Does a Defect of Energy Metabolism in the Nerve Fiber Underlie Axonal Degeneration in Polyneuropathies?

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A number of chemically unrelated neurotoxic compounds and several types of metabolic abnormalities cause strikingly similar patterns of distal symmetrical polyneuropathy in humans and animals. Experimental studies with laboratory species have demonstrated that many toxic polyneuropathies are associated with distal and retrograde axonal degeneration occurring in vulnerable nerve fiber tracts in the central as well as the peripheral nervous system. This has been termed *central-peripheral distal axonopathy*.

Recent observations from the authors' laboratories regarding (1) the spatial-temporal evolution of nerve fiber degeneration in experimental toxic neuropathies and (2) the inhibition of glycolytic enzymes by chemically unrelated neurotoxic compounds point to a common metabolic basis for many distal axonopathies. It is postulated that neurotoxic compounds deplete energy supplies in the axon by inhibiting nerve fiber enzymes required for the maintenance of energy synthesis. Resupply of enzymes from the neuronal soma fails to meet the increased demand for enzyme replacement in the axon, causing the concentration of enzymes to drop in distal regions. This leads to a local blockade of energy-dependent axonal transport, which produces a series of pathological changes culminating in distal nerve fiber degeneration. The idea provides a working hypothesis with which to study the cause of inherited and acquired human and animal polyneuropathies.

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Focus in recent years on demyelinating diseases and neuronal storage disorders has tended to obscure the fact that many neurological conditions do not result from diseases of the neuron or the myelin sheath, but from disease of the *axon*. Dysfunction and degeneration of the axon probably underlie a host of conditions, such as the spinocerebellar degenerations (e.g., Friedreich's ataxia), the many drug and toxin-related polyneuropathies, and the symmetrical distal neuropathies associated with diabetes mellitus, uremia, porphyria, vitamin deficiency, and old age. These many conditions are believed to display a characteristic picture of primary distal axonal degeneration that affects vulnerable tracts located in both the central and peripheral nervous systems [3, 25]. These conditions, which are together grouped under the term *central-peripheral distal axonopathy,* form the subject of this paper.

Distal Axonopathy

Little is known about the origin of axonal degeneration in distal axonopathies. Indeed, it has been a mystery why the axon appears to respond in such a stereotyped manner under so many different and apparently unrelated adverse conditions. Characteristically, degeneration begins in the distal parts of long and large-diameter axons before shorter and smaller axons become involved. With time, degeneration moves along affected nerve fibers toward their nerve cell bodies. This "dying-back" pattern of degeneration produces the familiar clinical pattern of symmetrical, ascending sensorimotor neuropathy, which begins in a stocking-and-glove distribution [3]. Subsequently degeneration in the nerves supplying the limbs progresses proximally until the patient is rendered quadriplegic. Cranial nerves and the autonomic nervous system may also be affected.

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Nosological differences exist in the distal axonopathy group of diseases: some have a slow course while others are rapid; some affect sensory more than motor functions, and vice-versa; some show greater expression in the central than in the peripheral nervous system; and some follow a progressive course while others are rapidly reversible.

Use of Toxic Chemical Probes

Ignorance concerning the morphological substrate of distal axonopathies is slowly giving way under intensive experimental investigation. Toxic chemicals have long been used as experimental probes of distal axonopathies because the timing and velocity of disease progression may be readily manipulated by varying the dose and duration of intoxication. Four poorly defined categories of experimental toxic distal axonopathy have been described based on morphological criteria, namely, distal axonal disease associated with accumulations of (1) 10 nm neurofilaments, (2) smooth membranous profiles, or (3) mitochondria, and (4) those unassociated with organelle accumulations. Since the pathological events may vary as a function of the velocity of axon breakdown, and because the type of disease depends both on the stage of degeneration and the locus sampled by the investigator, it is uncertain if this classification is realistic. Furthermore, most attempts to relate one morphological type of experimental distal axonopathy to a specific human disease meet with little success. A notable exception is the relationship between the rare childhood giant axonal neuropathy associated with abnormal hair [2] and the experimental and human neuropathies produced by the neurotoxic hexacarbon compounds methyl *n*-butyl ketone (M*n*BK) and *n*-hexane. These spontaneous and toxic diseases are both characterized by mixed, but predominantly motor, neuropathy in which axonal degeneration is heralded by multifocal accumulations of normal-appearing 10 nm neurofilaments that produce giant distal axonal swellings. The experimental study of the hexacarbon neuropathies has revolutionized our concept of the pathogenesis of the dying-back process and led to the present hypothesis of the cause of distal axonopathies.

Experimental Hexacarbon Neuropathy

The evolution of interest in experimental hexacarbon neuropathy is instructive. Like the majority of toxic models of neuropathy, the neurotoxic property of aliphatic hexacarbon solvents was recognized because of industrial outbreaks of human disease following occupational exposure. Isolated occurrences of *n*-hexane neuropathy in Japan and the United States [10] were received with little interest at first. It was not until the 1973 outbreak of M*n*BK neuropathy in a fabric-finishing factory in Ohio [1] that interest began to center on the neurotoxic properties of these metabolically related hexacarbon solvents. Investigators at several institutions produced identical patterns of giant axonal neuropathy in animals exposed to M*n*BK or *n*-hexane, or to 2,5-hexanedione (2,5-HD) [5, 13, 19, 24, 30], which was identified as a common metabolite of these solvents [4]. Our own observation of symmetrical distal and ascending degeneration in long spinal cord tracts and in peripheral nerves demonstrated that these neurotoxic hexacarbons produce a model dying-back process in experimental species [26, 27]. These compounds appeared to be uniquely powerful investigative probes because the spatiotemporal evolution of damage could be observed simply by examining with the light microscope the distribution of axonal swellings in teased nerve fibers at different stages of the disease process. As a result of these investigations, long-held notions on the nature and course of the dying-back process proved incorrect.

Changing Concepts of Pathogenesis

Until these studies it was generally believed that the dying back of axons in toxic neuropathies resulted from the toxin impairing the anabolic machinery of the neuronal perikaryon [3]. Because protein synthesis does not occur in the axon, it was believed that reduced amounts of synthesized materials exported from the diseased neuronal perikaryon would fail to meet the metabolic needs of the axon. This would cause the distal portion of the axon to receive an inadequate supply of materials and thus undergo degeneration. Although all neuronal perikarya would be similarly affected by the toxic assault, the longest axons would be the first to degenerate because their perikarya would bear the greatest metabolic load. As perikaryal function further deteriorated under continued toxic barrage, axons of smaller volume would become similarly compromised. This defect would first lead to axonal degeneration of the nerve terminal, and as neuronal dysfunction progressed, the disease would march steadily up affected fibers, which would appear to die back toward their nerve cell bodies.

The pattern of nerve fiber change observed in experimental hexacarbon neuropathy (Fig 1) demonstrated that this concept was incorrect for several reasons. First came the demonstration that PNS fiber diameter can be more important than axon length in determining the hierarchy of vulnerability. Thus, the large-diameter fibers leaving the tibial nerve to supply the calf muscles begin to degenerate before equivalent regions of longer but thinner tibial nerve fibers supplying plantar musculature. Second, it was found that giant axonal swellings develop in nerve

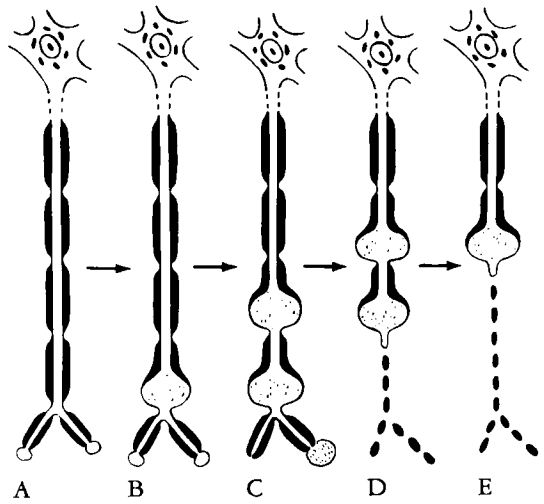

Fig 1. Distal (dying-back) axonopathy produced by neurotoxic hexacarbon compounds such as MnBK and 2,5-HD. (A) Normal axon. During chronic intoxication, transported materials (stippling) *accumulate, causing giant axonal swellings and myelin retraction to develop on the proximal sides of nodes of Ranvier in the distal portion of the fiber (B). Paranodal swellings appear at more proximal loci with time, as transport failure develops at these sites (C), while the distal portion below an axonal swelling undergoes wallerian-like degeneration (D, E).*

terminals only *after* swellings have appeared more proximally in the supporting nerve fiber. These swellings consistently develop first on the proximal sides of nodes of Ranvier and temporally move up the fiber to affect more proximal paranodes. Contrary to some reports, neurofilaments are not increased throughout the length of the axon; indeed, distal to giant axonal swellings, where the axon is attenuated and the myelin sheath corrugated, few neurofilaments are found. Further study of fibers showing different degrees of degeneration in the hexacarbon model revealed that nerve fiber breakdown commences adjacent to a giant axonal swelling, causing the portion below the swelling to undergo a more or less simultaneous disintegration. A third observation was the ability of distally damaged nerve fibers to regenerate axonal sprouts during the period of intoxication, a phenomenon which seems inconsistent with neuron perikaryal dysfunction.

Nerve Fiber Locus of Toxic Damage

These observations demonstrated that the classic concept of neuronal perikaryon disease was incorrect and encouraged us to develop the idea that these toxins might be acting directly on the nerve fiber. Similarly, these observations persuaded Cavanagh to abandon his long-held view that dying-back disease followed neuronal perikaryon dysfunction [21]. The new idea of local nerve fiber toxicity, initially suggested by Prineas [14], had evolved during our earlier studies of experimental acrylamide neuropathy [20, 23] and was strongly supported by the results of the hexacarbon investigation. The identification of 2,5-HD as the common neurotoxic metabolite of M*n*BK and *n*-hexane [4] set the stage for testing of this theory.

Recognition that 2,5-HD is a primary neurotoxic agent depended on the discovery of its long persistence time in vivo and the demonstration in 1974 that the compound could reproduce dying-back disease in organotypic CNS-PNS-muscle tissue cultures without the appearance of other metabolites [29, 32]. During this study we examined the entire evolution of axonal degeneration in living nerve fibers innervating functioning muscle. In addition to confirming the previous observations on the evolution of distal axonopathy in vivo, the tissue culture studies showed that axonal swellings frequently first appear proximal to a node of Ranvier marking the branching point between the parent efferent nerve fiber and the distal branches composing the motor nerve unit (see Fig 1). This showed that the disease commences at the end of the broadest part of the nerve fiber, proximal to the thinner branches supplying the motor nerve terminals, an observation which strengthened the notion that fiber diameter correlates with susceptibility to fiber degeneration.

Axonal Transport Studies

In 1975 investigations began to test the possibility that neurotoxins such as M*n*BK and 2,5-HD damage nerve fibers by impairing the axonal transport of perikaryal materials required for maintenance of axonal integrity. Mendell and collaborators [12] demonstrated that the rate of downflow in the proximal portion of sciatic nerves is impaired progressively during the course of the disease. Because this correlated with our observations of a progressive proximal spread of giant axonal swellings, it seemed possible that the swellings represented focal areas of slowed passage of transported materials. A focal slowing of fast transported materials within the giant axonal swellings was later demonstrated [7]. Subsequently Griffin and co-workers [6] showed that similar giant axonal swellings in proximal axons following β,β'-iminodipropionitrile (IDPN) intoxication resulted from a selective blockade of neurofilamentous proteins known to move along in a slow phase of axonal transport. The fast transport system appeared to remain intact in this condition. Because IDPN and hexacarbon-induced giant axonal swellings both contained 10 nm neurofilaments, it seemed likely that slow axonal transport was also impaired in hexacarbon distal axonopathy and that the

observed slowing of fast axonal transport was a secondary phenomenon.

Role of Energy Metabolism

Both the morphological and axonal transport findings in experimental hexacarbon neuropathies focused attention on distal nodes of Ranvier as sites of special vulnerability in distal axonopathies. It seemed possible that this phenomenon was related to the peculiar energy demands of the node of Ranvier associated with impulse conduction and axonal transport. If pathways synthesizing chemical energy were blocked within the fiber as a result of toxic assault, a reduced amount of energy would be available to drive these energy-requiring functions. Energy deprivation within the axon might be especially critical at nodes of Ranvier, accounting for the observed changes in conduction velocity and the accumulation of transported material in adjacent regions.

Several factors complicated this idea: First, the high energy demands of the nodal axon were only assumed. Second, although one of us (M. I. S.) had shown the fast axonal transport system to be energy dependent [18, 18a], a decrement in slow axonal transport, assumed to be the cause of neurofilament accumulation in hexacarbon neuropathy, may be related to another mechanism. Finally, the role of mitochondria located in the paranodal region of the Schwann cell had to be considered. It has been suggested that these mitochondria supply the presumed additional energy requirements of the axon at the node of Ranvier. Conceivably, as the axon swells and paranodal demyelination occurs, this energy source for the node disappears, thereby exacerbating the putative energy deficit in the nodal axon.

We pursued an investigation of the possibility that a blockade of energy-dependent axonal transport at nodes of Ranvier might cause the paranodal neurofilament accumulations seen in hexacarbon neuropathy. Previously investigators in Poland [31] and Finland [8] had reported that carbon disulfide intoxication also produced a neurofilamentous neuropathy of the dying-back type, similar to that caused by the neurotoxic hexacarbons. This appeared to be a major obstacle for a unitary hypothesis on the origin of distal axonopathies: how could *chemically unrelated* compounds, namely, 2,5-HD, acrylamide, and carbon disulfide, each produce distal CNS and PNS axonal degeneration associated with multifocal accumulations of 10 nm neurofilaments? Recalling the example of the gangliosidoses, in which related enzyme deficiencies produce common pathological features, it seemed reasonable that neurofilament distal axonopathies might also result from a common metabolic blockade, specifically, in pathways concerned with energy metabolism. The known protein reactivity of acrylamide, 2,5-HD, and carbon disulfide also suggested that enzyme study was a promising path to follow.

Neurotoxic Inhibition of Glycolysis

At the outset we were struck by the dimeric relationship between 2,5-HD and acetone. This caused us to embark on an in vitro investigation of the effect of the hexacarbon neurotoxins on α-glycerophosphate dehydrogenase (GPDH). It was postulated that GPDH might bind with the active dimer 2,5-HD in preference to the natural substrate dihydroxy*acetone* phosphate. Following preincubation of the crystalline enzyme with the toxin, substrate cleavage, as revealed by NADH oxidation, was greatly impaired [28].

Our subsequent biochemical investigations, which focused on energy metabolism, examined the possibility that key glycolytic enzymes might display a common sensitivity to the three chemically unrelated neurotoxic compounds (2,5-HD, acrylamide, and carbon disulfide). It was already known that disulfide ions inhibit crystalline glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity. Since GAPDH is a major gating enzyme on which axonal transport is known to depend [18], the sensitivity of this enzyme to the three toxins was next investigated. All three compounds were found to inhibit GAPDH activity as a function of both toxin concentration and duration of preincubation. This was true for crystalline enzymes as well as for enzymes present in brain and peripheral nerve tissue incubated in vitro. Subsequent examination of the sensitivity of phosphofructokinase (PFK), a major regulatory control step in glycolysis, gave comparable results ([15, 18a] and Sabri MI, Ederle K, Spencer PS: Studies on the biochemical basis of distal axonopathies. 3. Common metabolic defects in glycolysis produced by chemically unrelated neurotoxic agents. In preparation). In both cases enzyme inhibition was of mixed type, and enzyme reactivity could be preserved with sulfhydryl-providing reagents such as dithiothreitol. Lactate dehydrogenase was unaffected by these neurotoxic compounds, an observation which supported the idea that acrylamide [9, 22], 2,5-HD, M*n*BK, and carbon disulfide display specificity for sulfhydryl enzymes. As demonstrated in Figure 2, a blockade of enzyme activity at these sites in glycolysis would severely impair energy transformation.

The Pathogenesis of Distal Axonopathy

These observations have encouraged us to form a hypothesis on the mechanism of nerve fiber degeneration in distal axonopathies. We suggest that neurotoxins producing distal axonopathies act at

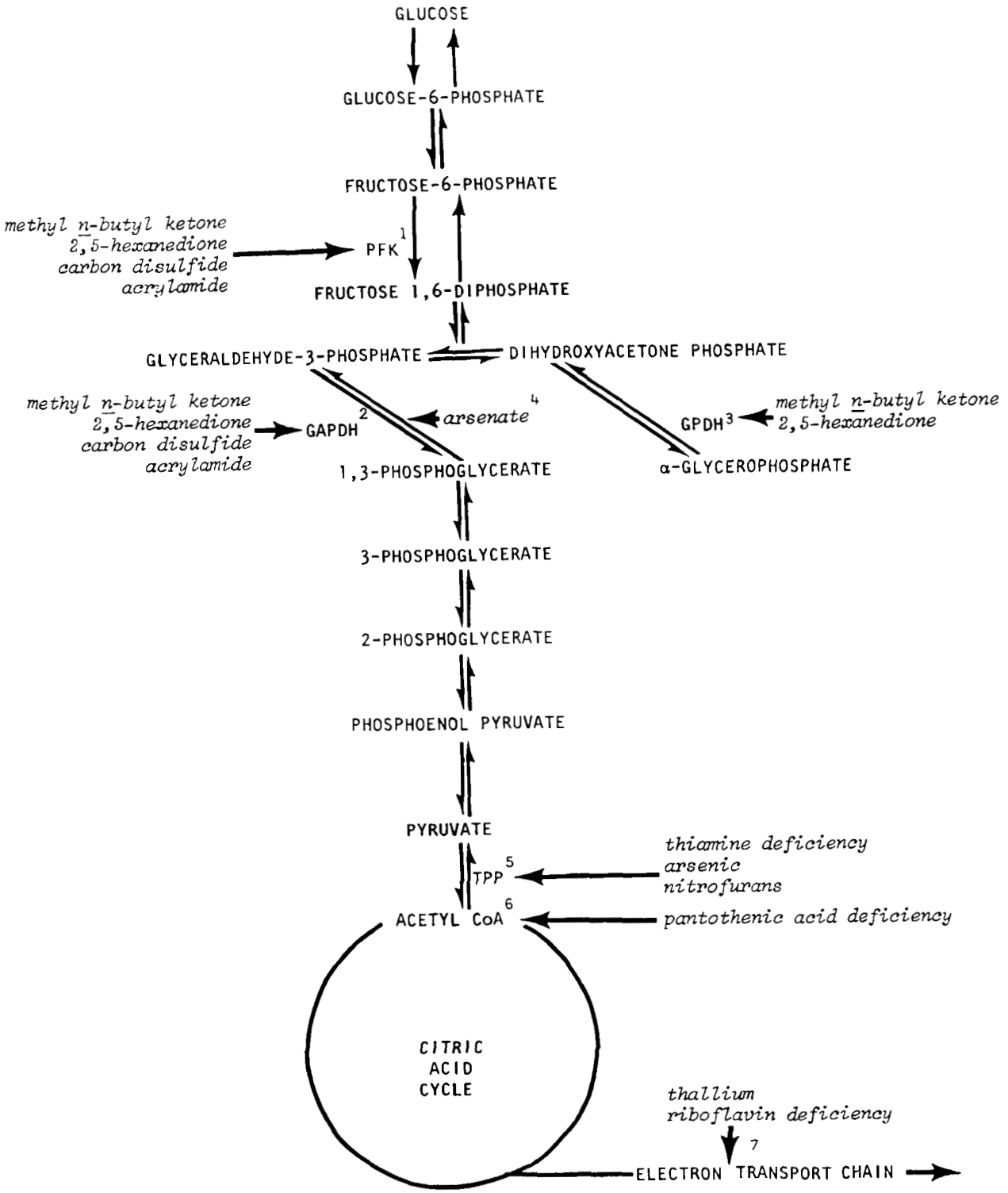

Fig 2. Energy-producing pathways showing putative target sites in distal axonopathies produced by neurotoxins and vitamin deficiency states. (1–3) *Phosphofructokinase (PFK), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and α-glycerophosphate dehydrogenase (GPDH) catalyze these reactions and are inhibited by the neurotoxins listed in italics ([15–17, 28] and Sabri MI, Ederle K, Spencer PS: Studies on the biochemical basis of distal axonopathies. 3. Common metabolic defects in glycolysis produced by chemically unrelated neurotoxic agents. In preparation).* (4) *Arsenic uncouples the oxidation of glyceraldehyde-3-phosphate by substituting for the phosphate radical.* (5) *Thiamine pyrophosphate (TPP) is a cofactor in this reaction. TPP production is decreased in thiamine deficiency states; arsenic interacts with TPP, and nitrofuran drugs act competitively with TPP for the oxidation of pyruvate [21].* (6) *Acetyl coenzyme A incorporates pantothenic acid in its structure. Deficiency of pantothenic acids in pigs produces degeneration of long spinal tracts as well as motor and sensory nerves [21].* (7) *Flavin nucleotides, required for the electron transport chain, may be decreased in riboflavin deficiency states or by thallium binding to riboflavin [21].*

nearby or related sites in metabolic pathways. Many distal axonopathies may result from impairment of energy synthesis—for example, by blockade of glycolysis—causing slowed axonal transport at nodes of Ranvier. This abnormality occurs first in the distal axon because the intraaxonal enzymes responsible for energy synthesis are supplied by axonal transport from the distant neuronal perikaryon. Under normal conditions, the perikaryon is able to meet the demand for glycolytic enzymes in the axon. However, when a toxin inhibits the activity of enzymes along the length of the nerve fiber (in axon or Schwann cells or both), the total axonal demand for the enzyme exceeds the ability of the neuronal perikaryon to respond. Under these conditions, transported enzymes are utilized to meet the raised demand of the proximal portion of the axon, leaving inadequate amounts of enzyme for the distal axon. The idea presupposes that enzymes are protected from the toxin during passage down the axon and that they are deposited progressively along the axon during transport. Failure of an adequate resupply of glycolytic enzymes to arrive in the distal axon would precipitate axonal transport difficulties, thereby causing the accumulation of neurofilaments which herald the onset of axonal degeneration and clinical neuropathy (see Fig 1).

Seven points support this hypothesis:

1. It is consistent with all known pathological features and biochemical aberrations identified in hexacarbon [15–17, 28] and acrylamide [9, 11, 22, 23] neuropathies, the best studied of the filamentous distal axonopathies.
2. It is consonant with the observed widespread in vivo distribution and protein reactivity of carbon disulfide, acrylamide, and 2,5-HD.
3. It explains the cause of other neuropathies such as those produced by arsenic, nitrofurans, thallium, and vitamin deficiencies [21], each of which may interrupt energy metabolism at different positions (see Figure 2 for explanation).
4. One can understand why long axons are more vulnerable than shorter axons of similar diameter because the axonal demand for enzyme replacement would be greater in longer fibers.
5. Paranodal giant axonal swelling would proceed up the fiber as the neuron failed to respond to the increasing axonal demand for enzyme replacement.
6. Degeneration would predominantly affect large-diameter myelinated fibers either because the energy demands are proportionately greater in these fibers or, alternatively, because swellings develop first in these fibers due to the mechanical problem posed by their special nodal architecture. Unlike small fibers, in which the nodal axon is only slightly attenuated, the nodal region of the large-diameter axon normally is shrunken to one-third of the internodal diameter. It is conceivable that failing axonal transport mechanisms could cause materials to accumulate within these fibers much more rapidly than in smaller-diameter fibers simply because of the attenuated structure of the nodal region. This idea is also consistent with the observation from tissue cultures that paranodal swelling frequently appears at the end of large-diameter portions of motor fibers before it occurs at more distally located paranodes in the smaller-diameter branches supplying end-plates (see Fig 1).
7. Observed axonal regeneration during intoxication could occur because the perikaryon is *not* undergoing progressive dysfunction. Furthermore, the small diameter of the regenerating axons would make them less vulnerable to fiber dysfunction.

In summary, this hypothesis provides a cohesive metabolic explanation for the cause of central-peripheral distal axonopathies. Two important corollaries for clinical neurology emerge: First, the hypothesis provides a rational basis for studying the origin of human inherited and acquired metabolic neuropathies of the distal axon. Some of these conditions may prove to be associated with a deficit in energy synthesis associated with blockade occurring at one or more of the many possible loci shown in Figure 2. Second, if specific metabolic lesions can be identified in human distal axonopathies, treatment by replacing enzyme or missing substrate becomes a realistic goal.

Finally, we should investigate the idea that patients with metabolic neuropathies akin to toxic neuropathies produce abnormal neurotoxic metabolites which cause the nerve damage. This idea is especially germane to diabetic polyneuropathy. Diabetic patients treated with insulin excrete the novel metabolite ethyl *n*-butyl ketone (E*n*BK) [33]. This compound undergoes subterminal carbon oxidation in animals to produce 2,5-heptanedione, which, like 2,5-HD, produces an experimental giant axonal neuropathy (O'Donoghue J, DiVincenzo G: personal communication). Methyl ethyl ketone, a non-neurotoxic component of diabetic (and normal) urine [33], would probably promote the neurotoxic effect of E*n*BK, as is known for M*n*BK. Such metabolic events occurring in the diabetic patient might account for the development of neuropathy. A comparable approach might yield new ideas on the cause of other neuropathies such as those associated with uremia and old age.

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