1983 usa

Neuromyopathy of Cyanide Intoxication due to "laetrile" (Amygdalin)

A Clinicopathologic Study

UMA P. KALYANARAMAN, MBBS, MSc,* KRISHNA KALYANARAMAN, MD, DM, FACP,†
STEPHEN A. CULLINAN, MD,‡ AND JOHN M. McLEAN, MD,§

A 67-year-old woman with lymphoma presented with a neuromyopathy following "laetrile" (amygdalin) treatment. She had significant elevation of blood and urinary thiocyanate and cyanide levels. Sural nerve biopsy specimen revealed a mixed pattern of demyelination and axonal degeneration, the latter being prominent. Gastrocnemius muscle biopsy specimen showed histochemically a mixed pattern of denervation and myopathy with Type II atrophy. It is concluded that cyanide toxicity secondary to laetrile therapy and nutritional deficiency caused the neuromyopathy, as the changes in peripheral nerve are similar to changes described in ataxic polyneuropathy occurring in Nigeria attributed to high cyanide content in the diet and nutritional deficiency. Although this patient received vincristine initially, the development of the neuromyopathy had no temporal relationship to its administration. The clinical profile, as well as peripheral nerve and muscle changes were not similar to either vincristine neuromyopathy or neuromyopathy due to paraneoplastic manifestation of lymphoma. Clinical improvement following discontinuation of "laetrile" by the patient further supports the toxic etiologic results for the neuromyopathy in this patient.

***Cancer* 51:2126–2133, 1983.**

LAETRILE with a lower case "l" is amygdalin, a cyanogenetic glycoside.[1] This is a naturally found toxic substance in the kernels of apricot pits, stone fruits, and nuts like almonds, cadamia nuts, etc.[2] Cyanogenetic glycosides promoted by backers of laetrile therapy for cancer are chemical substances composed of cyanide, aldehyde or ketone, and sugar. In a recent review of the poisonous side effects of laetrile, Herbert,[3] has concluded that laetrile can lead to cyanide poisoning and hence could be a public health hazard in view of recent legislation in several states allowing its use for the treatment of cancer. We present in this article a patient who developed a progressive polyneuropathy following laetrile therapy for lymphoma. We will present evidence based on biochemical and nerve and muscle biopsy studies, that this patient developed a neuromyopathy secondary to cyanide intoxication.

Case Report

A 66-year-old woman was admitted to the hospital for investigations because of progressive paresthesia of upper and lower extremities, difficulty in standing and walking all of 4–6 months duration. In 1970, based on a cervical lymph node biopsy specimen, she was diagnosed to have a poorly differentiated lymphocytic lymphoma and was treated with upper mantle radiation. She became apparently free of lymphoma, although she has since had a chronic normochromic normocytic anemia. In Februŭary 1980, she had a recurrence with an intra-abdominal mass which following a staging laparatomy, was diagnosed as IVE lymphoma. She underwent a palliative resection of the mass and splenectomy. Following this, she voluntarily took three tablets of laetrile (amygdalin) per day containing the equivalent of 25–75 mg of cyanide and had a short course of vincristine which was discontinued at least four months prior to the current admission because of intolerance.

Examination on admission revealed a moderately healthy

Presented at the annual meeting of the American Association of Neuropathologists held in Vancouver, British Columbia in June 1981.

From the Departments of Pathology, Neurosciences and Medicine, University of Illinois College of Medicine at Peoria.

* Assistant Professor of Pathology (Neuropathology).

† Associate Professor of Neurology.

‡ Clinical Instructor in Medicine.

§ Clinical Assistant Professor of Neurology.

Address for reprints: Uma P. Kalyanaraman, MBBS, MSc, One Illini Drive, P. O. Box 1649, Peoria, IL 61656.

The authors thank Robert Caughey and Linda Kroesen for their technical help and Larry Crossett for the photographs. They also thank W. Campbell, MD, for the follow-up on the patient and the Word Processing Department of the Peoria School of Medicine for typing the manuscript.

Accepted for publication March 8, 1982.

0008–543X/83/0601/2126 $1.20

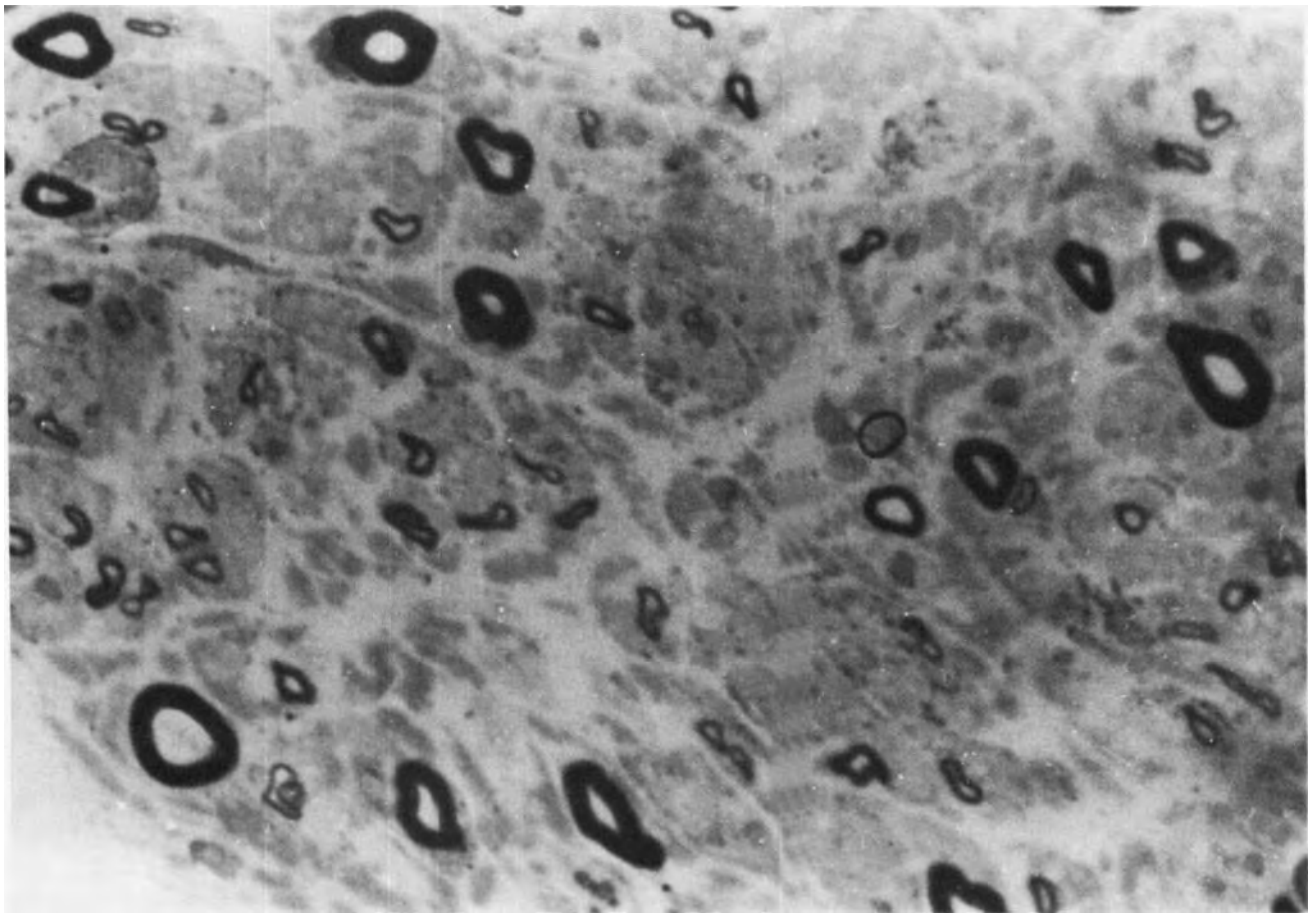


FIG. 1. One micron-thick section of the sural nerve biopsy specimen showing marked reduction in the number of large myelinated fibers (Toluidine blue ×1070).

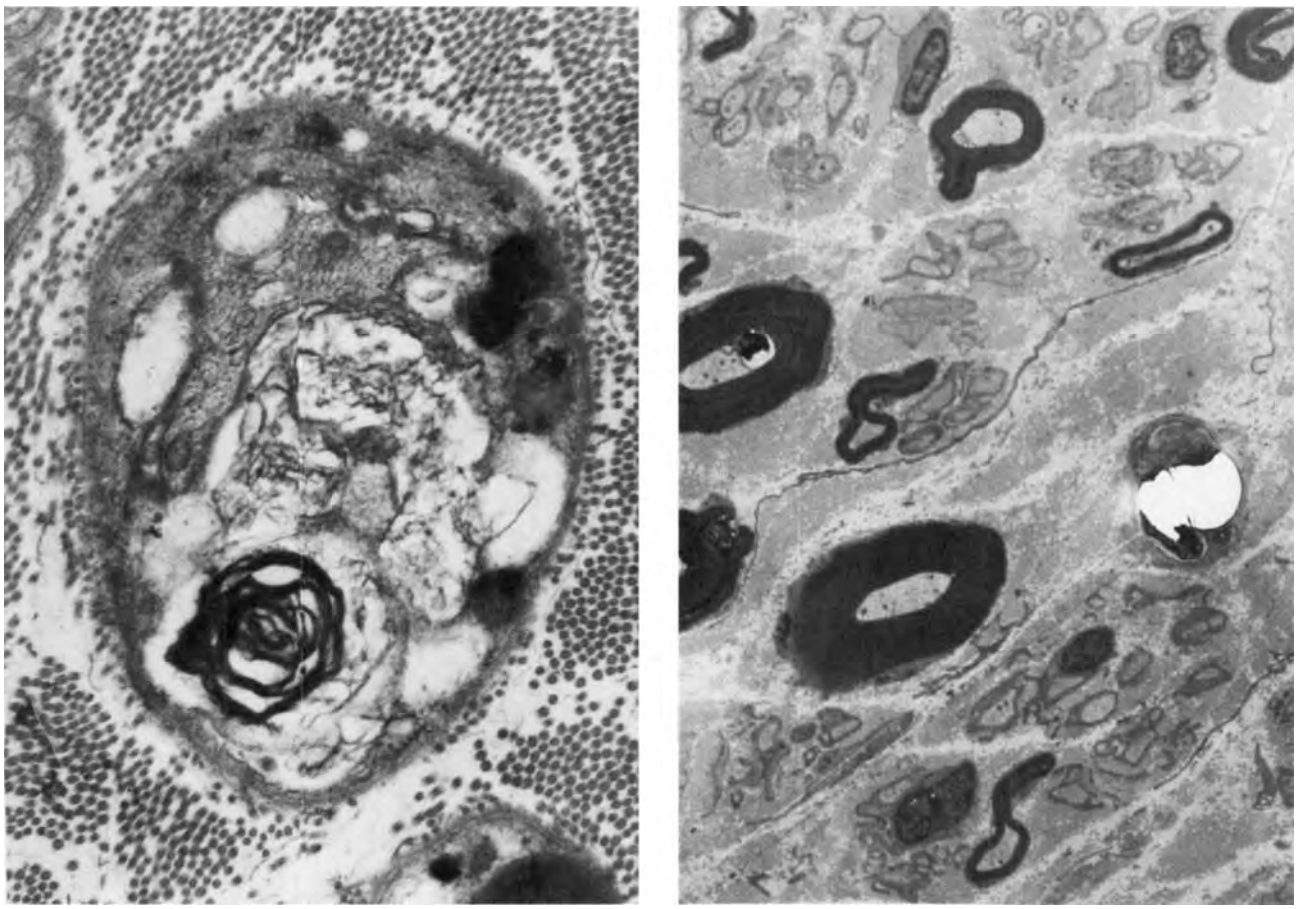
woman with no lymphadenopathy or organomegaly. Neuromuscular examination: Normal cortical and cranial nerve functions and speech. Gait was broad-based with positive Romberg's sign. She was weak diffusely with distal predominance. Sensory examination revealed a distal hypesthesia and hypalgesia of extremities, more marked in the legs with loss of proprioception distally. Tendon reflexes were present in upper extremities and absent in the lower extremities.

Laboratory Data

Routine urinalysis, electrolytes, serum proteins, calcium and phosphorous, thyroid profile, sedimentation rate, liver profile, x-ray chest, and EKG were normal. She showed a mild chronic normochromic, normocytic anemia and reticulocytosis. Serum glucose-6-phosphate dehydrogenase was normal. EMG and nerve conduction of lower extremities showed extensive partial denervation with unelicitable motor and sensory conduction velocities. Blood cyanide levels done on two different occasions were as follows: 191.8 mcg/100 ml and 39.4 mcg/100 ml (normal up to 15). Blood thiocyanate levels done at the same time were 12.3 mg/dl and 11.4 mg/dl (normal 2–4). Serum cobolamin levels on two occasions were 2000 pg/ml and 3230 pg/ml (normal 215–800). Urine thiocyanate levels two days apart were 6.8 mg/100 ml and 5.2 mg/100 ml (normal under 0.2 mg/100 ml). The patient underwent a left gastrocnemius and sural nerve biopsy.

Morphologic Studies

Sural nerve: Pieces of sural nerve were fixed in 3.6% glutaraldehyde for two hours followed by two ten minute washes in Sorenson's buffer. The nerve was then post fixed in 2% phosphate buffered osmium tetroxide. The material was again rinsed twice in phosphate buffer for five minutes. Following this in the alcohol dehydration step, the nerve was kept for five minutes each in 25%, 35%, 50%, 70%, 80%, and 95% ethanol. Then two changes in 100% ethanol for ten minutes each time was done as the next step in dehydration. The material was then processed for 15 minutes in 50% propylene oxide and 50% in Epon, followed by another 15 minute processing in 25% and 75% propylene oxide. The material was then kept in 100% Epon for one hour. The material in Epon molds were then left at 37°F overnight and then at 60°F for 24 hours after which it was sectioned by ultramicrotome. Toluidine blue stained one micron thick sections were studied by light microscope and a JEM 100c Transmission Electron Microscope was used to study the ultrathin sections.



FIGS. 2A AND 2B. (A, left) Ultrathin sections from the sural nerve biopsy specimen showing a totally demyelinated fiber. Also note the axonal degeneration and presence of myelin figure within the axoplasm (Uranyl acetate–lead citrate ×25,000). (B, right) Another area showing long tortuous fibers with thin myelin sheaths (Uranyl acetate–lead citrate ×3000).

Toulidine blue stained one micron thick sections showed a marked reduction in the number of large myelinated fibers (Fig. 1). Ultrastructural studies showed prominent myelin and axonal changes: myelin changes varied from totally demyelinated fibres to fibres with remyelination (Figs. 2A and 2B). Unravelling of myelin sheaths with granular disintegration was prominent. Regenerating fibres characterized by thin myelin sheath, tortuosity and elongation was prominent. Axonal changes consisted of presence of multilocular degeneration, myelin figures, increase of microtubules, microfilaments and mitochondria in the axoplasm (Fig. 3).

Muscle: Fresh snap frozen muscle in isopentane cooled by liquid nitrogen to −180°F was stained with H & E, modified trichrome, PAS, ATPase at PH 9.4, 4.6 and 4.3, NADH-TR and phosphorylase. Muscle necrosis, myophagia, vacuolization of fibers, fiber size variation, small group atrophy, and increase of connective tissue and fat indicative of a primary myopathy as well as neurogenic atrophy were prominent (Figs. 4A and 4B). Histochemical studies were consistent with the features found in a neurogenic atrophy like atrophic angulated fibres belonging to both fiber types by ATPase at PH 4.3 (Fig. 5). Target fibers, dark staining atrophic fibers as well as myofibrillary disintegration with dark staining of the center of the fibers by NADH-TR were seen (Fig. 6) ultrastructurally, changes were prominent in the Z-lines, consisting of smearing, zig zagging and haphazard arrangement (Fig. 7A). Intense thickening and widening of the Z-lines resulted in formation of structures resembling "pseudorods" in subsarcolemmal location (Fig. 7B).

Patient did not return for follow-up but was contacted by telephone. She had discontinued the laetrile as advised. She had recurrence of the abdominal swelling which responded to radiation. Her difficulty in walking had improved and she was ambulating doing volunteer work in hospitals.

Discussion

Ultrastructural changes of the nerve show unequivocally involvement of myelin and the axon. The muscle shows myopathic changes, in addition to the expected neurogenic atrophy with vacuolation and necrosis. Also, myofibrillar disintegration and prominent Z-line changes

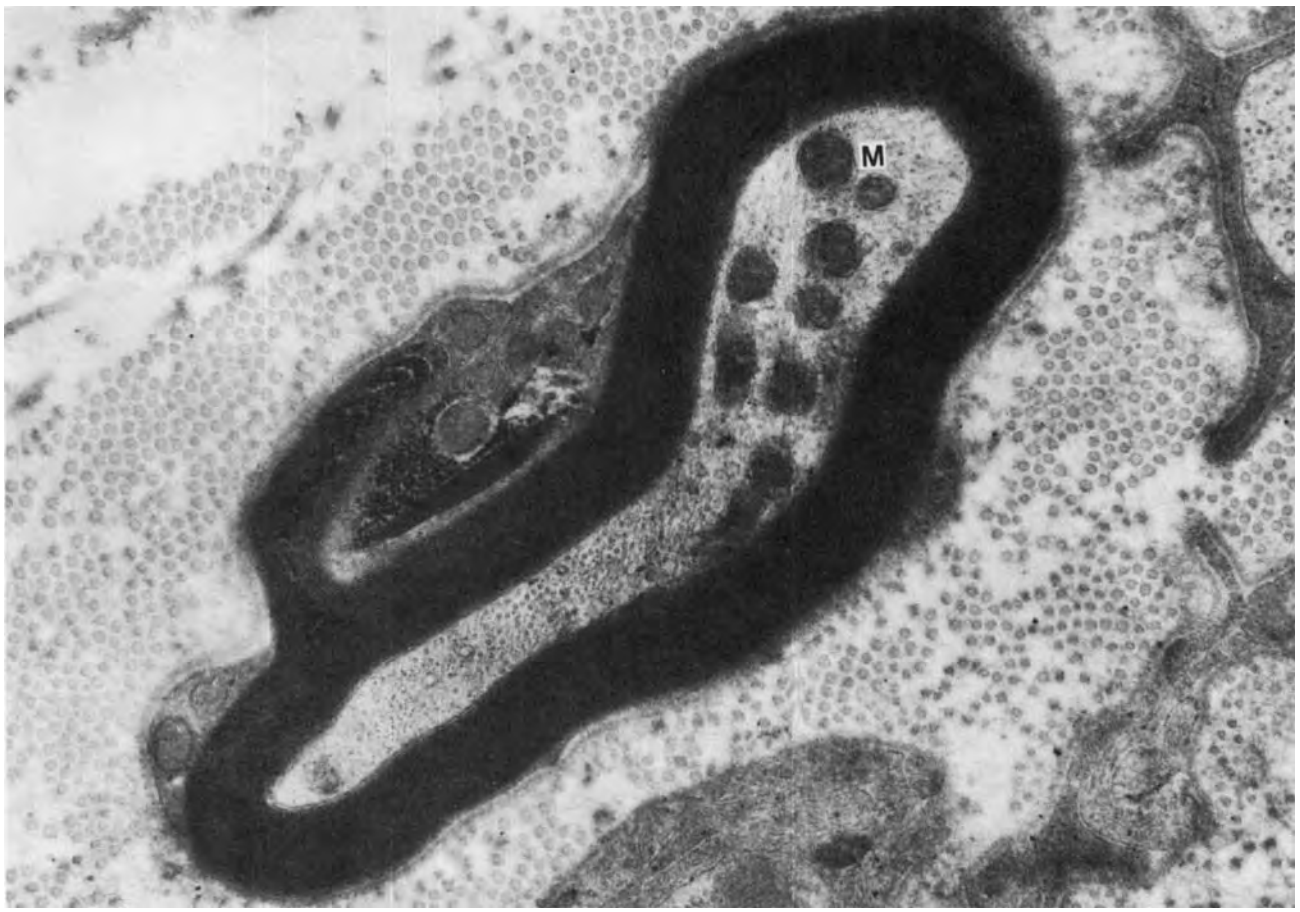
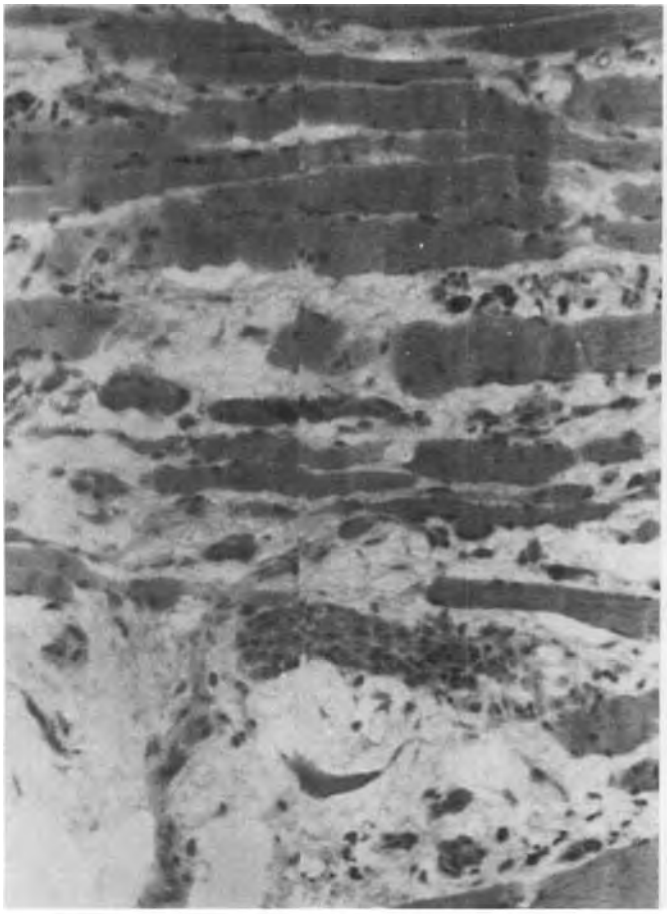
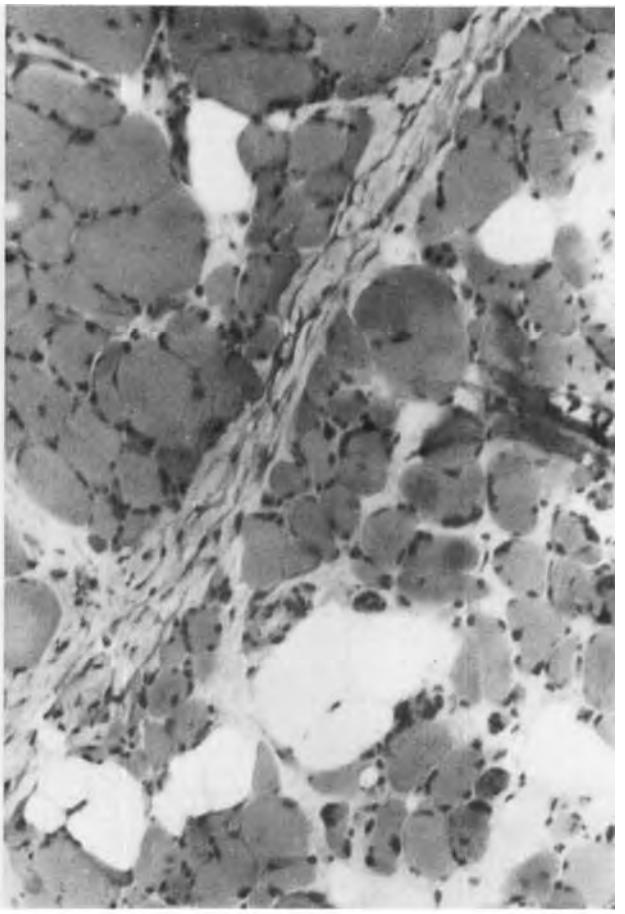


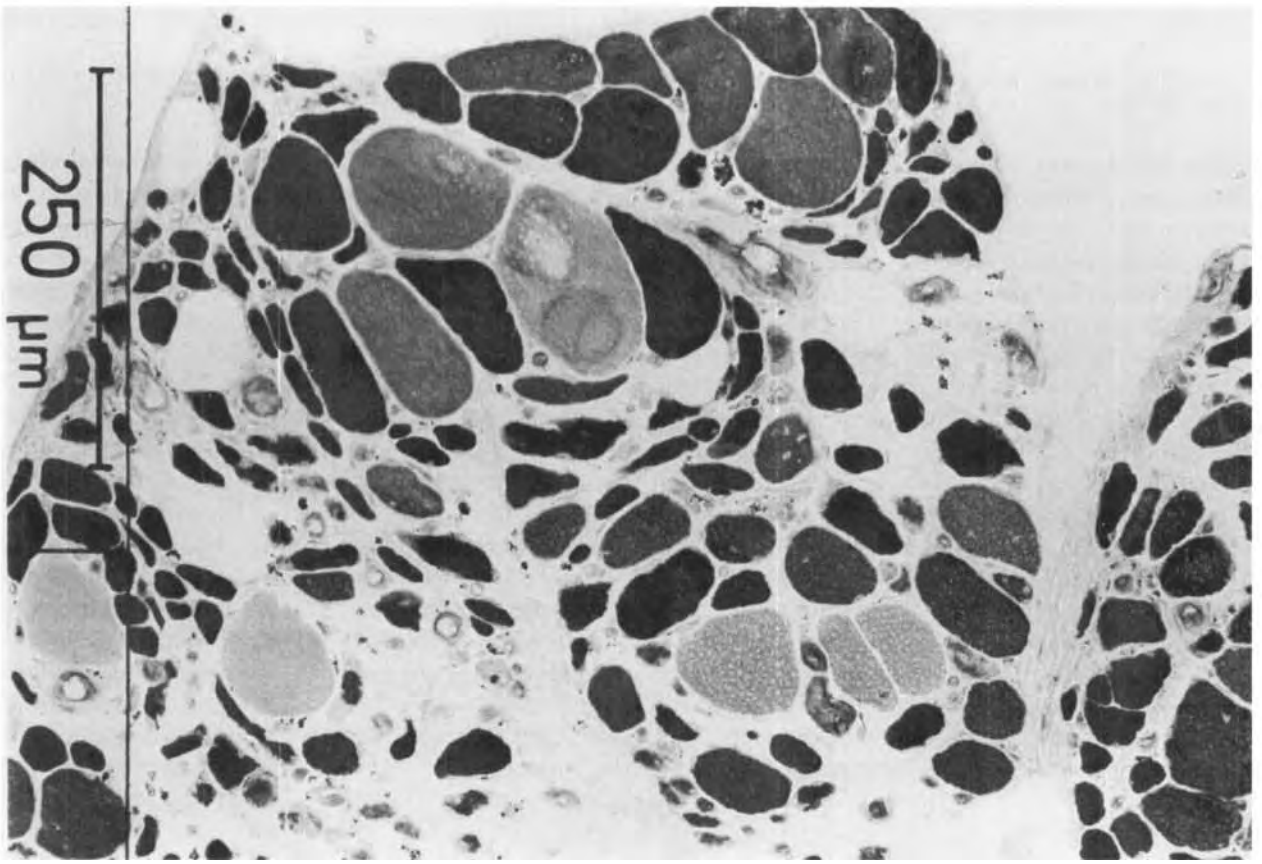
FIG. 3. Ultrathin section of sural nerve showing a fiber with increase of microfilaments, microtubules, and mitochondria (M) (Uranyl acetate–lead citrate ×34,000).

especially "pseudo rod formation" is unlikely to occur in neurogenic atrophy alone. The pathogenesis of the "neuromyopathy" in our opinion is caused by the toxic effect of cyanide and thiocyanate on the nerve and muscle. Laetrile consists of two parts of glucose, one part of benzaldehyde and a part of cyanide. The cyanide in laetrile is released as hydrogen cyanide (prussic acid) by hydrolysis in the presence of the enzyme B-glucosidase, or heat, or mineral acids.[3,4] The released hydrogen cyanide (hydrocyanic acid, HCN) is a colorless, weak acid boiling at 25.5°C (well below body temperature) to become a gas, which is lethal. Laetrile with a capital "L" is a synthetic substance that has never been marketed. Laetrile with a lower case "l" is amygdalin, the product marketed by Laetrile promoters. The popular term "laetriles" is a synonym for "cyanogenetic glycosides." Amygdalin, which the patient was taking is L-mandelonitrile-B-D-glucoroniside, 6B-glucoside, abundantly present in bitter almonds and apricot pits. Enzyme Beta-glucosidases catalyze the hydrolysis of glucositic bonds resulting in the dissociation of Mandelo-nitrile resulting in benzaldehyde and hydrogen cyanide formation, a reaction that can rapidly proceed at room temperature in the absence of lyases. Parenteral administration of laetrile is harmless as the substance is excreted without being degraded, whereas, oral administration results in the aforementioned reactions due to the presence of beta-glucosidases in the gastrointestinal tract.[4]

Our patient had been taking amygdalin containing an equivalent of 25–75 mg of cyanide/day and showed marked elevation of blood cyanide and thiocyanate levels as well as markedly increased urinary excretion of thiocyanate which show that she had cyanide and thiocyanate toxicity. Both cyanide and cyanate can produce toxic changes in humans due to chronic exposure.[5] Sodium cyanate (NaNCo) an agent which binds to the terminal NH_2 groups of the hemoglobin molecule has been used in the treatment of sickle cell anemia. Two individuals treated with 20–41 mg/kg/d for this entity experienced gradual onset of peripheral neuropathy after






250 µm

FIGS. 4A AND 4B. (A) Longitudinal section of muscle showing increased fat, muscle necrosis, myophagia and vacuolization (H & E, ×450). (B, right) Transverse section of muscle showing myopathic features and small group atrophy (H & E ×750).

FIG. 5. Transverse section of muscle showing atrophic fiber belonging to both fiber types and small group atrophy (ATPase PH 4.3 ×200).

8–20 months of treatment.[6] The clinical presentation as well as the histopathologic study of nerve biopsy specimen in both these and our cases are similar and the nerve biopsy specimen showed both myelin and axonal changes histologically. In that study the myelin changes were considered to be secondary to primary axonal changes.[7] Peterson *et al.*[6] studied 27 patients with sickle cell disease treated with sodium cyanate. They found that ten of them had clinical polyneuropathy and five had predominantly sensory symptoms. The clinical picture of polyneuropathy was proportional to the dose and time of treatment. All the patients improved following discontinuation of the treatment. Experimental studies of chronic cyanate intoxication, produced in rats extensive myelin vacuolization of spinal roots.[8] We did see myelin vacuolization in the nerve in our patient, although not prominently. Examples of chronic cyanide poisoning in humans are rare. Osuntokun[9] in 1968 described from Nigeria an obscure neurologic syndrome characterized by bilateral optic neuropathy and deafness, predominantly posterior column myelopathy with or without polyneuropathy and designated it as "Nigerian ataxic neuropathy." He pointed to chronic intake of food made from cassava plant rich in cyanide in his cases. All his patients had high plasma and urinary thiocyanates, which fell to normal levels after taking a diet containing little or no cassava. They also showed mild to moderate protein–caloric malnutrition as well as low intake of thiamine and clinical ariboflavinosis. Serum B_{12} and folate levels were high. Clinical and biochemical similarities of our patient to this syndrome of "Nigerian ataxic neuropathy" is striking. Cyanide and thiocyanate toxicity is the proposed etiology of "Nigerian ataxic neuropathy." Williams and Osuntokun[10] in a later report,

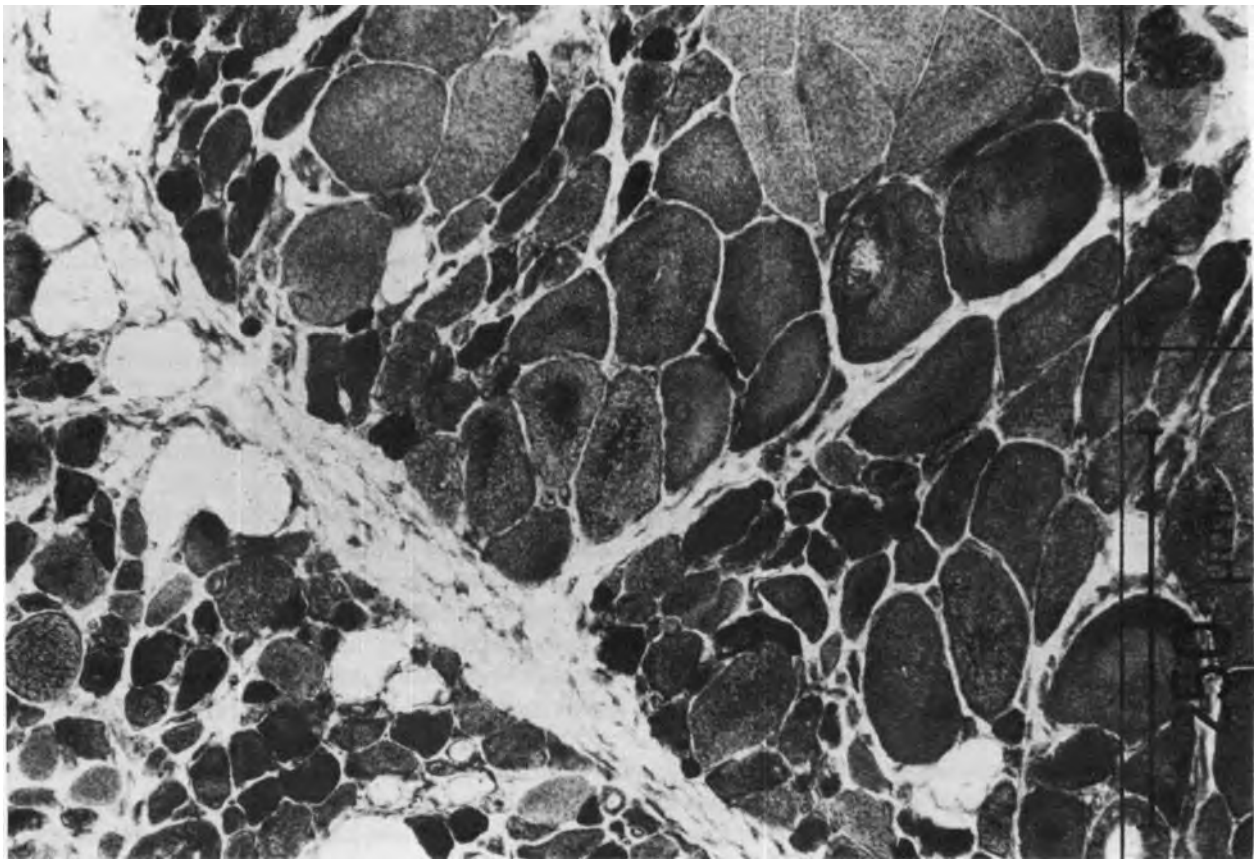
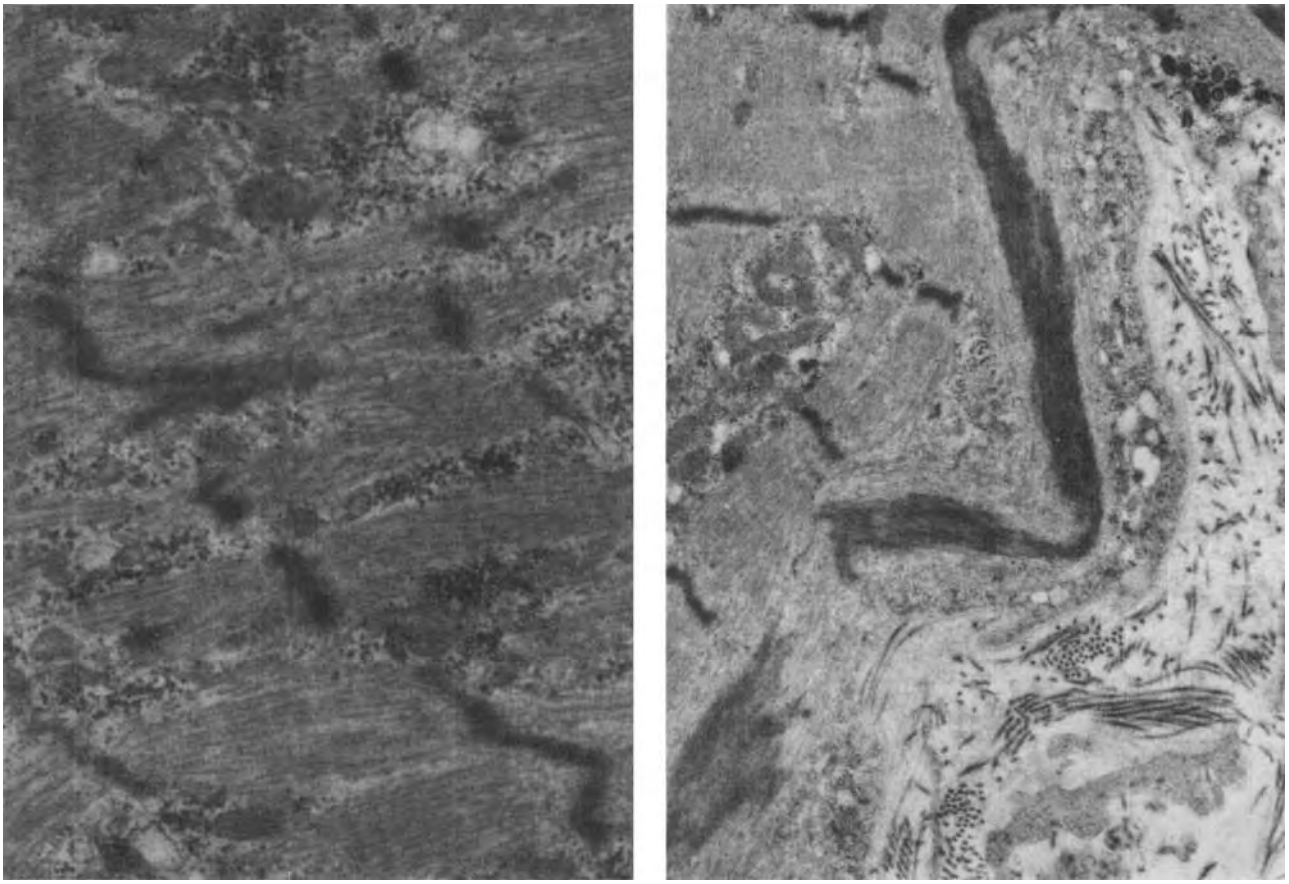


FIG. 6. Transverse section of muscle showing atrophic dark staining fibers and myofibrillar disintegration with dark staining of center of fibers (NADH-TR ×200).



FIGS. 7A AND 7B. (A) Ultrathin section of muscle showing Z-line smearing, zig zagging and haphazard arrangement (Uranyl acetate–lead citrate ×34,000). (B) Ultrathin section of muscle showing prominent Z-line changes leading to subsarcolemmel "pseudo rod" formation (Uranyl acetate–lead citrate ×13,400).

characterized the peripheral nerve pathology to be essentially "segmental demyelination," although their descriptions of changes, especially ultrastructural is quite similar to ours. There are no reports in the literature, of experimental chronic cyanide intoxication causing polyneuropathy. We could not find in the literature any reason for elevation of serum B_{12} and folate levels due to cyanide intoxication. This perplexing finding remains unexplained.

We believe that our patient has clinical and pathologically proven neuromyopathy due to cyanide toxicity secondary to amygdalin intake. The neuromyopathy is secondary to primary axonal degeneration with secondary myelin changes and the muscle changes represent in addition to neurogenic atrophy, a toxic myopathy. Questions may be raised as to whether vincristine could be the etiologic agent of the neuromyopathy in our patient. We do not believe vincristine to be the causative agent for the following reasons: vincristine administration was not temporally related to the onset of the neuromuscular symptoms which began at least four months after vincristine was discontinued. Sterman and Schaumberg[11] in their comprehensive review of vincristine neuropathy pointed to a general temporal sequence: disturbance of gastrointestinal motility was one of the cardinal clinical features which was absent in our patient. Also, autonomic dysfunction occurred in 50% of patients and cranial nerves were occasionally involved, again conspicuously absent in our patient. Bradley *et al.*[12] studied the pathologic changes in peripheral nerve and muscle in vincristine neuropathy in humans and described primarily an axonal degeneration of the nerve and a necrotizing myopathy with changes seen mostly at an ultrastructural level. From our findings in peripheral nerve and muscle, it is obvious that the pathologic results described by us: axonal neuropathy with prominent demyelination and prominent vacuolar myopathy with super-added neurogenic atrophy is quite different from the nerve and muscle changes in vincristine neuropathy. In the differential diagnosis we also considered the possibility of nonmetastatic effect of lymphoma on the peripheral nervous system. Walsh[13] in a study of 62 patients with lymphoma found electrophysiologic abnormalities suggestive of polyneuropathy in 35%. His-

tologic and ultrastructural study of sural nerve biopsy specimens in five of these patients showed evidence of axonal degeneration and segmental demyelination. He suggested toxic, metabolic or nutritional deficiency as possible causes in these cases. In a recent study of non-metastatic effect of lymphoma on the peripheral nervous system Posner[14] points to the exclusive occurrence of a subacute neuropathy with motor paresis and suggests virus infection of anterior horn cells as a possible etiologic factor. Schold *et al.*[15] in reviewing ten cases of subacute motor neuropathy occurring as a remote effect of lymphoma have described their clinical course and pathology. Their patients clinically had only motor symptoms unlike our patient who had a sensory-motor polyneuropathy. Histopathologically at autopsy in two patients they found primarily degeneration of anterior horn cells of the spinal cord and only mild demyelination of the posterior column and anterior nerve roots. Peripheral nerve changes similar to our cases were not seen. Morphologically, our case closely resembles the changes in peripheral nerve produced by cyanide intoxication[6-11] rather than the changes described by Walsh.[13] Also our patient had clinically improved to the point of becoming ambulatory following cessation of laetrile therapy although no follow-up serum cyanide or thiocyanide levels could be obtained. Although Posner[14] described a benign course in his patients with paraneoplastic peripheral nervous system involvement they were clinically and pathologically different as pointed out. We conclude that our patient had a toxic neuromyopathy secondary to cyanide intoxication due to intake of "laetrile."

REFERENCES

1. Conn EE. Cyanogenetic glycosides. In: Committee on Food Production, Food and Nutrition Board, National Research Council, eds. Toxicants Occurring Naturally in Foods, ed. 2. Washington, DC: National Academy of Sciences, 1973; 299–308.
2. Windholz M. The Merck Index. Ed. 9. Entries No. 630 (Amygdalin): 1057 (Benzaldehyde): 4688 (Hydrogen-cyanide): 5197 (Laetrile): 1976. New Jersey: Merck and Co., Inc, 1976.
3. Herbert V. Laetrile: The cult of cyanide promoting poison for profit. *Am J Clin Nutr* 1979: 32:1121–1158.
4. Lerner IJ. Laetrile: A lesson in cancer quackery. *CA* 1981; 3(2):91–95.
5. Politis MJ, Schaumburg HH, Spencer PS. Neurotoxicity of selected chemicals. In: Spencer PS, Schaumburg HH, eds. Experimental and Clinical Neurotoxicology. Baltimore: Williams and Wilkins, 1980; 617–618.
6. Peterson CM, Tsairis P, Ohnishi A *et al.* Sodium cyanate induced polyneuropathy in patients with sickle-cell disease. *Ann Intern Med* 1974; 81:152–158.
7. Onhishi A, Peterson CM, Dyck PJ. Axonal degeneration in sodium cyanate-induced neuropathy. *Arch Neurol* 1975; 32:530–534.
8. Tellez-Nagel I, Korthals JK, Vlassara HV, Cerami A. An ultrastructural study of chronic sodium cyanate-induced neuropathy. *J Neuropathol Exp Neurol* 1977; 36:351–363.
9. Osuntokun BO. An ataxic neuropathy in Nigeria: A clinical, biochemical and electrophysiological study. *Brain* 1968; 91:215–248.
10. Williams AO, Osuntokun BO. Peripheral neuropathy in tropical (nutritional) ataxia in Nigeria. *Arch Neurol* 1969; 21:475–492.
11. Sterman AB, Schaumburg HH. Neurotoxicity of selected drugs. In: Spencer PS, Schaumburg HH, eds. Experimental and Clinical neurotoxicology. Baltimore: Williams and Wilkins, 1980; 599–600.
12. Bradley WG, Lassman LP, Pearce GW *et al.* The neuromyopathy of Vincristine in man: Clinical, electrophysiological and pathological studies. *J Neurol Sci* 1970; 10:107–131.
13. Walsh JC. Neuropathy associated with lymphoma. *J Neurol Neurosurg Psychiat* 1971; 34:42–50.
14. Posner JB. Neurologic complications of systemic cancer. In: Dowling HE, ed. DM—Disease-a-Month. Chicago: Year Book Medical Publishers, Inc. 1978; 25(2):57–58.
15. Schold CS, Cho ES, Somasundaram M, Posner JB. Subacute motor neuromyopathy: A remote effect of lymphoma. *Ann Neurol* 1979; 5:271–287.