This article reviews current knowledge of the etiology of diabetic neuropathy and the outcomes and limitations of previous trials and discusses future directions for the investigation of its prevention and treatment. Proposed mechanisms for the development of diabetic neuropathy have been widely studied. It has been shown that there is improvement of nerve function associated with some short-term clinical trials of treatments that address a number of possible etiologic pathways. Improvement of morphometry has also been demonstrated in some short-term clinical trials. However, with the exception of the Diabetes Control and Complications Trial (DCCT), long-term trials with adequate statistical power to evaluate clinical outcome endpoints have not been conducted. The changes in nerve function are similar in most of the clinical trials. For instance, in four clinical trials directed at separate mechanisms (improved glucose control, high myo-inositol diet, therapy with an aldose reductase inhibitor, and therapy with supplementary y-linolenic acid), a similar improvement in peroneal motor velocity of 1-2 m/s is observed. This implies that each of the proposed mechanisms contributes equally to the development of neuropathy or that there is some redundancy to their mechanisms. In addition to an etiologic approach, non-specific neural stimulants, such as gangliosides and nerve growth factors, have also been investigated for the treatment of diabetic neuropathy. With the exception of the prevention of neuropathy by intensive glycemic control, the modest improvements with all other treatments have not led to sufficient evidence to approve any approach. Subanalyses of previous clinical trials suggest that treatment effects are greatest and most clear in patients with mild-to-moderate early neuropathy (stage I or early stage II). Thus, variation in composition and severity of baseline neuropathic disease in past clinical trials may have "washed out" any potential treatment effect. It is encouraging that more recent clinical trials have established more rigid inclusion and exclusion criteria so as to recruit only those patients with early or mild-to-moderate disease and a more homogeneous study population. Improvement with treatment has been measured with several markers including nerve conduction velocity, quantitative sensory testing, autonomic function testing, and morphometric changes. Presumably, the combined finding of improved nerve function and improved nerve morphometry will predict improvement in long-term clinical outcomes such as impaired sensation, painful neuropathy, insensitive feet, neurotrophic ulceration, and/or amputation. However, data to support this possibility are still lacking. It is our opinion that the overall design of neuropathy trials must consider present knowledge about complications in general and neuropathy specifically. We recommend that future trials be conducted over long periods with clinically significant outcomes as in the angiotensin-converting enzyme-inhibitor nephropathy trials and the DCCT with the recognition that reducing the development, rather than reversal, of complications is the best that can be reasonably expected. Patients with mild-to-moderate neuropathy (stage I or early stage II) with presumably more metabolic than structural neuropathy would be preferred subjects, and follow-up of 3-5 years is likely to be needed.

Diabetic neuropathy is an umbrella term encompassing two distinct groups of disorders, focal and diffuse neuropathies (Table 1), with different etiologies, progressions, and treatments.

D uring the past 20 years, numerous clinical trials have evaluated the efficacy of different agents for the treatment of diabetic neuropathy. However, there are still no definitive treatments available despite numerous trials and expanded understanding of the complexity of this complication of diabetes. We will review the current knowledge about the etiology of diabetic neuropathy and the outcomes and limitations of previous trials and then discuss future directions for the investigation of the prevention and treatment of diabetic neuropathy.
TABLE 1

Types of diabetic neuropathy

I. Focal neuropathies
   A. Mononeuropathies
      1. Sudden onset
      2. Asymmetrical
      3. Probably ischemic etiology
      4. Self-limited
      5. Examples
         - Mononeuropathies
         - Femoral neuropathies
         - Radiculopathies
         - Plexopathies
         - Cranial neuropathies
   B. Entrapment neuropathies
      1. Gradual onset
      2. Usually asymmetrical but can be bilateral
      3. Compression etiology
      4. Waxing and waning progressive course without spontaneous recovery
      5. Examples
         - Carpal tunnel syndrome
         - Ulnar entrapment
         - Lateral cutaneous femoral nerve entrapment
         - Tarsal tunnel syndrome

II. Diffuse neuropathies
   A. Insidious onset
   B. Symmetrical
   C. Abnormalities due to both structural and metabolic components
   D. Progressive
   E. Examples
      - Distal symmetrical polyneuropathy
      - Autonomic neuropathies

may take 18 months to subside and an additional 18 months in rehabilitation because of muscle wasting. In contrast, a cranial neuropathy may recover completely in days or weeks.

The entrapment neuropathies are caused by nerve compression within a bodily compartment and have a more gradual onset. They are usually asymmetrical in distribution, but may be bilateral, and have a waxing and waning progressive course without spontaneous recovery. Examples include carpal and tarsal tunnel syndromes.

The most common types of neuropathy attributed to diabetic complications are the diffuse neuropathies, which have been the focus of most clinical trials because of their increased prevalence and long-term impact on morbidity and mortality. They have an insidious onset (1) and present with a symmetrical distribution, right and left sides, upper and lower extremities, and motor sensory and autonomic nerves tend to correlate within an individual (2). These neuropathies generally have a progressive course with few (if any) spontaneous remissions. Examples include distal symmetrical polyneuropathy and the autonomic neuropathies. Abnormal neural function is the result of both metabolic and structural alterations. It is hypothesized that these alterations then lead to clinical signs and symptoms of neuropathy that predispose the patient to painful or insensitive extremities, foot ulcers, and amputation.

An understanding of the complex etiology and progressive nature of distal symmetrical polyneuropathy is important when considering the future direction of clinical trials. Figure 1 illustrates a hypothesis that encompasses the currently proposed mechanisms leading to neuropathy. According to this hypothesis, there are at least three different mechanisms (insulin deficiency, abnormal vasa nervorum, and autoimmunity) each of which initiates a cascade of biochemical alterations that in turn leads to structural changes. Complexity of the etiology results from the intermeshing, at several points, in the cascade of biochemical alterations. In this text, key studies will be used for illustration purposes, but this is not intended to be a comprehensive review of all studies related to each mechanism.

SYNOPSIS OF PROPOSED MECHANISMS

As with most diabetic complications, insulin deficiency and hyperglycemia are considered the initiating factors. Hyperglycemia causes a number of biochemical abnormalities that have been associated with neuropathy (Fig. 1). The results of the Diabetes Control and Complications Trial (DCCT) are the strongest evidence supporting this mechanism. The DCCT demonstrated slower loss of nerve function (nerve conduction velocities [NCVs] and autonomic function tests [APTs]) and less "confirmed clinical" neuropathy in the patients treated with intensive rather than conventional insulin therapy at 5 years (3,4). Confirmed clinical neuropathy in the DCCT was determined by a neurological exam and history performed by a physician in a standardized manner plus abnormal NCV or APT. This definition is assumed in all further references to confirmed clinical neuropathy in this Perspective. Unfortunately, morphometry was not evaluated in the DCCT. Long-term follow-up of the DCCT volunteers may demonstrate whether long-term clinical outcomes such as foot ulcers and amputations will be decreased or prevented.

It has also been proposed that an abnormal vasa nervorum causing local nerve ischemia will lead to poor nerve function (NCV, nerve amplitude, quantitative sensory test [QST], and APT) and abnormal morphometry. Lending credence to this mechanism, a recent study demonstrated that treatment with a prostaglandin I2 analog (beraprost sodium) resulted in improved nerve function by theoretically inducing relaxation of vascular smooth muscle and reducing nerve ischemia (5). Furthermore, Cameron et al. (6,7) showed a prevention of the decrease in NCV observed in untreated streptozotocin (STZ)-induced diabetic rats after treatment with an angiotensin-converting enzyme (ACE) inhibitor, lisinopril. This improvement was hypothesized to be secondary to vasodilation. A vascular mechanism is further supported by the work of Stevens et al. (8). In their hypothesis, insulin deficiency and hyperglycemia result in increased glucose metabolism through the polyol pathway via aldose reductase. In turn, increased aldose reductase activity competitively competes with nitric oxide synthetase for NADPH, resulting in decreased nitric oxide. Presumably, a decrease in nitric...
oxide reduces nerve blood flow, resulting in nerve ischemia. Thus, in this study (8), NCV did not decrease in STZ-induced diabetic rats if they were treated with sorbinil (an aldose reductase inhibitor [ARI]), but the effect of sorbinil could be blocked by nitric oxide synthetase inhibitor, reconciling the ARI and vasa nervorum mechanisms. In summary, it appears that there are credible animal data to support the vasa nervorum mechanism in humans are currently lacking.

Besides the competitive consumption of NADPH and the theoretical decrease in nitric oxide synthetase activity, the increased activity of the polyol pathway also decreases nerve myo-inositol through mechanisms that are not well understood. Thus, this decrease in nerve myo-inositol may also lead to a decrease in nerve function (NCV) and to abnormal morphometry. Clinical studies with ARIs have documented improved morphometry (9,10) and an improvement (1-2 m/s) in NCV (11-18). Only one study with an ARI has been done to evaluate prevention of clinical neuropathy (19). Results showed an improvement in peroneal motor, median motor, and median sensory NCV, but confirmed clinical neuropathy was not significantly improved. However, the statistical power of the study was noted to be inadequate. In summary, therapy with an ARI is associated with both an improvement of NCV and morphometry presumably via a restoration of nerve myo-inositol concentration and improved nerve blood flow. However, studies with ARIs with adequate statistical power to evaluate long-term clinical outcomes have not been conducted.

Hyperglycemia, per se, competitively inhibits neural uptake of myo-inositol (in addition to the polyol pathway decreasing nerve myo-inositol). It is hypothesized that Na⁺-K⁺-ATPase activity is decreased by lower myo-inositol concentrations and thus presumably slows NCV. In some studies, patients and animals placed on a high myo-inositol diet show improvement in NCV (20,21), but in other studies results were contradictory (22,23). Improvement in nerve morphometry and autonomic neuropathy has been shown in animals placed on high myo-inositol diets (24). Although these data are promising, studies to evaluate long-term clinical outcomes have not been conducted.

Increased levels of glycosylated neural proteins have also been attributed to hyperglycemia. Glycosylated neural proteins can cross-link, leading to the formation of advanced glycosylation end products (AGEs). Cross-linking changes the three-dimensional configuration of the proteins, and the proteins may become dysfunctional (25,26). This may account for the slowing of axonal transport observed in diabetic neuropathy (27). In addition, studies have shown an ARI-like effect on the polyol pathway by amino-γ-linolenic acid (28) as well as an effect on nitric oxide level and vascular flow (30,31). However, there are conflicting reports for both of these actions (32-34). Thus, the beneficial effects of amino-γ-linolenic acid may be secondary to prevention of AGE formation, inhibition of the polyol pathway, improvement in vascular flow, or a combination of these effects. Future clinical trials with products such as amino-γ-linolenic acid may provide further insight into the role of this pathway.

In diabetes, the 8-6-desaturation of linoleic acid to γ-linolenic acid (GLA) is impaired, causing depletion of subsequent metabolites (35,36). This forces prostaglandin metabolism down an alternate pathway, leading to a decrease in nerve function either directly or indirectly via nerve ischemia as a result of altered prostaglandin metabolism (as previously described). When patients were given evening primrose oil, which is high in γ-linolenic acid, in a double-blind placebo-controlled study, both peroneal and median motor NCV and thermal perception threshold improved in the patients randomized to GLA treatment compared with the control patients (37,38). However, clinical signs and symptoms were unchanged. Studies with adequate statistical power to evaluate long-term clinical outcome have not been conducted.

It also appears that treatment with acetyl-L-carnitine is associated with improved nerve function (39-41). Treatment with acetyl-L-carnitine normalized NCV, Na⁺-K⁺-ATPase and protein kinase C in STZ-induced diabetic rats (42). However, long-term studies with adequate statistical power to evaluate long-term clinical outcome have not been conducted with acetyl-L-carnitine.

Finally, neural antibodies have been suggested as an initiating agent of diabetic neuropathy. Although antibodies to nerve tissue are associated with the presence of diabetic neuropathy in both type I and type II patients (43-45), it is not clear that these antibodies play an initial etiologic role. These antibodies could simply be a response by the immune system to damaged nerves. However, once the autoantibodies have been produced, it is certainly feasible that they may further impair nerve integrity and function. Clinical trials of immune suppressive therapy for diabetic neuropathy have not been conducted.

In addition to etiologic approaches, gangliosides and nerve growth factor (insulin-like growth factor I) have been investigated as treatments of diabetic neuropathy. Distal dying back of nerves is a common morphometric finding in patients with diabetic nerve disease. Ganglioside therapy results in axonal sprouting (46) and could theoretically improve nerve function. Although clinical studies have not demonstrated a change in NCV in patients treated with gangliosides, in one clinical trial, there was less definite clinical neuropathy (47). However, it should be noted that this was not formally defined as confirmed clinical neuropathy. Although neurotrophic growth factors such as gangliosides and nerve growth factor hold promise, long-term studies with adequate statistical power to address clinical outcomes are still needed. Furthermore, it should be noted that mixed bovine gangliosides have been withdrawn from the market in Europe because of side effects (e.g., Guillain-Barré syndrome).

In summary, many proposed mechanisms for the development of diabetic neuropathy have been studied. It has been shown that there is improvement of nerve function associated with many short-term clinical trials of treatments that address specific portions of the etiologic pathway. Improvement of morphometry has also been demonstrated in some short-term clinical trials. However, with the exception of the DCCT, long-term trials with adequate statistical power to evaluate clinical outcomes have not yet been conducted. Interestingly, the changes in nerve function are similar in most of the clinical trials. Figure 2 represents four different treatment trials: improved glucose control (48), high myo-inositol diet (20), therapy with an ARI (11), and therapy with GLA supplement (37). All of these trials show an improvement in peroneal motor velocity of 1-2 m/s. This implies that each of the proposed mechanisms contributes to the devel-
FIG. 2. Effects of various treatments on peroneal motor NCV in diabetic patients (adapted from 11, 20, 37, 48). It should be noted that these studies result in similar changes in peroneal motor NCV. This implies that all pathways contribute to the pathophysiology of diabetic neuropathy, or that there is a common pathway that is not yet defined. This observation also suggests the possibility of combination therapy.

FIG. 3. Progression of distal symmetrical polyneuropathy. As duration of diabetes progresses, abnormalities in nerve function increase. Furthermore, the authors hypothesize that the reversible (metabolic) component gets proportionally smaller and the irreversible (structural) component gets proportionally larger.

FIG. 4. Theoretical impact of a successful intervention on distal symmetrical polyneuropathy, assuming all three patients present with similar clinical neuropathic findings. A successful therapy could have vastly different effects depending on the amount of reversible (metabolic) to irreversible (structural) abnormalities.

LIMITATIONS OF PREVIOUS TRIALS

The proposed complex mechanism of diabetic neuropathy could, by definition, result in a diverse patient population. In any single individual, one or more of these mechanisms may play a major or minor role. For example, therapies aimed at part of the cascade associated with the polyol pathway could have a dramatic effect if this is the main mechanism in an individual patient, or almost no effect if the primary mechanism is in a different part of the cascade (e.g., AGEs). Thus, it is anticipated that even with a successful treatment modality the beneficial effect might be variable depending on the patient cohort, since there is no method to identify the specific underlying pathophysiology of an individual patient.

Another confounding variable is shown in Fig. 3. It illustrates the concept that there is progressive deterioration of nerve function with time and duration of diabetes. Abnormal nerve function can be conceptually divided into a metabolic component, which theoretically would be rapidly reversed and theoretically is greatest in the early stages of neuropathy, and a structural component (more permanent) occurring later in the disease process. As with retinopathy and nephropathy, the structural component of diabetic neuropathy is most likely permanent or, if reversible, would be very slow to reverse. Although it is a matter of conjecture whether the structural component is irreversible, there is no evidence that structural changes are reversible. There is some evidence that treatment with neurotrophic factors that increase gene expression and the augmentation of structural proteins or increase Na⁺-K⁺-ATPase activity may be able to improve nerve function both clinically and electrophysiologically. Trials with nerve growth factor and acetyl-L-carnitine are now underway and will test the hypothesis that improvement is possible. Nevertheless, even with near normalization of blood glucose levels after a pancreatic transplant, for years there is only 1–2 m/s of improvement in NCV (49). On the other hand, reversibility has been shown in cases of nerve trauma or toxic insult. It is also a matter of conjecture that reversal of structural damage would be a slow process. However, this seems a reasonable conjecture in that numerous short-term clinical trials have been unable to show any significant improvement in nerve function. In addition, this conjecture is consistent with the DCCT results, which showed a small difference (the metabolic component) between treatment groups after 1 year and essentially no change thereafter.

Figure 4 illustrates three patients who all present with 75% of normal nerve function. One has a very large metabolic component, one has equal metabolic and structural components, and the third has a very small metabolic component. If a successful treatment modality (of any type) is used in all three patients, the responses might be vastly different. The patient with the largest metabolic component would experience rather dramatic improvement with the appropriate metabolic treatment, the second patient would theoretically have a more moderate improvement, and the third patient would have almost no improvement. The effect of a successful treatment of the reversible (metabolic) component of diabetic neuropathy is expected to be relatively rapid.
(months), but the possibility of demonstrating the effect depends on the number of patients with relatively large metabolic-to-structural component ratios. Thus, patient selection may be crucial to outcome. If patients with end-stage neuropathy are included in any study, the possibility of demonstrating a therapeutic effect is greatly diminished. The DCCT demonstrated this well. The DCCT showed little reversal of neuropathy in patients who already had neuropathy at the onset of the trial (3). Thus, we believe that reversal should not be an endpoint for neuropathy clinical trials any more than it is for retinopathy or nephropathy. Furthermore, the stage of neuropathy needs to be considered in trial design. Including patients with insensitive feet or foot ulcers would be similar to including diabetics in a nephropathy study or blind patients in a retinopathy study. Future clinical trials need to be based on past experience. It seems likely that the variation in composition and severity of baseline disease in past clinical trials may have washed out potential treatment effects. Subanalyses of previous clinical trials appear to support this concept in that treatment effects are greatest and most clear in patients with mild early neuropathy (stage I or early stage II, Mayo Clinic classification). It is encouraging that more recent clinical trials of diabetic neuropathy have established more rigid inclusion and exclusion criteria so as to recruit only those with early or mild-to-moderate disease, thus selecting a more homogeneous study population with more likelihood of a reversible component.

The relatively short duration of previous trials hinders the expectation of a significant clinical outcome when prevention or slowing of progression of neuropathy is the endpoint. In order to demonstrate these endpoints it is most likely that a clinical trial would need to last for several years, as was demonstrated by the DCCT. Therefore, clinical trials of diabetic neuropathy should not be conducted like clinical trials of B12 deficiency neuropathy or hypothyroidism-related neuropathy (where relatively rapid and complete reversal is possible) but should be conducted like clinical trials of the other chronic complications of diabetes (i.e., nephropathy and retinopathy).

Diabetic neuropathy lacks proven surrogate endpoints to facilitate clinical trials, as are available for other diseases. As an example, biochemical risk markers for the development of coronary artery disease (e.g., cholesterol), physiological markers of coronary artery disease (such as shown by ECG), and morphological determination (such as cardiac catherization) are all well established, clinically meaningful, quantitative tests. Intermediate clinical outcome endpoints, angina or myocardial infarction, and the ultimate clinical outcome, death, are easily identified and commonly agreed upon (Table 2). Chest pain, per se, is not assumed to be angina and secondary to coronary artery disease until it is confirmed by ECG and/or cardiac catherization. Thus, these tests confirm clinical coronary artery disease. It has been shown that improvement in cholesterol level, a biochemical risk marker, will result in improvement in the clinical outcomes (decrease in progression and mortality) of coronary artery disease. However, improvement in some parameters does not always relate to improved clinical outcome. For instance, a reduction in arrhythmias (a physiological marker) with antiarrhythmic drugs was associated with a higher death rate (50). Thus, it needs to be verified that improvement in any proposed surrogate is associated with an improvement in clinical outcomes. Similar analogies can be made with diabetic neuropathy (Table 2). Biochemical markers for distal symmetrical polyneuropathy may include an increased excretion of truncated nerve growth factor receptors in urine of patients with diabetic neuropathy (51). However, these measurements lack confirmatory evidence. Physiological measures include NCVs and amplitudes, AFTs, and QSTs. Morphological documentation is provided by sural nerve biopsy. Intermediate clinical outcomes would be confirmed clinical neuropathy, neuropathic pain, or insensitive lower extremities. The ultimate clinical outcomes, of course, would be foot ulcers and amputations. Fortunately, recent studies have included confirmation of clinical neuropathy as an endpoint (3). However, at present, we lack the validation and confirmation of any of these potential markers for diabetic neuropathy. To establish markers for neuropathy, at least one long-term clinical trial is needed to confirm that the markers predict clinical outcome. Then these markers can be used in lieu of long-term trials. This is a similar argument that was in existence before the glucose hypothesis was confirmed by the DCCT and the cholesterol hypothesis was confirmed by many multicenter lipid studies.

TABLE 2
Comparison of evaluation/documentation of coronary artery disease and diffuse diabetic neuropathy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coronary artery disease</th>
<th>Diabetic neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical connection</td>
<td>Cholesterol</td>
<td>Possibly truncated urine nerve growth factor receptor</td>
</tr>
<tr>
<td>Morphological measure</td>
<td>ECG</td>
<td>NCV/amplitude</td>
</tr>
<tr>
<td>Intermediate clinical outcome endpoints</td>
<td>Cardiac catherization</td>
<td>AFT</td>
</tr>
<tr>
<td></td>
<td>Angina</td>
<td>QST</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td>Sural nerve biopsy</td>
</tr>
<tr>
<td>Ultimate clinical outcome endpoints</td>
<td>Death</td>
<td>Neurotrophic pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insensitive foot</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Confirmed clinical neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foot ulcer</td>
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<tr>
<td></td>
<td></td>
<td>Amputation</td>
</tr>
</tbody>
</table>

Currently, a combination of morphometry and nerve function studies have been recommended as neuropathy clinical trial endpoints. Presumably, the combination of improved nerve function and nerve morphometry will predict improvement in long-term clinical outcomes such as painful neuropathy, insensitive feet, confirmed clinical neuropathy, neurotrophic ulceration, and/or amputation. Unfortunately, we do not have any study that documents that improvement in NCV, morphometry, or both will result in the lessening of intermediate or ultimate clinical endpoints of diabetic neuropathy. Future studies should be designed to show that an improvement in morphometry or NCV predicts improvement.
in clinical outcomes (less confirmed clinical neuropathy, fewer foot ulcers, fewer amputations, fewer insensitive feet, and fewer painful extremities). This is similar to neuropathy studies (e.g., the ACE-inhibitor trials) showing less end-stage renal failure or less dialysis, retinopathy studies (e.g., the laser trials) showing less worsening in vision or less blindness, and coronary artery disease studies (e.g., the blocker trials) showing less death or less myocardial infarction.

FUTURE DIRECTIONS
It is the opinion of the authors that future neuropathy study designs must consider present knowledge about complications in general and neuropathy in particular. Future trials should be conducted with an expectation similar to those of the ACE-inhibitor nephropathy trials and the DCCT (i.e., the slowing or prevention, rather than the reversal, of complications). Trial protocols should be designed to show prevention of the development of diabetic neuropathy (confirmed clinical outcome) or the slowing of the progression of diabetic neuropathy as defined by clinical endpoints (fewer insensitive extremities, fewer painful extremities, fewer neurotrophic ulcers, or fewer amputations). Patients with mild-to-moderate neuropathy (stage I or early stage II) with presumably more metabolic than structural alterations would be preferred subjects. If these trials are done, then it may obviate the need for nerve biopsy in future studies. Unfortunately, it is not certain that even if nerve morphometry shows improvement, this will necessarily correlate with improved long-term clinical outcome, any more than it was certain before the Cardiac Arrhythmia Suppression Trial study that suppression of arrhythmia would produce a better clinical outcome (50). Endpoint measures must have clinical and prognostic significance, as was learned in the early retinopathy trials (i.e., short-term increase in microaneurysms was not predictive of long-term clinical benefit). However, this approach will lengthen the course of these clinical trials to 3–5 years, similar to ACE-inhibitor studies, retinopathy trials, and other chronic complications trials.

CAVEAT
What are the practical considerations implicit in long-term clinical trials? Patient recruitment and compliance in a long-term study are possible but costly. Where will the funding be obtained? Cutbacks in funding and changes in priorities at the National Institutes of Health (NIH) make it unlikely that this is a potential source of funding, although diabetic neuropathy trials are clearly part of the NIH mission and should be conducted in spite of the apparent lack of interest. What is the possibility of the pharmaceutical industry funding these trials? The high cost and uncertain future of health care financing and regulation in the U.S. at present may not provide enough incentive to the pharmaceutical industry. Changes in patent law may provide the needed incentive, making long-term trials for chronic complications of diabetes more feasible. Perhaps the patent time clock should start at the time of clinical marketing (which might also allow the price of the drug to be lower). Regardless of the source of funding, we believe that trials aimed at reversal of neuropathy using only measures such as NCV, AFT, and QST with or without nerve morphometry (which have not been shown as of yet to relate to long-term clinical outcomes) are not the trial design of choice. Rather, trials aimed at clinical outcomes and slowing the progression of clinical neuropathy should be initiated.

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