PREVENTION AND TREATMENT OF THE COMPLICATIONS OF DIABETES MELLITUS

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DIABETES mellitus is a chronic disease characterized by hyperglycemia and by complications that include microvascular disease of the eye and kidney and a variety of clinical neuropathies. Although diabetes is also associated with premature macrovascular disease, this review is limited to a discussion of retinopathy, nephropathy, and neuropathy. The pathophysiology of these complications of diabetes was recently reviewed in the Journal.¹

The specific association of microvascular disease and neuropathy with diabetes and the relation of the two complications to the duration of diabetes suggest that they are linked to hyperglycemia or a concomitant metabolic abnormality. The Diabetes Control and Complications Trial (DCCT), conducted for nearly 10 years with 1441 patients between the ages of 13 and 39 years who had insulin-dependent diabetes mellitus (IDDM), demonstrated that the incidence of retinopathy, nephropathy, and neuropathy could be reduced by intensive treatment.²

Although the metabolic control of hyperglycemia should also limit the incidence and development of retinopathy, nephropathy, and neuropathy in patients with non-insulin-dependent diabetes mellitus (NIDDM), the extent of that effect has yet to be determined.³ The specific strategies for achieving metabolic control of the two types of diabetes also differ; diet, exercise, and oral antidiabetic drugs are the primary means of reducing blood glucose concentrations in patients with NIDDM. Moreover, the risks, for both children and middle-aged adults, of intensive attempts to lower blood glucose to nearly normal levels have not been defined, either for patients with IDDM or for those with NIDDM.²³

GENERAL PREVENTION

Intensive Treatment

In the DCCT, intensive treatment consisted of a series of steps intended to reduce blood glucose concentrations and glycosylated hemoglobin values to normal (Table 1). In patients with no initial retinopathy, this treatment reduced the risk of sustained disease by 76 percent, as measured by the three-step interim retinopathy scale of the Early Treatment of Diabetic Retinopathy Study (ETDRS), and the appearance of microaneurysms by 27 percent. In patients with mild initial retinopathy, intensive treatment reduced the risk of sustained retinopathy by 54 percent, the development of proliferative — or severe nonproliferative — retinopathy by 47 percent, and the need for laser treatment by 56 percent.² In the combined DCCT cohort, all of whose members initially excreted less than 200 mg of albumin per day, the risk that urinary albumin excretion would rise to more than 200 mg per day was decreased by 60 percent.² The incidence of cardiovascular events, although low in both groups, was lower in the intensively treated group than in the group that received conventional treatment. The chief side effects of intensive treatment were weight gain and hypoglycemia.

Interference with the Basic Pathophysiologic Mechanisms of Complications

The major tissues affected by diabetes — the retina, the kidney, and the nerves — are all freely permeable to glucose. Thus, increases in blood glucose concentrations increase the intracellular accumulation of both glucose and its subsequent metabolic products. The proposed mechanisms by which hyperglycemia may lead to microvascular and neurologic complications include the increased accumulation of polyols through the aldose reductase pathway¹⁵ and of advanced glycosylation end products.⁶

Aldose reductase catalyzes the reduction of glucose to sorbitol (Fig. 1). An increase in intracellular glucose leads to an increase in sorbitol, which in turn competitively inhibits both glomerular and neural synthesis of myo-inositol. This decrease in myo-inositol synthesis depresses phosphoinositide metabolism, which then decreases Na⁺/K⁺-ATPase activity.⁷ Clinical trials of aldose reductase inhibitors have been conducted to assess the drugs' effects in the treatment of neuropathy and in the prevention of neuropathy, retinopathy, and nephropathy.

Hyperglycemia also leads to the formation of advanced glycosylation end products (Fig. 2). Aminoguanidine, which inhibits the formation of advanced glycosylation end products, has beneficial effects on the kidney, nerves, and retina in studies in animals.⁸ In diabetic rats, it decreases the glomerular accumulation of advanced glycosylation end products, basement-membrane thickening, mesangial proliferation, and urinary albumin excretion⁹ and improves the animals' response to functional and structural abnormalities of the peripheral nerves.¹⁰¹¹ In addition, aminoguanidine decreases the formation of microaneurysms and the intercapillary deposition of protein in the retinas of diabetic rats.
Table 1. Intensive Treatment of Hyperglycemia in the Diabetes Control and Complications Trial. 2

Steps
Hospitalization for the initiation of therapy
Intensive education about diet and diabetes
Monthly outpatient visits and weekly telephone contacts
Monitoring of blood glucose levels by the patient four or more times daily
Multiple daily insulin injections (three or more) or use of an insulin-infusion device
Frequent adjustment of the insulin dose by the patient, on the basis of blood glucose level, diet, and exercise

Predefined goals
Blood glucose level*
Fasting, 70–120 mg/dl
Premeal, <180 mg/dl
3 a.m., >65 mg/dl
Glycosylated hemoglobin level, <2 SD above the mean value in normal subjects

*To convert blood glucose values to millimoles per liter, multiply by 0.0556.

An excellent review of the role of glycosylation and advanced glycosylation end products in the pathogenesis of diabetic complications was published last year. 9 No results of studies in humans have been reported.

**Retinopathy**

Diabetic retinopathy is the most important cause of visual impairment in the United States in persons under 60 years of age. The risk of proliferative retinopathy in the 20 years after diagnosis is higher for patients with IDDM (40 percent) than for those with NIDDM (20 percent). 13 However, there are many more patients with NIDDM; thus, patients with NIDDM constitute the majority of patients with all forms of diabetic retinopathy.

**Prevention**

As discussed above, intensive therapy in the DCCT reduced the risk of sustained progression of retinopathy and of the appearance of microaneurysms. 2 Once proliferative retinopathy develops, however, glucose control, achieved by pancreas transplantation, is not beneficial. 14–16 In all trials of the intensive treatment of patients who already had retinopathy, there has been transient early worsening of the condition. 17–19 This should not deter clinicians from intensive treatment, because despite the early worsening, which usually takes the form of soft exudates, there were long-term benefits of such an approach in the DCCT. 2

The aldose reductase inhibitors ponalrestat and sorbinil do not prevent the progression of early diabetic retinopathy. 20,21 In a study of epalrestat in 214 diabetic patients with either nonproliferative retinopathy or preproliferative retinopathy (defined as the presence of microaneurysms, retinal hemorrhages and exudates, and intraretinal vascular abnormalities), there was significantly less deterioration, as assessed by fluorescein angiography, in the patients treated with epalrestat than in those given placebo, but visual function was not reported. 22 Although a long-term retinopathy-prevention trial with the aldose reductase inhibitor tolrestat continues, the promise of the prevention of retinopathy by these agents has yet to be realized.

Antiplatelet agents can reduce the number of microaneurysms. The Dipyridamole Aspirin Microangiopathy of Diabetes and Ticlopidine Microangiopathy of Diabetes trials were double-blind, randomized, placebo-controlled studies of aspirin, aspirin plus dipyridamole, and ticlopidine. 23,24 In both studies, the treatment groups had fewer microaneurysms than the placebo groups. 23,24 Unfortunately, the presence of microaneurysms does not necessarily predict the subsequent development of vision-threatening retinopathy, and in the ETDRS there was no difference in the progression of retinopathy between a group of patients treated with 650 mg of aspirin daily and a placebo group. 25

**Detection**

The treatment of diabetic retinopathy and macular edema is most efficacious when started before any vision is lost. The prevention of further deterioration of vision, rather than improvement, is a more likely result of treatment, particularly in patients with macular edema. Every diabetic patient at risk should be routinely screened for retinopathy, even in the absence of any visual symptoms. Since the examination requires pupillary dilatation, most primary care practitioners refer their patients to an ophthalmologist for such an examination. Those at risk are postpubertal patients with IDDM who have had diabetes for five years and all patients with NIDDM. The examinations should be repeated annually. 26 In certain patients (e.g., pregnant
women, patients with known proliferative retinopathy, or patients who are beginning intensive insulin therapy, more frequent examinations may be required.

**Treatment**

The results of several major clinical trials serve as the basis for the treatment of proliferative diabetic retinopathy.\(^{27-29}\) In the Diabetic Retinopathy Study (DRS) and the ETDRS, photocoagulation, by argon laser or xenon arc light, prevented new visual loss in patients with proliferative retinopathy and macular edema, and it improved vision in some patients.\(^{28,30}\) In the DRS, a study of 879 patients (1758 individual eyes) conducted between 1972 and 1979, panretinal photocoagulation was followed by severe visual loss in only 16 percent of the treated eyes during the six-year follow-up period, but in 38 percent of the untreated eyes.

In the ETDRS, 3711 patients with macular edema who had either mild-to-severe nonproliferative retinopathy or mild early proliferative retinopathy were treated with panretinal photocoagulation followed by treatment with either aspirin (650 mg per day) or placebo.\(^{28,31}\) One eye of each patient was treated with panretinal photocoagulation by argon laser at the beginning of the study, and the other eye was examined every four months and treated with photocoagulation only if high-risk proliferative retinopathy was detected. During five years of follow-up, early panretinal photocoagulation resulted in a slightly lower rate of severe visual loss (2.6 percent) than deferred treatment (3.7 percent).\(^{31}\) However, many patients whose mild-to-moderate nonprolif-

### Nephropathy

Diabetic nephropathy is a leading cause of end-stage renal disease, accounting for nearly one third of all new cases.\(^{33}\) The incidence of end-stage renal disease is nearly 30 percent in patients with IDDM and ranges from 4 to 20 percent in patients with NIDDM. Given the higher prevalence of NIDDM, end-stage renal disease occurs in nearly the same numbers of patients with each type of diabetes.\(^{33}\) The incidence of diabetic nephropathy among patients who have had IDDM for 25 years or more is falling, perhaps as a result of better clinical control of hyperglycemia.\(^{34}\)

Hyperglycemia causes intraglomerular hypertension and renal hyperperfusion.\(^{35,36}\) Increased glomerular pressure results in the deposition of protein in the mesangium, ultimately leading to glomerulosclerosis and renal failure.\(^{36}\) Nonenzymatic glycosylation, as well as lipoprotein abnormalities, may also contribute to diabetic nephropathy.\(^{37}\) The four approaches to the prevention of diabetic renal disease are control of hyperglycemia, treatment of hypertension, restriction of dietary protein, and avoidance of nephrotoxic dyes or drugs (Table 2).

### Prevention

**Intensive Management**

Patients with IDDM who are treated with constant subcutaneous insulin have decreases in the thickness of capillary basement membranes in the skeletal muscles,\(^{38}\) reduced glomerular hyperfiltration,\(^{39,40}\) and stabilized albuminuria.\(^{41,42}\) In the DCCT, three stages of
diabetic renal disease were defined: microalbuminuria (urinary albumin excretion, ≥40 mg per day), albuminuria (urinary albumin excretion, ≥300 mg per day), and advanced nephropathy (urinary albumin excretion, ≥300 mg per day and creatinine clearance below 70 ml per minute per 1.73 m² of body-surface area).¹

Intensive treatment decreased the frequency of albuminuria by 60 percent.² As in patients with retinopathy, glycemic control resulting from pancreas transplantation does not ameliorate advanced nephropathy,¹⁶ but it does delay the progression of nephropathy in donor kidneys.⁶⁰

Angiotensin-Converting–Enzyme Inhibition

Angiotensin-converting–enzyme (ACE) inhibitors can delay the onset and progression of diabetic nephropathy.¹³,¹⁴ In a double-blind, randomized clinical trial of 409 patients with IDDM, treatment with the ACE inhibitor captopril resulted in a 50 percent decrease in the combined end point of death, dialysis, or transplantation.¹³ This decrease was independent of the small differences in blood pressure between the study groups, indicating that the renal protective effects of captopril are independent of its effect on systemic blood pressure. In normotensive patients with NIDDM who had microalbuminuria, ACE-inhibitor therapy resulted in long-term stabilization of serum creatinine concentrations and albuminuria.¹⁵ These studies suggest that ACE inhibitors prevent the progression of renal disease both in patients with IDDM and in those with NIDDM, even in the absence of hypertension.¹⁶

Aldose Reductase Inhibition

In 1991, ponalrestat was reported to reduce glomerular hyperfiltration in patients with IDDM.¹⁷ However, a large multicenter trial of the effects of ponalrestat on nephropathy and retinopathy was stopped because the

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Table 2. Strategies for the Prevention and Treatment of the Complications of Diabetes.

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<thead>
<tr>
<th>Complication</th>
<th>Strategy</th>
<th>Effectiveness</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Retinopathy</td>
<td>Clinical strategy</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Intensive treatment of hyperglycemia</td>
<td>Effective</td>
<td>DCCT²</td>
</tr>
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<td>Effective</td>
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<td></td>
<td>Experimental strategy</td>
<td></td>
<td></td>
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<td></td>
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<td>Kother et al.,²⁹ Sorbinil Retinopathy Trial,²² Hotta et al.²²</td>
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<td>Brownlee,⁶ Edelstein and Brownlee,⁶ Hammes et al.¹² ETDRS³³</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>Nephropathy</td>
<td>Clinical strategy</td>
<td></td>
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<td></td>
<td>Intensive treatment of hyperglycemia</td>
<td>Effective</td>
<td>DCCT²</td>
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<td></td>
<td>Antihypertensive drugs</td>
<td>Effective</td>
<td>DCCT²</td>
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<td></td>
<td>Dietary protein restriction</td>
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<td>Possibly effective in NIDDM Evanoff et al.,⁴⁶ Kuykens et al.,⁷⁷ Walker et al.,³⁴ Zeller et al.⁵⁰</td>
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<td>Experimental strategy</td>
<td></td>
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<td>Clinical strategy</td>
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</tr>
<tr>
<td></td>
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<td>Being tested in clinical trials</td>
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</tr>
<tr>
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<td>Effective</td>
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<td>Max et al.⁶⁹</td>
</tr>
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<td>Capsaicin</td>
<td>Effective</td>
<td>Fitzgerald⁶⁸</td>
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<td>Possibly effective</td>
<td>Ward,⁷¹ Apfel and Kessler⁷¹</td>
</tr>
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<td></td>
<td>Carbamazepine</td>
<td>Possibly effective</td>
<td>Ward,⁷¹ Apfel and Kessler⁷¹</td>
</tr>
<tr>
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<td>Clinical strategy</td>
<td></td>
<td></td>
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<td>Effective</td>
<td>Janssens et al.⁷¹</td>
</tr>
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<td></td>
<td>Metoclopramide</td>
<td>Effective</td>
<td>Snape et al.⁷⁸</td>
</tr>
<tr>
<td></td>
<td>Cisapride</td>
<td>Effective</td>
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</tr>
<tr>
<td></td>
<td>Experimental strategy</td>
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Drug had no effect. Aldose reductase inhibition must be considered as having no proved value in preventing nephropathy.

**Detection**

Microalbuminuria, defined as the excretion of 30 to 300 mg of albumin per day, is associated in diabetic nephropathy with both hemodynamic and morphologic changes. An increased rate of albumin excretion predicts impairment of renal function in patients with IDDM. Renal insufficiency subsequently develops in 80 percent of the patients with IDDM who have an albumin excretion rate of 20 μg per minute (29 mg per day) or more. By contrast, a rate of less than 20 μg per minute is associated with the subsequent development of diabetic nephropathy in only 4 percent of patients.

The progression of the stages of renal involvement is not as sharply characterized in patients with NIDDM as it is in those with IDDM. Some patients have microalbuminuria for years, yet renal failure never develops. In those in whom nephropathy does worsen, arteriolosclerosis, hypertension, or obstructive uropathy may be an important contributing factor. In patients with NIDDM, microalbuminuria has been found to be an independent risk factor for death due to cardiovascular disease.

Urinary albumin should be measured annually in all postpubertal patients who have had IDDM for five years or more and in all patients with NIDDM. Most standard dipsticks give positive results only when the rate of urinary albumin excretion is greater than 250 μg per minute (360 mg per day). Recently, products such as Micral (Boehringer–Mannheim) and Microbumitest (Ames) have been introduced to detect smaller amounts of albumin. Their specificities are fairly low (82 percent and 87 percent, respectively). Micral and Microbumitest are qualitative tests with a positive or negative result; a positive result corresponds to an albumin concentration greater than 40 mg per liter. Micral is a semiquantitative test with a range from 0 to 100 mg per liter. A value equal to or greater than 20 mg per liter is considered positive. These tests are useful for initial screening, but microalbuminuria is best diagnosed on the basis of quantitative assays. Quantitative-assay results with single-voided early-morning urine specimens, adjusted for their creatinine values, correlate well with measurements of 24-hour collections in terms of both sensitivity (94 percent) and specificity (96 percent). Thus, albumin levels in single-voided urine samples can be used to estimate 24-hour excretion. Microalbuminuria can be quite variable; albumin excretion should not be measured after exercise or during ketoacidosis or urinary tract infections.

**Treatment**

### Antihypertensive Therapy

Hypertension increases the rate at which diabetic nephropathy progresses; antihypertensive therapy slows its course. The prevalence of hypertension is higher in diabetic patients with microalbuminuria than in normal subjects matched for age and sex. In a prospective but uncontrolled study of 131 patients with diabetes, renal function, as measured by glomerular filtration, in the 47 patients with IDDM declined at a rate of 6 percent per year among those with systolic blood pressures of 140 mm Hg or higher and at a rate of 1 percent per year among those with systolic blood pressures of less than 140 mm Hg. The comparable rates among the 84 patients with NIDDM were 13.5 and 1 percent. The ideal blood pressure in patients with diabetes is probably 120/80 mm Hg. However, in many patients, particularly those with nephropathy, who have NIDDM — and in some who have IDDM — it may be difficult to achieve those values without side effects. For such patients the goal should be a blood pressure of 130/85 mm Hg.

As for treatment, thiazide diuretics have many dose-dependent side effects, including hyperglycemia, hypokalemia, and hyperlipidemia that make them unsuitable as first-line therapy for diabetic patients, and their use has been associated with increased mortality due to cardiovascular disease. Diabetic patients should therefore not be treated with more than 50 mg of hydrochlorothiazide per day or the equivalent. Beta-adrenergic–antagonist drugs also have metabolic side effects, including glucose intolerance and the masking of hypoglycemic symptoms. Alpha-adrenergic–antagonist drugs have minimal metabolic side effects and also decrease albuminuria.

ACE inhibitors or calcium-channel–blocking agents are the first choice for antihypertensive therapy in diabetic patients. Low-dose combinations of an ACE inhibitor and a calcium-channel–blocking agent may slow the decline of the glomerular filtration rate and restrain the development of albuminuria with fewer side effects than would a larger dose of either agent alone. Calcium-channel blockers vary in their effect on albuminuria. Both diltiazem and nicardipine, which decrease glomerular pressure by increasing efferent arteriolar dilatation, decrease albuminuria. By contrast, nifedipine, which dilates both afferent and efferent arterioles, increases it. Thus, for the control of hypertension in patients with diabetic nephropathy, diltiazem and nicardipine should be considered first.

### Protein Restriction

Diets low in protein decrease glomerular perfusion rates and albuminuria. In short-term studies, dietary protein restriction stabilized creatinine clearance, decreased systolic blood pressure, and increased serum albumin concentrations. In a crossover study of 19 patients with IDDM, in which the patients ate a high-protein diet (2.24 g per kilogram of body weight) for a mean of 29 months or a low-protein diet (0.67 g per kilogram) for a mean of 33 months, the glomerular filtration rate declined more in the group with the high-protein diet (0.61 ml per minute per month, vs. 0.14 ml per minute per month in the low-protein group). In a study of 35 patients with IDDM whose urinary albumin excretion exceeded 500 mg per day, one group was fed a daily diet containing 0.6 g of protein per kilo-
gram of ideal body weight, 500 to 1000 mg of phosphorous, and 2000 mg of sodium for a mean of 37 months; a second group received 1 g or more of protein per kilogram, 2000 mg of sodium, and 1000 mg of phosphorous per day. The creatinine clearance rate decreased by 0.33 ml per minute per 1.73 m² per month in the low-protein group and by 0.81 ml per minute per 1.73 m² per month in the high-protein group (P = 0.03).39 Currently, the American Diabetes Association recommends that nonpregnant diabetic patients limit their intake to 0.8 g of protein per kilogram of ideal body weight.46

**NEUROPATHY**

Diabetic neuropathy is one of the most common complications of diabetes mellitus and has myriad clinical presentations. The intensity and extent of the functional and anatomical abnormalities of diabetic neuropathy parallel the degree and duration of hyperglycemia. Acute hyperglycemia decreases nerve function. Chronic hyperglycemia is associated with the loss of myelinated and unmyelinated fibers, wallerian degeneration, and blunted nerve-fiber reproduction. The pathophysiologic mechanisms that underlie these changes are not clearly understood; proposed mechanisms include both the formation of sorbitol by aldose reductase and the formation of advanced glycosylation end products. Approaches to preventing or treating neuropathy include the intensive treatment of hyperglycemia, aldose reductase inhibition, and various symptomatic treatments (Table 2).

**Prevention**

Diabetic neuropathy is associated with reduced nerve conduction and increased blood glucose concentrations. In the DCCT, intensive treatment decreased the occurrence of clinical neuropathy by 60 percent.2

**Treatment**

Aldose reductase inhibitors improve nerve conduction velocity and increase the regeneration of damaged axons.61,62 However, clinical trials with sorbinil have shown only very small increases in conduction velocity,63-65 although biopsies of sural nerves show regeneration and repair of myelinated fibers in patients treated with the drug.66 Tolrestat, another aldose reductase inhibitor with similar morphologic effects,67 had clinical efficacy in a placebo-controlled trial.68 Although the benefits of these drugs are limited, they may have a role in preventing neuropathy or in easing the symptoms of some patients. None of the drugs are currently approved for use in the United States.

**Symptomatic Peripheral Neuropathy**

Current drug therapy for painful peripheral neuropathy includes tricyclic antidepressant drugs, phenytoin, carbamazepine, and topical capsaicin.69,70 Narcotic agents should be avoided because of their high potential for abuse. Nonsteroidal antiinflammatory drugs should be used judiciously in patients with microalbuminuria, because of the risk of renal toxicity. Amitriptyline is the most commonly used tricyclic antidepressant drug and is particularly effective in the treatment of dysesthetic pain. It should be started at doses as low as 25 mg at bedtime, and the dose may be increased gradually to a maximum of 150 to 200 mg per day. If the anticholinergic side effects of amitriptyline become dose limiting, other tricyclic antidepressant drugs can be tried. However, in a comparison study, amitriptyline was clearly more effective in relieving pain than desipramine and fluoxetine.69

Both phenytoin and carbamazepine have been used to treat diabetic neuropathy. Theoretically, these drugs dampen the abnormal discharge of sensory neurons.71 Questions about their efficacy, however, and the potential of carbamazepine to suppress bone marrow function limit their widespread use.72

Topical capsaicin, the active ingredient in hot peppers, has also been used in the treatment of painful diabetic neuropathy. Capsaicin promotes depletion of the pain-modulating substance P from the terminals of small sensory neurons. A double-blind, multicenter, vehicle-controlled study in 252 patients demonstrated a statistically significant decline in the intensity of pain, with pain relief evaluated by both patient and physician, in those who used a topical 0.075 percent capsaicin cream.70

**Autonomic Neuropathy**

Diabetic gastroparesis occasionally responds to metoclopramide or erythromycin.73,74 In a recent crossover study comparing erythromycin (750 mg per day) and metoclopramide (30 mg per day), erythromycin resulted in significantly more improvement in the gastric emptying of semisolid food and in the symptoms of gastroparesis.74 Domperidone, which like metoclopramide has an antidiopaminergic effect but does not cross the blood–brain barrier, also improves gastric emptying. Its efficacy, though, declines with time.79 Domperidone is not approved for use in the United States.

Cisapride, which stimulates the release of acetylcholine from the myenteric plexus of the gut, improves the rate of gastric emptying for both solid and liquid meals.75,76 The improvement may be sustained for up to one year, if cisapride is given orally in doses of 10 mg four times daily.77,78 However, cisapride is more expensive than erythromycin or metoclopramide. Erythromycin, by virtue of its low cost and effectiveness, should be the drug of first choice for diabetic patients with gastroparesis. It should be noted that severe gastroparesis often does not respond to any of these drugs and therefore can be a persistent problem.

Autonomic neuropathy can also cause diarrhea and orthostatic hypotension. In diabetic diarrhea, one or two doses of tetracycline (200 or 500 mg) can be effective at the beginning of an attack. Its mechanism of action is unknown but is probably not antibacterial. If tetracycline is ineffective, another anti diarrheal medication, such as diphenoxylate with atropine, should be given.72 Orthostatic hypotension is often difficult to treat, especially if accompanied by hypertension while recumbent. Practical measures include increased salt...
intake, the wearing of elastic tights, and sleeping with the head of the bed elevated. Fludrocortisone can help with postural hypotension by increasing arterial tone and expanding plasma volume.72

**Future Perspectives**

The future offers great hope for the treatment of patients with diabetes, with improved forms of insulin and other adjuncts to intensive treatment, pancreatic transplantation, and new drugs that interrupt the pathophysiologic mechanisms of the complications of diabetes. Currently, however, the most successful strategy for preventing complications of diabetes is intensive treatment of hyperglycemia. The DCCT demonstrated the value of this approach. In the DCCT, as in other studies, there was a curvilinear relation between glycated hemoglobin and the incidence of retinopathy. Thus, lowering the glycated hemoglobin 1 percent from a markedly abnormal value will be of more benefit than lowering it 1 percent from a slightly abnormal value. Because of the curvilinear relation between glycated hemoglobin and retinopathy, it is possible to generate break points by using two straight lines with differing slopes. Whereas this may represent a threshold below which complications do not occur, it may just be a reflection of the curvilinear relation between glycated hemoglobin and retinopathy. Recent data from the feasibility trial of a multicenter cooperative study by the Department of Veterans Affairs suggest that intensive insulin therapy to control hyperglycemia in patients with NIDDM is possible without adverse changes in weight, blood pressure, or plasma lipids and without hypoglycemia.39 Additional research will be needed to learn how intensive treatment of hyperglycemia can be widely applied and to identify the risks and appropriate strategies of intensive therapy in patients with NIDDM.

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