-yr survival (21). No differences were found in fasting insulin or insulin responses to an OGTT between patients and control subjects in a study of men <40 yr old who had had a myocardial infarction where both patients and control subjects had high serum cholesterol levels. Both patients and control subjects were not representative of the general population in that they all had high serum cholesterol and triglyceride levels, and these may have removed any changes in glucose and insulin levels (22).

A study of 120 patients undergoing coronary angiography found no correlation between fasting plasma in-
Insulin and atheroma

Insulin levels and the degree of coronary atherosclerosis (23). However, other studies that have shown elevated insulin response to oral glucose in relation to ischemic heart disease have shown normal fasting insulin levels, even though insulin responses to glucose have been increased.

Only one study has reported no difference in insulin responses to oral glucose between patients who had had myocardial infarctions and control subjects. Glucose levels were also similar in the two groups. However, 4-h glucose uptake, a measure of insulin sensitivity, was significantly increased in the patients with myocardial infarction. Thus, although the insulin levels were not different between the two groups, the effectiveness of the insulin appears to have been greater in the patients with myocardial infarction (24). The explanation for this is unclear.

Some of the actions of insulin on arterial smooth muscle cells are similar to those of insulinlike growth factor I (IGF-I). In one study, plasma insulinlike activity measured by the effect of plasma on adipose tissue was found to be higher in patients with clinical atherosclerosis (25). However, there was no association between plasma IGF-I levels measured by radioimmunoassay and the prevalence of myocardial infarction in diabetic or nondiabetic individuals (26).

An important question is whether the elevated insulin levels are effective. Measures of glucose assimilation in myocardial infarction have shown normal (27) or increased (24) glucose assimilation, although free-fatty acid assimilation has been normal (8,9,28-30).

Peripheral vascular disease. There have been several studies of insulin levels in patients with peripheral vascular disease. The earliest study looked at eight patients admitted for angiography for peripheral vascular occlusion and compared them with 45 nonobese healthy volunteers. The 1-h insulin response to a 50-g OGTT was elevated in the subjects with peripheral vascular disease (37).

Later studies with OGTTs showed similar results. Fifty-one men with peripheral disease demonstrated by angiography, but who had neither diabetes nor myocardial infarction, and weight-matched controls had a 50-g OGTT. There was an increased insulin and glucose response to oral glucose but no difference in the fasting levels. The total insulin response to oral glucose was also increased (38). Seventy-five percent of the patients had abnormal glucose or insulin responses, and the insulin area correlated with the degree of obesity (39). In 65 patients with peripheral vascular disease who did not have myocardial infarctions, high insulin responses to 100 g of oral glucose were found, independent of the effect of body weight and plasma glucose. Fasting insulin levels were unchanged (31). In a study of male patients with peripheral arterial disease of the lower limbs, 86 patients and 81 control subjects had OGTTs. There was no difference in the fasting insulin or glucose levels, but insulin and glucose responses to oral glucose were higher in the patients than the control subjects (40).

A study of intravenous glucose tolerance in 21 patients with angiographically demonstrated peripheral vascular disease showed higher fasting plasma insulin levels in the patients than in control subjects but no difference in the peak insulin secretion after a glucose infusion (41).

One study has reported contrary results. Sixteen nondiabetic patients who had intermittent claudication showed low plasma insulin levels after an OGTT. The patients were selected for an exercise program and were compared to physically well-trained control subjects. The insulin sensitivity in the muscles of these patients was increased, suggesting that the insulin had a greater effect than normal (42,43). The explanation for the difference between this and other studies is not clear.

Cerebrovascular disease. There have been only three reports of insulin levels in cerebrovascular disease, all from the same laboratory. These showed that in otherwise healthy subjects with cerebrovascular disease, there are increased insulin responses to oral glucose and often higher glucose levels but no difference in fasting glucose or insulin levels. The patients, who were age matched with the control subjects, were free from ischemic heart disease, obesity, and diabetes (44-46).

Summary. The overwhelming mass of evidence favors an increased insulin response to oral glucose in patients with ischemia of the heart, lower limbs, or brain. This is present with angiographically proved disease and thus appears not to be a nonspecific response to tissue injury but to be related to the arterial disease. There is less agreement on fasting insulin levels or insulin responses to intravenous stimuli, including glucose, tolbutamide, and arginine. This suggests that there is a gastrointestinal factor involved in the increased insulin response to oral glucose. Only one study has addressed this question, and it did not find evidence that GIP is the factor (18).

In patients with atherosclerosis, insulin sensitivity appears to be normal or enhanced with respect to glucose and lipid metabolism.

Population studies

Epidemiological studies of cardiovascular disease have identified populations at particularly high risk of developing the disease and have sought characteristics that might be related to the increased risk. There have been relatively few population studies of insulin levels. Ischemic heart disease is common in both Whites and Indians in South Africa but rare among Africans. In a group of African, Indian, and White healthy nondiabetic male subjects with no family history of diabetes, fasting insulin levels were similar in all three groups, but insulin levels after oral glucose were lower in Africans than Whites as was the mean area under the insulin curve. Glucose levels, both fasting and in response to glucose, did not differ between Whites and Africans (47).

The incidence of ischemic heart disease in men in their early 40s is ~3 times greater in Edinburgh than Stockholm (48). In a random sample of apparently healthy men in the two cities, there were no significant differ-
ences in plasma glucose levels fasting or in response to oral glucose, but Edinburgh men had higher peak plasma insulin concentrations and greater insulin release measured as the area under the insulin curve. Triglyceride concentrations were higher and HDL-chol concentrations were lower in Edinburgh than in Stockholm, and blood pressure was higher in Edinburgh. Thus, as found elsewhere, the combination of hyperinsulinemia, hypertension, hypertriglyceridemia, and low HDL levels was associated with an increased risk of ischemic heart disease (49).

Immigrants from the Indian subcontinent to England and Wales have higher morbidity and mortality from coronary heart disease than the general population. A study in East London of healthy Bangladeshis and European men and women 35–69 yr old found risk factors that were more frequent or higher in Bangladeshis, including cigarette smoking (in men only), plasma triglycerides, and serum insulin; HDL-chol was lower. Bangladeshi also had a much higher prevalence of diabetes. On the other hand, Europeans were more obese and had higher systolic blood pressure and plasma cholesterol levels. Thus, in this population, the combination of high insulin and triglyceride and low HDL-chol levels distinguishes the population at higher risk of cardiovascular disease, but obesity and blood pressure were not distinguishing features (50).

Another study of Asians and Whites in London found higher postglucose insulin and C-peptide levels in those of both ethnic groups who had had myocardial infarctions than in healthy control subjects. In both groups, insulin and C-peptide levels were higher in those with impaired glucose tolerance than those with normoglycemia. Insulin and C-peptide levels were also higher in Asians than Whites. High triglyceride and low HDL-chol levels were also found in the Asians and patients with myocardial infarctions of both ethnic groups compared with control subjects (51). Hyperinsulinemia seems to be a distinguishing feature for ischemic heart disease within and between populations.

Populations with high prevalence of diabetes are at risk for cardiovascular disease. The San Antonio Heart Study studied Mexican Americans, who have 3–5 times the prevalence of NIDDM as non-Hispanic Whites (52).

In a random sample of men and women 25–64 yr old in each population, Mexican Americans had higher fasting insulin concentrations and higher insulin and glucose responses to a 75-g oral glucose load but did not differ in fasting glucose levels. They also had higher values for all measurements of adiposity and fat distribution. When adiposity was taken into account, the difference in insulin responses to glucose between the two ethnic groups remained, but the fasting insulin levels did not differ. Thus, although Mexican Americans have more upper-body adiposity than non-Hispanic Whites, this does not entirely account for the hyperinsulinemia in the former population.

**Summary.** Five population studies have shown that insulin responses to glucose are higher in populations at greater risk of cardiovascular disease. The hyperinsulinemic populations often also have upper-body obesity, hypertriglyceridemia, and lower HDL levels, and some have higher blood pressure.

**PROSPECTIVE STUDIES**

There have been three prospective studies of the relationship between insulin and cardiovascular disease. Because these are the best available clinical evidence linking insulin to atherosclerosis, they will be considered in detail (Table 2).

The Helsinki Policeman Study comprised 1059 men between 30 and 59 yr old who were free of clinical evidence of coronary heart disease. Measurements made at baseline included a glucose tolerance test that used 60, 75, or 90 g glucose according to body surface area. Insulin levels were measured fasting and 1 and 2 h after glucose. The 5-yr follow-up data showed that both fatal and nonfatal myocardial infarctions were more common in those who had the highest fasting, 1-h, 2-h, and total plasma insulin responses to glucose (53), and the relationships were maintained at 9.5 yr (54). Multivariate analysis showed that high 1- and 2-h postglucose plasma insulin levels were independent predictors of coronary heart disease when BMI, blood glucose, plasma triglyc-

### TABLE 2

**Prospective studies of insulin and cardiovascular disease**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Oral glucose load (g)</th>
<th>Hours between glucose dose and blood sample</th>
<th>Duration of study (yr)</th>
<th>Cardiovascular end point</th>
<th>Other risk factors measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helsinki</td>
<td>1059</td>
<td>M</td>
<td>30–59</td>
<td>60, 75, or 90</td>
<td>Fasting, 1, and 2</td>
<td>9.5</td>
<td>MI, CHD death</td>
<td>Blood pressure, blood glucose, BMI, cholesterol, triglyceride, smoking, physical activity</td>
</tr>
<tr>
<td>Paris</td>
<td>7534</td>
<td>M</td>
<td>43–54</td>
<td>75</td>
<td>Fasting, 2</td>
<td>5.25</td>
<td>MI, CHD death</td>
<td>Blood pressure, blood glucose, BMI, cholesterol, smoking, triglyceride</td>
</tr>
<tr>
<td>Busselton, Australia</td>
<td>3390</td>
<td>M,F</td>
<td>21–70+</td>
<td>50 (not fasting)</td>
<td>1</td>
<td>6</td>
<td>CHD incidence, CHD death</td>
<td>Blood pressure, blood glucose, cholesterol, uric acid</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; CHD, coronary heart disease; BMI, body mass index.
erides and cholesterol, physical activity, smoking, and systolic blood pressure were taken into account (53). Fasting plasma insulin did not have a statistically significant independent contribution. Insulin was associated positively with triglyceride levels and negatively with HDL-chol levels, although the latter were measured 5 yr after the other baseline measurements were made. Although both blood pressure and plasma insulin were related to obesity, they were independently related to incidence of coronary heart disease.

The Paris prospective study investigated 7534 men 43–54 yr old working in the Paris civil service (55). The usual cardiovascular risk factors and anthropometric data were recorded at baseline, and a 75-g OGTT was performed with measurements of plasma glucose and insulin fasting and 2 h after the glucose had been consumed. There was no significant relationship between fasting or 2-h plasma glucose and the annual incidence of coronary heart disease. However, a higher incidence of coronary heart disease was found in those with the highest fasting and 2-h plasma insulin levels. In multivariate analysis, only the fasting insulin level was independently related to coronary heart disease incidence. The relationship was linear, was greater in obese than nonobese subjects, and was independent of glucose tolerance and blood pressure (56). Both fasting and 2-h postglucose insulin-glucose ratios were also related to coronary heart disease incidence. Other risk factors measured were cholesterol, systolic blood pressure, and BMI. HDL-chol was not measured, and there was no significant relationship between triglycerides and coronary heart disease incidence. Thus, in Paris, the fasting insulin level was the best predictor, whereas in Helsinki, the 2-h level showed the best relationship.

The Busselton, Western Australia, study was the only prospective study to include women and men (57). Subjects consumed 50 g glucose in the nonfasting state with blood glucose and serum insulin levels taken 1 h later. Other risk factors, but not HDL-chol, were measured at baseline. The serum insulin level was found to be significantly related to the 6-yr incidence of and 12-yr mortality from coronary heart disease in men 60–69 yr old but not in women of any age. Multiple regression analysis of the 13-yr mortality data of the Busselton data showed that deaths due to all causes were positively related to insulin in men 60–74 yr old but negatively related to insulin in men 40–59 yr old (58). It is difficult to compare these results with those of the Helsinki and Paris studies because the age and sex of the study populations differed and the glucose stimulus was given at any time of day without regard to nutritional status. This study provides further evidence for a predictive role of hyperinsulinemia in coronary heart disease but introduces a degree of inconsistency into the results of the prospective studies (59).

**Summary.** These prospective studies generally support an association between hyperinsulinemia and ischemic heart disease, although their results differ in detail. There is a need for further prospective studies, which should include both men and women in a wide age range.

**DIABETES MELLITUS**

For many years it was assumed that diabetes is a disease of absolute deficiency of insulin and hence that those with diabetes had low circulating insulin levels. It is now clear that this is not always the case.

In many NIDDM patients, insulin levels are higher than those in nondiabetic subjects. As glucose tolerance declines from normal, insulin responses to oral glucose in response to an OGTT and over 24 h become elevated (60–62). With severe glucose intolerance and fasting hyperglycemia, insulin levels become normal or subnormal (60). Although obesity with or without mild hyperglycemia is associated with elevated fasting insulin levels and insulin responses to oral glucose (63), the hyperinsulinemia of impaired glucose tolerance is also found in nonobese people (60). Thus, both normal-weight and obese people with impaired glucose tolerance and mild NIDDM have hyperinsulinemic responses to glucose and elevated 24-h insulin levels. The mechanism appears to be resistance to the action of insulin (60). This type of mild hyperglycemia is associated with doubling the mortality from myocardial infarction and stroke (64). Proinsulin levels are also elevated in NIDDM (65), and it has recently been suggested that in NIDDM much of what is measured as insulin by radioimmunoassay is in fact proinsulin or parts of the proinsulin molecule (66).

In insulin-dependent diabetes mellitus (IDDM), insulin therapy is delivered in nonphysiological ways with respect to route and control of delivery. Normally, insulin is secreted into the portal circulation, where 50% of insulin is cleared on first passage through the liver, so that insulin concentrations in the portal vein are several times higher than those in the peripheral circulation (67). Subcutaneous insulin circulates in high concentrations to achieve its desired effect on its main target organ, the liver. In normal physiology, insulin secretion is finely regulated, with increases in secretion stimulated by meals and a rapid fall to basal levels between meals and overnight. With subcutaneous insulin injections, the insulin levels remain high between meals and overnight (68,69). Thus, many patients with diabetes (both NIDDM and IDDM) have their tissues exposed to higher levels of insulin than those without diabetes.

There have been relatively few studies of insulin levels in relation to cardiovascular disease in diabetes. One study of insulin levels in patients with myocardial infarction found high insulin levels in a subgroup of diabetic patients (29). In another study, 101 diabetic patients with and without clinical evidence of cardiovascular disease were compared to 104 control subjects. Those with both diabetes and atherosclerosis had higher insulin-glucose ratios than diabetic patients without ath-
erosclerosis. Ponderal index, a measure of body weight, was identical in the two groups (70). A Japanese survey of 526 patients attending a diabetes clinic found that evidence of cardiovascular disease was more common in those who were obese or treated with oral agents or insulin (71). It was suggested that these features indicate hyperinsulinemia, but caution must be exercised in interpreting this type of study.

In a cross-sectional study from Finland of 133 newly diagnosed NIDDM patients 45–64 yr old and 144 nondiabetic control subjects, the serum insulin level 1 h after oral glucose was significantly higher in male nondiabetic subjects with myocardial infarction than those without, whereas fasting and postglucose serum insulin levels were consistently higher in female diabetic subjects with coronary heart disease than those without (72). Multiple logistic analysis showed a relationship between high 2-h postglucose serum insulin and coronary heart disease in females independent of other cardiovascular risk factors, including HDL and obesity. Although there are some inconsistencies in these results, they tend to support the hypothesis that hyperinsulinemia is related to cardiovascular disease in diabetic and nondiabetic people.

Because insulin levels are difficult to measure and interpret in insulin-treated diabetic patients, plasma C-peptide levels have been used as an indicator of endogenous insulin secretion. Two studies of C-peptide levels in relation to cardiovascular disease in diabetes have been reported, one measuring fasting C-peptide levels and the other C-peptide levels after glucagon. Glucagon-stimulated C-peptide levels were measured in 263 insulin-treated diabetic patients 45–64 yr old who were >30 yr old when their diabetes was diagnosed. The age-adjusted prevalence of myocardial infarction was three times higher in those with high C-peptide levels, whereas definite or possible coronary heart disease was nearly twice as high, and stroke was four times higher in this group (73). In multivariate analysis, high C-peptide levels were positively associated with definite or possible coronary heart disease independent of other cardiovascular risk factors.

One of the largest studies of the relationship of insulin to macrovascular disease in diabetes took place in Schwabing, Munich (74). In 323 patients with NIDDM and 178 matched control subjects, those with macrovascular disease—i.e., coronary artery disease, peripheral vascular disease, or carotid artery disease—had higher fasting C-peptide levels than those without evidence of cardiovascular disease. Conversely, both macrovascular disease and coronary heart disease were more frequent in those with the highest levels of fasting C-peptide, whether this was expressed in absolute terms or in relation to body weight. In the diabetic patients treated with insulin, those who had macrovascular disease had higher insulin doses, higher C-peptide levels, and higher free-insulin levels than those without cardiovascular disease. In the entire diabetic group, fasting C-peptide concentrations were associated with body weight and fasting serum triglycerides and inversely with HDL-cholesterol.

Only two prospective studies relating insulin to cardiovascular disease in diabetes have been reported. In Oxford, United Kingdom, diabetic patients who had new ECG changes after 5 yr of observation had higher baseline plasma insulin levels, both fasting and in response to an oral glucose load, than those whose ECGs remained unchanged. Three factors that were predictive for development of ECG abnormalities were age, insulin, and serum cholesterol (75). In the Paris prospective study of male civil servants 43–54 yr old, coronary heart disease mortality was closely and independently related to plasma insulin levels, both fasting and 2 h after 75 g of oral glucose (76). The relationship to plasma glucose levels was less close, although mortality was higher in those with impaired glucose tolerance and higher again in those with known diabetes. Most of the relationship of coronary heart disease mortality to the degree of glucose tolerance was related to fasting plasma insulin levels, systolic blood pressure, and to a lesser extent, plasma cholesterol. Thus, although the diabetic subjects were not analyzed separately, in a population that included those with diabetes, a relationship with insulin and cardiovascular disease was found.

Although the presence of diabetes confers an increased risk of cardiovascular disease, prevalence rates for cardiovascular disease in diabetes vary greatly between different countries and generally parallel the prevalence rates in the general population of each country. The prevalence of cardiovascular disease is lower in Japan than in the United States, but is higher in the Japanese-American population than in native Japanese. The prevalence of diabetes and impaired glucose tolerance is also higher in the Japanese-American population than in Japan. OGTTs with 75 g glucose were performed in 68 Japanese-American men (nisei) and 26 Tokyo Japanese men (77). All subjects had NIDDM treated with diet or sulfonylureas. The nisei men had higher fasting and postglucose insulin levels than the Tokyo men. Although the nisei men were more obese than the Tokyo men, they still had higher fasting insulin levels when body weight was taken into account. This is the only population study of insulin levels in diabetes, and its results are consistent with the clinical evidence linking hyperinsulinemia and cardiovascular disease in diabetes.

One study has not found a relationship between insulin levels and cardiovascular disease in diabetes. In the 10-year follow-up of the Bedford diabetes survey, the development of ischemic heart disease in those with borderline diabetes (impaired glucose tolerance) was not related to baseline plasma insulin levels (measured 2 h after a 50-g glucose load) (78).

Summary. Although the evidence is incomplete, and more prospective studies are urgently needed, almost all the reported studies have shown a relationship be-
between elevated insulin levels or measures of insulin secretion and cardiovascular disease in both NIDDM and IDDM subjects. As in those without diabetes, high triglyceride and low HDL-chol levels are often found in those with hyperinsulinemia and cardiovascular disease.

**HYPERINSULINEMIA AND OTHER Cardiovascular Risk Factors**

**Lipids.** Abnormalities in lipid metabolism are among the best-known cardiovascular risk factors. Raised cholesterol and low-density lipoproteins (LDLs) have a strong positive association with coronary heart disease (79), and HDLs have a negative association (80). There has been controversy over the question of whether triglycerides and very-low-density lipoproteins (VLDLs) have an independent relationship to coronary heart disease, although there is evidence that such a relationship exists (81). Insulin is most clearly associated with triglycerides and HDL.

It has been known for many years that insulin and triglyceride levels are closely related in normal and impaired glucose tolerance, in endogenous hypertriglyceridemia and obesity (82–87) and that hyperinsulinemia occurs in patients with hypertriglyceridemia (88,89). Abnormalities of fat cell size and metabolism are also related to high triglyceride levels (90). The postulated pathogenetic sequence is obesity causing insulin resistance and leading to hyperinsulinemia, increased triglyceride production, and increased levels of plasma triglycerides and VLDL (91).

More recently, there has been increased interest in relationships between insulin and HDL. Generally, HDL and VLDL levels are inversely related. Therefore, it is not unexpected that an inverse correlation between insulin and HDL levels is often found. The trio of hyperinsulinemia, raised triglyceride and VLDL levels, and decreased HDL-chol levels is a common finding in patients with cardiovascular disease. Other factors that may be involved in this interrelationship include obesity, hypertension, and sex hormones.

A study of 323 nondiabetic first-degree relatives of IDDM patients related insulin and glucose responses to OGTTs to lipids and lipoproteins (92). In general, the variations of the lipid levels with both sex and obesity could be accounted for mainly by changes in insulin and by age. In an Italian study of 610 factory workers 22–73 yr old, insulin measured fasting and 1 or 2 h after 75 g oral glucose and the area under the insulin response curve had a negative correlation with HDL and a positive correlation with triglyceride and body weight (93). Partial (negative) correlation coefficients between insulin and HDL-chol remained significant when the influence of body weight, glucose tolerance, triglycerides, smoking, alcohol, and physical activity was removed. Similar independent positive relationships occurred between insulin and triglycerides.

A study of nondiabetic men with the euglycemic-hyperinsulinemic glucose clamp showed a negative association between insulin-mediated glucose disposal and fasting triglyceride levels and VLDL-chol, VLDL triglycerides, and the total-cholesterol–HDL-chol ratio (94). The authors suggested that their findings support the view that hyperinsulinemia or insulin resistance may enhance the risk of coronary heart disease by adversely affecting lipoprotein levels, which themselves increase the risk of atherosclerosis. Similar results have been reported from a study with a hyperinsulinemic clamp in normolipidemic men and women with normal glucose tolerance in whom insulin resistance was directly related to triglyceride and inversely related to HDL levels (95). These investigations with direct methods of measuring insulin resistance support the conclusions of studies reporting an association between increased insulin secretion, high serum triglycerides, and low HDL levels (96). In a group of diabetic subjects, lower levels of HDL-chol and HDL<sub>2</sub>-chol and higher levels of total and VLDL triglycerides were found compared with those in non-diabetic control subjects, whereas plasma insulin and BMI were also higher in the diabetic patients (97). Plasma insulin correlated positively with total and VLDL triglycerides and negatively with HDL-chol and HDL<sub>2</sub>-chol. These relationships remained insignificant when other confounding factors were taken into consideration.

Attention is now being paid to combinations of cardiovascular risk factors. In an Israeli population-based study, hyperinsulinemia was associated with a combination of increased VLDL and LDL levels and reduced HDL levels (98). The relationship was independent of the effects of age, sex, glucose, body weight, blood pressure, and smoking. The adjusted risk ratio for the jointly disturbed lipoprotein profile in hyperinsulinemic subjects was 3.4.

**Summary.** Hyperinsulinemia is associated with raised triglyceride and decreased HDL-chol levels. Total cholesterol and LDL-chol are less closely related to hyperinsulinemia.

**Body fat distribution.** For many years there has been controversy over the relationship between obesity and the risk of ischemic heart disease. Although obesity is associated with increased mortality, it has not been clear whether it has an independent relationship to incidence of ischemic heart disease (99). Obesity is associated with other risk factors, including hypertension, diabetes, and hyperlipidemia, and hence its relationship to ischemic heart disease may be indirect. Insulin concentrations, both in the basal state and after a glucose challenge, are associated with increasing body weight and are reduced by weight loss (91,100,101).

More recently, attention has been paid to the distribution of adipose tissue. This is measured as waist-hip circumference ratio or subscapular skin-fold thickness, with higher values of each being indicators of abdominal, upper-body, or masculine body fat distribution. Positive independent relationships between upper-body adiposity and cardiovascular disease have been found.
in both men (102) and women (103). In NIDDM, abdominal adiposity measured by the waist-hip ratio, whether associated with being overweight or not, was associated with increased frequency of peripheral vascular disease, coronary artery disease, and hypertension, and with higher triglyceride and lower HDL-cholesterol values (104). In the Honolulu heart program, a study of 7692 men, subscapular skin-fold thickness had the closest relationship to incidence of coronary heart disease (105). In those with the highest third of subscapular skin-fold thickness, excess of coronary heart disease more than doubled. The relationship between subscapular skin-fold thickness and incidence of coronary heart disease was independent of the effects of BMI, age, cholesterol, glucose, triglycerides, hypertension, and cigarette smoking. Subscapular skin-fold thickness was also associated with raised cholesterol, glucose, triglyceride, and blood pressure levels and was inversely related to the proportion of people who smoked. In the prospective study, a measure of fat deposition was closely related to risk of coronary disease in middle-aged men (106).

Although obesity is associated with insulin resistance, hyperinsulinemia, and hyperglycemia, the closest relationship is with upper-body obesity (107). Upper-body obesity is also associated with hypertriglyceridemia, low HDL-cholesterol levels, impaired glucose tolerance, and increased risk of diabetes (108,109). Overt NIDDM was associated with a decrease in insulin response, although the insulin levels in those severely overweight were still higher than in those of normal weight (110).

In women, upper-body obesity was associated with increased glucose responses to an OGTT and an increase in insulin output, which was double that in those with lower-body-segment obesity and fourfold higher than in nonobese women (111). Fasting insulin levels were also higher in obese compared with control women. Presence of diabetes did not alter the relationship between insulin and distribution of body fat. The upper-body obese women also had higher fasting triglyceride levels than the lower-body obese subjects. Increasing waist-hip ratio was accompanied by progressively increasing fasting insulin levels, insulin and glucose levels after oral glucose, insulin resistance, and plasma triglyceride concentrations (112). These relationships were independent of the effect of body weight. Upper-body obesity is associated with large fat cells, which in turn tend to be resistant to the effects of insulin. Thus, it appears that in obese premenopausal women, sites of body fat localization influence the degree of insulin sensitivity and, in turn, plasma glucose, insulin, and lipid levels. Increased activity of androgens, manifested by decreased plasma sex hormone-binding globulin (SHBG) capacity and increased percentage of free testosterone, is also associated with increased waist-hip ratio and increased plasma glucose and insulin levels (both while fasting and in response to oral glucose challenge) and diminished in vivo insulin sensitivity (113).

Not only is the distribution of BMI important, but body weight does not take account of body composition. A detailed study of body composition showed that it is obesity that is most closely related to fasting insulin, insulin area, and other cardiovascular risk factors such as diastolic blood pressure, LDL, HDL, and estradiol-testosterone ratios (114). Thus, these findings conflict to some extent with others on body fat distribution.

Summary. Upper-body adiposity is associated (in separate studies) with coronary heart disease, diabetes, hyperinsulinemia, and hypertriglyceridemia. It is important to study the interrelationships of these and other measurements in relation to cardiovascular disease.

Hypertension. Hypertension is an important risk factor for cardiovascular disease, particularly for stroke but also for myocardial infarction and peripheral vascular disease (115). Diabetes is associated with increased frequency of raised blood pressure, which is not related entirely to the presence of kidney disease (116).

The first suggestion that there is a relationship between insulin and hypertension came from a study from London published in 1966 (37). Hypertensive patients had higher insulin levels in the fasting state and 30, 60, and 120 min after a 50-g OGTT than normotensive control subjects. The hyperinsulinemia was not related to age or therapy for hypertension (37). No further attention was paid to insulin-hypertension relationships for many years, but in the last decade, several new reports have appeared. These have included population surveys and studies of normotensive, hypertensive, diabetic, and obese subjects.

A population study of cardiovascular disease in Denmark showed a positive relationship between serum insulin and diastolic blood pressure, which was statistically significant but not of a high order (117). The Israel study of glucose intolerance, obesity, and hypertension, a longitudinal study of 5711 people, addressed the relationship of hypertension and insulin levels (118). In a subgroup of 2475 subjects, there was a highly significant association between hypertension and glucose intolerance independent of the effects of age, sex, obesity, and antihypertensive medications. Eighty-three percent of the hypertensive subjects were either glucose intolerant or obese. In another subgroup of 1241 subjects, fasting and postglucose insulin levels were significantly elevated in those with hypertension independent of obesity, glucose intolerance, age, and antihypertensive medication. The highest insulin levels were found in those who had a combination of hypertension, obesity, and abnormal glucose tolerance. Insulin resistance and hyperinsulinemia were present in most of the hypertensive subjects.

In a small study of 8 hypertensive subjects compared with 20 healthy control subjects, all with normal glucose tolerance, fasting insulin levels were unchanged in the hypertensive group, but the insulin responses 30, 60, and 120 min after a 75-g glucose tolerance test were significantly elevated. Diurnal profiles of insulin were
much higher in the postprandial state in hypertensive subjects than in control subjects (119).

Another study of the relationship of insulin to hypertension took place in war-injured bilateral above-knee amputees, a group at very high risk of cardiovascular disease (120). In 19 amputees, insulin responses to oral glucose were greatly increased compared with 12 age-matched control subjects. The insulin response was strongly and independently correlated with diastolic blood pressure, which was also correlated with percentage of body fat.

In a group of normotensive nondiabetic men and women, fasting insulin levels were significantly correlated with systolic and diastolic blood pressure, which were within the normal range. These remained significant when age and body weight were taken into account (121).

In 194 patients with impaired glucose tolerance in the Joslin Clinic, both fasting and postglucose insulin levels were closely related to the level of blood pressure (122). Sex, age, and glucose levels were not associated with hypertension, and differences in insulin persisted after correction for body weight. The relationship with insulin was closer for diastolic than systolic blood pressure and was most pronounced in those who were obese and hypertensive.

Obesity is often associated with raised blood pressure, and several studies have attempted to relate this association to hyperinsulinemia. Thirty-three very obese women who were neither diabetic nor hypertensive showed a significant positive correlation between fasting serum insulin and systolic and diastolic blood pressure (123). Insulin levels were slightly higher in those who had a positive family history of hypertension. The correlations between insulin and systolic and diastolic blood pressure remained significant when age, BMI, and serum glucose were controlled.

A contrary view came from a cross-sectional study of 2144 healthy middle-aged men not treated for hypertension or diabetes who were examined in the second Paris prospective study (124). Blood pressure was more strongly correlated with plasma glucose than with plasma insulin, and there was no relationship between insulin and blood pressure in subjects who were not overweight. The association between obesity and blood pressure was largely independent of plasma glucose and insulin, although simultaneous elevation of body weight, plasma glucose, and insulin was strongly associated with blood pressure. Plasma insulin was positively related to plasma triglycerides and negatively related to HDL-chol independent of plasma glucose and body weight.

In a study of people with newly diagnosed NIDDM, hyperinsulinemia was correlated with elevated blood pressure in diabetic and nondiabetic subjects, and the associations between insulin and blood pressure were independent of the effect of obesity (125). Eighteen obese hypertensive patients had similar fasting plasma insulin levels but higher 1- and 2-h postglucose insulin levels than 17 obese normotensive subjects (126). In the hypertensive group, there was a strong positive correlation between systolic blood pressure and the 2-h plasma insulin value. The glucose and insulin areas were significantly correlated with systolic blood pressure in a multiple regression model, and the degree of obesity and the 2-h plasma insulin value together explained ~65% of the variation in systolic blood pressure in the hypertensive group. The correlation between 2-h plasma insulin levels and diastolic blood pressure was not statistically significant.

In another approach to studying the relationship between insulin and hypertension, 50 obese adolescents were studied before and after weight loss achieved by diet with or without exercise. Compared with 10 nonobese adolescents of the same age, the obese subjects had higher systolic and diastolic blood pressure and higher fasting insulin levels and responses to a glucose load. After weight loss, blood pressure and insulin levels decreased, and there were significant correlations between the changes in insulin levels and the changes in blood pressure (127).

A study of obese hypertensive subjects, although finding a correlation between fasting serum insulin and mean arterial blood pressure, found that the relationship was eliminated if measures of body weight and body fat were taken into account. It was suggested that the relationship between serum insulin and blood pressure is indirect and is largely accounted for by a mutual association with body composition and fat distribution (128,129).

Confounding factors in the relationship between insulin and blood pressure are the frequent presence of glucose intolerance and obesity and the fact that age is also related to both insulin and blood pressure levels. A study that attempted to control for these different factors in a population of subjects in apparent good health found a significant correlation between diastolic blood pressure and plasma insulin levels after a glucose load (130). The relationship was independent of age and body weight. However, when obese and nonobese subjects were examined separately, the relationship only occurred in the nonobese subjects, in whom there was a significant relationship between postglucose plasma insulin and systolic and diastolic blood pressure. Similarly, when the subjects were divided into those who had high insulin responses and those with normal insulin responses, in the nonobese subjects, systolic and diastolic blood pressure was higher in the hyperinsulinemic subjects, but the levels were no different in the obese subjects.

Familial dyslipidemic hypertension is a recently described syndrome in which patients with familial hypertension have one or more of the following: high plasma triglycerides, high LDL-chol, or low HDL-chol (131). In some of these subjects, the lipid disorder has the characteristics of familial combined hyperlipidemia, and in these, increased fasting plasma insulin levels have been found after adjustment for BMI (132). Other subjects were obese and had high triglyceride and in-
Insulin levels and low HDL-chol levels. This syndrome provides another example of elevated insulin levels being associated with dyslipidemia, obesity, and hypertension.

In a study of young men with untreated essential hypertension who were neither obese nor diabetic, insulin-induced glucose uptake was markedly impaired (133). The insulin resistance involved glucose but not lipid metabolism and was located in the peripheral tissues and not in the liver. A group of Chinese men with hypertension, whether treated or untreated, had significantly elevated plasma glucose and insulin responses to an oral glucose load compared with healthy men irrespective of whether they were receiving antihypertensive treatment (134). Insulin-stimulated glucose uptake was diminished in the hypertensive men. In contrast, another study with different techniques found hyperinsulinemia and insulin resistance only in people who had both hypertension and NIDDM (135). Because serum C-peptide levels were the same in the normotensive and hypertensive diabetic subjects, it was inferred that the hyperinsulinemia was related to impaired hepatic extraction of insulin rather than to increased insulin secretion rates.

There are several possible mechanisms by which insulin might be causally related to hypertension (136). These include an effect of insulin on renal sodium reabsorption (137) and enhanced sympathetic nervous system activity in hyperinsulinemic states (138,139), although this may not entirely explain raised blood pressure in obesity (140).

Antihypertensive drugs may also cause increased insulin secretion, increased blood glucose and plasma triglyceride levels, and reduced HDL levels (141,142). It has been suggested that these metabolic changes may explain the fact that treatment of hypertension has little effect on the incidence of myocardial infarction. It is clear, however, that insulin resistance and hyperinsulinemia also occur in untreated hypertension and hence may contribute to the development of atherosclerosis in hypertensive people.

Summary. Insulin and blood pressure are closely related in normotensive and hypertensive people. Although obesity and diabetes are often found in people with hypertension, hyperinsulinemia also occurs in nonobese, nondiabetic hypertensive people.

Multiple risk factors. Hyperinsulinemia is associated with individual cardiovascular risk factors such as dyslipoproteinemia and hypertension but is also found in people with combinations of risk factors.

A survey of cardiovascular risk factors in 732 factory workers studied the relationship of serum insulin levels with plasma lipid levels and blood pressure in 32 subjects defined as having hyperinsulinemia (i.e., serum insulin >2SD above the mean) and compared these with 32 noninsulinemic subjects matched for age, sex, and BMI (143). The two groups had similar patterns of smoking, alcohol consumption, and physical exercise. Plasma triglyceride concentrations were significantly higher and HDL-chol levels lower in the hyperinsulinemic subjects, but plasma total cholesterol concentrations were not significantly different. Systolic and diastolic blood pressure was also higher in the subjects with normal glucose tolerance who were hyperinsulinemic. By multiple regression analysis, the plasma insulin response was independently associated with systolic and diastolic blood pressure and plasma triglyceride and was negatively associated with HDL-chol concentrations. Thus, patients with hyperinsulinemia and normal glucose tolerance, who are presumably insulin resistant, have a cluster of risk factors for atherosclerosis and possibly a common metabolic basis for these.

Similar interrelationships have been found in children (144). The Bogalusa heart study of 2856 children showed positive relationships between insulin and systolic and diastolic blood pressure and triglyceride and VLDL levels and an inverse relationship with HDL-chol. Similar relationships were found between glucose and the other risk factors, and glucose and insulin were significantly related. Partial correlation coefficients where adjustment was made for age and weight confirmed significant relationships between insulin and lipids but not blood pressure. It seems, therefore, that even in children, insulin and glucose correlate with other cardiovascular risk factors.

The Bogalusa heart study also addressed the question of clustering of cardiovascular risk factors (145). Lipid measurements, in this case the ratio of LDL- and VLDL-chol to HDL-chol, systolic blood pressure, and insulin, formed a cluster of risk factors, which were closely related to subscapular skin-fold thickness. More obese subjects showed greater clustering of risk factors than lean subjects, and truncal fat deposition had a greater impact on clustering for those with the higher rather than lower levels of risk factors. The highest insulin levels were found in those who were not obese, and insulin levels increased from normal to borderline as glucose tolerance became impaired.

Obesity is often a common feature of abnormal carbohydrate and lipid metabolism. In the San Antonio Heart Study, in both men and women, the glucose and insulin responses to an oral glucose load and measurements of weight and body fat distribution were positively related to triglyceride and negatively related to total HDL- and HDL2-chol levels (146). Insulin levels were also associated with total cholesterol and LDL-chol levels and with systolic and diastolic blood pressure in men but not in women, whereas glucose levels were positively associated with these variables in both men and women. Both hyperinsulinemia and overall obesity were independently associated with increased triglyceride levels and elevated blood pressure, and the findings suggest that the effect of body fat distribution and obesity on serum triglyceride levels and diastolic blood pressure may be mediated by increased glucose and insulin concentrations. In contrast, the relationship between adi-
Further clues to the relationship of coronary heart disease in men and women have come from studies of sex hormones in populations. In the San Antonio Heart Study, SHBG was negatively correlated with fasting insulin and insulin and glucose responses to an OGGT (152). The proportions of free estradiol and free testosterone were positively correlated with the same glucose and insulin variables. When partial correlation coefficients were calculated while controlling for obesity, free testosterone was positively associated with fasting and postglucose insulin levels, and SHBG remained significantly negatively correlated with insulin. The correlations of the percentages of free testosterone and free estradiol with insulin and glucose are similar to those with SHBG but are opposite in sign. Thus, in this group of premenopausal women, decreased levels of SHBG, and therefore increased free sex-hormone levels, were associated with increased glucose and insulin concentrations. In elderly men, serum testosterone and fasting insulin are strongly correlated (153).

It has been reported that men with premature myocardial infarction have evidence of feminization and that they have an increased ratio of estradiol to testosterone (E-T) (154). These findings have not been confirmed in all studies and in particular have not been found in patients with stroke (155). It has also been reported that there is a correlation between the E-T ratio and the insulin response to an OGGT (156). Estradiol levels are higher in patients with diabetes than control subjects; testosterone levels are the same, but the E-T ratio is higher in diabetes (157). Men who take regular physical exercise have lower glucose, insulin, and E-T ratio than those who are more sedentary (158). Testosterone levels have also been found to be low in men with diabetic ketoacidosis as in other acute illnesses; therefore, this abnormality may not be specific to carbohydrate abnormalities (159).

The role of insulin and sex hormones in coronary heart disease in diabetic and nondiabetic subjects was the topic of a workshop sponsored by the National Heart, Lung, and Blood Institute (160). There are methodological problems in assessing both hormone levels and hormone actions. Interrelationships between insulin, obesity, physical activity, blood pressure, and lipoproteins are complex and incompletely understood. Upper-body obesity, with its concomitants of hyperinsulinemia and increased androgenization, appears to be related to the risk of coronary disease, but whether genetic or environmental influences on body fat distribution are more important is unknown. Sex is one of the most important risk factors for coronary heart disease, but its role remains unexplained.

Summary. The sex differences in ischemic heart disease incidence and their absence in diabetes are intriguing and deserve much more investigation. There is a possibility that insulin has a role in these differences, but further work is required for its clarification.

Other risk factors. Some other associations with car-
diovascular disease are also associated with hyperinsulinemia. For example, those who exhibit type A behavior, described as “characterized by certain personality attributes and behavioral mannerisms suggestive of the presence of an excessive and incessant struggle against the exigencies of time or against the competitive efforts of other persons” are said to have increased risk of cardiovascular disease. Type A behavior is also associated with a hyperinsulinemic response to glucose challenge (161).

Anticonvulsant drugs, particularly phenytoin, increase HDLs and inhibit insulin secretion. A case-controlled study in Finland showed that mortality from ischemic heart disease was lower in those diagnosed as epileptic than in age- and sex-matched control subjects. This could not be attributed to an increase in the number of deaths from other causes. Those who were taking phenytoin either alone or with other drugs showed decreased mortality from ischemic heart disease in this study (162).

In a Norwegian population, a lipid-lowering diet used for 3 yr in a primary prevention trial of coronary heart disease resulted in lower insulin responses to glucose (163).

Plasminogen activator inhibitor-1 (PAI-1) is a physiological inhibitor of fibrinolysis and is synthesized in the liver and in endothelial cells. In 67 patients with angina pectoris, plasma insulin correlated strongly with PAI-1 activity (164). Thus, hyperinsulinemia, as well as stimulating atherogenesis, may also play a role in the development of myocardial infarction.

Summary. Hyperinsulinemia is associated with cardiovascular risk factors (Table 3). The combination of hyperinsulinemia, hypertension, hypertriglyceridemia, low HDL levels, hyperglycemia, and upper-body adiposity appears to be particularly closely associated with increased risk of cardiovascular disease. A mechanism linking the risk factors listed above with insulin resistance has been suggested and supported with experimental data. Although hyperinsulinemia may be linked to cardiovascular disease by the effects of other cardiovascular risk factors, evidence from prospective population studies that insulin has an independent predictive relationship to coronary heart disease and experimental evidence (to be reviewed) that insulin has biological activities on the arterial wall point to the possibility that insulin has a primary influence on development of atherosclerosis.

**BIOLOGICAL ACTIONS OF INSULIN ON ARTERIES**

**Experimental atherosclerosis.** The earliest evidence that insulin has a role in development of atherosclerosis was indirect and came from studies with dietary-cholesterol-induced arterial lesions in experimental animals (165, 166). Forty years ago, two groups of investigators found that alloxan-induced diabetes (ALX-D) caused increased serum cholesterol levels but decreased arterial lesions in cholesterol-fed rabbits. Animals that had been given ALX and that did not develop diabetes had the same degree of atherosclerosis as the controls, suggesting that the findings were not due to ALX itself. No effect of ALX on regression of arterial lesions was found. It was concluded that hypercholesterolemia is not the sole factor concerned in the genesis of experimental atherosclerosis but that another factor or factors must be essential to the production of the arterial lesions (165,166). Treatment of ALX-D animals with insulin restored the degree of cholesterol deposition in the aorta to that of the controls (167,168). Thus, it appeared that insulin is necessary for the full development of arterial lesions in cholesterol-fed rabbits, although alterations in plasma lipoprotein concentration and composition may also influence atherogenesis in this animal model (169,170).

Many other studies of experimental diabetes and large-vessel disease have been complicated by the fact that the animals were treated with insulin so that the effect of diabetes and the effect of its treatment could not be clearly distinguished.

Chickens have been extensively used for experimental atherosclerosis research and are said to have spontaneous arterial lesions similar to those in humans. In chickens that had developed atherosclerosis as a result of a high-cholesterol diet and were then changed to a low-cholesterol diet, insulin prevented the regression of the arterial lesions that normally occurred after this dietary change. Insulin also inhibited the effect of estrogen in protecting the coronary arteries against diet-induced atherosclerosis (171).

Several experiments have suggested an effect of insulin on atherosclerosis. In cholesterol-fed animals, the relationship between high serum cholesterol levels and arterial lesions is the same in pancreatectomized diabetic and nondiabetic animals, and the diabetic artery has the same susceptibility as the nondiabetic artery to atherogenic stimuli (172). On the other hand, treatment of diabetic animals with insulin reduced serum cholesterol levels but did not decrease the incidence or severity of the vascular lesions as occurred when a comparable reduction of hypercholesterolemia resulted from changes in diet (173). Insulin administration increased

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<th>TABLE 3</th>
<th>Cardiovascular risk factors associated with hyperinsulinemia</th>
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<td>Hypertension</td>
<td>Raised triglycerides</td>
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<tr>
<td>Raised cholesterol (evidence inconsistent)</td>
<td>Decreased high-density lipoprotein</td>
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<tr>
<td>Upper-body obesity</td>
<td>Decreased physical activity</td>
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<tr>
<td>Masculinity</td>
<td>Decreased plasminogen-activator inhibitor</td>
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| Decreased plasminogen-activator inhibitor | Type A personality |

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cholesterol turnover in the aortas of young rats but had no effect on old rats (174). ALX-D monkeys that had been treated with insulin developed hypercholesterolemia and more extensive atherosclerosis than the controls, both taking high-cholesterol diets (175). In rats predisposed to atherosclerosis, induction of ALX-D appeared to cause regression of the lesions (176,177). In cholesterol-fed nondiabetic rabbits, insulin administration led to a reduction in plasma lipids but increased development of arterial lesions; in regression experiments, insulin accelerated the rate of reduction of hypercholesterolemia when the diet was changed to an unsupplemented diet, but the regression of coronary atherosclerosis, which normally occurs with such a dietary change, was prevented by insulin treatment (178).

In dogs, administration of insulin stimulates synthesis of arterial mucopolysaccharides in certain parts of the arterial tree (179,180). In a different approach, insulin was injected into one femoral artery and saline into the other femoral artery in ALX-D dogs. The artery of the insulin-treated limb was compared to the controls and showed thickening of the media and an increase in its cholesterol content after 26–28 wk of treatment (181).

There have only been two experiments that studied the effect of insulin alone on arterial lesions. Chickens were divided into two groups and were fed a normal diet (182,183). One group was injected with ~3 U/day insulin-zinc suspension for 19 wk, and the other group was injected with the vehicle solution, which contained no insulin. The insulin-treated chickens had considerably more extensive stainable lipid in the intima and inner media of their aortas (Fig. 1). There was no correlation between the plasma and aortic lipid levels.

A recent study used rats, a species notoriously resistant to experimental atherosclerosis mainly because they do not develop diet-induced hypercholesterolemia (184). Thirty rats fed a standard diet were injected daily with 20 U/kg of lente insulin for 1 yr, and 20 control rats were treated with saline. At the end of the experiment, there was little difference in body weight and plasma glucose levels between the two groups of rats, but plasma insulin levels 4 h after injection were elevated in the insulin-treated group. Although plasma cholesterol, phospholipid, triglyceride, and free-fatty acid levels were slightly higher in the insulin-treated animals, none of the differences were statistically significant. The aortas of the insulin-treated animals contained significantly more triglyceride and had considerably greater thickening of the intima than those of the control animals. The thickening consisted of collagenous fibers and smooth muscle cells.

Summary. Long-term treatment with insulin results in lipid-containing lesions and arterial wall thickening in experimental animals. Insulin also inhibits regression of diet-induced experimental atherosclerosis, and insulin deficiency inhibits development of arterial lesions. Arterial wall metabolism. Although the major function of arteries is to transmit blood from one part of the body to another, they are not merely inactive conduits but consist of metabolically active tissue that, in its whole extent, is a large metabolic organ. Many early studies suggested that arterial tissue is insensitive to insulin; although experimental diabetes depressed lipid metabolism and decreased uptake of cholesterol into the isolated aorta, insulin added in vitro had no effect on the metabolism of aortas from healthy or diabetic animals (185–190) or cholesterol uptake from plasma into the aortic intima and media (191). The depressive effect of diabetes in vivo on aortic metabolism requires large or prolonged doses of insulin to correct (192). When great care was taken to ensure that any fatty adventitial material was absent from the tissue aortic preparations, insulin added in vitro had no effect on the metabolism of aortas from healthy or diabetic animals (185–190) or cholesterol uptake from plasma into the aortic intima and media (191). The depressive effect of diabetes in vivo on aortic metabolism requires large or prolonged doses of insulin to correct (192). When great care was taken to ensure that any fatty adventitial material was absent from the tissue aortic preparations, insulin added in vitro had no effect on the metabolism of aortas from healthy or diabetic animals (185–190) or cholesterol uptake from plasma into the aortic intima and media (191). The depressive effect of diabetes in vivo on aortic metabolism requires large or prolonged doses of insulin to correct (192).
deficient with streptozocin (STZ) and killed, and the aortas were incubated in vitro. There was a significant positive correlation between uptake of precursors into aortic lipids and serum insulin level in the animal when it was killed (193; Fig. 2). Similarly, when intact rats were injected with insulin, a positive correlation between aortic tissue metabolism and the insulin concentrations at death was found (198).

In the perfused rat aorta, STZ-induced diabetes reduced incorporation of glucose into lipids, but perfusion with insulin did not influence the suppressed metabolism of the media. However, treatment of intact diabetic animals with insulin increased glucose incorporation into lipids to levels higher than those found in nondiabetic rats (199). When the intravascular pressure of the isolated rat aorta perfused in situ was raised to a level similar to that in vivo, perfusion with insulin stimulated the uptake of labeled glucose into aortic lipids, whereas at low perfusion pressures, insulin had no effect on the aortic intima and media (200). This is the first and perhaps only study indicating a relationship between hemodynamic and metabolic effects on the aorta.

Another approach to the study of the effect of insulin on aortic metabolism used injections of insulin, which caused the production of anti-insulin antibodies, impaired glucose tolerance, and elevated plasma free-insulin and C-peptide levels. Aortic triglycerides were elevated and lipogenic enzyme activity increased in the pig aorta (201). In dogs, hyperinsulinemia induced by pancreatic grafts with venous drainage into the iliac vein caused elevated triglyceride levels in arterial smooth muscle cells and increased activity of lipogenic enzymes (202).

As well as stimulating synthesis of lipids, insulin may also inhibit the breakdown of lipids, particularly triglycerides, by inhibiting the effect of a triacylglycerol lipase in the arterial wall (203). The effects of insulin differ in different parts of the aorta and for different lipid fractions (204–207).

**Summary.** Insulin stimulates lipid synthesis in arterial tissue. The effect of insulin is influenced by hemodynamic factors and may be localized to certain parts of the artery.

**Arterial wall cell biology.** Four cell types are important in the pathogenesis of atherosclerosis. Two are cells from the circulation, monocyte macrophages and platelets, and two are cells of the arterial wall, endothelial cells and smooth muscle cells (208). Early changes in the process of atherogenesis include proliferation and migration of smooth muscle cells and infiltration of monocyte macrophages, which become the foam cells of the lesion. Insulin does not appear to have a direct effect on platelet activity, and large-vessel endothelial cells are resistant to the effects of insulin (209), even though they contain insulin receptors (210). The major cells in which insulin activity has been studied are vascular smooth muscle cells and monocyte macrophages.

Insulin in small concentrations causes proliferation of cultured primate (211; Fig. 3), rat (212,213), bovine (214), and human (215) smooth muscle cells, and insulin receptors have been identified in rat (216), bovine (217,218), and human (219) smooth muscle cells. It appears that the receptor for the proliferative effects of insulin is different from the receptor for its metabolic effects, which implies that in states of insulin resistance where the metabolic effects of insulin may be ineffective, the proliferative responses may still occur (217). Pericytes from capillaries, which are similar to smooth muscle cells, also proliferate in response to insulin (Fig. 4). This contrasts with endothelial cells, where those from large vessels are resistant to insulin and those from capillaries proliferate in response to insulin (220). The concentrations of insulin to which smooth muscle cells are sensitive are similar to those found in humans under physiological and pathophysiological conditions.

Cell culture studies are carried out in an artificial environment, and caution must be exercised in extrapolating cell culture data to the human artery. Evidence that the effects of insulin on the proliferation of smooth muscle cells may occur in vivo comes from studies in whole aortas, where it has been found that insulin stimulates DNA synthesis in the rat aorta and causes outgrowth of smooth muscle cells from cultured arterial pieces (221). This process has also been studied by incubating small pieces of intima-media from rat aorta and observing the outgrowth of cells (222). The tissues came from spontaneous autoimmune-diabetic BB/Wor rats, some of which were diabetes resistant, some were di-

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![Fig. 2. Insulin levels and uptake of glucose into aortic lipid in streptozocin-induced diabetic and control rats. Open bar, control; hatched bar, streptozocin (193). *Streptozocin vs. control.](image-url)
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Abnormalities in lipid metabolism may be involved in the pathogenesis of atherosclerosis, and low insulin levels may play a role in the development of atherosclerotic lesions (223) and increasing binding of LDLs to cell membranes of bovine smooth muscle cells (218). Insulin also stimulates LDL binding and inhibits HDL binding in fibroblasts (224).

As well as proliferating, smooth muscle cells migrate from the media to the intima in the early stages of atherogenesis. Insulin alone does not stimulate migration of smooth muscle cells or augment migration of smooth muscle cells induced by platelet-derived growth factor (225,226). However, if cells are pretreated with insulin in physiological concentrations, the migration induced by another chemotactant, 12-HETE, was increased in relation to the concentration of insulin. The stimulatory effect of insulin on migration also increased with duration of insulin treatment. Increasing glucose concentrations augmented the effects of insulin on 12-HETE-induced arterial smooth muscle cell migration (225).

In monocytes, insulin increases the activity of the enzyme in the cholesterol synthetic pathway, 3-hydroxy-3-methylglutaryl-CoA reductase, and stim-

FIG. 3. Effect of physiological concentrations of insulin on proliferation of cultured primate aortic smooth muscle cells. Insulin at dose of 10 μU/ml also caused significant proliferation of aortic smooth muscle cells (211).

FIG. 4. Effect of insulin on DNA synthesis in cultured endothelial and smooth muscle cells. Open bar, control; hatched bar, insulin (0.1 μU/ml serum-free medium; 209).
TABLE 4
Effects of insulin on arterial tissue

<table>
<thead>
<tr>
<th>Effect</th>
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<tbody>
<tr>
<td>Increased formation and decreased regression of lipid lesions</td>
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<tr>
<td>Lipid synthesis in arterial tissue</td>
</tr>
<tr>
<td>Connective tissue synthesis</td>
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<tr>
<td>Proliferation and migration of arterial smooth muscle cells</td>
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<tr>
<td>Sterol synthesis and low-density lipoprotein receptor activity in</td>
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<tr>
<td>arterial smooth muscle cells and monocyte macrophages</td>
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</tbody>
</table>

ulates LDL binding to the cell membrane (227, 228). Monocyte macrophages are the main source of the foam cells of the atherosclerotic lesion, and these actions of insulin may thus contribute to atherogenesis.

Summary. Insulin in physiological concentrations stimulates proliferation and migration of arterial smooth muscle cells. Insulin also stimulates cholesterol synthesis and LDL binding in arterial smooth muscle cells and monocyte macrophages.

The biological actions of insulin on arterial tissue are summarized in Table 4. The multiple effects of insulin provide evidence of a potential direct role for this hormone in the development of atherosclerosis.

CONCLUSIONS

Twenty years ago it was suggested that hyperinsulinemia is linked with atherosclerosis, diabetes, obesity, hyperlipidemia, lack of physical exercise, and hypertension and that the hyperinsulinemia is secondary to an impairment of insulin action on carbohydrate metabolism (1). This concept has been revived and given the name syndrome X (229).

It is interesting to trace the development of the original hypothesis between 1969 and 1989. The role of hypertriglyceridemia as a cardiovascular risk factor has waxed and waned and appears to be waxing again (81). HDL was known in 1969 but was only measured as a byproduct of lipoprotein analysis until its significance in cardiovascular disease was highlighted in 1975 (80). Since then, its relationship with carbohydrate metabolism and hyperinsulinemia has been explored. Hyperinsulinemia in hypertension was described in 1966 (37) but was not explored again until 1979 (117) and has only been seriously considered in recent years. Obesity has also had an uncertain role as a cardiovascular risk factor, but identification of the importance of upper-body adiposity and its relationship with hyperinsulinemia has clarified this (107). Knowledge of insulin resistance was incomplete in 1969, and since then, it has been measured directly. It was known that insulin levels were high in some diabetic subjects, but the concept of hyperinsulinemia in diabetes was unacceptable at that time. Insulin levels have since been found to be elevated in many NIDDM and IDDM patients (60, 68). In 1969, there had been 6 clinical studies showing hyperinsulinemia in patients with ischemic heart disease and 1 population study showing hyperinsulinemia in a population at risk of cardiovascular disease. There have now been >20 clinical studies, 5 population studies, and 3 prospective studies in nondiabetic subjects and 5 clinical studies, 2 prospective studies, and 1 population study in diabetic people. Most of these studies have found an association between hyperinsulinemia and cardiovascular disease.

The fact that hyperinsulinemia has been shown to have an independent predictive correlation with cardiovascular disease and that insulin has biological actions on arterial tissue, lipid metabolism, and renal sodium handling suggests that the primary abnormality may be hyperinsulinemia due to insulin resistance and that dyslipoproteinemia and hypertension may be secondary phenomena. Identification of nondiabetic people with insulin resistance and hyperinsulinemia (143) supports this suggestion.

A diagram can be constructed showing, in simplified form, the interrelationships between hyperinsulinemia and atherosclerosis and its major risk factors (Fig. 5). Such a schema can serve as the basis for further research to confirm or refute the hypothesis that hyperinsulinemia and atherosclerosis are directly related. The hypothesis would be strengthened by evidence that reducing insulin levels prevents cardiovascular disease. However, there are no means of changing insulin levels without bringing into play multiple regulatory and counterregulatory mechanisms, some of which might influence atherogenesis.

The hypothesis provides a theoretical basis for some simple measures for preventing atherosclerosis (6). Regular physical exercise and avoidance of obesity will reduce glucose and insulin levels in healthy people and those with NIDDM. In diabetic patients who require

![DIAGRAM]

FIG. 5. Schema linking hyperinsulinemia with atherosclerosis and some of its major risk factors.
insulin, the aim should be to secure good control of blood glucose with the lowest possible levels of circulating insulin.

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