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A TWO-YEAR TRIAL OF OLEIC AND ERUCIC ACIDS ("LORENZO'S OIL") AS TREATMENT FOR ADRENMYLEONEUROPATHY

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Abstract Background. Adrenomyeloneuropathy is an X-linked recessive disorder characterized by myelopathy, peripheral neuropathy, and cerebral demyelination, which develop in association with the accumulation of very-long-chain fatty acids. The administration of oleic and erucic acids inhibits the synthesis of very-long-chain fatty acids. Recently such dietary treatment has been widely publicized as a possible cure for this disease.

Methods. We conducted an open trial in 14 men with adrenomyeloneuropathy, 5 symptomatic heterozygous women, and 5 boys (mean age, 13 years) with preclinical adrenomyeloneuropathy. The patients ate a low-fat diet and received daily doses of glycerol trioleate oil (1.7 g per kilogram of body weight) and glycerol trierucate oil (0.3 g per kilogram). Clinical manifestations, cerebral and spinal cord magnetic resonance imaging (MRI) scans, nerve conduction, and brain-stem auditory and somatosensory evoked potentials were studied prospectively over 18 to 48 months. Plasma levels of very-long-chain fatty acids and the side effects of erucic acid were monitored monthly.

Results. By week 10, plasma very-long-chain fatty

acid levels declined nearly to normal. Nonetheless, over a mean follow-up of 33 months none of the 14 men with adrenomyeloneuropathy improved. In nine men there was functional deterioration, coincident in four with new cerebral lesions on MRI. In a single patient there was a reduction in cerebellar demyelination, but without clinical improvement. In one of the five asymptomatic boys signs of myelopathy developed. There were no changes in the symptomatic heterozygous women. There was some improvement in peroneal-nerve conduction, but no detectable clinical improvement. Conduction to the parietal cortex (T12–P37 interpeak latency) worsened in both the symptomatic men and the boys with preclinical adrenomyeloneuropathy. There was no change in other somatosensory evoked potentials or in brain-stem auditory evoked potentials. Asymptomatic thrombocytopenia (<100,000 cells per cubic millimeter) was noted in six patients.

Conclusions. In this open trial we found no evidence of a clinically relevant benefit from dietary treatment with oleic and erucic acids ("Lorenzo's oil") in patients with adrenomyeloneuropathy. (N Engl J Med 1993;329:745-52.)

X-LINKED adrenoleukodystrophy is a peroxisomal disease caused by a gene located in Xq28 and coding for an ATP-binding transporter.¹ One of the phenotypes, the cerebral form, occurs in young boys and is characterized by brain demyelination, with rapid deterioration or death, usually within three years.² Less frequent is adrenomyeloneuropathy, which involves the spinal cord and the peripheral nerves²⁻⁴ with severe spastic paraparesis, sensory loss in the legs, and sphincter disturbances that develop over a period of 5 to 15 years.²⁻⁴ Adrenomyeloneuropathy-like manifestations develop in about half of heterozygous women.^{2,5} Electrophysiologic abnormalities can be identified in boys

who have preclinical adrenomyeloneuropathy without neurologic disability.⁶

Adrenomyeloneuropathy and cerebral adrenoleukodystrophy are associated with impaired degradation of saturated very-long-chain fatty acids, which accumulate in cerebral white matter and the adrenal cortex.² Very-long-chain fatty acids are derived both from the diet and from endogenous synthesis by a microsomal system that elongates long-chain fatty acids.⁷ On the basis of the as yet unproved hypothesis that very-long-chain fatty acids are toxic to myelin sheaths,¹ therapeutic approaches have been developed to reduce their concentrations. The simple restriction of dietary very-long-chain fatty acids led to no biologic or clinical improvement.⁸ In 1986, oleic acid, an inhibitor of the elongation of fatty acids,⁹ was found to reduce the levels of very-long-chain fatty acids in cultured fibroblasts from patients with adrenoleukodystrophy.¹⁰ Trials using glycerol trioleate oil and a restricted diet decreased the plasma level of very-long-

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chain fatty acids by 50 percent in most patients.^{11,12} Small changes in sural- and peroneal-nerve conduction rates suggested a possible effect of glycerol trioleate oil,^{12,13} but no improvement was seen in clinical manifestations and on brain magnetic resonance imaging (MRI).^{12,13} Because of the apparently poor clinical results of glycerol trioleate oil alone, new trials using glycerol trierucate, a more potent inhibitor of the synthesis of very-long-chain fatty acids, were launched, allowing the normalization of plasma very-long-chain fatty acid levels within four to six weeks.¹⁴ However, despite the impression given by the recent popular movie, *Lorenzo's Oil*,¹⁵ erucic acid did not prevent neurologic deterioration in patients with cerebral adrenoleukodystrophy.^{14,16}

We studied the effects of glycerol trioleate and trierucate oils in men with adrenomyeloneuropathy, boys with preclinical adrenomyeloneuropathy, and symptomatic heterozygous women (i.e., subjects with the less severe forms of adrenoleukodystrophy).

METHODS

Patient Population

This open trial included 14 men with adrenomyeloneuropathy, 5 symptomatic heterozygous women, and 5 boys with preclinical adrenomyeloneuropathy. All the men with adrenomyeloneuropathy and all the heterozygous women had myelopathy²; 11 of the men and 2 of the women had mild neuropathy.² The five boys had no neurologic symptoms.⁶ The mean follow-up was 32.7 months in the men with adrenomyeloneuropathy (range, 18 to 48), 25.8 months in the symptomatic heterozygous women (range, 18 to 38), and 29.6 months in the boys with preclinical adrenomyeloneuropathy (range, 18 to 36). The study was approved by the institutional review board of the Hôpital St. Vincent de Paul, Paris. Informed consent was obtained from the patients or their parents.

Clinical Assessment

The patients underwent standard physical examination, electrocardiography, echocardiography, and chest radiography at entry, after 6 months, and then every 12 months, with measurement of electrolyte, liver-enzyme, vitamin A and E, lipid, and essential fatty acid concentrations in plasma.¹⁷ Plasma very-long-chain fatty acids (C22:0, C22:1, C24:0, C24:1, C26:0, and C26:1) were measured twice a month during the first three months, and then monthly.¹⁸ Platelet and leukocyte counts were obtained every three months.

At each visit, two neurologists performed standardized neurologic examinations. Clinical efficacy was assessed with the Expanded Disability Status Scale (EDSS)¹⁹ and the functional-system subscale of the Multiple Sclerosis Minimal Record of Disability and Ambulation Index.²⁰ The degree of perceived global change was rated independently by the neurologists and the patients according to the following scale: A, marked improvement; B, moderate improvement; C, no change; D, moderate worsening; and E, marked worsening.

Cerebral function was evaluated in the adults with the Mini-Mental State examination and in the boys with the revised Wechsler Intelligence Scale. Patients with abnormal results on these tests or abnormalities on brain MRI underwent a more extensive neuropsychological evaluation.

Neuroradiologic Evaluation

Cerebral and spinal cord MRI was performed with a 0.5-T unit (General Electric Medical Systems, Milwaukee),⁶ with identical sequential tomographic sagittal, coronal, and axial sections. The demyelinated areas were quantified,^{21,22} and lesions were graded as

mild, moderate, or severe. The estimated accuracy of measurement was within 9.6 percent, and variation in a single observer was within 2.3 percent.^{21,22}

Electrophysiologic Evaluation

We measured motor- and sensory-nerve conduction velocities, including F-wave latencies and bilateral H-reflexes; brain-stem auditory evoked potentials; somatosensory evoked potentials; and visual evoked potentials with pattern stimuli, as previously described.⁶ For somatosensory evoked potentials, the signals were registered as follows: for the lower limbs, at the spinal process to the iliac crest (T12) and in parietal areas of the scalp (2 cm behind the reference electrode Cz) (P37); for the upper limbs, at Erb's point (N10), at the level of the spinal process of the second cervical vertebra (N11), and in parietal areas of the scalp (2 cm behind and 7 cm lateral to the reference electrode Cz) (P14 and N20). To verify that changes were not due to variability in measurement, we determined that variation in a single observer for four nerve-conduction attributes (the amplitude and nerve conduction velocity of the peroneal and sensory median nerves) ranged from 2 to 4.5 percent.

Diet Design

The patients followed a low-fat diet that provided 10 percent of calories as fat, with less than 10 to 15 mg of C26:0 fatty acid per day. They received a mean ($\pm$ SD) of 1.7 ± 0.6 g of glycerol trioleate oil per kilogram of body weight per day and 0.3 ± 0.05 g of glycerol trierucate oil per kilogram per day. Glycerol trioleate and trierucate oils were kindly provided by the Société Industrielle des Oléagineux, Saint-Laurent-Blangy, France.

To avoid a deficiency of essential fatty acids, safflower oil (10 to 15 ml) and fish oil (2-g capsules) containing eicosapentaenoic acid (18 percent) and docosahexaenoic acid (12 percent) were added daily to the diet.

Statistical Analysis

Comparisons were performed with the chi-square test for trend for the global assessments by physicians and patients and with the Wilcoxon rank-sum test for other variables, including scores on the EDSS and the ambulation index. All reported P values are paired and two-sided.

RESULTS

Changes in Plasma Very-Long-Chain Fatty Acid Levels

In all the patients, plasma C26:0 concentrations decreased to normal or nearly normal values within 10 weeks of treatment (Fig. 1). In 9 of the 14 men with adrenomyeloneuropathy, the 5 boys with preclinical adrenomyeloneuropathy, and the 5 heterozygous women, C26:0 values were completely normal at the end of the follow-up period. In most patients, plasma C26:0 levels returned to normal when the plasma level of erucic acid was maintained between 125 and 160 μ mol per liter. All the patients complied with the diet.

Clinical Efficacy

In the men with adrenomyeloneuropathy the mean EDSS score increased by 1.0 point ($P < 0.02$) and the ambulation-index score by 1.26 points ($P < 0.001$) (Table 1). These changes reflected mainly the worsening myelopathy in four men (Patients 1, 2, 5, and 6) who became dependent on a wheelchair. The worsening scores on the EDSS or ambulation index were not correlated with the duration of disability before the diet began. There was no significant change in the

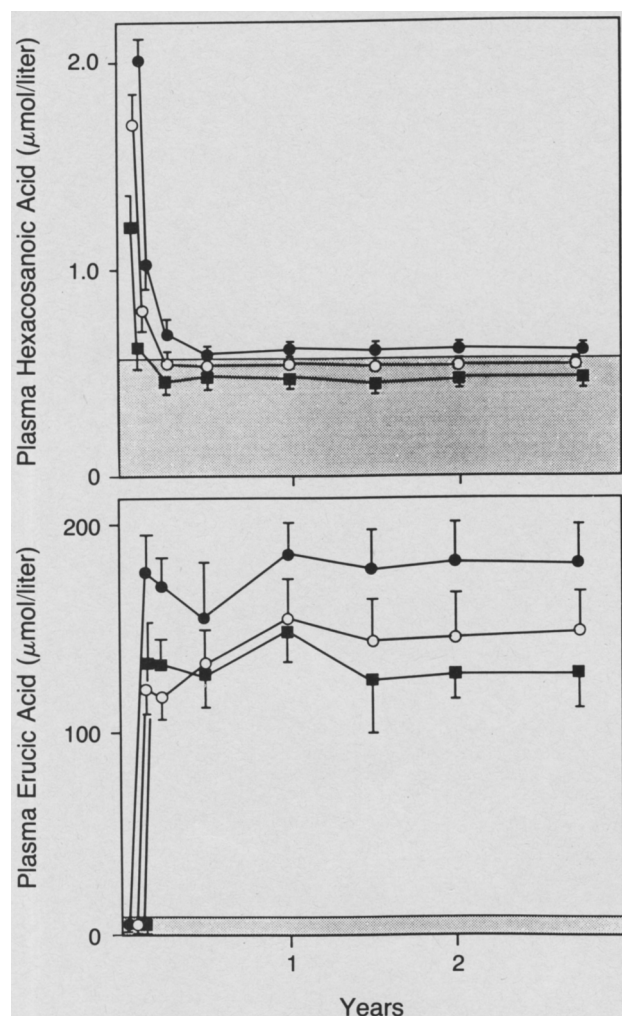


Figure 1. Changes in Plasma Hexacosanoic (C26:0) and Erucic (C22:1) Acid Levels in 14 Men with Adrenomyeloneuropathy (●), 5 Symptomatic Heterozygous Women (■), and 5 Boys with Preclinical Adrenomyeloneuropathy (○) during Glycerol Trioleate and Triteruic Therapy.

Hexacosanoic and erucic acid concentrations are expressed as means $\pm$ SE. The shaded areas correspond to mean ($\pm$ SD) normal levels.

symptomatic heterozygous women or the boys with preclinical adrenomyeloneuropathy, except Patient 21 (Table 1).

In the men with adrenomyeloneuropathy, pyramidal function worsened markedly according to the functional system subscale ($P < 0.05$ by the Wilcoxon rank-sum test). No changes were observed in cerebellar, sensory, and brain-stem function. Cerebral function also worsened ($P < 0.05$). In two men with adrenomyeloneuropathy (Patients 7 and 13) who began with moderate abnormalities in visuospatial function and working memory there was severe worsening of cognitive function, leading to dementia after 18 and 23 months, respectively, on the diet. Patient 4 had normal intellectual function at entry, but 42 months later had moderate abnormalities of language and atten-

tional and executive dysfunctions with the extension of demyelinating lesions in the left frontal lobe (Fig. 2). In Patient 1 visuospatial impairment and demyelinating lesions became apparent in the occipital lobes after 38 months on the diet.

No changes in function or cognition were observed in the symptomatic heterozygous women or the boys with preclinical adrenomyeloneuropathy, except Patient 21, in whom pyramidal signs developed.

According to the physician's assessment, 9 of the 14 men had more manifestations of the disease (Table 1). None of the men improved, even moderately. There was no change in the global assessment of the boys with preclinical adrenomyeloneuropathy or the symptomatic heterozygous women. Self-assessment by the patients was concordant (Table 1). The two men in whom dementia developed (Patients 7 and 13) could not give self-assessments.

Neuroradiologic Changes

Twelve men with adrenomyeloneuropathy had abnormal brain MRI scans before the diet (Table 2). In the seven with demyelination restricted to the internal capsule, the lesions remained unchanged in five and worsened markedly in two. In Patient 4, lesions that were initially in the left internal capsule increased five-fold and extended markedly into the left frontal lobe (Fig. 2). In Patient 1 demyelination appeared in the corpus callosum and occipital lobes after 24 months of the diet and doubled in size during the following 14 months.

Before the study diet, five of the men with adrenomyeloneuropathy had moderate demyelinating lesions within the parieto-occipital lobe (Patients 7, 11, and 13), frontal lobe (Patient 3), or cerebellum (Patient 12). In Patient 11, parieto-occipital lesions remained unchanged, whereas in two others (Patients 7 and 13) demyelination increased by 54 ± 12 percent and intellectual function declined. Demyelination increased by 27 percent in the patient with bifrontal lesions. A marked decrease (85 percent) in demyelinating cerebellar lesions was observed only in Patient 12, who in addition to adrenomyeloneuropathy had marked dysarthria and moderate cerebellar symptoms that remained unchanged.

In two symptomatic heterozygous women, demyelinating lesions of the internal capsule remained unchanged. MRI results remained normal in all the boys with preclinical adrenomyeloneuropathy. Spinal cord atrophy did not correlate with the severity of neurologic disability before the diet and did not change during follow-up.

Electrophysiologic Changes

The men with adrenomyeloneuropathy had an 8 percent improvement (95 percent confidence interval, 2.0 to 13.5 percent) in peroneal-nerve conduction at the end of the follow-up period, with no changes in average conduction velocities of the posterior tibial,

Table 1. Clinical Characteristics of the Study Patients.

PATIENT No.	AGE (YR)	DURATION OF DISEASE (YR)	EDSS*			AMBULATION INDEX†			PERCEIVED GLOBAL CHANGE (PHYSICIAN/PATIENT)‡
			BASE LINE	AFTER TREATMENT	STATUS	BASE LINE	AFTER TREATMENT	STATUS	
Men with adrenomyeloneuropathy									
1	42	22	5.5	6.5	Worse	4	7	Worse	E/E
2	37	14	5.5	6.5	Worse	5	7	Worse	E/E
3	26	8	3.5	3.5	Stable	2	3	Worse	C/C
4	22	3	3.0	4.0	Worse	2	3	Worse	E/E
5	35	9	6.0	6.5	Stable	4	7	Worse	C/C
6	29	6	5.5	6.5	Worse	4	7	Worse	D/D
7	33	9	4.5	8.0	Worse	3	4	Worse	E/—
8	30	5	4.0	6.0	Worse	3	5	Worse	E/E
9	29	9	4.0	4.0	Stable	3	3	Stable	D/C
10	34	9	3.0	3.0	Stable	2	2	Stable	C/B
11	33	11	5.0	5.5	Stable	3	3	Stable	C/C
12	28	12	4.0	4.0	Stable	3	3	Stable	C/C
13	26	3	4.5	7.5	Worse	3	5	Worse	E/—
14	31	4	4.0	4.0	Stable	2	2	Stable	D/D
Mean (±SD)	31.1±5.1	8.9±5.0	4.4±0.1	5.4±1.6		3.1±0.9	4.36±1.9		
Symptomatic heterozygous women									
15	54	5	4.0	4.5	Stable	3	3	Stable	D/D
16	32	10	3.5	3.5	Stable	2	2	Stable	C/D
17	42	3	3.5	3.5	Stable	3	3	Stable	B/B
18	39	4	3.0	3.0	Stable	2	2	Stable	C/C
19	53	4	3.5	3.5	Stable	2	2	Stable	C/C
Mean (±SD)	44.0±9.4	5.2±2.8	3.5±0.4	3.6±0.5		2.4±0.55	2.4±0.55		
Boys with preclinical adrenomyeloneuropathy									
20	11	0	1	1.5	Stable	0	0	Stable	C/C
21	16	0	0	1	Worse	0	1	Worse	D/C
22	11	0	0	0	Stable	0	0	Stable	C/C
23	11	0	0	0	Stable	0	0	Stable	C/C
24	17	0	1	1	Stable	0	0	Stable	C/C
Mean (±SD)	13.2±3.0	0.0±0.0	0.40±0.55	0.70±0.67		0.0±0.0	0.2±0.4		

*EDSS scores are as follows: 3.0, no more than mild disability, fully ambulatory; 3.5, moderate disability though fully ambulatory; 4.0, self-sufficient for up to 12 hours despite severe disability; 4.5, requires minimal assistance, has some limits on activity, but able to work a full day; 5.0, severe disability, cannot perform full daily activities, but ambulatory without aid; 5.5, severe disability precluding full daily activities, ambulates about 100 m; 6.0, requires constant assistance; 6.5, requires two canes or crutches to walk; 7.0, walks ≤5 m, essentially restricted to wheelchair; 7.5, restricted to wheelchair; and 8.0, restricted to bed or chair. An increase or decrease of 1 point was considered to indicate worsening or improvement; a change of 0.5 was considered to indicate that the patient's condition was stable.

†Scores on the ambulation index are as follows: 0, asymptomatic, fully active; 1, walks normally but with fatigue; 2, abnormal gait; 3, walks 25 ft (7.6 m) in 20 seconds or less; 4, requires cane to walk; 5, requires bilateral canes, needs >20 seconds to walk 25 ft; 6, uses wheelchair, requires bilateral support to walk; and 7, walking limited to several steps with bilateral support, uses wheelchair for most activities.

‡The perceived global changes, according to the impressions of the physician and the patient, are as follows: A, marked improvement; B, moderate improvement; C, no change; D, moderate worsening; and E, marked worsening.

sensory, and motor median nerves (Fig. 3). The conduction velocity of the posterior tibial nerve improved by 19 percent (95 percent confidence interval, 11.6 to 26 percent) in six of the men and declined by 6.5 percent (95 percent confidence interval, 4.7 to 8.4 percent) in three others. Similarly, sensory-median-nerve conduction improved by 20 percent (95 percent confidence interval, 15.7 to 25 percent) in six men and declined by 15 percent (95 percent confidence interval, 11 to 18 percent) in three.

The abnormal peroneal- and tibial-nerve conduction velocities observed in two heterozygous women before the study diet improved by 6 percent in one woman and 8 percent in the other. Motor- and sensory-median-nerve conduction velocities remained normal in all the heterozygous women during the study. In two boys with preclinical adrenomyeloneuropathy and abnormal peroneal-nerve conduction velocity before the diet, nerve conduction velocity improved by 6 and 20 percent.

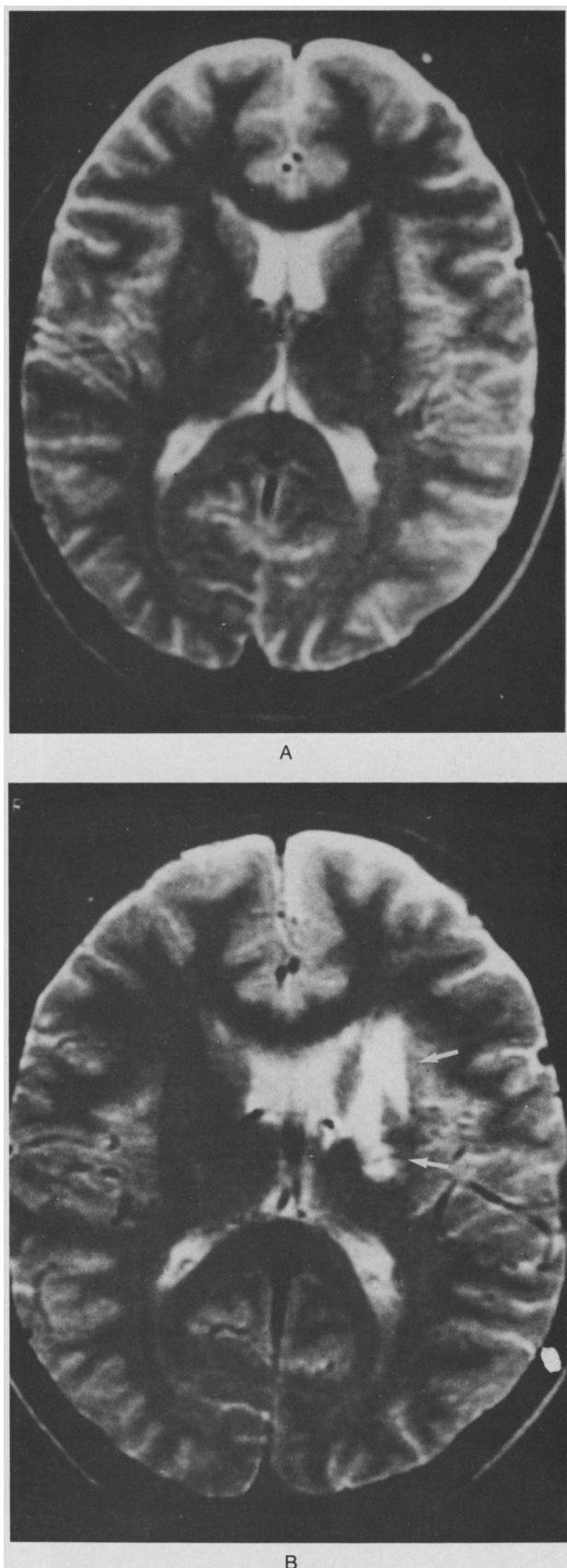
Auditory conduction in the brain stem (wave I–V

interpeak latency) was delayed in all the patients before the diet, and it remained unchanged in the men with adrenomyeloneuropathy and the symptomatic heterozygous women at the end of the follow-up period (Fig. 3). The average wave I–V interpeak latency worsened by 0.18 ± 0.04 msec in the five boys with preclinical adrenomyeloneuropathy.

We observed no change in median-nerve (N10 latency), medullothalamic, or thalamoparietal (N11–P14 and P14–N20 interpeak latencies) conduction times in any of the patients (Fig. 3).

The conduction velocity of the posterior tibial nerve (T12 latency) improved by 7 percent (95 percent confidence interval, 4.0 to 10 percent) in the men with adrenomyeloneuropathy (Fig. 3). Only one heterozygous woman had abnormal T12 latency before the study diet, and this variable improved by 5 percent. T12 latency improved by 1 SD in the five boys with preclinical adrenomyeloneuropathy ($P < 0.05$).

After stimulation of the posterior tibial nerve, conduction to the parietal cortex (T12–P37 interpeak la-



tency) could be measured in seven of the men with adrenomyeloneuropathy (the others had no identifiable P37 peak); it worsened by 17 percent (95 percent confidence interval, 2 to 31 percent) (Fig. 3). This variable remained unchanged in the heterozygous women. The boys with preclinical disease all had abnormal T12–P37 interpeak latency that increased by an average of 1 SD.

All but one man with adrenomyeloneuropathy (Patient 7) had normal visual evoked potentials at entry. P100 latency worsened in this patient and in Patient 13, whose demyelination increased in the parieto-occipital lobes. There was no change in visual evoked potentials in the other men, the heterozygous women, or the boys with preclinical disease.

Side Effects

The platelet count declined in 23 of the 24 patients,²³ with no correlation with plasma levels of erucic, arachidonic, and docosahexaenoic acid. Twelve of the patients had platelet counts between 100,000 and 150,000 per cubic millimeter, and six had counts below 100,000 per cubic millimeter. The lowest value during the period of dietary treatment was 52,000 per cubic millimeter. None of the patients had abnormal bleeding or hematoma. Three patients had asymptomatic neutropenia (500 to 700 cells per cubic millimeter). Two men with adrenomyeloneuropathy had mild asymmetric cardiac septal hypertrophy after 12 months of the study diet, but ventricular function remained normal. None of the patients had abnormal electrocardiograms or cardiac enlargement. A 12 percent decrease (95 percent confidence interval, 5 to 20 percent) in the cholesterol level was observed in the three groups, with a 13 percent increase (95 percent confidence interval, 4 to 24 percent) in high-density lipoprotein cholesterol only in the men with adrenomyeloneuropathy.

Although all the patients received safflower and fish oil rich in *n*-3 fatty acids, a 24 percent (95 percent confidence interval, 17 to 31 percent) decrease in plasma arachidonic acid levels and a 30 percent (95 percent confidence interval, 16 to 42 percent) decrease in plasma docosahexaenoic acid levels were observed in all the patients, but with no symptoms of essential fatty acid deficiency.

DISCUSSION

Early symptoms of adrenomyeloneuropathy usually appear when patients are between 24 and 28 years of age. These patients have myelopathy, often with mild peripheral neuropathy, and half of them have moderate cerebral involvement demonstrable by MRI

Figure 2. T₂-Weighted MRI Scans Showing the Absence of a Signal of Increased Intensity in the Left Internal Capsule of Patient 4 before the Study Diet (Panel A) and the Presence of Such Signals, Indicating Lesions, in the Same Region and in the Putamen and Claustrum (Panel B, Arrows) 42 Months Thereafter.

and neuropsychological tests.^{2,6,24} There are no data, however, that document the natural history of untreated adrenomyeloneuropathy. A review of the literature indicates that 35 percent of patients with adrenomyeloneuropathy have a marked progression of their disease within three years of diagnosis,^{3,4,6,25-48} the duration of the present trial. At least 30 percent of women who are heterozygous for adrenoleukodystrophy have spastic paraparesis, usually milder and of later onset (at about the age of 40) than in men with adrenomyeloneuropathy.^{2,5} Patients with preclinical adrenomyeloneuropathy may have sensory disturbances but no neurologic disability.⁶ Although one cannot be certain that these patients will have full expression of adrenomyeloneuropathy, the electrophysiologic abnormalities are predictive of clinical disease.

The myelopathy characteristically includes degeneration of the corticospinal and gracile tracts, medial lemnisci, and spinocerebellar pathways in the medulla.¹⁹ The glycerol trioleate and trierucate therapy did not protect the four men whose myelopathy worsened during the trial. In the other men with adrenomyeloneuropathy and the symptomatic heterozygous women, the clinical and MRI manifestations of myelopathy remained stable. A marked increase in T12-P37 interpeak latency in the patients with clinical and preclinical adrenomyeloneuropathy indicated a worsening.

Regarding peripheral neuropathy, the men with adrenomyeloneuropathy, the symptomatic heterozygous women, and the boys with preclinical disease had some improvement in peroneal-nerve conduction, and more limited improvement in posterior-tibial-nerve and sensory-median-nerve conduction, that

was more pronounced than with glycerol trioleate alone^{12,13,24} but still far from restoring normal conduction or reversing the disability. Since it is not known to occur spontaneously, this slight improvement could be due to the glycerol trioleate and trierucate therapy.

The lack of effect of dietary therapy on demyelinating lesions in our patients with adrenomyeloneuropathy is consistent with observations in patients with cerebral adrenoleukodystrophy, even when demyelination is moderate.^{14,16,24} We have confirmed the lack of benefit in a separate group of 35 children with cerebral adrenoleukodystrophy. Although the present data in patients with adrenomyeloneuropathy with cerebral lesions leave little likelihood of a positive effect of glycerol trioleate and trierucate oils, we cannot completely exclude the possibility that progression would have been more frequent or more rapid without the diet. Given the rapid extension of cerebral lesions in more than one third of the patients in our study, we consider any real benefit unlikely. On the other hand, the patients with clinical and preclinical adrenomyeloneuropathy and the symptomatic heterozygous women who had no cerebral lesions before the trial remained normal during the period of observation. Because of the limited frequency of cerebral demyelination in these forms of adrenoleukodystrophy, as well as its long and variable evolution,^{2,5,6,24} additional data are needed to determine whether a diet of glycerol trioleate and trierucate oils can prevent the development of the lesions.

Our trial documented various degrees of progression in preexisting myelopathy and cerebral lesions in a large fraction of patients with clinical or preclinical adrenomyeloneuropathy and heterozygous women. In the absence of an untreated control group, however, we could not determine whether glycerol trioleate and trierucate oils slowed the rate of deterioration. There are several obstacles to placebo-controlled trials in this disease. First, because of wide publicity, the public's high expectation of benefit from glycerol trioleate and trierucate has made the administration of a placebo ethically impossible. Second, adrenomyeloneuropathy affects only 1 in 45,000 people in Europe and the United States,^{1,2} which makes a controlled trial almost impossible. In fact, given the variability of the disease's manifestations and its long and variable course, such a trial would have to run for 5 to 10 years to allow the detection of any moderate therapeutic effect that could have escaped the present open trial. We

Table 2. Results of Brain MRI in Men with Adrenomyeloneuropathy Treated with Glycerol Trioleate and Glycerol Trierucate Oils.*

PATIENT No.†	INTERNAL CAPSULES		PARIETO-OCCIPITAL LOBE		FRONTAL LOBE		CEREBELLUM	
	BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT
10	—	—	—	—	—	—	—	—
14	—	—	—	—	—	—	—	—
2	+	+	—	—	—	—	—	—
5	+	+	—	—	—	—	—	—
6	+	+	—	—	—	—	—	—
8	+	+	—	—	—	—	—	—
9	+	+	—	—	—	—	—	—
1	+	+	—	++	—	—	—	—
4	+	+++	—	—	—	++	—	—
11	—	—	++	++	—	—	—	—
7	—	—	++	+++	—	—	—	—
13	—	—	++	+++	—	—	—	—
3	+	+	—	—	++	++	—	—
12‡	—	—	—	—	—	—	++	+

*Scans were graded as follows: — denotes no lesion, + mild lesions, ++ moderate lesions, and +++ severe lesions. Boxes indicate changes from base line.

†The patients are grouped according to the sites of their lesions.

‡The patient's lesions improved.

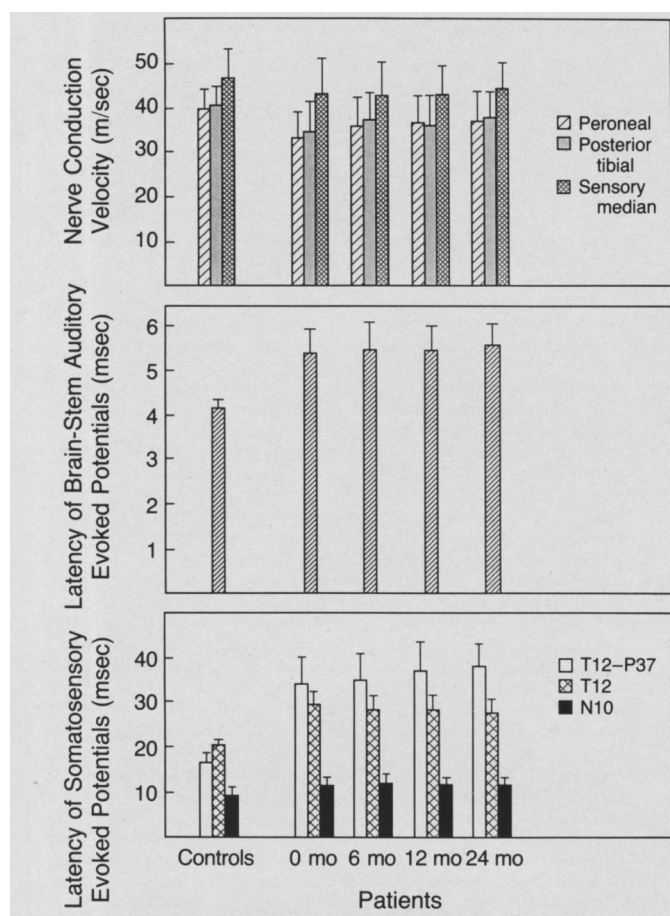


Figure 3. Mean ($\pm$ SD) Results of Electrophysiologic Testing in 14 Men with Adrenomyeloneuropathy during Glycerol Trioleate and Trierucate Therapy.

The top panel shows the conduction velocity of the peroneal, posterior tibial, and sensory median nerves. The middle panel shows the I-V interpeak latency, and the bottom panel the N10 peak, T12 peak, and T12-P37 interpeak latencies obtained by electrical stimulation of the median and posterior tibial nerves. The normal values obtained in controls are shown at the left in each panel.

do not think that a possible limited benefit from glycerol trioleate and trierucate merits the organization of large multicenter trials in patients with advanced myelopathy or cerebral lesions. In these patients, bone marrow transplantation is a promising therapy despite the associated morbidity.⁵⁰

To a limited extent, our data support a positive effect of glycerol trioleate and trierucate on peripheral-nerve conduction. These changes did not modify the clinical disabilities of patients with advanced adrenomyeloneuropathy, but they may be encouraging as a way to prevent the peripheral neuropathy. For patients in whom peripheral neuropathy predominates, early and prolonged therapy with glycerol trioleate and trierucate oils may be useful. Proof of a clinically important benefit from this dietary treatment requires a large, controlled trial. Since no clear benefits were evident in our small group of pa-

tients with preclinical adrenomyeloneuropathy, there should be no practical or ethical obstacle to the use of a placebo control.

The expectation that Lorenzo's oil would produce clinical benefits in patients with cerebral adrenoleukodystrophy or adrenomyeloneuropathy stemmed from its effects on the synthesis of very-long-chain fatty acids. Despite the near-normalization of plasma levels of very-long-chain fatty acids, we saw no improvement in preexisting myelopathy and cerebral lesions in our patients. No animal model of adrenoleukodystrophy is available, and therefore neither the manipulation of very-long-chain fatty acid levels nor the mechanisms of demyelination can be studied experimentally. The recent identification of the adrenoleukodystrophy gene¹ may lead to a "gene knock-out" murine model that could help in the search for therapies, including gene transfer to hematopoietic cells.

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