Dietary Factors in Epidemic Neuropathy on the Isle of Youth, Cuba[1]

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An epidemic neuropathy that broke out in Cuba in late 1991 has exhibited clinical manifestations similar to those of other polyneuropathies of nutritional origin. To investigate its possible association with diet, a study was conducted on the Isle of Youth in 1993, at the start of an outbreak there. Thirty-four subjects with cases and 65 controls were interviewed regarding their diets, measured anthropometrically, and evaluated.

As a whole, the subjects with cases demonstrated greater weight loss before the onset of disease, lower body mass indexes (BMI), lower percentages of body fat, and more deficient diets than the control subjects. Analysis of individual variables found associations between occurrence of the disease and the following: weight loss, low BMI, a broad range of specific dietary deficiencies, a sugar intake exceeding 15% of total caloric intake, alcohol consumption, and smoking. Also, protective associations were found between absence of the disease and regular consumption of certain foods at or above specified levels.

Multivariate analysis indicated that while smoking and alcohol consumption reinforced the effects of the dietary deficiencies, they did not account for occurrence of the disease by themselves. Overall, the results indicate that diets which are deficient in caloric energy, protein, fat, and the micronutrients included in the study, and which reflect an imbalance resulting from a relative excess of sugar, with consequent effects on body weight, are strongly associated with, and causally related to, the occurrence of epidemic neuropathy in Cuba.

In late 1991 an increase was detected in the number of cases of bilateral optic neuropathy in Cuba's Pinar del Río Province. These cases were characterized ophthalmologically by the presence of central or cecocentral scotomata, loss of red and green vision, pallor in the temporal border of the optic disc, and loss of axonal fibers in the papillomacular bundle. During the course of 1992, cases began to be recorded in other provinces, and a change was observed in that forms of peripheral neuropathy as well as mixed forms of the disease began to appear. These diverse manifestations were lumped together under the classification "epidemic neuropathy" (EN).

From 1 January 1992 through 18 June 1993, 45 584 of these cases were reported in Cuba, indicating an incidence of 418.7 cases per 100 000 inhabitants. The disease is concentrated in the 25–64 year age group, being found only occasionally in other age groups. Slightly over half of all patients have the optic form of the disease (*1*).

In the etiology of the polyneuropathies, among the matters considered are nutritional and toxic factors. However, it is recognized that cases of nutritional origin usually show generalized signs of

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undernutrition such as loss of subcutaneous fat and muscle volume. Such cases can rarely be ascribed to something as simple as a single vitamin deficiency, the vast majority appearing to arise instead from several nutrient deficiencies acting together (*2, 3*).

Recent evolution of the epidemic on Cuba's Isle of Youth (Isla de la Juventud), involving a pattern of occurrence similar to that observed in Pinar del Río at the outset, permitted those conducting the study reported here to assess the diets of those afflicted prior to onset of the disease. The aim of this study was to evaluate the hypothesis that the EN epidemic was associated with dietary deficiency.

MATERIALS AND METHODS

The study was conducted in June 1993. Thirty-four patients (21 men and 13 women) of the 44 with recorded cases on the Isle of Youth were included in the study population. While all 34 subjects had been diagnosed as having bilateral optic neuropathy, some also showed manifestations of peripheral neuropathy. It was not possible to examine the 10 remaining patients because they had moved away from the area or had changed their address.

Sixty-five control subjects (people not exhibiting any symptoms of the disease) were selected at random from the same residential blocks where cases had been identified or from adjoining blocks. By applying a pairing process, the same age (± 5 years) and sex proportions were maintained in the case and control populations.

Measurements were taken of weight, height (without stretching), and subscapular, tricipital, bicipital, and suprailiac skin folds; body mass index (BMI = weight/height^2) was calculated; estimates were made of body composition, i.e., the relative percentages of fat (adipose tissue) and lean mass (fat-free tissue) (*4*); and the subjects were classified by weight for height using the standard Cuban reference tables (*5*). All measurements were made by the same technician using the same equipment.

Food consumption data were collected by performing a semiquantitative study of intake frequency based on direct individual interviews (the method most recommended for case-control studies) (*6*). These interviews lasted between 30 and 40 minutes. Addition of a column and certain open-ended questions to the survey form made it possible to further individualize the survey by recording the size of the portion normally consumed by each subject and specifically identifying certain foods consumed. This made it possible to reduce certain errors attributable to the standard instrument (*7, 8*).

The survey retrospectively recorded the frequency of consumption for the 90-day period immediately preceding appearance of the disease in subjects with cases. In order to avoid possible bias related to the seasonal influence of crops, the questions asked the control subjects applied to the same time period and season as those asked of the subjects with cases.

The survey was designed and performed by two specialized professionals. For operational reasons, there was no way to avoid the interviewers' knowing which individuals were case subjects and which were controls.

The energy and nutrient content of each subject's diet was estimated using the NUTRISIS program system (*9*). The recommended daily amount of energy intake was estimated for each individual based on the subject's sex, age, desirable body weight, and the intensity of habitual physical activity in the months preceding onset of the disease (*10*). The respondents were also asked questions regarding loss of body weight during the 12 months preceding the appearance of symptoms. In calculating each subject's percentage of recommended nutrient in-

take, the nutritional recommendations for the Cuban population were employed (*11*).

To evaluate smoking, respondents were queried as to the number of cigars and cigarettes they smoked per day; one cigar was considered the equivalent of five cigarettes.

Regarding the anthropometric and dietary variables, percentile distributions were computed and the medians for study cases and control subjects were compared using the Kruskal-Wallis test.

A subject's weight for height was deemed low when the value found was below the range considered "acceptable" according to the standard reference tables for the Cuban population (*5*). The cutoff points for establishing the risk criteria with regard to particular foods were selected on the basis of the consumption or nonconsumption of certain foods and the arbitrary size of the portions. The cutoff points for daily intake of energy and nutrients were 50% of the daily recommended amounts, as values below these are more consistent with the appearance of deficiency manifestations.

Using these risk criteria, the variables were dichotomized. In order to evaluate the strength of the association between the risk factors being studied and the occurrence of EN, odds ratios (OR) and their corresponding confidence intervals (CI) were calculated for each separate variable.

To remove the effect of potentially confounding concomitant variables from the analysis, logistic regression was employed. Since the hypothesis of interest concerned the effect of low consumption of nutrients, and since deleterious habits were recognized as elements favoring processes similar to those being investigated, adjustments were made for the variables of smoking and alcohol consumption, both of which were also addressed at the bivariate level (by asking whether the subject did or did not smoke and did or did not consume more than 10 grams of alcohol per day).

RESULTS

The mean age of female study subjects with cases of EN was 44.0 years, with a range of 20 to 64 years, while that of male subjects with cases was 42.7 years, with a range of 25 to 56 years. The mean age of female control subjects was 41.9 years, with a range of 26 to 68 years, while that of male control subjects was 43.3 years, with a range of 23 to 60 years.

Overall, compared to the control subjects the subjects with cases exhibited greater weight loss prior to falling ill, a lower BMI, a lower percentage of body fat, lower consumption of the various foods selected with the exception of leafy vegetables, a less varied diet, greater consumption of alcohol, and a markedly lower intake of caloric energy and nutrients. As indicated in Tables 1 through 5, all of these differences exhibited statistical significance.

The percentage contributions of total protein and protein of animal origin to total caloric energy intake (without considering the energy provided by alcohol) were lower among the subjects with cases than among the controls, but the contribution of sugar to this energy intake was higher among the cases (Table 6).

The OR obtained by analyzing each individual variable indicated possible associations between occurrence of the disease and the following: weight loss, a BMI below 23 kg/m^2, low body weight (in terms of weight for height), low intake of bread, low intake of rice, a relatively unvaried diet, nonconsumption of milk, a sugar intake accounting for over 15% of total caloric energy, alcohol consumption (over 10 grams per day), and a daily intake at or below 50% of the recommended amount of caloric energy (excluding energy derived from alcohol), protein, fat, or various micronutrients (folic acid, niacin, pyridoxine, riboflavin, thiamine, vitamin A, or vitamin E) (Tables 7–9). In addition, observed associations indicated that con-

Table 1. Anthropometric variables of the study cases (N = 34) and controls (N = 65), showing values obtained for the 25th, 50th, and 75th percentiles of each group and the statistical significance of the differences observed between the medians of the two groups.

Variables		Percentile			P
		25	50	75	
Weight loss (kg) in 12 months	Cases	1.0	4.5	12.0	
	Controls	0.0	1.0	7.0	0.041
Relative weight loss (% of total body weight lost in year before survey)	Cases	2.0	8.0	16.0	
	Controls	0.0	2.0	9.0	0.017
BMI (kg/m^2)	Cases	20.2	21.5	22.6	
	Controls	21.7	24.9	27.1	<0.001
Fat (kg)	Cases	9.4	12.9	19.5	
	Controls	13.2	18.7	25.5	0.011
Lean mass (kg)	Cases	39.9	44.6	50.9	
	Controls	38.8	46.4	56.1	0.193
Fat (% of body weight)	Cases	16.3	21.5	32.2	
	Controls	21.7	27.8	36.1	0.025
Lean mass (% of body weight)	Cases	67.8	78.5	83.7	
	Controls	63.8	72.3	78.4	0.025

sumption of the following conferred protection: tubers and starchy roots (>125 g/day), beans (>120 g/day), oil (>15 g/day), and meat products extended with soybean flour (>15 g/day) (Table 8). No association was found (P = 0.501) between the estimated intensity of physical activity and occurrence of the disease.

The median value for the number of cigarettes smoked per day was 20 among the subjects with cases and three among the control subjects (P < 0.001). When smoking was considered by itself, it emerged as a significant factor associated positively with the disease (OR = 4.25; CI = 1.41 to 13.41). This association increased with the number of cigarettes smoked, values for those smoking over 20 cigarettes per day (as compared to nonsmokers) being higher (OR = 18.37; CI = 4.40 to 105.27) than for those smoking over 10 per day (OR = 11.30; CI = 3.71 to 37.89).

The multivariate analysis showed that the effect of smoking persisted when the confounding effect attributable to alcohol consumption was taken into account in the model (OR = 3.82; CI = 1.37 to 10.63). However, the effect of alcohol consumption disappeared when the data were adjusted for smoking.

When the nutritional data were in turn adjusted for these two habits, the OR values for intake of protein, caloric energy (excluding energy from alcohol), fat, pyridoxine, thiamine, vitamin E, niacin, folic acid, riboflavin, and vitamin A remained substantially in excess of 1.0 (see Table 9). In contrast, the presumed effect of smoking and alcohol use was diluted when the two variables were included in a trivariate model containing any of these nutritional variables. Specifically, the presumed effect of smoking disappeared (the OR became statistically nonsignificant, the lower limit of the CI being less than 1.0 while the upper limit exceeded 1.0) when this variable and alcohol use were included in a trivariate model containing energy, protein, pyridoxine, thiamine, vitamin E, niacin, folic acid, or riboflavin. Likewise, the presumed effect of alcohol use disappeared when this variable and smoking were included in a trivariate

Table 2. Intakes of selected foods by the study cases (N = 34) and controls (N = 65), showing values (in g/day of ready-to-eat foods) obtained for the 25th, 50th, and 75th percentiles of each group and the statistical significance of the differences observed between the medians of the two groups.

Variables		Percentile 25	50	75	P
Milk (g/day)	Cases	0	0	15	
	Controls	0	96	156	0.001
Ground beef extended with soybean flour (g/day)	Cases	1	4	6	
	Controls	8	12	16	<0.001
Hamburgers made with ground beef extended with soybean flour (g/day)	Cases	0	0	6	
	Controls	0	8	30	0.001
Beans (g/day)	Cases	48	112	136	
	Controls	112	200	256	<0.001
Rice (g/day)	Cases	149	160	299	
	Controls	224	320	352	<0.001
Bread (g/day)	Cases	28	75	91	
	Controls	70	107	158	<0.001
Tubers and starchy roots (g/day)	Cases	50	82	125	
	Controls	63	116	173	0.026
Leafy vegetables (g/day)	Cases	2	15	30	
	Controls	1	10	56	0.967
Oil (g/day)	Cases	10	10	12	
	Controls	10	11	18	0.003
Sugar (g/day)	Cases	39	56	79	
	Controls	49	90	128	0.002
Alcohol (g/day)	Cases	0.0	8.5	47.0	
	Controls	0.0	0.0	7.0	<0.001
Number of foods/ month	Cases	17	19	21	
	Controls	20	23	27	<0.001

model containing energy, pyridoxine, vitamin E, folic acid, or riboflavin.

The OR for vitamin C intake was not significant when energy intake (excluding energy from alcohol), smoking, and alcohol consumption were included in the same model. In contrast, low energy intake (without alcohol) at or below 50% of the recommended amount continued to show a significant association with occurrence of the disease (OR = 54.88; CI = 10.18 to 295.97) after the data were adjusted for smoking, alcohol consumption, and vitamin C intake.

When adjustments were made for protein intake, this eliminated associations between the disease and deficient calcium and iron intakes (see Table 5) that had been observed when the effects of calcium and iron intakes were assessed individually without adjustment.

DISCUSSION AND CONCLUSIONS

Weight loss has been a frequent finding in neuropathy epidemics similar to this one (*2, 12, 13*). Within our study population, the greater weight loss detected among subjects with cases can be attributed to greater dietary deficiency, as no difference in estimated physical activity was found between cases and controls.

Table 3. Intakes of total caloric energy, caloric energy excluding alcohol, total protein, animal protein, fat, and carbohydrate by the study cases (N = 34) and controls (N = 65), showing amounts (in kcal or g) and percentages of the recommended amounts recorded for the 25th, 50th, and 75th percentiles of each group. In every instance the difference between the medians of the two groups was statistically highly significant ($P < 0.001$). The category "animal protein (%)" was not included because a broad consensus on the recommended dietary intake of animal protein has not been reached, and this value is not generally furnished by most normative literature.

		Percentile		
Variables		25	50	75
Total energy (kcal)	Cases	883	1 280	1 968
	Controls	1 671	2 180	2 620
Total energy (%)	Cases	38	49	74
	Controls	70	87	108
Energy without alcohol (kcal)	Cases	862	1 153	1 484
	Controls	1 667	2 093	2 526
Energy without alcohol (%)	Cases	32	41	51
	Controls	70	84	106
Total protein (g)	Cases	20.6	28.0	35.8
	Controls	49.1	65.0	79.7
Total protein (%)	Cases	23	38	44
	Controls	69	82	97
Animal protein (g)	Cases	4.0	5.4	12.7
	Controls	14.1	21.8	32.3
Fats (g)	Cases	15.2	18.7	26.2
	Controls	27.6	36.1	47.1
Fats (%)	Cases	18	25	31
	Controls	34	48	61
Carbohydrates (g)	Cases	151	227	273
	Controls	304	381	466
Carbohydrates (%)	Cases	40	53	65
	Controls	79	98	126

Physical activity has increased in most of the Cuban population as a result of the economic difficulties currently affecting the country, a phenomenon that has taken place together with a decrease in the amount and variety of foods consumed. National per capita food availability in 1992 represented only 82% of the estimated caloric energy and 75% of the estimated protein of food available in 1989, with protein providing 9% of the total energy and fat providing 15% (*14*). However, it should be noted that priority has been given to children in the distribution of certain foods, which may explain the low incidence of EN among individuals under 15 years of age.

The toxic action of the cyanogenic glucosides contained in foods such as yuca (cassava), cabbage, and beans (*15*) has been discussed as a possible factor in the current epidemic neuropathy, based on experiences elsewhere (*16–18*). However, the results of this study suggest that consumption of these foods had neutral or protective effects—contradicting this hypothesis, especially since yuca predominated among the tubers and starchy roots consumed, while cabbage predominated among the leafy vegetables.

Table 4. Intakes of vitamin B complex components by the study cases (N = 34) and controls (N = 65), showing amounts (in mg or μg) and percentages of the recommended amounts recorded for the 25th, 50th, and 75th percentiles of each group. In every instance the difference between the medians of the two groups was statistically highly significant ($P < 0.001$).

Variables		Percentile		
		25	50	75
Thiamine (mg)	Cases	0.27	0.44	0.69
	Controls	0.68	0.87	1.06
Thiamine (%)	Cases	20	32	44
	Controls	57	67	83
Riboflavin (mg)	Cases	0.21	0.32	0.47
	Controls	0.62	0.82	1.04
Riboflavin (%)	Cases	13	19	28
	Controls	14	53	66
Pyridoxine (mg)	Cases	0.44	0.68	0.95
	Controls	1.09	1.37	1.70
Pyridoxine (%)	Cases	28	43	58
	Controls	78	90	114
Niacin (mg)	Cases	2.86	4.81	6.23
	Controls	7.58	9.64	12.97
Niacin (%)	Cases	16	26	34
	Controls	46	54	70
Folic acid (μg)	Cases	77	117	151
	Controls	182	224	306
Folic acid (%)	Cases	31	47	60
	Controls	73	90	122

The widespread introduction of soybeans into the Cuban population's diet has aroused suspicion among some researchers, because of the neurotoxic effects of possible residues of hexane in extract flours and the adverse influence of certain soybean constituents on intestinal absorption (*19*). However, the protective association found in the present study between soybean intake and being a control subject suggests this suspicion is unfounded.

No food item was ingested in greater amounts by the subjects with cases as opposed to the controls, and hence it was not possible to assign any particular item the attribute of being a potential carrier of some toxic substance.

The median energy intake (including alcohol) of the subjects with cases was similar to the estimated per capita energy value of the rationed supply of food, whereas that of the control subjects was similar to the per capita energy intake for the Cuban population in 1992, as estimated using the food balance sheet method—a method that includes rationed supplies, public feeding programs, and food obtained through self-grown crops and other means (*14*).

The diet of the subjects with cases in this study was low in animal protein. The lack of essential amino acids combined with a low energy intake can be presumed to have increased the catabolism of tissue proteins and favored the loss of body weight. In addition, these circumstances also appear to have influenced, among other things, the methylation reactions that lead to the synthesis of myelin, detoxification of cyanide (*20*), and synthesis of taurine (*21*). Also, a com-

Table 5. Intakes of vitamins A, C, and E, of calcium, and of iron by the study cases (N = 34) and controls (N = 65), showing amounts (in mg or μg) and percentages of the recommended amounts recorded for the 25th, 50th, and 75th percentiles of each group and the statistical significance of the differences observed between the medians of the two groups.

Variables		Percentile 25	50	75	P
Vitamin A (μg)	Cases	80	153	344	
	Controls	220	442	729	<0.001
Vitamin A (%)	Cases	10	20	43	
	Controls	31	62	91	<0.001
Vitamin C (mg)	Cases	21	50	111	
	Controls	49	98	151	0.004
Vitamin C (%)	Cases	35	84	185	
	Controls	82	164	252	0.004
Vitamin E (mg)	Cases	3.90	4.63	5.46	
	Controls	6.10	7.25	9.25	<0.001
Vitamin E (%)	Cases	44	50	59	
	Controls	66	78	100	<0.001
Calcium (mg)	Cases	104	164	256	
	Controls	284	403	589	<0.001
Calcium (%)	Cases	13	20	32	
	Controls	36	50	74	<0.001
Iron (mg)	Cases	4.03	6.20	7.71	
	Controls	9.40	12.47	14.64	<0.001
Iron (%)	Cases	29	46	64	
	Controls	56	94	116	<0.001

Table 6. A comparison of the percentages of total caloric intake derived from different sources (excluding alcohol) by the 25th, 50th, and 75th percentiles of the study cases (N = 34) and controls (N = 65) and the statistical significance of the differences observed between the medians of the two groups.

Variables		Percentile 25	50	75	P
Energy (excluding alcohol-derived energy) from:					
Total protein (%)	Cases	7.8	10.2	11.8	
	Controls	10.9	11.8	13.6	0.001
Animal protein (%)	Cases	1.4	2.5	3.6	
	Controls	2.9	4.6	5.5	<0.001
Fat (%)	Cases	14.6	15.8	21.0	
	Controls	12.9	14.8	18.6	0.206
Carbohydrate (%)	Cases	67.8	74.4	77.4	
	Controls	68.8	72.1	75.4	0.280
Sugar (%)	Cases	15.5	19.5	23.6	
	Controls	12.6	15.4	21.4	0.041

Table 7. Percentages of cases and controls at risk because of their low body mass index, low body weight for height, or loss of weight; odds ratios (OR) and confidence intervals (CI) are shown for the differences observed.

Risk criterion	% of individuals at risk			
	Cases (n = 34)	Controls (n = 65)	OR	CI (95%)
BMI < 23 kg/m²	76.5	30.8	7.31	2.56 to 21.54
Low body weight (weight for height)	67.6	27.7	5.46	2.02 to 15.09
Loss of weight (in 12-month period)	79.4	56.9	2.92	1.01 to 8.71

Table 8. Percentages of cases and controls at risk (*) or protected (†) by their reported intakes of the selected foods indicated; odds ratios (OR) and confidence intervals (CI) are shown for the differences observed.

Risk criterion	% of individuals at risk (*) or protected (†)			
	Cases (n = 34)	Controls (n = 65)	OR	CI (95%)
Bread <105 g/day*	85.3	49.2	5.98	1.87 to 20.41
Rice <160 g/day*	55.9	18.5	5.59	2.01 to 15.88
<18 foods/month*	50.0	16.9	4.91	1.74 to 14.10
Nonconsumption of milk*	70.6	33.8	4.69	1.74 to 12.91
Sugar >15% of energy*	73.5	49.2	2.86	1.06 to 7.91
Alcohol >10 g/day*	47.1	24.6	2.72	1.03 to 7.28
Leafy vegetables >30 g/day†	20.6	33.8	0.51	0.17 to 1.49
Tubers and starchy roots >125 g/day†	17.6	41.5	0.30	0.10 to 0.91
Ground beef extended with soybean flour >15 g/day†	11.8	33.8	0.26	0.07 to 0.92
Hamburgers made with ground beef extended with soybean flour >15 g/day†	8.8	33.8	0.19	0.04 to 0.76
Oil >15 g/day†	11.8	40.0	0.20	0.05 to 0.70
Beans >120 g/day†	32.4	69.2	0.21	0.08 to 0.57

bined decrease in the intake of tryptophan and pyridoxine compromises the synthesis of niacin (*22*). All these effects favor the appearance of neuropathies of nutritional origin.

The greater consumption of alcohol observed among the study subjects with cases increased the risk of undesirable collateral manifestations. That is because the net effect of chronic alcohol ingestion is reduction in the tissue concentrations of ATP, increased weight loss, and the appearance of micronutrient deficiencies—whether as a result of limited food intake or interference with the absorption, deposit, metabolism, and excretion of multiple nutrients such as folic acid, methionine, niacin, thiamine, zinc, and vitamins A, B_6, and E (*2, 23*).

Dietary deficiencies have been identified as a factor in the pathogenesis of both optic and peripheral neuropathies. The importance of vitamin deficiencies in these neuropathies is widely recognized (*2, 3, 24*). By the 1940s Beam (*25*) had already noted that amblyopia was probably due to vitamin, mineral, and protein deficiencies; intoxications of a chemical

Table 9. Percentages of cases and controls deemed at risk because their reported intakes of the listed nutrients were at or below 50% of the recommended amounts. (The 50% values were estimated for each subject, based on that subject's sex, age, desirable body weight, etc.) For each variable, the OR and CI on the bottom line represent figures obtained when working with that variable alone, while the figure on the top line represents the result of a multivariate analysis in which values were adjusted for smoking and alcohol consumption.

Risk criterion	% of individuals at risk: Cases (n = 34)	% of individuals at risk: Controls (n = 65)	OR	CI (95%)
Low protein	82.4	6.2	109.86	20.05 to 601.78
			71.17	15.93 to 363.85
Low pyridoxine	67.6	3.1	83.31	14.41 to 481.54
			65.86	12.02 to 480.83
Low thiamine	82.4	9.2	76.51	15.17 to 385.92
			45.89	11.79 to 196.73
Low energy (excluding energy from alcohol)	67.6	3.1	60.56	11.83 to 310.09
			65.86	12.02 to 480.83
Low vitamin E	52.9	1.5	54.63	6.66 to 448.20
			72.00	8.74 to 1 583.35
Low niacin	91.2	41.5	17.65	4.87 to 63.98
			14.54	3.65 to 67.59
Low folic acid	52.9	6.2	15.25	4.53 to 51.38
			17.16	4.51 to 71.44
Low fat	91.2	56.9	6.42	2.03 to 20.32
			7.82	1.97 to 36.24
Low riboflavin	85.3	46.2	5.48	1.81 to 16.54
			6.77	2.11 to 23.12
Low vitamin A	79.4	41.5	5.10	1.84 to 14.15
			5.43	1.88 to 16.26

and biological nature; and the effect of intense physical activity combined with insufficient energy intake (*25*).

The relatively high sugar content in the diet of the subjects with cases, together with their relatively low intake of thiamine and high consumption of alcohol, could be expected to increase the likelihood of clinical manifestations of thiamine deficiency (*26*). However, the clinical pictures of these subjects did not precisely match those of cases involving thiamine deficiency alone.

The subjects with cases had markedly lower average intakes of niacin, riboflavin, pyridoxine, and folic acid than did the control subjects. Niacin and riboflavin, in addition to thiamine, participate in cellular metabolism of glucose, the primary source of energy for nerve cells. Also, pyridoxine is the cofactor in the decarboxylation reactions that lead to synthesis of the central and peripheral nervous system neurotransmitters. In addition, pyridoxine and folic acid participate in key functions of sulfur compound metabolism necessary for methylation reactions that lead to synthesis of myelin and to cyanide detoxification (*27*).

The clinical manifestations of EN in Cuba include weight loss, blurred vision, photophobia, gradual loss of visual acuity, neurosensorial auditory loss, dysphonia, dysphagia, sensory ataxia, pain in the extremities, increased urinary frequency, weakness in the legs, dysesthesias and paresthesias (primarily in the ankles), and a burning sensation on the

soles of the feet (*1*). References to these clinical manifestations appear in the literature, together with references to manifestations of combined dietary deficiencies involving the B complex vitamins that include cheilosis, glossitis, angular stomatitis, and pellagroid cutaneous alterations (*2*).

The average intake levels of B complex vitamins that were found for the subjects with cases (less than 50% of the recommended daily intakes) are consistent with the appearance of multiple deficiency manifestations.

Also, in studies of neuropathies of nutritional origin, combined vitamin A and B complex deficiencies have been reported (*13, 25*). In our survey, vitamin A intake among the subjects with cases averaged only 20% of the recommended daily intake.

In addition, vitamin E intake among the subjects with cases was low. This nutrient, in conjunction with selenium and vitamin C, prevents peroxidation of lipids in the cell membranes. In vitamin E deficiency, neuroaxonal dystrophy-type neuropathies can occur (*28, 29*).

The diet-related results observed in the subjects with cases in this study are compatible with the distal axonal lesions found in biopsies of the sural nerves of patients studied in other provinces. These latter lesions may be of nutritional, toxic, or metabolic origin (*1*).

The noxious effect of tobacco on the optic nerve is attributed to an inability to detoxify cyanide to thiocyanate with formation of other products that may interfere with myelinization and the turnover of myelin (*30*). This alteration may also be provoked by inadequate nutrition involving proteins and a number of different vitamins (*31*). In our study, diet may have played a major role in the association observed between smoking and EN, which increased with the number of cigarettes smoked per day.

Following adjustment of the data for smoking and alcohol consumption, the results of the multivariate analysis showed that the association between EN and nutrition remained unconditionally present. This finding strongly supported the assumption that, although these deleterious habits reinforced the effect of dietary deficiency, they were not sufficient to account for the association between dietary deficiency and occurrence of the disease by themselves.

The favorable response of most Cubans with EN to vitamin treatment (*1, 14*) supports the principal hypothesis advanced in this study. The study results also permit the conclusion that a diet deficient in caloric energy, protein, fat, and the various micronutrients studied—and unbalanced by a relative excess of sugar, with consequent effects on body weight—is strongly associated with EN and bears a causal relationship to it.

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