

## **DIABETES MELLITUS AND THE SURGEON**

The importance of diabetes mellitus as a cause of mortality and morbidity is shown by the 8,253 titles admitted to MEDLARS in the 30 months from January 1, 1983 to June 30, 1985. The disease affects about 1 to 5% of the U.S. population,<sup>49, 145</sup> about 10 million people. According to the 1976 Health Interview Survey, 80% of diabetic patients in the United States are older than 45 years, 57% are women, and 15% are black.<sup>101</sup> Type I (insulin-dependent diabetes) occurs in 20%, and Type II (insulin-independent diabetes or maturity-onset diabetes) affects 80% of the diabetic population. Surgeons frequently take care of diabetics either because diabetes is incidental to another disease requiring operation, or because of some complication of diabetes such as occlusive vascular disease, neuropathy, or infection. Approximately 50% of diabetics have at least one, often several, operations during their lifetimes.<sup>122</sup> In one study, 23% of patients were found to have diabetes at the time of admission to hospital for elective or emergency operations.<sup>52, 136</sup> Emergencies comprised 5% of operative procedures and 80% of them were performed for infections.

### **PROBLEMS WITH THE MANAGEMENT OF DIABETIC PATIENTS**

Over the course of 15 to 20 years many diabetic patients develop lesions involving multiple organs. Among these lesions are hypertension, myocardial infarction, cerebrovascular accidents, gangrene of the limb, peripheral and autonomic neuropathy, retinopathy, cataracts, progressive renal failure, and infections. (Ophthalmic problems will not be discussed in this monograph.) Once a patient has developed a major complication of diabetes he or she is likely to have other problems as well. For example, a diabetic with foot problems often has coronary artery disease, retinopathy, and nephropathy.<sup>107, 108</sup> The incidence of coronary artery disease is five to ten times higher in diabetics than in nondiabetics.<sup>102</sup> In diabetics with neuropathy, the incidence of retinopathy is 65 to 90% (increasing with age) compared with 18 to 30% in those without neuropathy.<sup>44</sup> Patients with neuropathy have a 70 to 75% incidence of nephropathy com-

pared with 10 to 45% in those without neuropathy.<sup>44</sup> Vascular lesions in the lower limbs are two or three times more common in diabetics with neuropathy than in those without it.<sup>44</sup> Some authors have reported an increased incidence of cerebrovascular accidents in diabetics<sup>145</sup> (see "Cardiovascular Complications"). The incidence of all complications increases with the duration of the diabetes. The importance of complications at other sites (causing ischemia of the heart, brain, and kidney) is borne out by a significantly decreased life expectancy, irrespective of the age at which diabetes developed.<sup>60, 107, 108</sup> In fact, diabetes with its complications is the third most common cause of death in the United States.<sup>145</sup> Once a leg has had to be amputated, two thirds of patients will be dead within five years.<sup>102</sup>

## RISKS OF OPERATION IN DIABETICS

Preoperatively, the patient needs to be thoroughly evaluated to determine the extent of damage by the disease and to take appropriate preventive measures. Increased mortality and morbidity in diabetics undergoing operation is related mainly to cardiovascular complications, infections, and reduced rates of wound healing.<sup>136</sup> An increased incidence of cardiovascular disease makes myocardial infarction, congestive heart failure, and stroke responsible for more than 50% of deaths of diabetics after operation<sup>52, 172</sup> (see "Cardiovascular Complications"). It is therefore imperative that the surgeon, working together with the anesthesiologist, internist, or diabetologist, make every effort to prevent cardiovascular complications in the peri- and postoperative periods.

Infection is another major cause of mortality and morbidity. During periods of hyperglycemia and ketoacidosis, host defenses against infection are impaired. Hence the importance of adequate control of the blood glucose. In one series, infections of the urinary tract, lower limbs, and lungs contributed to the deaths of 16% of patients.<sup>52</sup>

Neuropathy, particularly involving the autonomic nervous system, may impair vascular responses during and after operation.<sup>105</sup> The surgeon also should be aware of the risks of urinary retention, acute gastric dilatation, and ileus in patients with neuropathy involving the urinary bladder and gastrointestinal tract.

Impaired renal function as a result of nephropathy may make management of fluid and electrolyte balance difficult. Uncorrected hyperglycemia leading to osmotic diuresis and glycosuria may cause severe fluid losses and the development of nonketotic hyperosmolar coma,<sup>135</sup> which may result in vascular thrombosis because of hyperviscosity.<sup>136</sup>

Depending on the magnitude of the operation, the stress associ-

ated with it may adversely affect the patient's metabolic status.<sup>4</sup> Minor operations or well-planned elective procedures cause minimal changes, but profound catabolic alterations may occur after extensive operations, particularly if complicated by hemorrhage and sepsis. In response to stress the neuroendocrine system releases multiple catabolic hormones that profoundly affect metabolism. Increased secretion of catecholamines depresses insulin secretion and suppresses the peripheral action of insulin, leading to reduced insulin sensitivity. Liberation of glucagon causes ketogenesis, gluconeogenesis, and glycogenolysis.<sup>124</sup> Increased secretion of cortisol causes protein breakdown with an increased flow of amino acids to the liver for gluconeogenesis. In addition, cortisol reduces the binding affinities of insulin to its tissue receptors. Increased secretion of growth hormone inhibits glucose uptake by the tissues and stimulates the use of fatty acids and ketones as alternative fuels. All these catabolic hormones also suppress the uptake of branched-chain amino acids by muscle. All the above changes deprive the patient of needed stores of fuel and cause protein wastage that adversely affects wound healing and recovery from the stress of operation. To prevent increased gluconeogenesis and maintain peripheral glucose utilization in diabetics during major operations, it is necessary to administer insulin. The surgeon has to tread the fine line between giving too little insulin on the one hand, with the risks of inducing hyperosmolar nonketotic coma or ketoacidosis, and on the other, giving too much, with the attendant hazard of hypoglycemia. Hypoglycemia may cause serious cerebral dysfunction, impaired cardiac function, pulmonary edema, and death. To avoid these problems one should aim to keep the blood glucose between 120 and 200 mg/dl.<sup>136</sup>

Problems with wound healing, especially in the lower extremities, may occur in diabetics.<sup>69</sup> Multiple factors play a role. Cardiovascular disease (see "Cardiovascular Problems") may hamper compensatory mechanisms following injury and decrease of circulating blood volume. In addition, leukocyte defense and fibroblast function are defective in areas poorly supplied with oxygen because of microvascular disease. Peripheral neuropathy with sensory loss may result in injury due to repeated unperceived trauma to the healing area (see "Diabetic Foot Problems"). Under certain conditions, diabetics are prone to infection (see "Infections in Diabetics"). Insulin deficiency suppresses collagen deposition and may worsen energy deficiency in the wound.<sup>69</sup> Failure of glucose to enter the cell may interfere with anaerobic as well as aerobic metabolism. To meet the challenge of a nonhealing wound in a diabetic patient, the surgeon may have to adjust blood volume, correct anemia, increase arterial PO<sub>2</sub>, administer antibiotics, and apply skin grafts. If local necrosis persists, de-

spite all these measures, there is little alternative to amputation or to operative creation of a new vascular supply to the unhealed area.<sup>69</sup>

## **MANAGEMENT OF DIABETES DURING OPERATION**

### *MINOR SURGERY*

Insulin is not required in Type II patients who are being managed with diet alone or with an oral antidiabetic agent.<sup>136</sup> The latter should be discontinued until after the operation. The blood glucose is monitored before and after operation and regular insulin is given, as described below, if the blood glucose is not controlled preoperatively or if hyperglycemia develops postoperatively.

### *MAJOR ELECTIVE OPERATIONS*

Several protocols are available for the administration of insulin.<sup>131, 136, 175</sup> One method is used for the patient whose blood glucose is under control with long-acting insulin therapy and in whom an uncomplicated course is expected. On the day of operation the patient is started on 5% dextrose solution intravenously (IV) and is given half the usual insulin dose (both NPH and regular) subcutaneously. Postoperatively, the remainder of the usual dose is given. If the postoperative blood glucose is below 140 mg/dl, the dose is reduced by half. On the day after operation, the usual dose of insulin is given in the morning before breakfast or while continuing the IV glucose infusion. A modification of this approach is to use small doses of regular insulin subcutaneously during the postoperative period altering dosage according to the blood glucose level. Patients who have been treated with single daily injections of long-acting insulin, but who are not under control before operation, should be switched to a regular insulin regimen.

Intravenous regular insulin is frequently used in Type I or Type II patients who require major operations.<sup>131, 136</sup> Type I patients are stabilized preoperatively on NPH or Lente insulin, and regular insulin is given twice a day. In Type II patients, oral antidiabetic agents are stopped one day before operation if the blood glucose level is less than 120 mg/dl. The operation is scheduled for the morning if possible. If not, breakfast is replaced with a dextrose-insulin infusion that is continued throughout the day. All IV fluids contain 5% dextrose whether in water, or in half normal or normal saline. If fluid restriction is desirable, 1 or 2 L of 5% dextrose are replaced with 500 ml of 10% dextrose solution.<sup>136</sup> Insulin absorption by the delivery system can be avoided by using plastic containers, high concentra-

tions of insulin, prior flushing of the system with 50 ml of a mixture of insulin and glucose, and avoidance of filters in the IV line.<sup>131, 136</sup> The amount of insulin added to each liter of 5% dextrose ranges from 6 to 20 units.<sup>136</sup> Six to twelve units are added in patients whose daily insulin requirements are 20 to 40 units, 15 units for those who usually receive 50 to 80 units daily, and 20 units for those with higher insulin requirements. These doses are ordered for each of 3 L of 5% dextrose solution given during the day of operation. Each infusion should also have 20 to 40 mEq of potassium chloride.

Another method of administering insulin and glucose IV utilizes two infusion pumps.<sup>131, 175</sup> One delivers 5% dextrose in Ringer's lactate at 2 ml/kg/hour, while the other infuses insulin from a plastic bag containing 250 ml of normal saline and 50 units of U-100 regular insulin. The blood glucose level determines the rate of insulin infusion. No insulin is given for levels below 80 mg/dl, and 20 units/hour are given for levels greater than 200 mg/dl. The operation is not started until the level is below 200 mg/dl. Greater amounts of insulin will be required to keep the blood glucose below this level in emergency operations or in operations complicated by infection. In extreme cases bolus injection of 0.1 to 0.4 units/kg may be needed as an additive.

Irrespective of the method of insulin administration 5e blood glucose should be monitored intraoperatively during long operations, and postoperatively, in the recovery room, and then every four to six hours to determine requirements for additional insulin or additional glucose, depending on whether hyper- or hypoglycemia develops.<sup>136</sup> If the blood glucose is below 120 mg/dl, the concentration of IV insulin must be reduced. If hyperglycemia is present one may increase the amount of insulin in the IV infusion, or, an additional six units may be given subcutaneously for a blood glucose level above 250 mg/dl, or 8 to 10 units for a level above 350 mg/dl.<sup>136</sup> Intravenous glucose and electrolyte solutions may be required for several days after operation until oral feeding can be resumed and the patient can be returned to the preoperative usual daily dose of insulin.

Should the patient's surgical condition require IV hyperalimentation this should be used in much the same way as in the nondiabetic patient.<sup>136</sup> Regular insulin is added to the hyperalimentation solution in a dose of 15 to 20 units/L, and may be supplemented by subcutaneous injections of regular insulin if the blood glucose rises above 250 mg/dl. The dose of insulin in the hyperalimentation fluid may be raised to 30 units/L or more if hyperglycemia persists, the decision being made on four to six hourly blood glucose determinations. One should avoid using filters in the IV line as insulin is lost in them by absorption.

## **EMERGENCY SURGERY IN PATIENTS WITH KETOACIDOSIS**

Diabetic patients with severe sepsis, acute gangrenous cholecystitis, perforated diverticulitis, and other surgical emergencies often develop hyperglycemia, hypokalemia, dehydration, and ketonemia, which may progress rapidly to ketoacidosis.<sup>136</sup> Emergency blood levels are obtained of glucose, ketones, electrolytes, arterial blood gases and pH, blood urea nitrogen (BUN), creatinine, and blood cell counts. Treatment commences with the rapid infusion of normal saline, giving 1 L in 90 minutes and 500 ml/hour thereafter. An IV bolus of 10 to 20 units of regular insulin is given together with a continuous IV infusion of normal saline containing regular insulin (50 units per 500 ml of saline) delivering 100 ml/hour or 10 units/hour of insulin. Hypokalemia is corrected by giving potassium chloride alternating with buffered phosphate. Sodium bicarbonate should be given for severe acidosis. A Swan-Ganz catheter should be placed to monitor circulatory hemodynamics.

Four hours of the above treatment should suppress ketogenesis and partially correct hyperglycemia.<sup>136</sup> The blood glucose level should decline by 80 to 100 mg/dl/hour. In the presence of sepsis the insulin dose required to produce such a fall averages 10 to 30 units/hour. Blood glucose and electrolyte measurements are performed every two hours to determine the need for additional insulin and potassium administration. When the blood glucose level declines to 250 to 300 mg/dl, saline solution should be replaced with 5% dextrose in half- or full-strength saline. Operation should be undertaken after a period of three to five hours for fluid and electrolyte replacement and insulin therapy. One cannot afford to wait longer fully to correct the ketoacidosis, as the underlying surgical problem that caused it will continue to progress and a vicious circle will develop. During operation insulin and fluids are continued, the amounts being determined by periodic checks of the blood glucose, electrolytes, and arterial blood gases. Subsequent treatment with IV insulin in dextrose solution is continued as described under "Major Elective Surgery." In the postoperative period the patient can be stabilized on combined NPH and regular insulin.

## **CARDIOVASCULAR COMPLICATIONS OF DIABETES**

Vascular disease is the most important cause of mortality and morbidity in diabetics.<sup>82</sup> It may cause large, small, and microvessel disease, that is, macroangiopathy, arteriolar disease, and microangiopathy. Diabetic nephropathy and retinopathy are caused by microangiopathy. Disease of the large and small vessels causes myocardial infarction, stroke, and gangrene of the lower limbs.

Several factors contribute to the development of large and/or small

vessel disease in diabetics. Hyperglycemia may impair cellular function by the intracellular accumulation of sorbitol, or by excessive nonenzymatic glucosylation of various proteins, causing high levels of hemoglobin A<sub>1c</sub>, which has an unusually high affinity for oxygen, and contributes to tissue hypoxia.<sup>33, 173</sup> Smoking results in a further shift to the left of the oxyhemoglobin dissociation curve, and also contributes to the increased incidence of atherosclerosis. Diabetics who smoke have a significantly greater risk of developing vascular lesions than those who do not.<sup>38</sup> Glucosylation of collagen may contribute to the development of vascular lesions.<sup>130</sup> Poor diabetic control is associated with high plasma levels of low density or very low density lipoproteins, which are rich in cholesterol and triglycerides.<sup>33, 142</sup> Hypertension, another risk factor for atherosclerosis, is increased in diabetics.<sup>33</sup> Increasing attention is being paid to abnormalities of blood clotting in the pathogenesis of vascular problems in diabetics. An "increased thrombotic tendency" has been described with elevated levels of coagulation factors VII, X, Von Willebrand factor and fibrinogen, increased platelet adhesiveness, increased platelet aggregation, and decreased fibrinolytic activity.<sup>33, 51</sup> The circulation is further impaired by elevated plasma viscosity and increased erythrocyte aggregation.<sup>33</sup> Other risk factors for vascular disease include the frequent occurrence of obesity in diabetics, immunologic injuries to the vessels, and possible genetic predisposition to vascular disease.<sup>33, 145</sup>

#### *PERIPHERAL VASCULAR DISEASE*

Atherosclerosis has a higher incidence in diabetics, occurs at an earlier age, is more rapidly progressive, and has a more serious prognosis than in nondiabetics.<sup>11, 63, 102, 107, 108, 145</sup> Approximately 50% of patients have evidence of peripheral arterial disease ten to 15 years after the onset of diabetes.<sup>16</sup> The distribution of the lesions is different in diabetics than in nondiabetics in that the more peripheral and smaller vessels tend to be involved, including the small arteries, arterioles, and capillaries.<sup>43, 107, 108, 145</sup> The aorta and iliac vessels are relatively infrequently affected, whereas severe disease occurs in the profunda femoris, distal superficial femoral, popliteal and tibial vessels (Fig 1A and B). The higher incidence of more severe lesions of the profunda femoris in diabetic patients may account, in part, for the poorer prognosis of their arterial disease.<sup>63</sup>

Whereas the occlusive process frequently involves a single segment of an artery in the nondiabetic, atherosclerosis tends to be multisegmental in the diabetic.<sup>63</sup> In one study two of the three leg arteries were occluded in 69% of diabetics compared with 35% of nondiabetics.<sup>63</sup> In addition, the frequent occlusions of the popliteal and tibial arteries in diabetics means that a good runoff is three



**FIG 1.**  
**A**, diabetic patient with mild atherosclerosis of femoral arteries. **B**, same patient with occlusions of popliteal and tibial vessels on right side.  
**C**, same patient after arterial bypass. (Courtesy of Dr. Richard Fowl, University of Cincinnati.)

times less frequent than in nondiabetics. These findings explain why reconstructive arterial surgery is less commonly possible in diabetics than in nondiabetics.<sup>63</sup> Occlusive lesions are also frequent in the large vessels of the foot, the dorsalis pedis, the pedal arch, and the metatarsal arteries. In one study, significant occlusions were found in 60% of the metatarsal arteries of diabetics compared with 21% in nondiabetics.<sup>48</sup> In addition, the digital arteries showed occlusions in 19% of diabetics compared with 10% of nondiabetics. Calcification adjacent to the internal elastic lamina is common in the medium-sized and small arteries, including the tibial arteries, the pedal arch, the metatarsal arteries, and the proximal portions of the digital arteries.<sup>48</sup> Forty percent of diabetic patients who have no pedal pulses and gangrenous lesions of the foot still have a palpable popliteal pulse, indicating patency of the aorta, iliac, and femoral arteries. This finding is rarely encountered in nondiabetics in whom gangrene is almost invariably associated with occlusion of the arteries at or above the level of the knee.<sup>102</sup>

Depending on the severity of arterial insufficiency, patients may present with intermittent claudication, rest pain, ischemic ulceration, or gangrene. In one study of 332 patients who presented with rest pain, ulceration, or gangrene, 75% of diabetic patients had ulceration or gangrene compared with 41% of nondiabetics.<sup>144</sup> Ischemic ulcers must be differentiated from neuropathic ulcers, as the prognosis and therapy of the two conditions are different.<sup>107, 108</sup> Patients with ischemic ulcers often have a history of progressive intermittent claudication. The ulcers are extremely painful and usually occur on the toes. In contrast, neuropathic ulcers are painless and are found on the ball of the foot, over the metatarsal heads, or on the plantar aspect of the big toe.<sup>145</sup>

Whether all vascular lesions in diabetics are caused by atherosclerosis or whether the small vessel disease may represent a specific diabetic disorder is a subject of controversy. Some investigators failed to detect any specific small vessel disease peculiar to diabetes.<sup>148</sup> LoGerfo and Coffman<sup>89</sup> collected data from light microscopy, vascular casting, and physiologic studies to support the view that there is a widespread misconception about the existence of occlusive microvascular disease in diabetics, but suggest that there may be functional abnormalities of the diabetic microcirculation.<sup>89</sup> However, small vessel disease is known to occur in the retina (diabetic retinopathy) and in the glomeruli (diabetic nephrosclerosis), and similar lesions are believed to occur in small vessels of virtually all tissues, including those of the feet and toes.<sup>174</sup> This microangiopathy consists of intimal thickening involving mainly the basement membrane. It is present in 88% of diabetics as compared with 23% of nondiabetics. It has a patchy distribution, normal segments of vessels separating diseased areas. Basement membrane thickening is

more pronounced in the more distal vessels of the extremity, possibly indicating that venous hydrostatic pressure may play a role in its development.<sup>82</sup> The basement membrane thickening tends to increase with the duration of diabetes, suggesting that hyperglycemia may be etiologically significant.<sup>174</sup> However, basement membrane thickening is not related to the severity of the diabetes nor to its regulation, and occurs in both Type I and II diabetes. Some investigators believe that the intimal thickening may occlude the lumen,<sup>58</sup> but other workers dispute this conclusion.<sup>9, 48, 61, 132</sup> Other suggestions are that the basement membrane thickening interferes with the diffusion of nutrients through the vessel wall and hampers the migration of leukocytes into areas of infection.<sup>9</sup>

A factor that may aggravate arterial insufficiency is edema of the lower limbs, caused by congestive heart failure or venous insufficiency.<sup>160</sup> Edema causes increased tissue pressure with impairment of the collateral circulation. In addition, edema secondary to heart failure is accompanied by decreased cardiac output, which is more harmful in an ischemic limb than in other areas. In 66% of 247 diabetic patients who developed gangrene, there was a close temporal relationship between the development of edema and the appearance of gangrene.<sup>88</sup>

When using noninvasive vascular studies to evaluate the arterial blood supply in the lower limbs of diabetics, erroneously high segmental pressure readings may be obtained, as the vessels are difficult to compress because of increased arterial stiffness or calcification.<sup>10, 13, 17</sup> The analogue wave form of the Doppler signal may confirm that the pressure measurements are inaccurate. All other factors being equal, the pressure necessary for healing in diabetics is higher than in nondiabetics.<sup>160</sup> In part, this is due to the aggregate effect of occlusive disease of both large and small arteries, which causes greater resistance and less blood flow at any given pressure.<sup>154</sup> For example, Raines et al.<sup>117</sup> found that healing was likely in nondiabetics at ankle pressures greater than 65 mm Hg, whereas pressures more than 90 mm Hg were necessary in diabetics. However, reliance on ankle pressures alone fails to consider patency of the pedal arch and digital arteries. Thus, if forefoot plethysmography demonstrates pulsatile metatarsal vessels, the chances of healing are 90%.<sup>117</sup> However, absent or weak pulsations may be misleading in diabetics. In one study, forefoot plethysmography predicted failure in 50% of diabetics whose amputations healed at that level.<sup>54</sup> As the digital arteries of diabetics are much less likely to be calcified than the more proximal vessels, measurement of digital pressures should be attempted.<sup>160</sup> In one study, all lesions healed when these pressures exceeded 30 mm Hg in nondiabetics, whereas in diabetics 94% healed if pressures exceeded 55 mm Hg.<sup>24</sup> Other investigators mentioned healing with much lower pressures provided they were

higher than 25 mm Hg.<sup>10</sup> At times, application of a toe cuff for pressure measurements may not be possible because of lesions of the toe, the webspace, or distal forefoot. The above studies emphasize the need to consider the noninvasive vascular findings together with clinical observations before making decisions regarding treatment of vascular problems in diabetics.

In contrast with nondiabetics, far fewer diabetic patients undergo reconstructive vascular procedures because the centrifugal distribution of their disease frequently precludes these operations.<sup>144</sup> For example, in a study of 332 patients with lower extremity ulceration or gangrene, only 14% of diabetic patients had reconstructive vascular operations compared with 43% of nondiabetics.<sup>144</sup> Before undertaking operation, detailed arteriography is essential. In addition to an aortoiliofemoral arteriogram one must visualize all arteries down to, and including, the dorsalis pedis and the plantar arch.<sup>7, 145</sup> In suitable candidates, vascular reconstruction has drastically altered the prognosis of diabetic foot problems. Many patients who would have had above-knee amputations in the past now have vascular reconstructions followed by major or minor debridements.<sup>103</sup> These are individuals with ulceration or gangrene associated with low-grade infection. One must emphasize that bypass grafting, even with autogenous saphenous vein, is contraindicated in the presence of active infection because of the danger of infecting the graft.<sup>160</sup> One prefers a primary amputation under such circumstances. If vascular grafting is feasible I usually do not perform debridement at the same time, but several days later. In those patients with lesions suitable for arterial reconstruction the type of operation performed is no different from that in nondiabetics. In one study, approximately two thirds of each group required femoropopliteotibial bypass procedures.<sup>144</sup>

#### ***Illustrative Case Report***

A 66-year-old man with a long history of diabetes and tobacco use presented with a gangrenous ulcer of the right heel. There was a palpable femoral pulse but absent distal pulses. An arteriogram showed mild atherosclerosis of the femoral arteries (see Fig 1,A) and marked atherosclerosis and occlusions of the popliteal and tibial vessels, especially on the right side (see Fig 1,B). The pulse volume recording demonstrated a flat transmetatarsal tracing. After conservative management the ulcer did not heal. It was thought that arterial reconstruction was indicated. A right femoral-anterior tibial bypass using *in situ* saphenous vein was performed (see Fig 1,C). Postoperatively, the patient's ulcer is healing.

At times diabetes may be associated with a higher operative mortality after reconstructive arterial surgery.<sup>146</sup> We must bear in mind that a patent bypass graft does not ensure limb salvage. All vascular surgeons have had the frustrating experience of having to perform a

major amputation in the presence of a patent femoropopliteal graft in a diabetic patient, because blood flow failed to improve in the presence of significant distal small vessel disease. In general, vascular reconstruction of the leg has a good prognosis if there is inflow to the pedal vascular arches.<sup>36</sup> However, several surgeons have had successful outcomes in patients who failed to show a pedal arch on arteriography.<sup>7</sup> Long-term femoropopliteal graft patency rates and symptomatic improvement in diabetic patients have been similar<sup>7,146</sup> to or even better than those obtained in nondiabetics.<sup>70</sup> Follow-up studies of up to ten years indicate that revascularization procedures in diabetics are durable and should be undertaken if technically feasible.<sup>70,119</sup>

The importance of attempting to salvage an ischemic lower extremity in a diabetic is emphasized by the presence of occlusive disease in the contralateral limb that soon may threaten its viability. Fifty percent of diabetics who undergo a unilateral amputation develop ischemic problems on the opposite side within two years.<sup>59</sup>

In patients who are not suitable candidates for vascular reconstruction one may consider performing a lumbar sympathectomy, but the procedure may be of little help because associated neuropathy frequently has already caused an "autosympathectomy."<sup>107,108</sup> Successful five-year results after lumbar sympathectomy were obtained in only 19% of diabetics compared with 51% of nondiabetics.<sup>37</sup> In contrast, another study showed that 30% of diabetics in whom sympathectomies were done as "last ditch" procedures had significant improvement in skin blood flow and healing of indolent ulcers.<sup>71</sup> The role of sympathectomy remains controversial.

Limb salvage is not possible in many diabetics. In individuals who presented with rest pain, ulceration, or gangrene, 54% required some form of amputation compared with 16% in nondiabetics.<sup>144</sup> Amputation in diabetics is discussed in the section entitled "Diabetic Foot Disorders."

## CORONARY ARTERY DISEASE

Diabetes is a well-established risk factor for coronary artery disease (CAD). In various series it was from 1.2 to 6.6 times more frequent in diabetics than in nondiabetics.<sup>46</sup> Autopsy studies show CAD in 45% to 70% of diabetic patients compared with 8% to 30% in nondiabetics.<sup>81</sup> One study suggests that asymptomatic heart disease is more common in diabetics than in nondiabetics and that it progresses more rapidly.<sup>23</sup> Coronary artery disease is the most common cause of death in Type II diabetes, but also frequently occurs in Type I diabetics. Myocardial infarction (MI) may be the cause of death in as many as 20% of diabetics.<sup>91</sup> Other features in diabetics include a high incidence of congestive heart failure, cardiogenic

shock, myocardial rupture, recurrent MI, and painless infarction (probably related to neuropathy of the cardiac nerves).<sup>46</sup> The extent of the atherosclerotic lesions is greater in diabetics than nondiabetics, as seen in pathologic material and in coronary angiograms.<sup>46, 47</sup> In one angiographic study there was a lower incidence of single-vessel and a higher incidence of multivessel disease in diabetics.<sup>165</sup> While more vessels are affected in diabetics, findings conflict as to whether atherosclerosis is more diffuse within any coronary vessel than in nondiabetics.<sup>46, 165</sup> Some reports indicate that atherosclerotic involvement is greater in the distal portion of the vessels in diabetics, whereas involvement of the proximal segments is more common in nondiabetics. Other studies have not shown these differences.

Diabetes is not per se a reason to avoid operation for severe coronary artery disease as long as the diabetes is under control.<sup>73</sup> In a series of 261 diabetics and 1931 nondiabetics who underwent coronary artery bypass grafting (CABG) between 1972 and 1977, the percentage of patients with relief of angina was the same in both groups.<sup>73</sup> Short- and long-term mortality was higher in the diabetics than in the nondiabetics and hospital stay was longer. Of the diabetics 17.2% had serious postoperative complications, including 7.7% hospital deaths. Higher incidences of sternal<sup>45</sup> and groin wound infections have been reported.<sup>30</sup> Despite the increased mortality and morbidity five-year survival after CABG in diabetics still exceeds survival of any reported series of medically treated diabetics with comparable disease.<sup>73</sup> In a series of 312 patients (including 73 diabetics) who survived simultaneous CABG and carotid endarterectomy, cumulative five-year survival rates were 69% for diabetics and 87% for nondiabetics ( $P < .025$ ).<sup>66</sup>

#### CEREBROVASCULAR DISEASE

Complications of Type I diabetes are so severe that few patients survive long enough to develop carotid artery disease.<sup>23</sup> Those that do, develop it at a younger age (50.5 years) than other diabetics and nondiabetics (63 years).<sup>23</sup> Type II diabetes is a strong risk factor for carotid arterial disease, stroke, or both.<sup>78, 170</sup> In a prospective study utilizing Duplex scanning to followup 162 asymptomatic patients with cervical bruits, 19 (12%) were diabetic. Progression of disease was more frequent (58%) in the diabetic group than in the nondiabetics (35%,  $P = .04$ ).<sup>121</sup> Progression was particularly common in patients less than 65 years old. In another study of 482 diabetics (mean age,  $57 \pm 12$  years), 20% had evidence of carotid artery occlusive disease (CAOD) demonstrated by noninvasive tests using oculoplethysmography and phonoangiography.<sup>78</sup> Those with CAOD had a higher incidence of retinopathy, proteinuria, neuropathy, and more atherosclerosis in the leg arteries. Of 35 diabetics with transient isch-

emic attacks, 20% developed a stroke within one year and 37% within five years.<sup>106</sup> In contrast, in a series of 124 patients (of whom two thirds were diabetic) with hemispheric transient ischemic attacks, none developed a stroke in a follow-up of two to ten years after surgical treatment of their carotid artery disease, demonstrating the efficacy of carotid endarterectomy in preventing stroke.<sup>23</sup> However, these excellent results were tempered by the fact that there was a highly significant increased death rate from MI (55%) among diabetics compared with nondiabetics (25%) among those patients followed up more than four years.

The incidence of stroke is twice as high in diabetics as in the non-diabetic population and three times as high in diabetic women.<sup>75</sup> Major strokes seem to occur after age 60 or 70; however, involvement of small vessels leading to encephalomalacia may be present at a younger age.<sup>83</sup> In a series of 5,479 autopsies of which 677 patients were diabetic, the brain weights were less and encephalomalacia was greater in diabetics than in nondiabetics.<sup>6</sup> Factors other than extracranial carotid disease may be responsible for some irreversible strokes, including proliferative changes in the intracranial vessels causing local thrombosis; increased platelet adhesiveness in diabetics causing irreversible platelet plugs following temporary cerebral ischemia; and hyperglycemia, which may hamper the recovery of cerebral function following temporary ischemia, through the production of lactic acid or by causing an increase in cerebral edema.<sup>170</sup>

#### VASCULAR ACCESS FOR HEMODIALYSIS

Increasing numbers of patients with end-stage renal disease caused by diabetic nephropathy are being treated with hemodialysis. Problems arise in creating arteriovenous fistulas at the wrist because suitable vessels are often absent due to previous IV therapy and advanced atherosclerosis of the forearm arteries. Suggestive evidence of the latter includes digital ischemic skin changes, an incompressible radial pulse, or radiographs of the forearm showing extensive vessel calcification.<sup>2</sup> In one study,<sup>2</sup> radiocephalic arteriovenous fistulas were successful on the first attempt in only 30 of 50 diabetics in contrast to 98 of 110 nondiabetics ( $P < .001$ ). In diabetics only 49 usable radiocephalic fistulas were obtained in 101 attempts, compared with 19 brachiocephalic fistulas in 26 attempts ( $P < .05$ ). Brachiocephalic fistulas are preferable to wrist fistulas in diabetics.<sup>2</sup>

Because of the increased susceptibility to infection in diabetics with renal failure, insertion of prosthetic vascular grafts for access should be avoided whenever possible. If the surgeon is compelled to use them he or she must emphasize to the dialysis staff the need for extra care in performing aseptic cannulation of the grafts.

We digress for a moment to mention peritoneal dialysis in diabet-

ics. It has the advantage that retinopathy, which seems to progress in patients on hemodialysis, does not do so with peritoneal dialysis.<sup>104</sup> However, other complications, such as neuropathy and vascular disease, once established, usually progress. The blood glucose level is controlled with intraperitoneal insulin in addition to the patient's regular insulin. Survival is significantly worse than in nondiabetics, chiefly because of progression of diabetic complications, with a one-year survival of 44%.<sup>104</sup>

#### PENILE BLOOD FLOW

Diabetes is probably the most common organic cause of sexual impotence.<sup>112</sup> It occurs in 40% to 50% of all long-term diabetic men of all ages, and occurs in both Type I and Type II diabetics. The two major causes are neuropathy affecting the autonomic nerve supply to the corpora cavernosa, and reduced blood flow to the penis.<sup>112</sup> The latter may be caused by aortoiliac disease (Leriche syndrome) or by stenoses of the internal pudendal arteries.<sup>78, 79</sup> Deficient penile blood flow may be confirmed by penile plethysmography, comparison of penile to brachial arterial blood pressures, recording of Doppler arterial blood flow signals, and by arteriography, which may necessitate highly selective views of the distal pudendal and penile arteries. Major aortoiliac reconstructions may be necessary to relieve lower limb ischemic symptoms and improve penile blood flow by restoring either prograde or retrograde circulation to the internal iliac arteries. To avert postoperative impotence, nerve sparing techniques must be used that avoid injury to the autonomic nerves responsible for erection of the penis, and embolism from the internal iliac arteries must be prevented.<sup>40, 41</sup> Pudendal artery disease may be bypassed by bilateral anastomosis of the inferior epigastric arteries to the corpora cavernosa.<sup>40, 41</sup>

Atherosclerosis of these arteries is a contraindication to this procedure. In patients unsuitable for arterial reconstruction, or whose primary problem is diabetic neuropathy, satisfactory sexual function can be restored by insertion into the corpora cavernosa of rigid silicone Small-Carrion or inflatable Scott-type penile prostheses.<sup>112</sup> Some words of warning. Patients with diabetes and vascular disease may be at risk for penile ischemia and gangrene, which has been reported three weeks after implantation of solid penile prostheses.<sup>134</sup> In addition, prosthetic graft failure may occur because of infection, which, in diabetics is often caused by *Staphylococcus epidermidis*.<sup>110</sup>

#### INFECTIONS IN DIABETES

There is a widely held belief that diabetics have increased susceptibility to infection. This is probably not true in the well-controlled

diabetic, but the poorly controlled patient has impaired immune defenses and is very prone to infection.<sup>72</sup> The mechanisms are poorly understood and conflicting explanations have been advanced.<sup>25</sup> As engulfment and intracellular killing of bacteria are energy-requiring processes, there is defective phagocytosis and killing of bacteria by the leukocytes of poorly controlled diabetics. Two factors play a role, hyperglycemia and ketoacidosis. Hyperglycemia impairs phagocytosis and also facilitates the growth of bacteria that enter the tissues.<sup>72</sup> Ketoacidosis delays the migration of granulocytes to the site of a lesion, and depresses the phagocytic and bactericidal functions of these cells.<sup>72</sup> Conflicting reports have been published concerning antibody production in response to bacterial antigens and regarding the opsonic capacity of the blood of diabetics.<sup>25</sup> Microangiopathy may facilitate the development of infection because of decreased tissue perfusion and lowered oxygen levels. It also impairs the delivery of granulocytes, antibodies, and antibiotics to an area of infection. A host defense that is frequently breached in diabetics is the skin. Defects caused by ischemia (see "Cardiovascular Complications") or by neuropathy (see "Diabetic Foot Disorders") serve as portals for the entry of bacteria.

A severe infection in the diabetic induces a series of catabolic disturbances.<sup>72</sup> There is negative nitrogen balance, increased gluconeogenesis, hyperglycemia, mobilization of fatty acids, and acidosis. The net result is an increase in insulin "resistance" and a consequent increase in insulin requirements for maintenance of control. Thus a vicious circle is established: poorly controlled diabetes, with its accompanying hyperglycemia and ketoacidosis, impairs host defense mechanisms, and that in turn facilitates progression of the infectious process.<sup>72</sup>

Infection is the most common precipitating factor in diabetic ketoacidosis. In different series it accounts for 28% to 77% of such cases.<sup>97, 99, 141</sup> Infection is a major cause of mortality and morbidity in diabetics.<sup>25</sup> In a study of patients with ketoacidosis the overall mortality was 6%, but 43% of the deaths were caused by infection.<sup>141</sup> Diabetics have a worse prognosis than nondiabetics with certain infections, such as staphylococcal bacteremia or acute pyelonephritis, if complicated by papillary necrosis or emphysematous pyelonephritis.<sup>25</sup>

## *SPECIFIC INFECTIONS IN DIABETIC PATIENTS*

### *Foot Infections*

These are discussed in the section entitled "Diabetic Foot Disorders."

### *Skin and Soft-Tissue Infections*

Increased skin and nasal carriage of staphylococci<sup>25</sup> may predispose diabetics to an increased incidence of infections with these

organisms. Although conflicting reports have been published, on the whole, staphylococcal infections seem to be more common in diabetics than in nondiabetics.<sup>25</sup> One study showed a higher incidence of infections of clean postoperative wounds in diabetics than in non-diabetics—10.7% in the former group and 1.8% in the latter.<sup>34</sup> Gram-negative wound infections are three times more frequent in diabetic than in nondiabetic individuals.<sup>143</sup> However, in one study, infections in clean orthopedic wounds were not more frequent in diabetics.<sup>86</sup>

In healthy persons, infection of a hair follicle (folliculitis) or of several adjacent follicles (furunculosis) is a minor and self-limiting condition. In susceptible individuals, such as diabetics, this may progress to form a carbuncle. This is a multilocular suppurative extension of a furuncle into the subcutaneous tissues.<sup>32, 139</sup> Most common locations are the nape of the neck, dorsum of the trunk, hands and digits, and hirsute areas of the chest and abdomen. Separation of compartments in a carbuncle is maintained through persistence of fascial attachments to the skin.<sup>32</sup> As the individual locules tend to point separately there are multiple draining sites. Most carbuncles are caused by pyogenic cocci, usually *Staphylococcus aureus*, but gram-negative bacilli and streptococci may be found coincidentally.<sup>32</sup> Fever and systemic toxicity are common. Incision and drainage and appropriate antibiotic therapy are necessary. In order to secure adequate drainage extensive incisions and undermining of flaps are often required to divide adherent septa. Carbuncles may recur years after otherwise successful therapy.<sup>139</sup> In my experience, carbuncles have become uncommon in recent years, perhaps because of early use of antibiotics in treating folliculitis or furunculosis.

Necrotizing soft-tissue infections, caused by a mixture of aerobic and anaerobic organisms, cause extensive necrosis of the skin and subcutaneous tissues (fasciitis) or the underlying muscles (cellulitis). In a series of 30 patients with necrotizing fasciitis more than 75% of patients had diabetes and atherosclerotic vascular disease.<sup>90</sup> Reasons for the predisposition to necrotizing soft-tissue infections are not known. Perhaps vascular insufficiency and tissue hypoxia caused by diabetic microangiopathy create favorable conditions for mixed aerobic-anaerobic infections.<sup>171</sup> These may begin in the perianal or pelvic regions (where anaerobes are common), or in the extremities (where the vascular supply is compromised), or in the deep fascial planes of the neck (by spread from infected teeth).<sup>25</sup> Necrotizing cellulitis is a life-threatening disorder with a mortality of over 60% despite optimal therapy.<sup>171</sup> Death is usually due to overwhelming sepsis, respiratory failure, renal failure, or multiple organ failure.<sup>90</sup> Patients rapidly become acutely ill and develop ketoacidosis. Despite severe tenderness, superficial gangrene is rarely extensive. Small skin ulcers develop that drain thin, reddish-brown, foul-smelling fluid. Subcutaneous emphysema occurs in 25% of cases. Fever and leukocytosis

are frequently present. The most common microorganisms are anaerobic streptococci, bacteroides, aerobic or facultative gram-negative bacilli, including pseudomonas and enterococci. Bacteremia with organisms similar to those in the wound occurs in 50% of patients.<sup>171</sup> Necrotizing fasciitis is less severe than necrotizing cellulitis,<sup>171</sup> but still has a mortality of 38%.<sup>90</sup> Both conditions require thorough drainage of abscesses and removal of necrotic material, antibiotics to cover aerobic and anaerobic gram-negative and positive organisms, correction of ketoacidosis, control of diabetes, and aggressive supportive therapy, which may include respiratory support, central cardiovascular monitoring, hemodialysis, and oral or IV hyperalimentation.<sup>90</sup>

### ***Illustrative Case History***

A 69-year-old diabetic man with hypertension, atherosclerotic heart disease, and renal insufficiency developed a painful swelling in the right side of the groin. Examination showed tenderness, erythema, and induration of the upper third of the right thigh. There was crepitance and a discharging sinus that emitted foul-smelling brown fluid. The patient was clinically dehydrated. The blood glucose level was 770 mg/dl with moderate ketonemia. Serum electrolytes were sodium, 124 mEq; potassium, 5.3; chloride, 83; CO<sub>2</sub>, 20; BUN, 98 mg/dl; and creatinine, 3.5 mg/dl. Arterial blood gas analysis with the patient breathing room air showed pH, 7.29, PaO<sub>2</sub>, 72 mm Hg, PaCO<sub>2</sub>, 34 mm Hg, and HCO<sub>3</sub>, 17 mm Hg. The white blood cell count was 17,900/cu mm. In the SICU a Swan-Ganz catheter, arterial cannula, and Foley catheter were passed and fluid and electrolyte resuscitation and continuous IV insulin therapy given for approximately six hours, by which time the blood glucose level had fallen to 400 mg/dl when the patient was taken to the operating room. An area of necrotizing fasciitis, which started superiorly at the anterior iliac crest and lower abdomen, and extended down to the superior trochanter and then medially to approximately 6 in. below the medial attachment of the inguinal ligament, was thoroughly debrided. The underlying muscles were normal. Culture revealed two strains of *S. epidermidis*, as well as peptococcus, diphtheroids, and *Bacillus* species. Antibiotic therapy was with thienamycin. The patient's condition rapidly improved and within 48 hours the blood glucose level was 250 mg/dl on treatment with 10 to 15 units of regular units every four hours. Arterial blood gases and electrolytes were close to normal and the BUN and creatinine levels had fallen to 48 and 1.9 mg/dl, respectively. Further wound debridement was performed three days after the initial operation. For the most part the wound granulated satisfactorily and 20 days later some further debridement was performed and the wound covered with a meshed split-thickness skin graft. Satisfactory healing occurred over a period of several weeks. The diabetes was stabilized on an 1,800-calorie diet and NPH insulin 15 units every morning.

Hand infections, although not as common as those of the lower limbs, may require amputation of fingers to control infection in as

many as 30% of cases.<sup>25</sup> One problem is that because of neuropathy and poor vision, patients are not aware of the onset of infection that may progress to involve underlying bones and joints.

#### *ACUTE CHOLECYSTITIS AND EMPHYSEMATOUS CHOLECYSTITIS*

Until quite recently it was accepted that morbidity was increased after cholecystectomy for acute cholecystitis in diabetics, a viewpoint that was supported by several large studies.<sup>98, 161, 162</sup> A major medical textbook recommended cholecystectomy in diabetics with asymptomatic gallstones, while at the same time not recommending the operation for asymptomatic nondiabetic patients.<sup>93</sup> However, several recent studies showed no increased mortality or morbidity in diabetics who underwent cholecystectomy for acute or chronic cholecystitis.<sup>67, 111, 166</sup> These findings support my own experience. Therefore, there seem to be no valid reasons to offer different treatment of diabetics and nondiabetics with gallstones or acute cholecystitis. The decision to operate should be made independently of whether or not the patient is diabetic. An entity that does require an aggressive attitude is acute emphysematous cholecystitis. This disorder, characterized by the radiographic demonstration of gas in and around the gallbladder, is caused by a mixed aerobic and anaerobic infection. Cultures of bile are positive in 50 to 90% of cases, of which 25% to 50% are caused by *Clostridia*.<sup>171</sup> *Escherichia coli*, streptococci, staphylococci, and *P. aeruginosa* are also frequently isolated. Diabetics account for more than one third of patients with this rare disease.<sup>171</sup> The clinical findings are similar to those of acute cholecystitis, but in emphysematous cholecystitis gas may be seen radiologically within the first 48 hours of infection and may extend to the surrounding tissues within the next 48 hours. Some workers recommend abdominal radiographs for at least four days in diabetic patients with clinical features of acute cholecystitis who are being treated nonoperatively.<sup>171</sup>

The outcome is very different from that in acute cholecystitis.<sup>25, 171</sup> Gallbladder perforation and gangrene are frequent and the mortality rate is 3 to 10 times higher than in acute cholecystitis. The male to female ratio is approximately 3:1, the reverse of that seen in acute cholecystitis. Arterial insufficiency may play a role in the pathogenesis of emphysematous cholecystitis.<sup>171</sup> Treatment consists of early cholecystectomy and broad-spectrum antibiotic coverage.

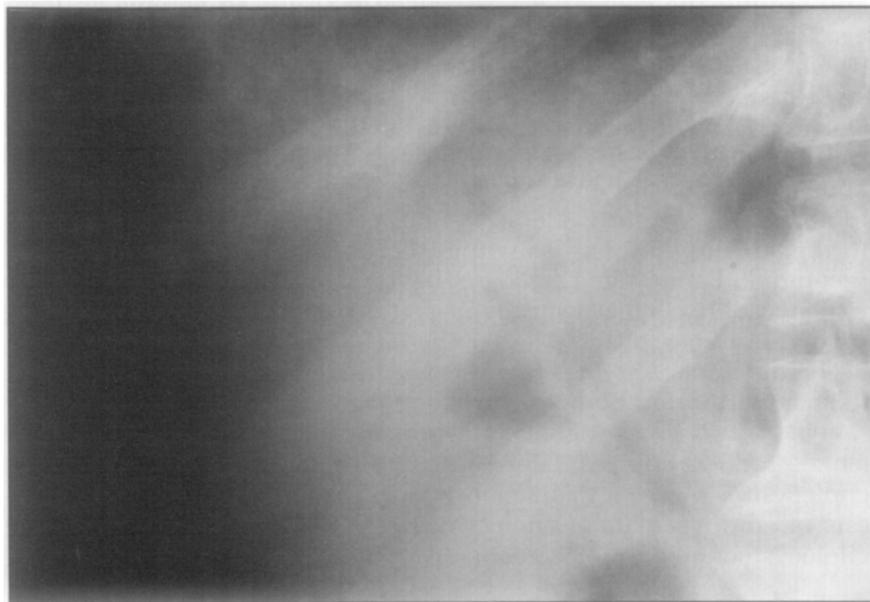
#### *Illustrative Case History*

A 79-year-old nondiabetic man presented with a three-day history of nausea and anorexia. He denied emesis or significant abdominal pain. Apart from hypertension he had not been ill previously. The temperature was

99.8°F and there was tenderness with mild guarding in the right upper quadrant of the abdomen. The white blood cell count was 13,800/cu mm. Radiographs of the abdomen showed air in the biliary tree (Fig 2), but no signs of intestinal obstruction to suggest the possibility of gallstone ileus. A diagnosis of emphysematous cholecystitis was made and confirmed at operation when a large tense edematous gallbladder, with multiple necrotic areas in the wall, was found. Cholecystectomy was performed. No stones were found in the specimen. Operative cholangiogram was normal. The abdomen was drained and the skin and subcutaneous tissues were left open. Antibiotic therapy with clindamycin, ampicillin, and gentamicin proved satisfactory to control infection that was later found to have been caused by *C. Perfringens*. Delayed primary closure of the wound was performed and the patient had an uneventful recovery.

#### *INTRABDOMINAL INFECTIONS*

Diabetic ketoacidosis may cause difficulty in differentiation from acute abdominal problems. Patients with this disorder may have severe abdominal pain, vomiting, and sometimes rigidity of the abdominal wall simulating a local inflammatory lesion such as acute appendicitis.<sup>138</sup> If the abdominal symptoms and signs do not rapidly subside under treatment for the ketoacidosis one



**FIG 2.**

Nondiabetic patient with air in the biliary tree and gallbladder caused by emphysematous cholecystitis.

should suspect an acute intra-abdominal condition that may have indeed precipitated the ketoacidosis.

#### *Illustrative Case Report*

A 35-year-old schizophrenic woman with a strong family history of diabetes complained of upper abdominal pain, nausea, vomiting, constipation, and increasing thirst and urinary frequency. The pulse rate was 124 beats per minute, the temperature was 99.2°F, and the blood pressure was 122/70 mm Hg. The abdomen was distended with diffuse tenderness. Bowel sounds were present. Abdominal radiographs showed small and large bowel distension consistent with ileus. The white blood cell count was 22,600 cells/cu mm, and the blood glucose level was 675 mg/dl with marked ketonemia. On room air the blood gases showed pH, 7.08, PaO<sub>2</sub>, 137 mm Hg, PaCO<sub>2</sub>, 14 mm Hg, HCO<sub>3</sub>, 5.0 mm Hg. Urinalysis showed a glucose level of 0.5 gm/dl and ketones of more than 80 mg/dl. The BUN level was 17 mg/dl, creatinine, 1.2, sodium, 133 mEq/L, potassium, 4.8, chlorides, 86, and CO<sub>2</sub>, 6.0. No evidence of any infection was found. The patient was admitted to the intensive care unit, where a triple lumen central venous line and an arterial line were placed as well as a Foley bladder catheter. She was started on normal saline at 200 ml/hour supplemented over several hours with several ampoules of sodium bicarbonate. Insulin was given by IV drip at 10 units/hour and potassium chloride at 20 mEq/hour. After 18 hours of treatment there was a dramatic improvement in the patient's overall condition. Within 48 hours the vomiting had ceased and the patient had a bowel movement. She still had some epigastric discomfort and the abdomen remained distended. However, she was able to take food by mouth. The blood glucose level was 318, sodium, 143, potassium, 4.0, chloride, 120, CO<sub>2</sub>, 9, and the ketonemia had disappeared. Arterial blood pH was 7.31, PaO<sub>2</sub>, 101 mm Hg, PaCO<sub>2</sub>, 22 mm Hg, and HCO<sub>3</sub>, 12 mm Hg. Insulin therapy was changed to 20 units of lente and 10 units of regular insulin subcutaneously in the morning and 15 units of regular insulin in the evening while receiving 5% dextrose in half-strength normal saline at 150 ml/hour IV. Thereafter the patient's abdominal complaints rapidly cleared up. Over the course of the next three days she was stabilized on an 1,800-calorie diabetic diet and therapy with human insulin, 30 units of lente and 10 units regular, in the mornings.

Diabetes contributes to the mortality of intra-abdominal sepsis. In a series of 187 patients the overall mortality was 24%, but it was 48% in the 21 diabetic patients.<sup>39</sup>

#### *URINARY TRACT INFECTIONS*

Controlled studies have shown a two- to fourfold higher incidence of bacteruria in diabetic women (but not in men) than in control groups.<sup>171</sup> Nosocomial urinary tract infections are also more common in diabetics.<sup>143</sup> Several factors contribute to their susceptibility

to urinary tract infections.<sup>25,171</sup> Bladder dysfunction resulting from neuropathy is probably the most important. Urologic manipulations, such as catheterization, play a role. In addition, high concentrations of urinary glucose impair the phagocytic function of polymorphonuclear leukocytes. The upper urinary tract appears to be involved in nearly 80% of cases.

Although the majority of urinary tract infections in diabetics are asymptomatic, diabetes appears to predispose patients to more severe infections.<sup>25,171</sup> Thus, of 52 patients with perinephric abscesses, 36 were diabetic. The diagnosis should be suspected in any diabetic with urinary tract infection who does not respond to antibiotic therapy within three or four days. Renal papillary necrosis is another complication of urinary tract infection in diabetics. In fact diabetics account for more than 50% of patients with this complication. The diagnosis should be suspected in patients who respond poorly to antimicrobial therapy or who develop renal insufficiency.<sup>171</sup> The diagnosis is made on retrograde pyelography, which shows dilatation of a calyceal fornix, irregularity of the papillary tip, extension of contrast medium into the renal parenchyma, or, in late cases, a club-shaped cavity.

Gas-forming infections of the kidney, renal pelvis, ureter, or bladder are uncommon and most occur in diabetics.<sup>25</sup> It is believed that gram-negative microorganisms utilize glucose and liberate gas and cause a severe necrotizing infection in areas of vascular insufficiency. Urinary tract obstruction may be a contributory factor.<sup>56</sup> The prognosis is worse when the renal parenchyma rather than the urinary collecting system is involved. As with other renal complications, the disorder should be suspected whenever a diabetic does not respond quickly to appropriate antibiotics. Abdominal radiographs show mottled lucencies in the kidney, ureter, or bladder.

The urinary tract is the most frequent source of microorganisms in patients with bacteremia caused by gram-negative rods. *Escherichia coli* is the major organism and may cause septic shock or pneumonia.<sup>25</sup>

### FUNGAL INFECTIONS

Moist warm areas of the thighs, genitalia, and breasts are prone to candida skin infections, especially in diabetics who are overweight, or are being treated with antibiotics.<sup>25</sup> Breakdown of the skin may permit entry of more virulent organisms and set the stage for infections such as necrotizing fasciitis.

Fungal infections of the urinary tract are also more frequent in diabetics.<sup>171</sup> *Candida* was cultured from the urine of 35% of glycosuric diabetics, and diabetics accounted for 20% to 90% of urinary tract infections with *Torulopsis glabrata*.<sup>171</sup> Although the majority of

fungal urinary tract infections are insignificant, some are serious and both candida and *T. glabrata* can cause cystitis, pyelonephritis, renal or perinephric abscesses, fungus balls, and a clinical picture resembling gram-negative sepsis. Amphotericin B, 5-fluorocytosine, or ketoconazole have been used to treat fungal urinary tract infections.<sup>171</sup>

Diabetics account for more than two thirds of cases of rhinocerebral mucormycosis, which occurs usually in those who are acidotic. This rare but life-threatening infection starts suddenly with periorbital or perinasal pain, induration and discoloration, bloody nasal discharge, unilateral headache, swelling of the eyelid, and lacrimation.<sup>171</sup> Extension of infection from the nose or paranasal sinuses may occur through the cribriform plate and orbit to the brain and meninges, and causes paralysis of cranial nerves II to V, seizures, hemiparesis, coma, and cavernous sinus thrombosis.<sup>25, 171</sup>

Diabetes is present in 10 to 20% of patients with cryptococcal infections, histoplasmosis, coccidiomycosis, and blastomycosis.<sup>171</sup>

### BACTEREMIA

While most bacterial pathogens may invade the bloodstream, certain varieties seem to pose a particular threat to diabetic patients.<sup>25</sup> Bacteremia with aerobic gram-negative rods may complicate urinary tract infections, gallbladder or gastrointestinal tract disease, or the use of IV catheters. In one study gram-negative shock followed operation in 7% of diabetic patients compared with less than 1% of nondiabetics.<sup>5</sup> *Escherichia coli* was the most common organism involved, and 86% of the bacteremias arose from the urinary tract. Another study showed that nosocomial gram-negative bacteremia was three times more frequent in diabetics than in nondiabetics.<sup>143</sup> A third study showed a higher mortality rate (39%) in diabetics than in nondiabetics (20%).<sup>84</sup>

Bacteremia due to group B streptococci was more common in diabetics than in nondiabetics in several studies, particularly in patients with gangrene of an extremity.<sup>25, 171</sup> Fifteen of 42 patients with staphylococcal bacteremia were diabetic.<sup>25</sup> Skin infections and intravascular catheters were common sources of the microorganisms. In one series, staphylococcal bacteremia had a higher mortality (69%) in diabetic patients than in nondiabetics (17%).<sup>31</sup>

### PNEUMONIA

Diabetics are prone to develop pneumonia caused by *S. aureus* or *Klebsiella pneumoniae*, possibly related to increased carriage in the nose of the former microorganism and in the throat of the latter.<sup>25, 171</sup> Why diabetics should be predisposed to these types of pneumonia but not to pneumococcal pneumonia is not clear. Among factors

that may contribute to pneumonia are defective phagocytosis of inhaled bacteria by pulmonary macrophages and impaired bactericidal mechanisms of the lung in patients with ketoacidosis. Infections with either *S. aureus* or aerobic gram-negative rods may cause severe necrotizing pneumonias, with a nearly 40% mortality rate.<sup>25, 171</sup>

### **OTHER INFECTIONS**

Malignant external otitis occurs almost exclusively in diabetics and most frequently is caused by *P. aeruginosa*.<sup>25, 171</sup> Usually there is persistent ear pain and purulent discharge occurring in patients over 35 years of age. Granulation tissue or polyps can be observed in the external canal. Infection may spread to involve deep soft tissues, the parotid gland, temperomandibular joint, mastoid bone, and cranial nerves. The mortality is over 50%.

Tuberculosis was once a common problem in diabetics, but its incidence in them has declined parallel to the decrease in the general population. However, diabetes still ranks second only to alcoholism as a major factor in reactivation of tuberculosis.<sup>25, 171</sup>

Periodontal disease is more common and more severe in diabetics than in nondiabetics.<sup>25</sup>

### **PREVENTION AND TREATMENT OF INFECTION**

The single most important factor in prevention of infection is good control of the diabetes, especially prevention of ketoacidosis.<sup>72</sup> Personal hygiene, particularly of the feet, is also important. Other preventive and/or therapeutic measures are discussed in the sections entitled "Management of Diabetes During Operation" and "Prevention of Complications of Diabetes."

### **DIABETIC FOOT DISORDERS**

The reader will observe that most illustrations in this monograph deal with foot problems. This is no coincidence, and emphasizes the frequency of foot disorders in diabetics. The magnitude of the problem is revealed by the following facts: lesions of the feet are responsible for more than one fifth of hospitalizations of diabetics.<sup>114</sup> Lower extremity disease is the most common disorder necessitating operation in diabetics.<sup>107, 108</sup> Gangrene is 53 times more frequent in diabetic men and 71 times more frequent in diabetic women over 40 years of age than in nondiabetic atherosclerotic people.<sup>11</sup> It is often bilateral. Approximately one half of all nontraumatic lower extremity amputations performed in the United States are related to diabetes.<sup>43</sup>

Three percent of diabetics are amputees.<sup>13</sup> At autopsy 29% of diabetics have gangrene or have had an amputation of a limb.<sup>167</sup> In approximately two thirds of diabetics with gangrene, this complication is a principal or contributory cause of death.<sup>82, 107, 108</sup>

There are three major causes of foot problems in diabetics: peripheral arterial disease, peripheral neuropathy, and infection.<sup>82, 107, 108</sup> Any of these disorders may occur alone, but combinations of two or of all three are often present. In approximately one third of patients the underlying cause is ischemia; neuropathy accounts for another third, and the remainder are of mixed etiology.<sup>107, 108</sup> These disorders greatly affect prognosis and treatment. The foot of a patient with early diabetes, who has normal circulation and sensation, responds to injury and infection like that of a nondiabetic. But, in the diabetic with neuropathy or vascular insufficiency, or both problems, infections that otherwise would be trivial may have disastrous effects, threatening loss of limb or life.

Patients with diabetes of more than ten to 15 years' duration usually have neuropathy.<sup>107, 108</sup> The cause is unknown, but possibilities include accumulation of sorbitol metabolites in nerves, decreased levels of myoinositol, defective myelin synthesis, malnutrition in poorly controlled diabetics, and microvascular disease of peripheral nerves.<sup>145</sup> Important pathologic features are severe nerve fiber loss,<sup>3</sup> and segmental demyelination and remyelination of remaining axons.<sup>27</sup>

Peripheral neuropathy causes variable effects on the motor, sensory, and sympathetic nerve supply of the lower limbs. It may damage the motor nerves of the small intrinsic muscles of the feet, may cause diminished sensation or complete absence of pain, and may affect the sympathetic nerves, producing dry, nonsweating, vasodilated feet ("autosympathectomy"). The muscular weakness results in deformities such as medial deviation of the lateral three toes, hallux valgus, bunionette of the fifth toe, and hammer toes, showing dorsal subluxation of the proximal phalanges and plantar prominence of the metatarsal heads.<sup>102, 107, 108, 160</sup> Loss of the intrinsic muscles upsets the normal balance between the flexors and extensors, which is necessary for proper weight distribution during walking. The protrusion of the metatarsal heads causes excessive load on the underlying soft tissues during standing or walking. In addition, the amount of weight borne by the toes is reduced and is shifted to the metatarsal area. As a consequence of all these changes, excessive weight is borne under the metatarsal heads, particularly the first,<sup>13, 35, 87, 160</sup> and calluses develop over the bony prominences. In persons with normal sensation such lesions cause pain and compel them to reduce weight bearing. Diabetics, who have diminished or absent sensation in the feet, continue full weight bearing. As a result the calluses

cause pressure necrosis of the underlying plantar skin, leading to neuropathic or mal perforans ulcers, most of which occur under the first, second and fifth metatarsophalangeal joints in that order.<sup>102</sup> The ulcers may serve as portals for spreading infection.<sup>102</sup>

#### *Illustrative Case History*

A 56-year-old insulin-dependent diabetic man required several debridements of a  $2 \times 2$  cm draining mal perforans ulcer on the plantar surface of the right foot overlying the second metatarsophalangeal joint. The flexor tendons to the toe lay exposed in the ulcer bed and were excised. The patient was also treated with cefazolin for the infection, which was caused by beta-hemolytic streptococci, coagulase-negative staphylococci, and rare *E. coli* organisms. Two and a half weeks later he was readmitted to the hospital because of extension of the ulcer, fever (100°F), leukocytosis (19,400 cu mm), hyperglycemia (blood glucose, 462 mg/dl), and glycosuria and ketonuria. The second and third metatarsophalangeal joints were visible in the base of the ulcer. A ray amputation of the second and third toes was performed and the wound left open. *Staphylococcus aureus* was grown from it. After operation and treatment with cefoxitin the infection and the diabetes were brought under control. The wound healed gradually over several months (Fig 3). The patient subsequently developed a mal perforans ulcer over the plantar aspect of the opposite first metatarsal head.

Patients with poor sensation in the feet are likely to traumatize them in other ways.<sup>102</sup> Because of poor eyesight, caused by cataracts or retinopathy, they may stub the toes, or injure the skin when cutting the nails, or may tread on sharp objects. I have seen several patients with a sharp object projecting into or embedded in the foot for several days or weeks, who were blissfully unaware of its presence until severe sepsis supervened.

#### *Illustrative Case History*

A frail 49-year-old diabetic woman had been treated with cisplatin for metastatic ovarian cancer. She also had renal failure that required hemodialysis. She had trod on a needle but did not come to the hospital until a week later when she was desperately ill with a deep plantar abscess, a white blood cell count of 27,000/cu mm, blood glucose level of more than 900 mg/dl, and ketoacidosis. A radiograph showed a needle in the sole of the foot (Fig 4). After stabilization with fluids and electrolytes, insulin therapy, and antibiotics, the needle was removed and a large plantar abscess laid wide open. *Staphylococcus aureus* was cultured from the wound. However, the sepsis progressed and as the patient adamantly refused to have an amputation, further radical debridements of the foot were performed four and eight days later. She developed *S. aureus* sepsis of the polytetrafluoroethylene (PTFE) graft used for dialysis and subsequently of a Quinton hemodialysis catheter. Episodes of hyperglycemia and ketoacidosis recurred because of uncontrolled sepsis and the patient died almost four weeks after initial drainage of the foot abscess.



**FIG 3.**

Diabetic man with neuropathy complicated by hallux valgus and a mal perforans ulcer over the fifth metatarsal head. Badly infected mal perforans ulcer involving the metatarsophalangeal joints of the second and third toes had previously required an open ray amputation.

Pressure necrosis may occur when the external pressure exceeds capillary pressure, for example, on the skin of the heel, when insensitive feet lie unprotected against the bed for prolonged periods.

#### *Illustrative Case Report*

A 73-year-old man with Type II diabetes treated with 250 mg of diabinase twice a day was admitted to the hospital because of bilateral heel ulcers of



**FIG 4.**

Diabetic patient with needle embedded in sole of foot that caused a deep plantar abscess. Note also calcified vessels and small gas bubbles on medial side of foot.

five weeks' duration, which had failed to heal despite treatment with antibiotics and elevation of the feet (Fig 5). The patient had neuropathy of both lower limbs. The lower extremity pulses were femorals 2+, popliteals 1+, but with absent dorsalis pedis and posterior tibial arteries. Noninvasive vascular studies showed an ankle-brachial index of 1.0 on the right, but 0.8 on the left, indicating some distal disease. The ulcers were thoroughly debrided, but very little bleeding was noted on the left side and necrosis was



**FIG 5.**

Diabetic patient with deep neuropathic ulcer of left heel.

found to extend down to bone. When the patient signed himself out of the hospital a week later the ulcer remained indolent and showed no signs of granulation tissue.

Patients may also injure their feet by using excessively hot baths or heating pads or by applying strong chemical liniments on corns and calluses.

Autonomic neuropathy causes a dry fissured skin that cracks easily, making it susceptible to secondary infection.<sup>13</sup> Another effect of autosympathectomy is arteriovenous shunting, which may hamper tissue oxygenation. In addition, denervated blood vessels may be hypersensitive to cold, further increasing skin ischemia.<sup>13</sup>

The small joints of the foot are supported by capsules and ligaments. Additional stability is provided by the muscles that control their movements. As more load is shifted to the static joint structures of neuropathic feet, they undergo gradual weakening and destruction, leading to painless, severely osteoarthritic or Charcot's joints.<sup>102</sup> Those most frequently affected are the ankle, subtalar, tarsal, or tarsometatarsal joints. The abnormal stresses applied to ligaments, synovial sheaths, articular surfaces, and bones cause an inflammatory reaction, which manifests itself clinically as swelling and increase in local temperature, which may be mistaken for osteomyelitis or pyogenic arthritis. Treatment consists of keeping an affected foot at rest until the inflammation subsides. This is accomplished

initially using a short-leg walking cast, which is replaced later with a molded polypropylene orthosis to provide continuing support for the foot.

Infection in neuropathic or ischemic feet often begins in an apparently trivial break in the skin.<sup>102</sup> The initial lesion frequently originates near the nails, which are often abnormal in ischemic neuropathic diabetic feet.<sup>102, 107, 108</sup> Stubbing the toes or wearing new shoes may cause breaks in the skin of patients with long ingrown, or incurved nails, or onychogryphosis. In some individuals poor foot hygiene cause excess keratin and debris to accumulate under the nails and in the nail folds, which may facilitate the growth of bacteria. Web space infections may follow the accumulation of moist detritus in the webs and the development of epidermophytosis and fissuring of the skin, which permits bacteria to enter. What often begins as minor trauma, followed by minor infection, may progress to a major infection because the circulation is inadequate to control the micro-organisms, and because neuropathy permits the spread of infection.<sup>102</sup> The normal foot has a rich collateral circulation, but in diabetics multiple occlusions in effect may convert the vessels supplying the toes into end arteries, similar to those in the heart or kidney. Progressive infection may cause thrombotic occlusions and gangrene of the area supplied by these vessels. This pattern contrasts with gangrene in nondiabetic atherosclerotic patients, which, almost invariably, is associated with occlusions at or above knee level. A further problem in diabetics with severe neuropathy is failure to localize infections, because affected areas are not put at rest, as feet with normal sensation would be, with resultant dissemination of infection along fascial planes. I have often observed that diabetics with severe infections of the feet have little or no discomfort.<sup>108</sup>

Several types of major infection occur in the feet of diabetics.<sup>80, 102</sup> One variety is the mal perforans ulcer on the plantar surface of the toes or under the heads of the metatarsals. It occurs in patients with neuropathy, frequently with no evidence of ischemia. If untreated, infection ultimately spreads to the underlying fascia, joints, tendons, and bones.

#### *Illustrative Case Report*

A 38-year-old woman with Type I diabetes of more than 30 years' duration developed glomerulosclerosis and chronic renal failure, which was treated with two cadaver kidney transplants, each of which failed because of chronic rejection, and currently is being maintained on hemodialysis. She also has marked peripheral neuropathy, complicated by a severe Charcot's osteoarthropathy of the right ankle (Fig 6). Despite this she has been able to walk. During the past year she has been admitted to the hospital on at least three occasions because of neuropathic ulcers on the medial side



**FIG 6.**

Diabetic patient with severe Charcot's osteoarthropathy of the right ankle. **A**, anteroposterior view, **B**, lateral view. Note calcified vessels on both views.

of the instep or on the big toe, which were complicated by infection and cellulitis. On each occasion the problem was controlled by debridement, systemic antibiotic therapy, and bed rest.

A second variety of major infection is a group of necrotizing skin and subcutaneous tissue infections<sup>80</sup> including necrotizing fasciitis, and necrotizing cellulitis (see "Infections in Diabetes").

A third type of major infection is an abscess in the deep spaces of the sole. Usually it occurs in the central plantar space, and less commonly the medial or lateral plantar space.<sup>102</sup> Infection may result from direct penetration by sharp foreign bodies, or by spread from a web space, or from the plantar surface of a toe, or from an ulcerated bunion or bunionette. Inflammatory edema causes obliteration of the concavity of the longitudinal arch and disappearance of the skin creases of the sole, followed later by swelling of the dorsum of the foot. Fever, malaise, and other systemic signs of severe infection are also present. In severe cases infection causes thrombotic occlusion of small- and medium-sized vessels, and progressive necrosis of plantar fascia, tendons, bones, and joints. Gangrene of one or more

toes may occur. In addition, infection may spread proximally up tendon sheaths into the leg.

Infections are caused by multiple organisms, which may be gram-positive or negative, aerobic, or anaerobic.<sup>80, 102, 108</sup> The most frequent aerobes are gram-negative bacilli, enterococci, and *S. aureus*. Gram-negative bacilli (especially *Bacteroides*, and *Fusobacterium*), *Clostridia*, and anaerobic cocci are the most common anaerobes encountered. Anaerobes outnumber aerobes by more than tenfold.<sup>126</sup> One should suspect anaerobic infections whenever there is a fetid discharge, or crepitus, or subcutaneous gas. It is important to obtain cultures from the depths of the wound at the time of debridement or amputation, as the bacterial population in the depths may differ significantly from that in the superficial tissues.<sup>133</sup> The great variety of bacteria in the lesions necessitates the use of broad-spectrum antibiotics. As many as 20% of patients with gangrene of the foot may have subcutaneous gas,<sup>12, 107, 108</sup> which is usually produced by gram-negative rods and enterococci and rarely by clostridia.

Besides clinical assessment of the extent and severity of the infection, and the presence or absence of neuropathy and vascular insufficiency, radiographic study of the foot is necessary to search for foreign bodies, Charcot joints (indicative of advanced neuropathy), septic arthritis, or osteomyelitis. In the presence of gangrene or infection, the absence of osteoporosis or other lytic lesions is an unfavorable sign, as good blood flow is necessary to cause such changes.<sup>103</sup> Performed when indicated, sinograms may demonstrate underlying joint involvement, or extension into the deep tissues of the foot.<sup>160</sup>

The diabetic with a septic foot needs emergency treatment. Large doses of broad-spectrum antibiotics should be given until culture and sensitivity tests are completed, when changes in antibiotic therapy can be made, as indicated. As infection may cause loss of control of the diabetes it may be necessary to institute temporary therapy with regular insulin and frequent monitoring of the blood glucose until the infection is under control. If septic shock or severe ketoacidosis is present, a Swan-Ganz catheter should be placed to help monitor blood volume replenishment. Usually six to 12 hours of treatment is necessary to prepare the patient for operation. During this time any ketoacidosis and hyperglycemia are controlled, extracellular fluid volume is replenished, and adequate blood levels of antibiotics are established.<sup>160</sup> During hospitalization great care must be taken to protect the foot and other susceptible areas from developing decubitus ulcers.<sup>107, 108</sup>

Operation is indicated in all patients except those with superficial ulcers that can be managed conservatively, or a superficial cellulitis (without necrosis) that will respond to bed rest and antibiotics. One must stress the need for prompt surgical drainage, debridement, or

amputation as indicated. Unfortunately, needless delays on the part of the patient or primary care physician often result in spreading infection, vascular thrombosis, and proximal extension of the destructive process, threatening the patient's limb and even his life.

Surgical treatment may range from minor debridement of a paronychia and removal of an ingrown toe nail to a major amputation of a foot that has been destroyed by infection.<sup>103</sup> Aggressive local treatment is possible only if there is an adequate blood supply. A patient with severe sepsis and extensive popliteotibial occlusive disease should have a guillotine amputation just above the ankle.<sup>160</sup> If the foot has a good blood supply, extensive drainage and debridement of all infected and necrotic tissues should be performed without regard to subsequent reconstruction. This may include removal of several digits and metatarsals. The amount of devitalized tissue needing excision is invariably greater than suggested by the initial clinical examination of the foot.

Whenever performing debridement or drainage procedures in diabetic feet, adjacent tissues must be handled very gently because of associated neuropathy or impaired blood supply. The goal is to avoid amputation, or to perform it at the lowest possible safe level.<sup>103</sup> Rough handling of the tissues may defeat this objective by causing necrosis of the wound margins. Local anesthesia should be avoided because the injection itself may aggravate ischemia. Skin hooks should be used in preference to forceps. Absorbable ligatures should be used in the wound, which should be left open and should not be tightly packed. One should avoid using constricting dressings or bandages.

In treating a mal perforans ulcer one should assess its depth, clinically and radiographically, to determine whether tendon, bone, or joints are affected.<sup>107, 108</sup> If it involves only the skin and subcutaneous tissues, it will heal if the patient avoids weight bearing and local care is given to the ulcer. A sinus tract must be laid wide open, and all necrotic tissue, including infected bone, removed. As the circulation in a neuropathic foot is often good, small ulcers will heal spontaneously, but if the defect is large skin grafting may be required. Weight bearing must be avoided by bed rest or the use of crutches. Often the patient's compliance is a problem because poor vision and the absence of pain create a false sense of complacency.

Once the lesion is healed, a weight-transferring prosthesis must be fitted to the shoe to prevent recurrent problems. If a mal perforans ulcer involves an underlying joint, a ray amputation, removing the toe and the head of the related metatarsal, often is the procedure of choice.<sup>108</sup> If more than one ulcer is present in the distal foot, a transmetatarsal amputation may give the best results. This procedure not only removes the ulcers, but, when neuropathy is confined

to the forefoot, places the insensitive skin on a non-weight-bearing part of the foot.

Necrotizing skin and soft-tissue infections should be treated with antibiotics and prompt surgical drainage and debridement.<sup>107, 108</sup> Amputation may be necessary if extensive necrosis is present.

An abscess of the medial or lateral plantar space may be drained dorsal to the print line of the sole to avoid a scar on the weight-bearing surface.<sup>103</sup> An abscess of the central plantar space is opened from the original site of infection proximally toward the calcaneus. All necrotic and devitalized tissue should be removed. At the end of the procedure all wound surfaces should be bleeding. The primary aim is to control sepsis.<sup>103, 108</sup> Later, a formal amputation at a higher level might be necessary if there has been so much destruction of the soft tissues that the foot is useless for walking. If infection has extended proximally along tendon sheaths the incision must be continued proximally into the leg as far as is necessary. Such extension should be suspected if there is pain in the heel or the calf.<sup>160</sup> In late cases crepitus may be present.

#### *Illustrative Case Report*

A 31-year-old Type I diabetic woman underwent a kidney transplant operation from her mother and had satisfactory renal function on maintenance immunosuppressive therapy with azathioprine, prednisone, and cyclosporine. She also had peripheral neuropathy, which, after her transplant operation, was complicated by deep ulceration of the medial aspect of the right heel with recurrent cellulitis. An abscess in this area was drained eight months after transplantation but the wound failed to heal. Eight months later the patient developed swelling of the foot and foul-smelling drainage. She looked sick and toxic, had a pulse rate of 120 beats per minute and a temperature of 102°F. The white blood cell count was 26,500/cu mm with 69% polymorphonuclear leukocytes. The blood glucose level was 450 mg/dl with mild ketonemia. There was crepitance and foul-smelling purulent drainage from the medial aspect of the foot along the instep. The infected area appeared to be quite separate from the heel ulcer. Radiographic examination of the foot showed marked osteoporosis, vascular calcification in the metatarsal artery between the first and second toes, and mottled gas densities in the soft tissues along the medial aspect of the proximal foot and ankle (Fig 7). Intravenous fluids of 5% dextrose in normal saline were given at 125 to 150 ml/hour. The patient was maintained on her usual dose of human lente insulin (30 units in the morning and 6 in the evening) and human regular insulin (6 units in the morning and 6 in the evening). The blood glucose level was checked by finger stick every six hours and supplemental regular insulin was given as needed according to a sliding scale of 0 units for blood glucose levels of 0 to 200 mg/dl, 5 units for levels of 200 to 250, 8 units for levels of 250 to 300, 10 units for levels of 300 to 350, and 12 units for levels of 350 to 400. She also was placed on therapy with clindamycin and Fortaz (ceftazidime). With the patient under general anesthesia, the entire infected area was laid wide open from the big toe to the heel



**FIG 7.**

Diabetic patient with severe soft-tissue infection of foot with gas bubbles in tissues on medial side of foot. Note also calcified metatarsal artery between first and second metatarsal bones.

ulcer. All necrotic skin, subcutaneous fat pad, deep fascia, and the long flexor tendon of the big toe were excised and the wound packed wide open. Culture of organisms from the depths of the wound revealed a mixed growth of *Morganella morganii*, *Proteus vulgaris*, enterococcus, *Bacteroides fragilis*, and peptococcus species.

Within 36 hours of operation it was obvious that infection and necrosis were spreading despite wide drainage and debridement and appropriate antibiotic therapy. Amputation was advised, but the patient refused. At this stage she looked less toxic, there was no ketonemia, and she was placed on an 1,800-calorie diabetic diet. However, control of the blood glucose level was difficult and lente insulin therapy was discontinued and regular insulin administered according to the sliding scale. The white blood cell count remained elevated (23,200/cu mm). Despite daily debridement necrosis pro-

gressed and six days after the drainage operation the patient finally consented to a below-knee amputation, which was performed using a long posterior musculocutaneous flap and hemovac drainage. Postoperatively, the leukocytosis disappeared. During the first few days after amputation the blood glucose level was brought under control, and the patient was returned to lente and regular insulin therapy at levels similar to those used preoperatively. Antibiotic treatment was discontinued eight days after amputation. The stump healed satisfactorily.

After drainage of a major foot infection the wound must be reassessed on a daily basis. If pus is found on the dressings one should suspect an inadequately drained pocket, which must be opened widely.<sup>108</sup>

The wound will granulate in and close spontaneously if the blood supply is satisfactory and the defect is small. Split-thickness skin grafts can be applied to large defects to shorten the healing process. Occasionally a viable toe may be sacrificed and filleted to provide a full-thickness pedicle flap to close a fairly large distal defect.<sup>160</sup> When two or more toes have been lost a transmetatarsal amputation often is the best treatment.

In some patients, despite satisfactory drainage of infection, the wound may fail to heal because of inadequate blood supply. Such patients should be evaluated for vascular reconstruction. One may have to perform bypass grafting procedures in limbs that are infected distally, bearing in mind the risk of involvement of the operative wound. The danger should be minimized with the use of autogenous material whenever possible, use of monofilament sutures, and appropriate antibiotic coverage.<sup>71</sup> If the patient is not a satisfactory candidate for arterial reconstruction and daily examinations reveal extension of necrosis in the skin edge or in exposed muscles, an amputation is necessary at a level with good blood supply.

#### *LOWER LIMB AMPUTATIONS IN DIABETICS*

Amputation may be necessary in patients with severe rest pain that is not amenable to vascular reconstruction or when neuropathy, ischemia, or infection have caused tissue destruction.<sup>108</sup> More than half the patients who undergo amputations for ischemic disease are diabetic.<sup>145</sup> The aim of treatment is to save as much of the foot as possible to enable the patient to continue walking. Unfortunately, problems are frequently bilateral, and at least 30% of all diabetic amputees will lose the contralateral limb within three years.<sup>59</sup>

If possible, the definitive operation should be the first one. However, this may not be feasible when severe sepsis is present and the initial procedure will need to be wide drainage and debridement or a guillotine amputation.

Any decision regarding the level of amputation can be made only

after careful evaluation of each patient's problems, taking into consideration the general condition and local factors, including the extent of ulceration or gangrene, severity of infection, degree of circulatory impairment, and severity of pain.<sup>108</sup> Ancillary tests such as vascular laboratory studies (see "Cardiovascular Complications in Diabetes") and angiography may be helpful in some patients. Social circumstances such as whether the patient is working or is retired also enter into the decision-making. However, when all these factors are taken into consideration the only definitive test that will indicate whether healing will occur is trial of distal amputation.<sup>113</sup>

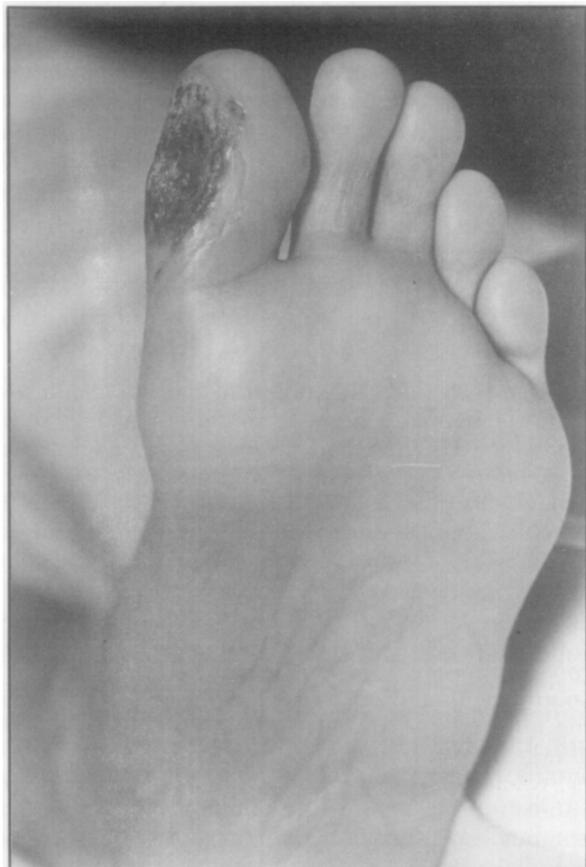
#### *Illustrative Case Report*

A 65-year-old man was seen with Type II diabetes, Parkinson's disease, hypertension, and glaucoma. He had a six-month history of ulceration of the left big toe, which recently had become larger (Fig. 8). There was no history of claudication or rest pain. Peripheral pulses were femoral 2+, popliteal 1+, but with absent dorsalis pedis and posterior tibial pulses. Noninvasive vascular studies showed no evidence of arterial occlusive disease and an ankle-brachial index of greater than 1.0, but distal calcification could not be ruled out. Pulse waveform analysis suggested flow compatible with wound healing. Therefore, the big toe was amputated under appropriate antibiotic cover. (*Staphylococcus aureus*, coagulase-negative staphylococcus, *Enterobacter aerogenes*, and *Morganella morganii* were grown from the ulcer.) Good bleeding was noted at operation. Postoperatively, the wound became infected and despite antibiotic therapy and debridement, failed to heal. (*M. morganii* was grown from the wound.) An arteriogram showed diffuse calcification in both femoral arteries and occlusion of the tibial and peroneal arteries above the ankle. No major arteries were visualized in the foot, but small musculocutaneous branches were seen distally. In view of the excellent pulse waveforms obtained in the forefoot, a transmetatarsal amputation was performed 17 days after the toe amputation. Good bleeding was again noted. This wound also became infected and broke down. (*M. morganii* was grown from the wound.) Despite debridement and appropriate antibiotic therapy, there were no signs of healing, and a below the knee amputation was performed three weeks later. This healed without any problems.

Amputation in diabetics may be performed at one of six levels. The lower the level the better, as healed amputations in the foot permit walking without prostheses. Large parts of the foot may be excised with eventual healing and successful ambulation.<sup>113</sup>

#### *Illustrative Case Report*

A 51-year-old Type II diabetic man developed wet gangrene of the right lateral foot after dropping a heavy weight on it. There was diminished sensation in both feet but no history of claudication or rest pain. Noninvasive vascular studies showed bilateral superficial femoral artery occlusions. The ankle-brachial index was 0.79 on the right side. Analysis of forefoot puls-



**FIG 8.**

Diabetic patient with ulceration on medial side of left big toe. Noninvasive vascular studies suggested sufficient flow to permit healing of a big toe amputation. (Courtesy of Dr. Richard Fowl, University of Cincinnati.)

tions showed excellent waveforms and it was anticipated that the foot would heal after operation. A ray amputation of the fourth and fifth toes was performed under appropriate antibiotic coverage. *Staphylococcus aureus* was grown from the septic area. Seven months later the patient underwent a ray amputation of the opposite big toe for an infected mal perforans ulcer and osteomyelitis. Two months later, after wearing ill-fitting shoes, he developed gangrene of the right third toe, which was amputated. In addition a plantar abscess, caused by *S. aureus*, coagulase-negative staphylococci, beta-hemolytic streptococci, and diphtheroids, was drained and a necrotic area on the dorsum of the foot was debrided (Fig 9). One month later, a gangrenous right second toe was amputated. A meshed split-thickness skin graft was applied to the granulating areas on the dorsum and plantar aspect of the right foot. This healed satisfactorily.



**FIG 9.**

Diabetic patient's right foot after amputation of the lateral three toes for gangrene and drainage of a plantar abscess.

Fortunately, a minor amputation is frequently possible because of the distal location of vascular occlusion in many diabetics, or because amputation is needed for a neuropathic ulcer without vascular compromise. In one series the initial treatment was a minor amputation in 40% of diabetics as compared with 4% of nondiabetics.<sup>144</sup>

Prolonged hospitalization to obtain the most distal amputation is justified because overall mortality is related to the length of the contralateral extremity. Many studies have shown that only a few vascular amputees, particularly those with above the knee amputations, are able to walk with the aid of a prosthesis.<sup>113</sup> On the other hand, it is important at an early stage to recognize those patients in whom a distal amputation is contraindicated, and thus avoid prolonged hospitalization during which successive amputations are performed progressing up the foot and leg.<sup>103, 104</sup>

The most common amputation is of an individual toe, through the base of the distal or proximal phalanx.<sup>113</sup> Amputation through the distal part of the metatarsal bone is preferred to disarticulation through the metatarsophalangeal joint, as the exposed avascular cartilage delays healing.<sup>103</sup> Medial and lateral flaps, which contain the digital blood vessels, are used in performing amputation of the lesser toes, and dorsal and plantar flaps are used for the big toe. Loss of this toe interferes with walking, as it plays an important role in stepping off.

A ray amputation may be performed for complications of neuropathy if the foot has a good circulation.<sup>108</sup> The wound should be packed open in the presence of sepsis; otherwise primary closure is indicated. When gangrene or ulceration involves two or more toes, a transmetatarsal amputation may be the operation of choice. A satisfactory blood supply in the distal foot is essential to ensure healing after all these operations. A Syme amputation, rarely done,<sup>108</sup> is used mainly in patients who do not have enough healthy skin to permit a transmetatarsal amputation or in whom a transmetatarsal amputation has failed. It is of value in patients who have visual disturbances or who would do poorly with crutches or prostheses.<sup>103</sup> A palpable posterior tibial pulse is essential to ensure healing of the stump.

An amputation either below the knee (BKA) or above the knee (AKA) may be necessary whenever a major arterial occlusion unsuitable for vascular reconstruction is present or when there is extensive tissue destruction. It is possible to save the knee in more than 80% of diabetics<sup>113</sup> provided that a BKA is not contraindicated by the level of infection or ischemia, or by a flexion contracture of the knee.<sup>108</sup> Primary closure of the stump is safe if there is no evidence of spread of infection above the ankle.<sup>160</sup>

A tourniquet must not be used when performing any amputation as it may damage an already tenuous blood supply. Tissues must be handled gently and complete hemostasis must be obtained. If possible, drains should be avoided, as they may serve as a portal for infection. The skin flaps should be approximated without tension with fine monofilament sutures.

The rate of primary wound healing is similar in diabetics and non-

diabetics,<sup>113</sup> but the incidence varies in different series. Healing is reported in 33 to 71% of toe amputations, 50 to 70% of transmetatarsal procedures, 28 to 80% of Syme's amputations, 68 to 83% of BKAs, and 82 to 100% of AKAs. Failure of healing occurs as a result of inadequate arterial blood supply, excessive operative trauma, uncontrollable invasive infection, or combinations of these problems. One study suggests that high hemoglobin levels, perhaps by increasing blood viscosity, adversely affect the outcome of amputations at the digital, metatarsal, and transmetatarsal levels.<sup>8</sup> All 18 amputations done in patients with a preoperative hemoglobin less than 12 gm/dl were successful, while all 30 amputations in those with a level more than 13 gm/dl failed. In a series of 312 lower limb amputations in which 51% of the patients were diabetic, overall primary healing occurred in 75% and amputation not requiring a prosthesis was accomplished in 31%.<sup>113</sup> Prolonged periods of hospitalization and intensive wound care were needed to obtain this high rate of foot salvage. In the past, amputations in diabetics had mortality rates of 20 to 40% and the majority were AKAs. More recent reports show decreased mortality rates and a definite trend toward use of more distal amputations. The improvement results from a more aggressive approach to lower extremity revascularization, improved perioperative management, and the concentration of patients in a single surgical service.<sup>113</sup> One study shows that death after lower limb amputation in diabetics occurs mostly in terminally ill bedridden patients and the rate can be kept down to about 5%, a figure similar to that obtained in nondiabetics.<sup>113</sup>

Amputation must not be looked on as a last ditch procedure. In fact it is an important step in rehabilitation. Best results are obtained with the use of a skilled and concerned team, including surgeons, nurses, prosthetists, physical and occupational therapists, social workers, the family practitioner or internist, and the patient's family.

## SURGICALLY CORRECTABLE DIABETES

In many endocrine disorders excessive secretion of a counter-regulatory hormone such as growth hormone, cortisol, catecholamines, or glucagon is accompanied by varying degrees of glucose intolerance.<sup>53</sup> However, because of feedback control mechanisms, overt diabetes with symptomatic hyperglycemia, glycosuria, and ketosis is relatively uncommon, unless an underlying genetic diabetic diathesis is also present. Surgical treatment may eradicate the diabetes or glucose intolerance in several disorders. Transsphenoidal excision of pituitary microadenomas,<sup>14</sup> or adrenalectomy are used in the treatment of Cushing's disease.<sup>116</sup> Surgical removal of pheochromocytomas usually restores or improves glucose tolerance within several weeks of the operation.<sup>55, 164</sup>

In hyperthyroidism mild glucose intolerance occurs in 2 to 57% of patients.<sup>65</sup> Glucose tolerance usually improves with return to the euthyroid state,<sup>65</sup> but may not necessarily do so, since Type I diabetes in some patients may have arisen from autoimmune mechanism similar to that causing hyperthyroidism and the two conditions may coexist.<sup>53</sup> The clinical hallmark of a glucagonoma (an islet cell glucagon-producing tumor of the pancreas) is a triad of glucose intolerance, a distinctive skin rash known as necrolytic migratory erythema, and a normocytic normochromic anemia.<sup>53</sup> The condition should be suspected whenever a diabetic presents with the characteristic skin rash. The diabetes is usually mild and its systemic complications are distinctly uncommon. Significant weight loss is a fairly constant finding and is probably caused by the catabolic effects of glucagon. Of the more than 50 tumors reported most have been malignant. After complete excision total regression of all manifestations of the syndrome has occurred in only a minority of patients.<sup>53, 79</sup> For patients with nonresectable tumors, chemotherapy with streptozotocin, streptozotocin and fluorouracil, or dimethyltriazenoimidazole carboxamide (DTIC) has been used.<sup>53</sup>

Diabetes of mild-to-moderate severity occurred in seven patients with somatostatinomas (somatostatin-secreting tumors) of the pancreas but was absent in two patients with extrapancreatic neoplasms.<sup>53</sup> Raised circulating somatostatin levels may be responsible for other clinical manifestations, including gallbladder disease, diarrhea (with or without steatorrhea), hypo or achlorhydria, anemia, and weight loss. One patient had successful excision of the pancreatic tumor, with complete disappearance of diabetes, and remained asymptomatic six years later, but the others were diagnosed at a late stage when they had significant metastases, culminating in a fatal outcome or necessitating chemotherapy.<sup>53</sup>

## SURGICALLY INDUCED DIABETES

Patients who require partial or total pancreatectomy for chronic pancreatitis or carcinoma should be warned of the risk of developing diabetes. In patients with chronic pancreatitis who underwent 80 to 95% distal resections, the incidence of diabetes increased from a preoperative 28% to a postoperative level of 72%, of whom 80% required insulin.<sup>50</sup> After 40 to 80% resections the incidence of diabetes increased from 17% to 32%, of whom 60% required insulin.<sup>50</sup> Even longitudinal pancreaticojejunostomy (Puestow) was followed by diabetes in 20 to 40% of patients,<sup>115, 168, 169</sup> but this was attributed to the natural progression of islet cell destruction seen in chronic pancreatitis.

After total pancreatectomy initial diabetic management involves adding 10 units of regular insulin to each liter of IV 5% dextrose

solution, augmented by a sliding scale based on periodic blood glucose measurements. When oral feedings start, the IV glucose can be reduced and discontinued after three to four days, while insulin is given subcutaneously as indicated by measurement of blood glucose levels. When oral feeding is adequate the patient is switched to a longer acting insulin, usually in a dose of 20 to 30 units daily.<sup>15</sup> Subsequent management differs from that of ordinary diabetes in that the blood glucose level should be kept higher, at 150 to 200 mg/dl, to prevent hypoglycemia, which is prone to occur in these patients, perhaps because of the absence of pancreatic glucagon.<sup>15, 96</sup> Hypoglycemia may be avoided by augmenting food intake slightly and reducing the insulin dose, particularly when physical activity is increased. Sugar should be carried at all times and should be kept at the bedside. In particular the patient should avoid missing the evening meal, as hypoglycemia is most likely to occur at night if a long-acting insulin has been used. It may be beneficial for the patient to experience a hypoglycemic attack (sweating, tachycardia, undue nervousness) before leaving the hospital and learn that the symptoms can be easily relieved by taking sugar.<sup>96</sup>

## **ORGAN TRANSPLANTATION IN DIABETICS**

### ***RENAL TRANSPLANTATION***

Over the course of approximately 20 years diabetic patients are likely to develop proteinuria, hypertension, and deterioration of renal function. The catabolic and metabolic disturbances of uremia are superimposed on the complications of diabetes, and there may be progression of peripheral neuropathy, retinopathy, and vascular disease.<sup>85</sup> At present there is no treatment that can prevent the development of diabetic glomerulosclerosis and its ultimate progression to end-stage renal failure. That the disease can be reversed is shown by experience with transplantation of two kidneys from a Type I diabetic cadaver donor, which had histologic evidence of diabetic nephropathy, and which were transplanted into two *nondiabetic* recipients. Biopsies seven months after transplantation showed almost complete resolution of the nephropathy.<sup>1</sup>

Diabetics comprise 20 to 30% of all patients referred for dialysis or renal transplantation.<sup>76</sup> Each year approximately 2,000 to 2,500 new patients with Type I diabetes require treatment for end-stage renal disease. Transplantation as treatment for such patients began slowly in the 1970s. At that time diabetics were considered to be a high-risk category, especially when treated with large doses of steroids. With improvements in management, transplantation, as opposed to dialysis, is now regarded as the optimum form of treatment for many diabetics with end-stage renal disease.<sup>76, 85, 149</sup> Besides restoring renal

function, transplantation may result in improvement of motor neuropathy and stabilization or improvement of retinopathy. Variable results have been reported following renal transplantation at various centers. The largest experience at a single center (534 patients with Type I diabetes treated since 1968) has been obtained at the University of Minnesota.<sup>149</sup> In a study of 190 diabetic and 242 nondiabetic patients who received primary renal allografts between July 1979 and December 1982, patient and graft survival rates at two years posttransplantation were very similar in diabetic and nondiabetic recipients of kidneys from HLA-nonidentical related living donors (90% vs. 92% for patient survival, and 86% vs. 83% for graft survival).<sup>149</sup> The corresponding figures for recipients of cadaver kidneys showed somewhat lower patient survival rates in diabetics (83% vs. 90%) and equivalent graft survival rates (73%). However, pooled data from many transplant centers do not show such good results. The Kidney Transplant Histocompatibility study involving 2,418 consecutive cadaver donor transplants showed three-year graft survivals that were statistically significantly inferior in diabetic patients.<sup>77</sup> Similar findings, using a different patient population, were obtained in an analysis of 1,549 transplants reported to the South Eastern Organ Procurement Foundation.<sup>77</sup> Analysis of the large data base at the UCLA registry involving more than 100 transplant centers and approximately 20,000 patients showed one-year graft survivals in diabetic patients vs. nondiabetic recipients, whose underlying disease was pyelonephritis, to be 56% vs. 79% in recipients of parental kidneys, 75% vs. 90% in recipients of HLA-identical sibling kidneys, and 45% vs. 60% in recipients of cadaver kidneys.<sup>26</sup>

The above studies were almost exclusively done on patients treated with what was formerly conventional immunosuppressive therapy (azathioprine, prednisone, and anti-lymphocyte globulin). The introduction of cyclosporine produced no improvement over conventional therapy in one study but a significant improvement in another. In a randomized trial at the University of Minnesota of 129 diabetic and 101 nondiabetic patients, the differences between diabetic and nondiabetic recipients and between cyclosporine and conventionally treated patients were not statistically significant.<sup>149</sup> In another study of 43 diabetic patients, two-year graft and patient survivals in cyclosporine-treated patients were 70% and 93% compared to 65% and 83% in 17 conventionally treated patients.<sup>123</sup> However, these results must be treated with caution as historical controls were used rather than a randomized approach.

In the University of Minnesota study, although microscopic evidence of diabetic nephropathy was detected in biopsies performed four or more years after transplantation, no allografts failed because of this complication, even in patients followed up more than ten years.<sup>149</sup> However, despite the restoration of satisfactory renal func-

tion, diabetes continued to exert its toll. Of 26 patients who survived more than ten years after transplantation five (19%) had myocardial infarctions, four (15%) had strokes, 19 (73%) had cataracts, ten (38%) were blind, and eight (31%) had had lower extremity amputations. Ten years after transplantation, six patients (23%) were "active." As cardiovascular disease is the major cause of death of diabetic transplant patients,<sup>85,149</sup> some workers perform routine coronary angiography, even in asymptomatic individuals, and avoid transplantation in those with severe coronary artery disease.<sup>76,85</sup> In one study 45% of patients had significant coronary artery disease. Patient and graft survival were much better in patients without such disease.<sup>85</sup> To avoid other vascular complications after transplantation, diabetics should also have preoperative noninvasive studies of the cerebral and peripheral vascular systems.

### PANCREATIC TRANSPLANTATION

The first human pancreatic transplant was performed in 1966. Only small numbers of transplants were performed until the 1980s, when, as a result of technical improvements and better immunosuppressive management, the whole field of pancreatic transplantation has opened up. Thus, in the two-year period starting in January 1983 more transplants were performed than in the preceding 17 years.<sup>150-152</sup> Up until January 1985, 561 pancreas transplants (excluding islet cell transplants) had been performed on 525 patients at 60 institutions. Cadaver donors were the source of most of the grafts, but living donors were used in 41 instances. Currently, pancreatic transplantation is being offered to diabetics whose complications are, or potentially will be, more serious than the potential side effects of long-term immunosuppressive therapy.<sup>150-152</sup> Patients who need or have had a renal transplant, and who are already receiving immunosuppressive therapy, are major candidates. Others are those diabetics who have preproliferative retinopathy and who are likely to become blind, or who have albuminuria and will ultimately develop progressive nephropathy. Patients who have hypoglycemic reactions while on insulin pump or other intensive insulin regimens may also benefit from pancreatic transplantation. Pancreatic transplantation is the most physiologic method of obtaining a euglycemic state.

Either the whole organ or the distal segment (body and tail), comprising about 50% of the gland, may be transplanted. In the former case the pancreas is removed with the portal vein and an aortic patch bearing the celiac axis or this vessel together with the superior mesenteric artery. Vascular anastomoses are made to the recipient's iliac vessels. When the distal segment is used, the celiac axis or splenic artery, and the portal or splenic vein are used for revascularizing the organ by anastomosis to the iliac vessels. One group anas-

tomoses the donor splenic vessels to those of the recipient so that the hormones secreted by the gland will be directed into the portal rather than the systemic circulation.<sup>22</sup> Another group has used the recipient's inferior mesenteric vessels for the same purpose.<sup>57</sup> Whether there is a metabolic advantage in providing portal drainage is not clear at present. Some surgeons leave the spleen attached to the pancreatic graft to increase blood flow and thus reduce the risk of thrombosis of the splenic vessels. However, this procedure has no advantages and may cause serious graft-versus-host disease. Major differences in technique exist regarding the handling of the exocrine secretions of the pancreas. Using the whole organ some surgeons transplanted it together with the duodenum. As leaks occurred because of rejection or technical problems, most surgeons abandoned this approach and either retained a segment of duodenum adjacent to the ampulla of the Vater, or only the ampulla itself, or have removed all the duodenum and used the pancreatic duct for anastomosis. Dissection of the entire duodenum from the pancreatic allograft reduces the risk of enteric contamination from the donor. The exocrine secretions from the whole gland or the distal pancreatic segment have been drained into a Roux loop of small bowel, the stomach, the ureter, or bladder.<sup>150-152</sup> In the latter two cases no damage to these structures occurs, as the enzymes are secreted into the urine in an inactive form. Patients with drainage into the urinary system may have problems with acidosis because of loss of sodium bicarbonate in the pancreatic secretions being voided in the urine.<sup>158</sup> This complication is avoided with a duct-enteric or duodenenteric anastomosis. Because of problems with pancreatic fistulas, pancreatitis, or sepsis with the use of these techniques, some surgeons have left the pancreatic duct open and draining freely into the peritoneal cavity from which the secretions are safely absorbed, provided that they are not activated. However, as some patients developed pancreatic ascites after this procedure it has largely been abandoned. Other surgeons have tried to obliterate the exocrine drainage by ligating the pancreatic duct or injecting the entire ductal system with a synthetic polymer such as neoprene. The disadvantage of the latter technique is that it stimulates fibrosis in the pancreas, which eventually may encompass the islets and cause failure of the graft.

If a living related donor is used the donor must have a normal glucose tolerance test preoperatively.<sup>150-152</sup> The body and tail are removed with ligation of the splenic artery and vein near the splenic hilum, leaving the spleen *in situ*. It usually remains viable because of the collateral blood supply from the stomach. No donors have died. However, two required reoperations, one having a splenectomy, and the other requiring ligation of the pancreatic duct at the level of transection.<sup>150-152</sup> In some donors there was a change in the

glucose tolerance tests postoperatively, but this was physiologically significant in only one individual. In using cadaver donors the surgeon usually has the option of removing the whole gland or only the distal segment. However, because of the shortage of donors some are being used for harvest of both the liver and pancreas. In such cases only the distal pancreas (with the splenic vessels) is removed in order to leave the maximal length of portal vein with the liver allograft.

In some cases, as with the use of a living related donor, the pancreas can be transplanted immediately after removal from the donor. In others the graft must be preserved using hypothermic electrolyte solutions. Although early graft loss was less with organs preserved for less than six hours than with those preserved for longer periods, the differences in graft survival at one year were not significant (34% vs. 26%).<sup>150-152</sup>

Approximately 80% of pancreatic transplant recipients have had renal transplants either at the same operation or prior to the pancreatic transplant.<sup>150-152</sup> The success rate of the pancreatic grafts was much the same in those who had kidney transplants as in those who did not. However, patient survival rates were higher in patients who received pancreas grafts only than in those who had kidney transplants as well. The difference is easy to explain, as the former group did not have uremia and other advanced complications of diabetes. However, the fact that patient survival rates were also higher in uremic diabetics who received a kidney transplant before undergoing pancreatic transplantation suggests that there is a penalty for transplanting both organs at the same operation rather than metachronously.<sup>152</sup> The lesson is that in uremic diabetic patients the first step should be to correct the uremia with renal transplantation before attempting to cure the diabetes with pancreatic transplantation.

Before 1977 one-year patient survival rates after pancreatic grafting were only 39% and graft survivals were 3%.<sup>150-152</sup> The results have been steadily improving since then. In 1983 and 1984 the one-year patient survival rate was 77% and one-year graft survival was 40%. The introduction of cyclosporine has contributed to these improved results. If only technically successful grafts are considered, the one-year graft survival rate in 257 recipients treated with cyclosporine was 46%, compared with 26% in 143 patients treated with conventional immunosuppressive therapy.<sup>150-152</sup> The graft survival rate is higher for pancreases from related donors (15/35, 43% functioning) than from cadaver donors (9/51, 18% functioning).<sup>150</sup>

Of the 561 transplants reported to the Pancreas Transplant Registry, 110 (20%) were technical failures for reasons including vascular thrombosis, infection, ascites, bleeding, inadequate preservation, pancreatitis, and pancreatic fistulas. Another 231 grafts (41%) failed because of rejection or from undetermined causes, and 79 (14%)

technically successful grafts functioned until the patients died. As of May 15, 1985 140 patients were alive with functioning grafts. The longest survivor is now 5.7 years posttransplant with a functioning graft.<sup>150</sup>

The diagnosis of pancreatic allograft rejection is difficult. Often it is suspected because an associated renal allograft shows clinical, biochemical, or histological evidence of rejection. However, renal or pancreatic allograft rejections may occur quite independently. In patients with urinary drainage of pancreatic secretions, rejection may be suspected if there is a significant drop in the 24-hour output of urinary amylase. Otherwise, rejection should be suspected whenever there is hyperglycemia. Therefore, home monitoring of blood glucose levels with glucometers by the patient or spouse is important. However, hyperglycemia may be a late feature of rejection and frequently indicates irreversible islet destruction.<sup>74</sup> On the other hand, hyperglycemia may result from steroid therapy and may not necessarily reflect graft dysfunction.

Although C-peptide levels (decreases suggest islet cell destruction) can distinguish these causes of high blood glucose, they are rarely available in time to be of clinical value.<sup>74</sup> Cyclosporine may also cause impairment of glucose tolerance, perhaps by causing insulin resistance.<sup>62</sup> Serum amylase levels are of little value in the diagnosis of rejection.<sup>156</sup> Ultrasound studies, while helpful in detecting intra- or extrapancreatic fluid collections, have been of limited value in diagnosing rejection and cannot distinguish between pancreatitis and rejection.<sup>75</sup> Selenomethionine scans are of little value because the long half-life (70 days) of the agent leads to a persistent image that precludes sequential imaging of the graft, and also gives a relatively high dose of radiation to the patient. <sup>99m</sup>Tc DTPA scans and arteriography are unlikely to detect early rejection, as both techniques rely on deterioration of graft perfusion as an indicator of rejection. As platelets are deposited in organs undergoing rejection use of 111-indium oxine labeled autogenous platelets has been found to be of value in the diagnosis of rejection.<sup>74</sup> Early use of graft biopsy may also be of value.<sup>150</sup> Percutaneous needle biopsy is not used because of risks of hemorrhage or fistula formation. Open biopsy requires laparotomy and carries risks of morbidity and even mortality.<sup>74</sup> Biopsy may be helpful in distinguishing between rejection (characterized by vasculitis), fibrosis caused by duct injection, and recurrence of the autoimmune disease (with "isletitis" and selective beta-cell destruction).<sup>137</sup> However, it is remarkable that in ten of 31 biopsies the islets appeared normal despite clinical and pathological evidence of rejection. With treatment rejection can be reversed in a third of histologically proven cases.<sup>137</sup>

Another problem with pancreatic transplantation is recurrence in

the graft of the original autoimmune disease that caused the diabetes in the first place. This has been observed in pancreas transplants between identical twins.<sup>150, 153</sup>

#### *ISLET CELL ALLOTTRANSPLANTATION*

A theoretical advantage of using only the islets for transplantation is the simplicity of the method—there are no needs for vascular anastomoses and no problems with handling of the pancreatic exocrine secretions. The pancreas is removed from the donor, minced into small pieces, treated with collagenase to separate off as much of the exocrine tissue as possible, and the residue injected into the recipient. Various sites have been used, including subcutaneous, intramuscular, intraperitoneal, intraportal, and intrasplenic. The latter two routes have been used most commonly in humans.

Up to June 1984, 166 pancreatic islet allografts in humans were reported to the International Registry.<sup>151</sup> However, no patient is currently insulin-independent. Various reasons have been advanced for the high failure rate.<sup>156</sup> (1) An insufficient number of islets transplanted. Yields of islets varying from 5% in most cases to less than 20% in one study have been reported. (2) The islets are more immunogenic than the whole pancreas. A major problem is the difficulty in distinguishing between technical failures due to transplantation of inadequate numbers of islet cells and graft rejection. Transplants of neonatal and fetal islets have been done in an attempt to increase yields of islets, and to decrease immunogenicity.<sup>155</sup> Other attempts to reduce immunogenicity include culture of the islets prior to transplantation to remove passenger leukocytes and/or dendritic cells, pretreatment with antidendritic cell antibodies, graft irradiation (2,000 rad), pretreatment with antilymphocyte globulin, treatment of the islets with ultraviolet light, and placement of the islets in diffusion chambers at the time of transplantation in an attempt to protect them from rejection.<sup>64, 155</sup> (3) Corticosteroid administration disturbs carbohydrate metabolism and increases the load on the beta-cells of the islets. (4) Transplantation to inappropriate sites outside the portal venous drainage area.

#### *PANCREATIC AUTOTRANSPLANTATION*

Total or near-total pancreatectomy to relieve the severe pain of chronic pancreatitis usually leads to insulin-dependent diabetes mellitus (see "Surgically Induced Diabetes"). Although it produces pain relief the operation has been used sparingly because of the risk of inducing a brittle diabetes in a patient who may continue to consume alcohol in large quantities. Attempts have been made to pre-

vent this complication either by autotransplantation of a segment of the pancreas or of the pancreatic islets. Before undertaking such procedures islet cell function should be evaluated, since diabetes occurs in 12 to 45% of patients with chronic pancreatitis.<sup>100, 156</sup> Function can be evaluated by performing an oral glucose test and measuring blood levels of glucose, insulin, and C-peptide.<sup>156</sup> An arginine stimulation test followed by repeat measurements of these three compounds can also be done.

### *Islet Cell Autografting*

The technique of preparing the islets and the sites of injection are the same as with islet cell allografting. A problem not encountered with harvesting islets from a normal pancreas is a lower yield of islets from the fibrotic gland affected by chronic pancreatitis.<sup>156</sup> The intraportal site was used in 59 of 64 cases reported.<sup>156</sup> However, unlike allotransplantation, use of this site for autografting results in complications.<sup>15</sup> Transient elevations of portal pressure during infusion are relatively common, and death has resulted in at least three cases. Other complications, probably resulting from infusing large volumes of enzymatically active nonpurified tissue into the portal circulation, include systemic hypotension, elevated liver enzymes, portal vein occlusion, and disseminated intravascular coagulation. Two cases of fatal hepatic infarction have been reported.<sup>157</sup> Some surgeons have injected pancreatic islets underneath the renal capsule, as this may be an immunologically privileged site.<sup>156</sup> Long-term follow-up of patients so treated is needed. By March 1982, 76 cases of pancreatic islet cell autotransplantation had been reported to the International Registry. Withdrawal of insulin therapy was possible in 25 to 40% of patients treated at several large centers.<sup>156</sup> The extent of pancreatectomy varied from 70 to 100%. A problem in interpreting the results of islet cell autotransplantation is that the pancreatic remnant may produce some or all of the insulin needed to control the blood glucose. This may account for the better results seen when lesser amounts of pancreas were resected.<sup>156</sup>

### *Segmental Pancreatic Autotransplantation*

The body and tail of the pancreas removed from patients undergoing near-total or total pancreatectomy can be transplanted to the femoral triangle with anastomosis of the splenic to the femoral vessels. An arteriovenous fistula may be created between the splenic vessels to maintain flow. The pancreatic duct is ligated.

Segmental autografts have been successful, with no need for insulin in six of eight reported cases, seven for chronic pancreatitis, and one for pancreatic cancer involving the head of the gland.<sup>68, 92, 159</sup> The latter patient remains well eight months after operation.<sup>92</sup>

## **NEW METHODS OF INSULIN ADMINISTRATION (INSULIN PUMPS)**

Over the past half century, our ability to alter the development and progression of macro- and microvascular complications of diabetes has changed very little. The advent of reliable methods for measurement of blood glucose concentrations by the patient provided an impetus for the development of new methods of insulin administration, which are aimed at maintaining blood glucose concentrations in the nondiabetic range in the hope of preventing chronic complications.<sup>120</sup>

### ***POR TABLE PUMPS***

Portable pumps carried in a harness have been devised for continuous infusion of insulin subcutaneously, intravenously, or intraperitoneally. These are programmed to deliver insulin at variable rates. The intraperitoneal method should provide the most physiological approach, as studies in animals have shown that such insulin is absorbed into the portal venous system.<sup>124</sup> However, there is no clinical evidence that intraperitoneal delivery is any better than IV administration. Absorption of insulin delivered subcutaneously is slow and variable,<sup>127</sup> and the method requires frequent glucose measurements and consistency in both diet and exercise to maintain normoglycemia. In consequence, a substantial number of patients are unable to comply with the demands.<sup>95</sup> Complications include catheter obstruction and infection at the injection site. Hypoglycemia is a risk of intensive insulin therapy and is particularly a problem in patients with hypoglycemic unawareness or counterregulatory defects or in individuals who become obsessed with "total normalization" of blood glucose levels.<sup>120</sup> On the other hand severe hyperglycemia and ketoacidosis may occur through occlusion of the catheter, leakage, or pump failure.

In a study of 161 patients treated with subcutaneous insulin pumps, 42% developed infected infusion sites, ketoacidosis, and hypoglycemic coma, which occurred once in every 27, 78, and 175 patient months, respectively.<sup>94</sup> Whereas skin infections at injection sites are virtually nonexistent in patients receiving conventional insulin therapy, they are by far the most common complication associated with the use of insulin pumps. An infected pump site was implicated in the development of toxic shock syndrome and another caused fatal bacterial endocarditis.<sup>94</sup> In Mecklenberg's series,<sup>94</sup> 46 patients (29%) had a total of 109 infected infusion sites. Most had cellulitis, but eight patients had abscesses that required incision and drainage. *Staphylococcus aureus* was the most common organism.

Insulin delivered IV may be given at a constant basal rate that is augmented at meal times.<sup>109</sup> The overnight basal rate is adjusted to maintain fasting normoglycemia. Intravenous delivery systems have been complicated by phlebitis, infection, kinking of the catheter, disruption of flow, and limitation of activity. These problems can be avoided by using biologically inert central venous catheters that are surgically placed under full aseptic conditions and tunneled subcutaneously.<sup>109</sup>

### ***IMPLANTABLE PUMPS***

Portable pumps are cumbersome, restrict the patient's daily activities, prevent contact sports, swimming, and showering, and carry a major risk of infection at the site of entry of the catheter into the body. To avoid these problems, surgeons have used, in animal and human studies, a variety of implantable pumps placed subcutaneously, much like a pacemaker battery pack.<sup>18,21</sup> These deliver insulin via a Silastic catheter either into the superior vena cava or the peritoneal cavity.

Desirable features of an implantable insulin delivery system include (1) reliability and fail-safe operation, (2) implantability and explantability under local anesthesia, (3) long battery life, (4) multiple insulin delivery rates, (5) small size and weight, (6) biocompatible materials, (7) remote programmability based on recipient blood glucose monitoring, and (8) ability to deliver concentrated insulin with infrequent reservoir refilling.<sup>128</sup> Three basic varieties of pump are under investigation.<sup>18</sup> One is a vapor-pressure-powered pump that is divided into two compartments by a metal bellows that is the only movable part. The charging fluid (a fluorocarbon), placed in the outer chamber, expands at a fixed rate at body temperature to a vapor phase, which exerts pressure on the bellows and thus on the inner chamber from which the infusate is expelled through a bacterial filter, a capillary drop pressure mechanism and a silicone rubber catheter into the desired location. Most parts of the pump are made of titanium. The device is refilled biweekly by a percutaneous needle injection that simultaneously fills the infusate chamber and recompresses the fluorocarbon power source. A variety of peristaltic pumps are available. They rely on a series of rollers that compress a flexible tube carrying insulin from a reservoir and force it onward through the catheter. They are powered by lithium batteries with a two-year life. A third type of pump is a pulsatile pump that uses a solenoid-driven reciprocating chamber with two check valves to move infusate out from the reservoir and through the delivery catheter. It is powered by a lithium battery estimated to have ten years of function *in vivo*. Peristaltic or pulsatile solenoid pumps are programmable so that infusion rates can be varied.<sup>18</sup>

Early results with these pumps have shown improvement in mean postprandial glucose and mean fasting glucose values and normalization of glycosylated hemoglobin levels. The pumps with IV delivery systems have been of particular benefit in a small group of high-risk patients who are resistant to subcutaneous or intramuscular insulin.<sup>20</sup> Most effective control of the blood glucose requires constant rate insulin infusion by the pump, with supplemental prandial injections of subcutaneous insulin. Such treatments have decreased the frequency of hyper- and hypoglycemic episodes. Although not always eliminated, hypoglycemic episodes were nearly always minor. There are body counter-regulatory mechanisms that seem to compensate even for the continuous flow of insulin from the device during the night.<sup>20</sup> An improvement in some of the lipid abnormalities of diabetes even in the absence of concurrent improvement in glycemic control (measured by glycosylated hemoglobin) also has been reported.<sup>29</sup> Patient acceptance of the pumps has been high, with minimal interference with the recipient's life-style and with minimal risk of infection.<sup>18-20</sup> Problems encountered include battery failure, electronic failure, catheter damage, and late plugging of IV catheters by fibrin, or the formation of an occluding fibrinous "cocoon" around intraperitoneal catheters. Some investigators have abandoned the intraperitoneal route in favor of the IV approach because of this complication. Others have used laparoscopic removal of fibrous adhesions in an attempt to restore function to intraperitoneal catheters.<sup>21</sup>

A theoretical risk of continuous insulin infusion is the development of secondary amyloidosis due to chronic administration of insulin aggregates.<sup>120</sup> Another theoretical risk of systemic hyperinsulinemia is acceleration of development of atherosclerosis.<sup>147</sup>

At present we do not know whether lowering the blood glucose level will reduce the severity or progression of the microvascular and other complications of diabetes. We need large-scale clinical trials such as the ongoing Diabetes Control and Complications trial to assess the long-term benefits and risks of intensive insulin therapy.<sup>118</sup>

## **PREVENTION OF DIABETIC COMPLICATIONS**

In recent years, advances in self-monitoring of blood glucose levels and in self-administration of insulin have provided better control of the metabolic abnormalities of diabetes, and hopefully will reduce the vascular, neurologic, and infectious complications associated with poorly controlled diabetes.<sup>140, 163</sup> Long-term follow-up of such patients with conventionally treated controls may provide the answer to this very important question. In addition, it may be possible to reduce the risk factors associated with vascular disease by control of obesity, hyperglycemia, hypercholesterolemia, hypertriglyceride-

mia, and hypertension, and by avoidance of cigarette smoking and sedentary habits.<sup>28,42</sup> Preventive measures include a diet containing reduced amounts of saturated fats, cholesterol, and total calories, and a high fiber content. Drugs that lower serum cholesterol or lipid levels are also being evaluated. Up to the present time, pancreatic transplantation has been used only in patients with advanced disease. With more experience this operation will be done earlier before the onset of serious complications and hopefully, by providing a source of insulin, which responds to the body's varying needs, will provide complete control of the diabetes and arrest the progression of retinopathy, vascular disease, neuropathy, and nephropathy.

Patients must be seen at regular intervals by their physicians, who should evaluate them as a whole, paying particular attention to the condition of cardiovascular, neurologic, renal, and ophthalmic systems and to the lower extremities. The patients must be taught to recognize signs of infection such as fever, malaise, redness, swelling, or discharge, and should report promptly to their physicians if these develop, or if they develop a significant break in the skin that fails to heal. In particular, the lower limbs should be evaluated. The feet should be examined for nail abnormalities, fungal infections, corns, calluses, and bony exostoses. Correction of these abnormalities may prevent the development of more serious complications.

A great effort must be made to educate patients about the care of their feet, particularly those who already have neuropathy. Some patients are remarkably unconcerned about their problems, have little insight, and are guilty of self-neglect.<sup>38</sup> Good foot care is essential.<sup>13,80,82,108</sup> This includes daily examination of the feet by patients or their spouses, if the patient's vision is poor. The feet should be kept clean and dry, and tight-fitting shoes or socks should not be worn. Patients should avoid using mended socks, or socks with seams, and should change the socks daily. If the feet are cold at night, the patients should wear bed socks, but should not use hot water bottles or heating pads. They should avoid trauma to the feet, including application of strong chemicals in the form of "corn removers." Patients should not walk barefooted, especially on hot surfaces such as sandy beaches and around swimming pools. Shoes should be inspected daily for foreign objects, nail points, and torn linings. Toenails, corns, and minor foot problems should be given proper care, usually by a podiatrist. Epidermophytosis should be treated promptly. Patients or spouses should be given a set of written instructions outlining the various preventive measures. Patients must be taught to seek medical care promptly even for a trivial lesion, such as an ulcerated callus or an infected ingrown toenail, because if it is left unattended it may progress to a potentially life-threatening complication requiring a major amputation.

## REFERENCES

1. Abouna GM, Al-Adnani MS, Kremer GD, et al: Reversal of diabetic nephropathy in human cadaveric kidneys after transplantation into non-diabetic recipients. *Lancet* 1983; 2:1274-1276.
2. Adams MA, Majewski JT, Kiselow MC, et al: Diabetic vascular access: Dialysis. *Transplantation* 1986; 15:307-308.
3. Adams RD, Asbury AK: Diseases of the peripheral nervous system, in Petersdorf RG, Adams RD, Braunwald E, et al: *Harrison's Principles of Internal Medicine*, ed 10. New York, McGraw-Hill Book Co, 1983, p 2161.
4. Allison SP, Tomlin PJ, Chamberlain MJ: Some effects of anaesthesia and surgery on carbohydrate and fat metabolism. *Br J Anaesth* 1969; 41:588-593.
5. Ariyan S, Halasz NA: The incidence of postoperative gram-negative shock in diabetics. *Am J Med Sci* 1967; 254:808-815.
6. Aronson SM: Intracranial vascular lesions in patients with diabetes mellitus. *J Neuropathol Exp Neurol* 1973; 32:183-196.
7. Auer I, Hurley JJ, Binnington B, et al: Distal tibial vein grafts for limb salvage. *Arch Surg* 1983; 118:597-602.
8. Bailey MJ, Johnston CLW, Yates CJP, et al: Preoperative haemoglobin as predictor of outcome of diabetic amputations. *Lancet* 1979; 2:168-170.
9. Benson BB, Lacy PE: Diabetic microangiopathy in human toes, with emphasis on the ultrastructural change in dermal capillaries. *Am J Pathol* 1964; 45:41-58.
10. Barnes RW: Discussion of Gibbons GW, Wheelock FC Jr, Siembieda C, et al: Noninvasive prediction of amputation level in diabetic patients. *Arch Surg* 1979; 114:1253-1257.
11. Bell ET: Incidence of gangrene of the extremities in non-diabetic and in diabetic persons. *Arch Pathol* 1950; 49:469-473.
12. Bessman AN, Wagner W: Non-clostridial gas gangrene: Report of 48 cases and review of the literature. *JAMA* 1975; 233:958-963.
13. Boulton AJM: Detecting the patient at risk for diabetic foot ulcers. *Pract Cardiol* 1983; 9:135-145.
14. Bigos ST, Somma M, Rasio E, et al: Cushing's disease: Management by transsphenoidal microsurgery. *J Clin Endocrinol Metabol* 1980; 50:348-354.
15. Braasch JW, Rossi RL: Total pancreatectomy for chronic pancreatitis, in Brooks JR (ed): *Surgery of the Pancreas*. Philadelphia, WB Saunders Co, 1983, pp 247-262.
16. Brandman O, Redisch W: Incidence of peripheral vascular changes in diabetes mellitus. *Diabetes* 1953; 2:194-198.
17. Bridges RA, Barnes RW: Segmental limb pressures, in Kempczinski RF, Yao JST (eds): *Practical Noninvasive Vascular Diagnosis*. Chicago, Year Book Medical Publishers Inc, 1982, pp 79-92.
18. Buchwald H: Implantable drug infusion devices. *Surg Rounds* 1984; 7:16-23.
19. Buchwald H, Chute EP: Implantable infusion devices: Gadgets for the future. *Bull Am Coll Surg* 1985; 70:16-17, 24.
20. Buchwald H, Chute EP, Goldenberg FJ, et al: Implantable infusion pump management of insulin resistant diabetes mellitus. *Ann Surg* 1985; 202:278-282.
21. Buchwald H: Personal communication, 1986.
22. Calne RY: Paratopic segmental pancreas grafting: A technique with portal venous drainage. *Lancet* 1984; 1:595-597.

23. Campbell DR, Hoar CS Jr, Wheelock FC Jr: Carotid artery surgery in diabetic patients. *Arch Surg* 1984; 119:1405-1407.
24. Carter SA: The relationship of distal systolic pressures to healing of skin lesions in limbs with arterial occlusive disease, with special reference to diabetes mellitus. *Scand J Clin Lab Invest* 1973; 31(suppl 128):239-243.
25. Casey JI: Host defense and infections in diabetes mellitus, in Ellenberg M, Rifkin H (eds): *Diabetes Mellitus. Theory and Practice*, ed 3. New York, Medical Examination Publishing Co Inc, 1983, pp 667-678.
26. Cats S, Terasaki PI, Perdue S, et al: Increased vulnerability of the donor organ in related kidney transplants for certain diseases. *Transplantation* 1984; 37:575-579.
27. Chopra JS, Hurwitz LJ, Montgomery DAD: The pathogenesis of sural nerve changes in diabetes mellitus. *Brain* 1969; 92:391-418.
28. Christlieb AR: Treating hypertension in the patient with diabetes mellitus. *Med Clin N Am* 1982; 66:1373-1388.
29. Chute EP, Barbosa JJ, Rupp WM, et al: Reduction of plasma cholesterol and LDL-cholesterol by continuous intravenous insulin infusion. *Surgery* 1985; 98:656-661.
30. Chycota NN, Gau GT, Pluth JR, et al: Myocardial revascularization: Comparison of operability and surgical results in diabetic and non-diabetic patients. *J Thorac Cardiovasc Surg* 1973; 65:856-862.
31. Cluff LE, Reynolds RC, Page DL, et al: Staphylococcal bacteremia and altered host resistance. *Ann Intern Med* 1968; 69:859-873.
32. Cohn I Jr, Bornside GH: Infections, in Schwartz SE (ed): *Principles of Surgery*, ed 4. New York, McGraw-Hill Book Co, 1984, pp 165-198.
33. Colwell JA, Halushka PV, Sarji KE, et al: Vascular disease in diabetes: Pathophysiological mechanisms and therapy. *Arch Intern Med* 1979; 139:225-230.
34. Cruse PJE, Foord R: A five-year prospective study of 23,649 surgical wounds. *Arch Surg* 1973; 107:206-210.
35. Ctereteck GC, Dhanendran M, Hutton WC, et al: Vertical forces acting on the feet of diabetic patients with neuropathic ulceration. *Br J Surg* 1981; 68:608-614.
36. Dardik H, Bernhard VM, Mannick JA, et al: Tibial peroneal arterial reconstruction (symposium). *Cont Surg* 1979; 14:83-117.
37. DaValle MJ, Baumann FG, Mintzer R, et al: Limited success of lumbar sympathectomy in the prevention of ischemic limb loss in diabetic patients. *Surg Gynecol Obstet* 1981; 152:784-788.
38. Delbridge L, Appleberg M, Reeve TS: Factors associated with the development of foot lesions in the diabetic. *Surgery* 1983; 93:78-82.
39. Dellinger EP, Wertz MJ, Meakins JL, et al: Surgical infection stratification system for intraabdominal infection. *Arch Surg* 1985; 120:21-29.
40. De Palma RG: Impotence in vascular disease: Relationship to vascular surgery. *Br J Surg* 1982; 69(suppl):S14-S16.
41. De Palma RG, Kedia K, Persky L: Surgical options in the correction of vasculogenic impotence. *Vasc Surg* 1980; 14:92-103.
42. Dunn FL: Hyperlipidemia and diabetes. *Med Clin N Am* 1982; 66:1347-1360.
43. Ecker ML, Jacobs BS: Lower extremity amputation in diabetic patients. *Diabetes* 1970; 19:189-195.
44. Fagerberg SE: Diabetic neuropathy: A clinical and histological study on the significance of vascular affections. *Acta Med Scand* 1959; 164(suppl 345): 1-99.
45. Farrington M, Webster M, Fenn A, et al: Study of Cardiothoracic wound infection at St. Thomas Hospital. *Br J Surg* 1985; 72:759-762.

46. Fein FS, Scheuer J: Heart disease in diabetes, in Ellenberg M, Rifkin H (eds): *Diabetes Mellitus: Theory and Practice*, ed 3. New York, Medical Examination Publishing Co Inc, 1983, pp 851-861.
47. Feldman M, Feldman M Jr: The association of coronary artery occlusion and infarction with diabetes mellitus: A necropsy study. *Am J Med Sci* 1954; 228:53-56.
48. Ferrier TM: Comparative study of arterial disease in amputated lower limbs from diabetics and non-diabetics. (with special reference to feet arteries). *Med J Aust* 1967; 1:5-11.
49. Foster DW: Diabetes mellitus, in Petersdorf RG, Adams RA, Braunwald E, et al (eds): *Harrison's Principles of Internal Medicine*, ed 10. New York, McGraw-Hill Book Co, 1983, p 661.
50. Frey CF, Child CG III, Fry W: Pancreatectomy for chronic pancreatitis. *Ann Surg* 1976; 184:403-414.
51. Fuller JH, Keen H, Jarrett RJ, et al: Haemostatic variables associated with diabetes and its complications. *Br Med J* 1979; 2:964-966.
52. Galloway JA, Shuman CR: Diabetes and surgery: A study of 667 cases. *Am J Med* 1963; 34:177-191.
53. Ganda OP, Soeldner JS: Diabetes secondary to endocrinopathies, in Ellenberg M, Rifkin H (eds): *Diabetes Mellitus. Theory and Practice*, ed 3. New York, Medical Examination Publishing Co Inc, 1983, pp 1005-1020.
54. Gibbon GW, Wheelock FC Jr, Hoar CS Jr, et al: Predicting success of forefoot amputations in diabetics by noninvasive testing. *Arch Surg* 1979; 114:1034-1036.
55. Glenn F, Mannix H Jr: The surgical management of chromaffin tumors. *Ann Surg* 1968; 167:619-629.
56. Godec CJ, Cass AS, Berkseth R: Emphysematous pyelonephritis in a solitary kidney. *J Urol* 1980; 124:119-121.
57. Sutherland DER, Goetz FC, Moudry KC, et al: Use of recipient mesenteric vessels for revascularization of segmental pancreas grafts: Technical and metabolic considerations. *Transplant Proc* 1987; 19:2300-2304.
58. Goldenberg S, Alex M, Joshi RA, et al: Nonatheromatous peripheral vascular disease of the lower extremity in diabetes mellitus. *Diabetes* 1959; 8:261-273.
59. Goldner MG: The fate of the second leg in the diabetic amputee. *Diabetes* 1960; 9:100-103.
60. Goodkin G: Mortality factors in diabetes: A 20 year mortality study. *J Occup Med* 1975; 17:716-721.
61. Guggenheim W, Koch G, Adams AP, et al: Femoral and popliteal occlusive vascular disease: A report on 143 diabetic patients. *Diabetes* 1969; 18:428-433.
62. Gunnarsson R, Klintmalm G, Lundgren G, et al: Deterioration in glucose metabolism in pancreatic transplant recipients given cyclosporine. *Lancet* 1983; 2:571-572.
63. Haimovici II: Peripheral arterial disease in diabetes mellitus, in Ellenberg M, Rifkin H (eds): *Diabetes Mellitus: Theory and Practice*. New York, McGraw-Hill Book Co, 1970, pp 890-911.
64. Hardy MA, Lau H, Weber C, et al: Pancreatic islet transplantation: Induction of graft acceptance by ultraviolet irradiation of donor tissue. *Ann Surg* 1984; 200:441-450.
65. Harrison LC, Flier JS: Diabetes associated with other endocrine diseases, in Podolsky S, Viswanathan M (eds): *Secondary Diabetes: The Spectrum of the Diabetic Syndromes*. New York, Raven Press, 1980, pp 269-286.

66. Hertzer NR, Loop FD, Taylor PC, et al: Combined myocardial revascularization and carotid endarterectomy: Operative and late results in 331 patients. *J Thorac Cardiovasc Surg* 1983; 85:577-589.
67. Hjortrup A, Sorensen C, Dyremose E, et al: Influence of diabetes mellitus on operative risk. *Br J Surg* 1985; 72:783-785.
68. Hogle H, Reemtsma K: Pancreatic autotransplantation following resection. *Surgery* 1978; 83:359-362.
69. Hunt TK: Fundamentals of wound management in surgery, in *Wound Healing: Disorders of Repair*. South Plainfield, NJ, Chirurgescom, Inc, 1976, pp 46-47.
70. Hurley JJ, Auer AI, Hershey FB, et al: Distal arterial reconstruction: Patency and limb salvage in diabetics. *J Vasc Surg* 1987; 5:796-799.
71. Jacobs RL, Karmody AM, Wirth C, et al: The team approach in salvage of the diabetic foot, in Nyhus LM (ed): *Surgery Annual*. New York, Appleton-Century-Crofts, 1977, 9:231-264.
72. Johnson JE III: Infection and diabetes, in Ellenberg M, Rifkin H (ed): *Diabetes Mellitus: Theory and Practice*. New York, McGraw-Hill Book Co, 1970, pp 734-745.
73. Johnson WD, Pedraza PM, Kayser KL: Coronary artery surgery in diabetics: 261 consecutive patients followed four to seven years. *Am Heart J* 1982; 104:823-827.
74. Jurewicz WA, Buckels JAC, Dykes JGA, et al: 111-Indium platelets in monitoring pancreatic allografts in man. *Br J Surg* 1985; 72:228-231.
75. Kannel WB, McGee DL: Diabetes and cardiovascular disease: The Framingham study. *JAMA* 1979; 241:2035-2038.
76. Khauli RB, Novick AC, Steinmuller DR, et al: Patient survival and rehabilitation of diabetics with end-stage disease: Comparison of therapeutic modalities. *Transplant Proc* 1985; 27:178-181.
77. Krakauer H, Spees EK, Vaughn WK, et al: Assessment of prognostic factors and projection of outcomes in renal transplantation. *Transplantation* 1983; 36:372-378.
78. Kuebler TW, Bendick PJ, Fineberg SE, et al: Diabetes mellitus and cerebrovascular disease: Prevalence of carotid artery occlusive disease and associated risk factors in 482 adult diabetic patients. *Diabetes Care* 1983; 6:274-278.
79. Lawrence AM, Dorsch T: The glucagonoma syndrome, in Podolsky S, Viswanathan M (eds): *Secondary Diabetes: The Spectrum of the Diabetic Syndromes*. New York, Raven Press, 1980, pp 287-295.
80. LeFrock JL, Molavi A: Foot infections in diabetic patients, in Andriole VT (ed): *Mediguide to Infectious Diseases*. West Haven, Miles Pharmaceuticals, 1983, vol 3, pp 1-5.
81. Leland OS Jr: Diabetes and the heart, in Kozek GP (ed): *Clinical Diabetes Mellitus*. Philadelphia, WB Saunders Co, 1982, pp 302-326.
82. Levin ME, O'Neal LW: *The Diabetic Foot*, ed 3. St Louis, CV Mosby Co, 1983.
83. Levin ME, O'Neal LW: Peripheral vascular disease, in Ellenberg M, Rifkin H: *Diabetes Mellitus. Theory and Practice*, ed 3. New York, Medical Examination Publishing Co, 1983, pp 803-828.
84. Lewis J, Fekety FR Jr: Gram-negative bacteremia. *Johns Hopkins Med J* 1969; 124:106-111.
85. Libertino JA, Zinman L, Salerno R, et al: Diabetic renal transplantation. *J Urol* 1980; 124:593-595.
86. Lidgren L: Postoperative orthopaedic infections in patients with diabetes mellitus. *Acta Orthop Scand* 1973; 44:149-151.

87. Lippmann HI, Farrar R: Prevention of amputation in diabetics. *Angiology* 1979; 30:649-658.
88. Lithner F, Tornblom N: Gangrene localized to the lower limbs in diabetics. *Acta Med Scand* 1980; 208:315-320.
89. LoGerfo FW, Coffman JD: Vascular and microvascular disease of the foot in diabetes: Implications for foot care. *N Engl J Med* 1984; 311:1615-1619.
90. Majeski JA, Alexander JW: Early diagnosis, nutritional support, and immediate extensive debridement improve survival in necrotizing fasciitis. *Am J Surg* 1983; 145:784-787.
91. Malins J: *Clinical Diabetes Mellitus*, ed 1. London, Eyre and Spottiswood Ltd, 1968.
92. McDonald JC, Rohr MS, Tucker WY: Recent experiences with autotransplantation of the kidney, jejunum, and pancreas. *Ann Surg* 1983; 197:678-687.
93. McPhee MS, Greenberger NJ: Diseases of the gallbladder and bile ducts, in Petersdorf RG, Adams RD, Braunwald E, et al (ed): *Harrison's Principles of Internal Medicine*, ed 10. New York, McGraw-Hill Book Co, 1983, pp 1821-1832.
94. Mecklenberg RS, Benson EA, Benson JW Jr, et al: Acute complications associated with insulin infusion pump therapy: Report of experience with 161 patients. *JAMA* 1984; 252:3265-3269.
95. Mecklenberg RS, Benson EA, Benson JW Jr, et al: Long-term metabolic control with insulin pump therapy: Report of experience with 127 patients. *N Engl J Med* 1985; 313:465-468.
96. Moosa AR: Total pancreateoduodenectomy for cancer of the pancreas, in Nyhus LM, Baker RJ (eds): *Mastery of Surgery*. Boston, Little Brown & Co, 1984, pp 795-808.
97. Müller WA, Faloona GR, Unger RH: Hyperglucagonemia in diabetic ketoacidosis: Its prevalence and significance. *Am J Med* 1973; 54:52-57.
98. Mundth ED: Cholecystitis and diabetes mellitus. *N Engl J Med* 1962; 267:642-646.
99. Nabarro JDN: Diabetic acidosis: Clinical aspects, in Leibel BS, Wrenshall GA (eds): *On the Nature and Treatment of Diabetes*. New York, Excerpta Medica Foundation, 1965, pp 545-562.
100. Najarian JS, Sutherland DER, Steffes MW: Isolation of islets of Langerhans for transplantation. *Transplant Proc* 1975; 7:611-613.
101. National Diabetes Data Group: *Selected Statistics for Health and Medical Care of Diabetes*. Bethesda, Md, National Institutes of Health, 1980.
102. O'Neal LW: Surgical pathology of the foot and clinicopathologic correlations, in Levin ME, O'Neal LW (eds): *The Diabetic Foot*, ed 3. St Louis, CV Mosby Co, 1983, pp 162-200.
103. O'Neal LW, Wagner FW Jr: Debridement and amputation, in Levin ME, O'Neal LW (eds): *The Diabetic Foot*, ed 3. St Louis, CV Mosby Co, 1983, pp 274-302.
104. Oreopoulos DG: Peritoneal dialysis, in Massry SG, Glasscock RJ (eds): *Textbook of Nephrology*. Baltimore, Williams & Wilkins Co., 1983, vol 2, pp 8.30-8.37.
105. Page MM, Watkins PJ: Cardiorespiratory arrest and diabetic autonomic neuropathy. *Lancet* 1978; 1:14-17.
106. Palumbo PJ, Elveback LR, Whisnant JP: Neurologic complications of diabetes mellitus: Transient ischemic attack, stroke, and peripheral neuropathy. *Adv Neurol* 1978; 19:593-601.

107. Penn I: Management of the diabetic foot. *Contin Educ Fam Phys* 1980; 13: 37-44.
108. Penn I: The impact of diabetes mellitus on extremity ischemia, in Kempczinski RF (ed): *The Ischemic Leg*. Chicago, Year Book Medical Publishers Inc, 1985, pp 51-69.
109. Perlman K, Ehrlich RM, Filler RM, et al: Waveform requirements for metabolic normalization with continuous intravenous insulin delivery in man. *Diabetes* 1981; 30:710-717.
110. Persky L, Luria S, Porter A, et al: *Staphylococcus epidermidis* in diabetic urological patient. *J Urol* 1986; 136:466-467.
111. Pickleman J: Controversies in biliary tract surgery. *Can J Surg* 1986; 29:429-433.
112. Podolsky S: Diagnosis and treatment of sexual dysfunction in the male diabetic. *Med Clin N Am* 1982; 66:1389-1396.
113. Porter JM, Baur GM, Taylor LM Jr: Lower extremity amputations for ischemia. *Arch Surg* 1981; 116:89-92.
114. Pratt TC: Gangrene and infection in the diabetic. *Med Clin N Am* 1965; 49:987-1004.
115. Prinz RA, Kaufman BH, Folk FA, et al: Pancreaticojejunostomy for chronic pancreatitis: Two to 21-year follow-up. *Arch Surg* 1978; 113:520-525.
116. Prinz RA, Brooks MH, Lawrence AM, et al: Cushing's disease: The role of adrenalectomy and autotransplantation. *Surg Clin N Am* 1979; 59:159-165.
117. Raines JK, Darling RC, Buth J, et al: Vascular laboratory criteria for the management of peripheral vascular disease of the lower extremities. *Surgery* 1976; 79:21-28.
118. Raskin P, Rosenstock J: Blood glucose control and diabetic complications. *Ann Intern Med* 1986; 105:254-263.
119. Reichle FA, Rankin KP, Tyson RR, et al: Long-term results of femoroinfrapopliteal bypass in diabetic patients with severe ischemia of the lower extremity. *Am J Surg* 1979; 137:653-656.
120. Rizza RA: New modes of insulin administration: Do they have a role in clinical diabetes? *Ann Intern Med* 1986; 105:126-129.
121. Roederer GO, Langlois YE, Jager KA, et al: The natural history of carotid arterial disease in asymptomatic patients with cervical blocks. *Stroke* 1984; 15:605-613.
122. Root HF: Preoperative medical care of the diabetic patient. *Postgrad Med* 1966; 40:439-444.
123. Rosenthal JT: Transplantation in diabetics with end stage renal disease (letter). *Transplant Immunol* 1985; 1:6-7.
124. Russell RCG, Walker CJ, Bloom SR: Hyperglucagonaemia in the surgical patient. *Br Med J* 1975; 1:10-12.
125. Salomon NW, Page US, Okies JE, et al: Diabetes mellitus and coronary artery bypass: Short-term risk and long-term prognosis. *J Thorac Cardiovasc Surg* 1983; 85:264-271.
126. Sapico FL, Canawati HN, Witte JL, et al: Quantitative aerobic and anaerobic bacteriology of infected diabetic feet. *J Clin Microbiol* 1980; 12:413-420.
127. Schade DS, Eaton RP: Insulin delivery: How when and where (editorial). *N Engl J Med* 1985; 312:1120-1121.
128. Schade DS, Eaton P, Carlson GA, et al: Future therapy of the insulin-dependent diabetic patient: The implantable insulin delivery system. *Diabetes Care* 1981; 4:319-324.
129. Schade DS, Eaton RP, Davis T, et al: The kinetics of peritoneal insulin absorption. *Metabolism* 1981; 30:149-155.

130. Schnider SL, Kohn RR: Glucosylation of human collagen in aging and diabetes mellitus. *J Clin Invest* 1980; 66:1179–1181.
131. Schwartz SI: Diabetes mellitus, in Schwartz SI: *Principles of Surgery*, ed 4. New York, McGraw-Hill Book Co, 1984, pp 467–470.
132. Semple R: Diabetes and peripheral arterial disease: A clinical study. *Lancet* 1953; 1:1064–1068.
133. Sharp CS, Bessman AN, Wagner FW Jr, et al: Microbiology of superficial and deep tissues in infected diabetic gangrene. *Surg Gynecol Obstet* 1979; 149:217–219.
134. Shelling RH, Maxted WC: Major complications of silicone penile prosthesis: predisposing clinical situations. *Urology* 1980; 15:131–133.
135. Shin B, Joseph SI: Hyperglycemic hyperosmolar nonketotic coma following diazoxide, anesthesia and operation. *Anesthet Analg* 1977; 56:506–514.
136. Shuman CR: Surgery and diabetes, in Ellenberg M, Rifkin H (eds): *Diabetes Mellitus. Theory and Practice*, ed 3. New York, Medical Examination Publishing Co, 1983, pp 679–687.
137. Sutherland DER, Casanova D, Sibley RK: Role of pancreas graft biopsies in the diagnosis and treatment of rejection after pancreas transplantation. *Transplant Proc* 1987; 19:2329–2331.
138. Silen W: *Cope's Early Diagnosis of the Acute Abdomen*, ed 16. New York, Oxford University Press, 1983, pp 84, 266.
139. Simmons RL, Ahrenholz DH: Infections of the skin and soft tissues, in Simmons RL, Howard RJ (eds): *Surgical Infectious Diseases*. New York, Appleton-Century-Crofts, 1982, pp 507–583.
140. Skyler JS: Self-monitoring of blood glucose. *Med Clin N Am* 1982; 66:1227–1250.
141. Soler NG, Bennett MA, Fitzgerald MG, et al: Intensive care in the management of diabetic ketoacidosis. *Lancet* 1973; 1:951–954.
142. Sosenko JM, Breslow JL, Miettinen OS, et al: Hyperglycemia and plasma lipid levels: A prospective study of young insulin-dependent diabetic patients. *N Engl J Med* 1980; 302:650–654.
143. Stamm WE, Martin SM, Bennett JV: Epidemiology of nosocomial infections due to gram-negative bacilli: Aspects relevant to development and use of vaccines. *J Infect Dis* 1977; 136:S151–S160.
144. Steer HW, Cuckle HS, Franklin PM, et al: The influence of diabetes mellitus upon peripheral vascular disease. *Surg Gynecol Obstet* 1983; 157:64–72.
145. Stemmer EA: Vascular complications of diabetes mellitus, in Moore WS (ed): *Vascular Surgery: A Comprehensive Review*. New York, Grune & Stratton Inc, 1983, pp 415–429.
146. Stipa S, Wheelock FC Jr: A comparison of femoral artery grafts in diabetic and non-diabetic patients. *Am J Surg* 1971; 121:223–228.
147. Stout RW: The role of insulin in atherosclerosis in diabetics and nondiabetics: A review. *Diabetes* 1981; 30(suppl 2):54–57.
148. Standness DE Jr, Priest RE, Gibbons GE: Combined clinical and pathologic study of diabetic and nondiabetic peripheral arterial disease. *Diabetes* 1964; 13:366–372.
149. Sutherland DER: Transplantation in diabetic patients: conventional therapy (letter). *Transplant Immunol* 1985; 1:2–4.
150. Sutherland DER, Goetz FC, Najarian JS: One hundred pancreas transplants at a single institution. *Ann Surg* 1984; 200:414–440.
151. Sutherland DER, Kendall D: Clinical pancreas and islet transplant registry report. *Transplant Proc* 1985; 17:307–311.

152. Sutherland DER, Kendall D, Goetz FC, et al: Pancreas transplantation. *Surg Clin N Am* 1986; 66:557-583.
153. Sutherland DER, Sibley RK, Chinn PL: Twin-to-twin pancreas transplantation: Reversal and reenactment of pathogenesis of Type 1 diabetes (abstract). *Clin Res* 1984; 32(2):561A.
154. Tenembaum MM, Rayfield E, Junior J, et al: Altered pressure flow relationship in the diabetic foot. *J Surg Res* 1981; 31:307-313.
155. Toledo-Pereyra LH: Practical immunologic aspects of clinical pancreas and islet cell transplantation. *Dialy Transplant* 1986; 15:514-520.
156. Toledo-Pereyra LH, Cederna J: Islet cell transplantation. *Contemp Surg* 1984; 24:15-24.
157. Toledo-Pereyra LH, Rowlett AL, Cain W, et al: Hepatic infarction following intraportal islet cell autotransplantation after near-total pancreatectomy. *Transplantation* 1984; 38:88-89.
158. Tom WW, Munda R, First MR, et al: Physiologic consequences of pancreatic allograft exocrine drainage into the urinary tract. *Transplant Proc* 1987; 19:2339-2342.
159. Tosatti E, Valentini U, Campisi C, et al: Segmental pancreas autotransplantation in man following total or near total pancreatectomy for serious recurrent chronic pancreatitis. *Transplant Proc* 1980; 12(suppl 2):15-18.
160. Towne JB: Management of foot lesions in the diabetic patient, in Rutherford RR (ed): *Vascular Surgery*, ed 2. Philadelphia, WB Saunders Co, 1984, pp 661-669.
161. Turner RJ III, Becker WF, Coleman WO, et al: Acute cholecystitis in the diabetic. *South Med J* 1969; 62:228-231.
162. Turrill FL, McCarron MM, Mikkelsen WP: Gallstones and diabetes: An ominous association. *Am J Surg* 1961; 102:184-190.
163. Unger RH: Benefits and risks of meticulous control of diabetes. *Med Clin N Am* 1982; 66:1317-1324.
164. Van Heerden JA, Sheps SG, Hamberger B, et al: Pheochromocytoma: Current status and changing trends. *Surgery* 1982; 91:367-373.
165. Vigorito C, Botocchi S, Bonzani G, et al: Severity of coronary artery disease in patients with diabetes mellitus: Angiographic study of 34 diabetic and 120 nondiabetic patients. *Am Heart J* 1980; 100:782-787.
166. Walsh DB, Eckhauser FE, Ramsburgh SR, et al: Risk associated with diabetes mellitus in patients undergoing gallbladder surgery. *Surgery* 1982; 91:254-257.
167. Warren S, LeCompte PM, Legg MA: *The Pathology of Diabetes Mellitus*, ed 4. Philadelphia, Lea & Febiger, 1966.
168. Warshaw AL, Popp JW Jr, Schapiro RH: Long-term patency, pancreatic function, and pain relief after lateral pancreaticojejunostomy for chronic pancreatitis. *Gastroenterology* 1980; 79:289-293.
169. Way LW, Gadacz T, Goldman L: Surgical treatment of chronic pancreatitis. *Am J Surg* 1974; 127:202-209.
170. Weinberger J, Biscarra V, Weisberg MK, et al: Factors contributing to stroke in patients with atherosclerotic disease of the great vessels: The role of diabetes. *Stroke* 1983; 14:709-712.
171. Wheat LJ: Infection and diabetes mellitus. *Diabetes Care* 1980; 3:187-197.
172. Wheelock FC Jr, Marble A: Surgery and diabetes, in Marble A, White P, Bradley RF, et al (eds): *Joslin's Diabetes Mellitus*, ed 11. Philadelphia, Lea & Febiger 1971, pp 599-620.
173. Williamson JR, Kilo C: Vascular complications in diabetes mellitus (editorial). *N Engl J Med* 1980; 302:399-400.

174. Williamson JR, Vogler NJ, Kilo C: Regional variations in the width of the basement membrane of muscle capillaries in man and giraffe. *Am J Pathol* 1971; 63:359-367.
175. Woodruff RE, Lewis SB, McLeskey CH, et al: Avoidance of surgical hyperglycemia in diabetic patients. *JAMA* 1980; 244:166-168.