0025-7974/91/7004-0229$03.00/0
MEDICINE

Vol. 70, No. 4
Printed in U.S.A.

Neurologic Aspects of Cobalamin Deficiency

EDWARD B. HEALTON, M.D., DAVID G. SAVAGE, M.D., JOHN C. M. BRUST, M.D., T. J. GARRETT, M.D. AND JOHN LINDENBAUM, M.D.

Introduction

The neurologic disorders associated with pernicious anemia were well described in the literature of the late nineteenth century and the first decades of this century (5, 17, 31, 54, 67, 89, 91, 94). Much of the classic literature on the topic is subject to certain limitations, including uncertainty as to underlying diagnosis and problems in evaluating therapy with liver preparations of varying potency. No large detailed series of patients with vitamin B_{12} (cobalamin, Cbl) deficiency affecting the nervous system has been published since the introduction of various modern diagnostic and therapeutic measures, including the Schilling test, serum Cbl level and treatment with purified vitamin B_{12}, although many reports involving single patients or small numbers of patients have appeared (7, 17, 28, 38, 43, 47, 49, 65, 71, 87, 91, 98). It has been noted that clinical presentation of patients with Cbl deficiency during the modern era has been different and less advanced than in the past (22). It is possible that neurologic disorders due to lack of Cbl seen in recent years may be more responsive to therapy and show a higher degree of reversibility than has been observed previously (8, 17, 27, 31, 43, 44, 67, 75, 88, 89, 96). We present here a review of the presentations and responses to treatment of a large series of patients with well-documented Cbl deficiency who were studied at 2 university hospitals during a recent 17-year period.

Methods

Patients

The records of all patients with low serum Cbl levels evaluated at Columbia-Presbyterian Medical Center and Harlem Hospital Center between July 1968 and September 1985 were reviewed. In addition, the records of 2 patients with low normal serum Cbl levels in whom subsequent therapy with cyanocobalamin produced striking neurologic improvement were reviewed because of their neurologists' conviction that Cbl deficiency was present before treatment. Clinical Cbl deficiency was defined as a syndrome involving the tongue, nervous system, and/or hematopoetic system characteristic of lack of Cbl which responded to therapy with the vitamin; in those cases in which there was no follow-up after therapy, Cbl deficiency was the only plausible explanation for the syndrome.

In 369 patients there were 389 such episodes of documented clinical Cbl deficiency; some patients had recurrent episodes after discontinuation of maintenance treatment with vitamin B_{12}. One hundred eighty-nine of these patients (with 199 episodes) had neurologic symptoms, signs, or both. In 46 patients, neurologic evaluation was inadequate or a neurologic disorder was present that did not clearly respond to therapy with cobalamin and was explained by an alternative diagnosis (Alzheimer's disease 11, idiopathic parkinsonism 3, stroke 4, diabetes mellitus 4, chronic alcoholism 3, hereditary spinal cerebellar degeneration 1, normal pressure hydrocephalus 1, and motor neuron disease 1) or by normal aging (diminished vibration sense and loss of Achilles tendon reflex, 3 patients). In the remaining 143 patients (153 episodes; 39.3% of the 389 episodes), the neurologic disorders were attributed to Cbl deficiency. These patients form the basis for this report. Neurologic examinations were performed by a neurologist or were considered complete in 136 episodes (89%). In the other 17 episodes the examination was sufficiently complete for documentation and classification of the neurologic abnormalities. Forty of the 143 patients included in this study have been previously reported (58).

Definitions

Neurologic syndromes: Based on the presumed anatomic localization of the clinical findings, we attributed the neurologic abnormalities in our patients to one or more of the clinical syndromes listed in Table 1. In this classification distal, symmetrical, cutaneous sensory loss and absent tendon reflexes were attributed to peripheral nerve disease, and spasticity, extensor plantar responses, hyperreflexia, and a segmental vibratory or cutaneous sensory level were considered spinal cord dysfunction. Some patients had either 1) distal symmetrical loss of vibratory sensation and/or proprioception or 2) autonomic abnormalities, findings that could signify either peripheral nerve or spinal cord disease; they were classified as having "myelopathy and/or neuropathy" (M/N). Paresthesias without abnormal findings on neurologic examination constituted a separate category. A combination of clinical syndromes was frequently required to completely explain the neurologic abnormalities.

From the Departments of Neurology (E.B.H., J.C.M.B.) and Medicine (D.G.S., T.J.G., J.L.), Columbia-Presbyterian Medical Center, Harlem Hospital Center, and the College Of Physicians and Surgeons, Columbia University, New York, New York.

Address reprint request to: Dr. John Lindenbaum, Department of Medicine, Columbia-Presbyterian Medical Center, 630 West 168th Street, New York, NY 10032.

Severity scores: In order to better quantitate the severity of neurologic involvement and overall functional disability before and after therapy, a grading system was devised (Table 2) so that each episode could be given a point score. Neurologic abnormalities were scored according to the level and severity of involvement of sensory, motor, reflex, autonomic, and visual systems and according to functional disability of gait or intellectual function. Lower and upper limbs were scored independently.

Treatment response: In determining whether a neurologic response to cobalamin therapy had occurred, the available information was considered adequate in those patients who either improved after treatment with the vitamin or who failed to improve after at least 6 months of therapy. In patients treated and followed for less than six months who did not improve, response was considered uncertain. Neurologic improvement was considered complete when all neurologic symptoms disappeared and the neurologic examination and functional level became normal (severity score = 0); partial, when there were residual neurologic abnormalities or functional impairment after initial improvement (severity score decreased by 1 point or greater); or absent, if the neurologic abnormalities or functional level remained unchanged or worsened (severity score unaltered or increased). All patients were treated with parenteral cyanocobalamin in 1000 μg doses but the number and timing of the initial injections were quite variable. Most patients received the same dose monthly as maintenance therapy.

Serum Cbl concentrations were determined by microbiologic assay with *Lactobacillus leichmannii* (83), radioassay using purified intrinsic factor (Quantaphase, Bio-Rad Laboratories, Richmond, CA), or both methods. Serum folate levels were assayed employing *Lactobacillus casei* or milk-binder radioassays.

The statistical analysis employed a variety of techniques, including Student t test, the chi-square method for fourfold tables with correction for continuity, and multiple linear regression to determine the effect of a number of variables (including age, sex, duration of symptoms, ethnic group, hematocrit, ethyrocyte mean cell volume [MCV], hospital, year of diagnosis, serum Cbl and serum folate) on three different dependent variables: severity scores before and after treatment and percent improvement over pre-treatment status (see below). In each analysis, the most strongly related predictor variables were selected by stepwise linear regression using the BMDP2R system (13). A further regression was then done using this set of predictor variables by all-possible-subset regression (BMDP9R) and a best subset chosen (13, 25).

Results

Patient profile

The 143 patients with neurologic disorders included 62 blacks, 56 whites, 24 Caribbean hispanics (predominantly from Puerto Rico or the Dominican Republic) and 1 Native American. The age of onset of the symptoms of Cbl deficiency varied from 17 to 98 years (mean, 61.4). Mean age of onset was similar among the various ethnic groups. Nearly 40% of the patients developed symptoms before the age of 60 (Fig. 1) and 22% before the age of 50. Pernicious anemia was the most common underlying cause of Cbl deficiency (Table 3). Of the 3 patients considered to have food Cbl malabsorption (24), one was found to have serum antibodies to intrinsic factor and an abnormal Schilling test 9 years after an initially normal Schilling test. This patient was thought to have food Cbl malabsorption evolving into pernicious anemia (16, 23).

Symptoms at onset of cobalamin deficiency

Neurologic symptoms attributed to Cbl deficiency occurred first and were the dominant symptoms in 114 episodes (Table 4). Paresthesias, most commonly described as tingling, "pins and needles" sensation or numbness, were the most common initial complaints and occurred in more than 70% of the patients with neurologic symptoms. Ten patients complained bitterly of them and considered them disabling. Paresthesias were typically bilateral and were experienced in the feet or the feet and hands. In 22 episodes, however, paresthe-

TABLE 1. Definitions of neurologic syndromes

Syndrome	Definition
Peripheral neuropathy	Bilateral symmetrical impairment of cutaneous sensation distally in the limbs (without a segmental level) or absent or diminished tendon reflexes, with or without distal symmetrical atrophic limb weakness
Myelopathy	Spasticity, extensor plantar responses, or pathologic hyperreflexia with or without bilateral limb weakness; or a segmental vibratory or cutaneous sensory level
Myelopathy and/or neuropathy	Impaired proprioception, non-segmental diminished vibratory sensation, or autonomic symptoms such as postural hypotension, urinary or rectal incontinence, or impotence
Altered mental status	Impairment of attention span, memory, abstraction, fund of knowledge or other intellectual function with or without abnormalities of behavior, mood, affect, or logical thought
Optic neuropathy	Bilateral predominantly central or centrocecal visual impairment, with or without optic atrophy
Paresthesias without abnormal neurologic findings	Spontaneous prickling, tingling, burning, numbness or related sensory complaints perceived predominantly in the feet or feet and hands without abnormal findings on neurologic examination

TABLE 2. Point system for numerical severity scoring

Abnormality	Finding	Points	Comments
Sensory	Paresthesias in the feet or hands	2	
	Diminished proprioception		When a sensory modality was absent, 1 additional point for each affected level was added
	At the toes or fingers	2	
	At the ankles or wrists	4	
	At the knees or elbows	6	
	Diminished vibratory sensation		
	At the toes or fingers	1	
	At the ankles or wrists	2	
	At the knees or elbows	3	
	Segmental vibratory level	4	
	Diminished cutaneous sensation		
	In the toes or fingers	2	
	At the ankles or wrists	4	
	At the knees or elbows	6	
	Segmental cutaneous sensory level	8	
Motor	Weakness		When complete paralysis occurred, 2 additional points for each affected level were added. If spasticity was present in the limbs, 4 additional points were added
	At or below the ankles or wrists	2	
	At or below the knees or elbows	4	
	At or below the hips or shoulders	6	
Reflexes	Extensor plantar responses, clonus, or hyperreflexia	4	
	Areflexia (other than absent Achilles' tendon reflex in the elderly)	2	
Autonomic	Urinary or fecal incontinence, postural hypotension, or impotence	4	
Gait	Unable to maintain the Romberg position	2	Points were assigned according to the degree of support required for ambulation
	Gait ataxia but able to walk unsupported	3	
	Substantial support required for ambulation	6	
	Wheelchair or bed bound	9	
Mental	Intellectual or behavioral impairment present but requiring no social support	3	Points were assigned based on the degree of support required to carry out activities of daily living
	Partially dependent for activities of daily living	6	
	Completely dependent for all activities of daily living	9	
Vision	Visual acuity impaired but better than 20/200	3	
	Visual acuity 20/200–20/800	6	
	Able to only count fingers or recognize hand movements	9	

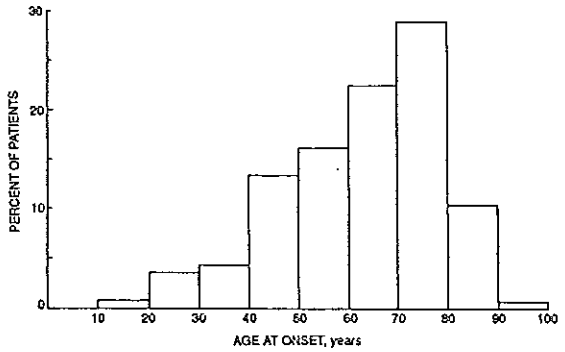

FIG. 1. Distribution by decade of age of onset of symptoms of Cbl deficiency in 143 patients with neurologic manifestations. For patients who had more than 1 episode, age at first episode was used.

sias were reported exclusively in the hands or hands and arms; in 3 others the symptoms occurred first in the hands and later in the feet and legs. One patient described prominent paresthesias in the gluteal and genital regions in addition to the lower limbs. Thirty-two patients with paresthesias also reported other symptoms such as gait ataxia and weakness of the legs or the legs and arms. Ataxia of gait was an initial complaint in 34 episodes. Less common initial symptoms are listed in Table 4. The median duration of neurologic symptoms before diagnosis and treatment with vitamin B_{12} was 4.0 months (mean, 13.1 ± 31.6).

In 37 episodes the initial complaints attributable to Cbl deficiency were non-neurologic. In 6 of these episodes, paresthesias (4 episodes), ataxia (1), or ataxia and memory loss (1) developed subsequently. In 120 episodes (78%), therefore, neurologic symptoms were present by the time Cbl deficiency was ultimately diagnosed. In 31 episodes, neurologic symptoms were not reported from onset to the time Cbl deficiency was diagnosed and treated.

Two patients (1 episode each) were free of all symptoms when anemia and Cbl deficiency were diagnosed as the result of a "routine" complete blood count.

TABLE 3. Causes of cobalamin deficiency in 143 patients

Etiology	Number of Patients (%)
Pernicious anemia	
Proven*	95 (66.4)
Probable†	17 (11.9)
Tropical sprue	8 (5.6)
Gastric resection	6 (4.2)
Ileal resection	4 (2.8)
Jejunal diverticula	3 (2.1)
Dietary cobalamin malabsorption (probable)‡	3 (2.1)
Multiple etiologies§	4 (2.8)
Etiology not established	3 (2.1)
Total	143 (100.0)

* Based on the presence of serum antibodies to intrinsic factor, correction of cobalamin malabsorption by intrinsic factor in Schilling tests, or both.

† All had evidence of achlorhydria. In 7 only the first part of the Schilling test was done which demonstrated malabsorption of cobalamin. One patient died before a Schilling test could be performed but the serum gastrin was elevated and gastric atrophy was demonstrated at autopsy. Nine achlorhydric patients did not have Schilling tests; gastrointestinal x-rays were normal.

‡ The patients had normal gastrointestinal x-ray films, normal Schilling tests and evidence of achlorhydria.

§ Proven pernicious anemia and gastric resection; proven pernicious anemia and ileal resection; proven pernicious anemia and ileal Waldenströom disease; gastric and ileal resection.

TABLE 4. Symptoms at onset of 153 episodes of cobalamin deficiency

Initial Symptoms	Number of Episodes (%)
Neurologic	114 (74.5)
Paresthesias and/or numbness	51
Paresthesias and/or numbness with	
Gait ataxia	14
Gait ataxia + anosmia, diminished taste	1
Gait ataxia + fecal incontinence	1
Gait ataxia + leg weakness	1
Leg weakness	6
Impaired manual dexterity	5
Impaired coin recognition	2
Memory loss	1
Impotence	1
Gait ataxia	14
Gait ataxia with	
Leg weakness	1
Impaired manual dexterity	1
Urinary incontinence	1
Personality change	1
Memory loss	4
Leg weakness	2
Orthostatic lightheadedness	2
Anosmia, diminished taste	2
Paranoid psychosis	2
Diminished visual acuity	1
Non-neurologic symptoms*	37 (24.2)
Asymptomatic	2 (1.3)
	153 (100.0)

* Sore tongue, gastrointestinal symptoms (anorexia, vomiting, diarrhea), weight loss, generalized weakness, syncope associated with severe anemia.

Progression of neurologic symptoms

In 40 episodes, progression of neurologic symptoms was documented in the medical record. Progression in each instance was considered unequivocal and not simply a reflection of subtle differences in history and examination by different observers. In 14, ataxia or paresthesias became more severe or paresthesias moved more proximally in the extremities or from the lower to upper limbs. In 26 episodes, 1 or more new neurologic symptoms were reported, including gait ataxia (11 episodes), limb weakness and stiffness (8), paresthesias (5), impaired tactile recognition of coins (2), impaired memory (2), difficulty buttoning clothes (1), personality change (1) and decreased libido (1). Six patients developed autonomic symptoms including urinary urgency, frequency, or incontinence in 5, and impotence in 1. Six patients (none of whom were anemic) became bed- or wheelchair-bound while under observation. In all patients with progression, symptoms increased over weeks to months rather than more rapidly.

Many in whom delays in diagnosis occurred were considered to have other disorders, such as spinal cord compression, amyotrophic lateral sclerosis, peripheral neuropathy due to alcoholism, diabetes or unknown cause, and Alzheimer's disease, before serum cobalamin levels were finally obtained. In these patients a number of unnecessary procedures were performed, including myelograms in 6 and sural nerve biopsy in 1.

Neurologic findings at diagnosis

In 31 of the 153 episodes (20.3%), neurologic symptoms were present but the neurologic examination was normal at the time of diagnosis. These patients complained of distal symmetrical limb paresthesias (28 episodes), paresthesias and ataxia (2), or paresthesias, ataxia and impaired memory (1). In the other 122 episodes (89 of which were associated with neurologic symptoms), there were sensory, motor, autonomic, mental, or visual abnormalities on examination (Table 5). The most common abnormality was diminished vibratory sensation, which was found in 107 episodes (87.7%). Vibratory sensation was usually diminished or absent in the feet or feet and legs up to the knees. In more severely affected patients, vibratory sensation was substantially diminished up to the iliac crest (6 episodes), lower thoracic area (2 episodes), midthoracic area (2 episodes), hands and elbows (3 episodes), and shoulders (1 episode).

Proprioception was diminished or absent in the toes or ankles in 72 episodes. In 8, position sense was also impaired in the fingers (7 episodes) or wrists (1). Position sense loss was always accom-

TABLE 5. Abnormal neurologic findings in 122 episodes of cobalamin deficiency

Neurologic Abnormality	Alone	Combined with						Number of Episodes (%)
		Ataxia	PP	QP	MI	MI + PP	MI + QP	
Impaired VS + PS	29	11*	1		2			43 (35.2)
Impaired VS	21	4	4		2		1†	32 (26.2)
Impaired VS, PS + CS	7†	5	3‡§	3‡‖	2	2‡	2¶	24 (19.8)
Impaired VS + CS	3¶	1			2			6 (4.9)
Impaired CS	4**				2			6 (4.9)
Impaired PS+ ?VS††	3	1			1‡‡			5 (4.2)
Ataxia	1				1			2 (1.6)
Postural hypotension + impaired VS	2							2 (1.6)
Mental impairment	1							1 (0.8)
Reduced visual acuity					1			1 (0.8)
Total								122

Abbreviations: PP = paraparesis, QP = quadriparesis, MI = mental impairment, VS = vibratory sensation, PS = joint position sense, CS = cutaneous sensation.

* 2 episodes with urinary incontinence.
† 1 episode with fecal incontinence.
‡ 1 episode with urinary incontinence.
§ 2 episodes with ataxia.
‖ 1 episode with urinary urgency, ataxia and impotence.
¶ 1 episode with urinary urgency and frequency.
** 1 episode with impotence.
†† Testing of vibratory sensation inadequate.
‡‡ Ataxia present.

panied by abnormal vibratory sensation, with the exception of 5 episodes, in which the latter modality was not tested or was inadequately tested. In 3 patients with diminished vibratory sensation and normal proprioception, corticospinal tract abnormalities (2 episodes) or impaired 2-point discrimination (1 episode) were noted. Ataxia of gait, commonly with associated sensory impairment, was observed in 28. The Romberg sign and Lhermitte phenomenon (14) were present in 14 and 3 episodes, respectively.

Cutaneous touch and pain sensation was reduced in 36 episodes; in 6 of these the sensory examination was otherwise normal. Cutaneous sensation was usually impaired in "stocking" distribution in the feet or feet and legs up to the knees. In 8 episodes, however, the arms were also involved up to the wrists (5 episodes), forearms (2), or biceps (1); in 3 there was a cutaneous sensory segmental level at L1 (1 episode) or T5 (2 episodes).

Weakness of the limbs was found in 16 episodes, always together with sensory deficits. The weakness affected the lower limbs symmetrically in all episodes except 1, in which bilateral leg weakness was very asymmetric. Six patients had weakness of the upper as well as the lower extremities. Hyperreflexia, extensor plantar responses, and spasticity were noted in 7 episodes. In 1 patient with extensor plantar responses, reflexes were absent in the legs. Reflexes were normal, diminished or absent in the remaining 9 patients with limb weakness, 4 of whom also had distal atrophy. Tendon reflexes were absent or substantially reduced in 41 episodes and hyperactive in 13.

Autonomic abnormalities were uncommon. In several episodes urinary incontinence (5 episodes), urinary frequency and urgency (3), fecal incontinence (2), or impotence (2) accompanied other motor or sensory abnormalities. In 2 additional episodes, involving the same patient, severe postural hypotension (30 to 40 mm drop in systolic blood pressure) and syncope occurred with a variable increase in heart rate on standing in the absence of other autonomic symptoms. In both of these episodes vibratory sensation was also impaired.

Visual impairment with bilateral centrocecal scotomas attributed to Cbl deficiency occurred in only 1 patient whose visual acuity was 20/800 in the right eye and limited to counting fingers in the left. This previously reported patient (85) had subacute visual loss without optic atrophy.

Mental impairment appeared to be caused by Cbl deficiency in 18 episodes. In 17 this was characterized either by global dementia (8) or predominantly recent memory loss with mildly reduced attention span and otherwise normal cognitive function (9). In 5 of these episodes, depression (2 episodes), agitation (2), and hypomania (1) were superimposed on intellectual impairment, and in 2 episodes, acute paranoid psychosis or depression and "personality change" dominated the mental status. In the other episode there were no intellectual abnormalities but the patient had a blunted affect and emotional lability.

In 17 of the 18 episodes with mental impairment,

there were other neurologic abnormalities. In 14, decreased vibration sense was found, frequently in association with other findings. In 1, impairment of vision was the only other neurologic abnormality, and in 2 episodes there were paresthesias and an ataxic broad-based gait requiring assistance. In the other patient with mental impairment the only finding was an amnestic syndrome but the neurologic examination was incomplete because of poor cooperation.

Neurologic syndromes

The various neurologic presentations were classified according to the definitions outlined in Table 1 and are summarized in Table 6. The category of myelopathy and/or neuropathy was the most common neurologic syndrome. Peripheral neuropathy and myelopathy were also common but were usually associated with other neurologic syndromes. In 61 episodes (39.9%), more than 1 syndrome was present.

Neurologic diagnostic tests

Quantitative values of electromyographic studies were available in 10 patients, 9 of whom had clinical signs of peripheral neuropathy. Seven of the 9 had decreased peroneal or posterior tibial nerve conduction velocities (29 to 40 m/sec). In 6 of the 7, however, there was also evidence of axonal damage (fibrillation potentials and positive sharp waves, accompanied by decreased amplitude of evoked motor and sensory potentials in 4, absent responses to surface recording of stimulated sensory nerves in 3 and of stimulated motor nerves in 2). One of the 9 patients with clinical signs of peripheral neuropathy had a normal study, and 1 showed only cervical radiculopathy. Electromyography was normal in a tenth patient with "myelopathy and/or neuropathy."

Somatosensory evoked response testing revealed cervical conduction delay in 3 patients with myelopathy and 1 with peripheral neuropathy plus myelopathy and/or neuropathy, but was normal in another patient with signs of myelopathy. Three patients with either myelopathy, peripheral neuropathy, or altered mental status, but no visual or brainstem symptoms or signs, had normal visual evoked potentials. Two of these patients also had normal brainstem auditory evoked responses.

Electroencephalography showed diffuse slowing in 2 patients with altered mental status secondary to cobalamin deficiency and in 2 with probable Alzheimer's disease. It was normal in 3 others with altered mental status secondary to cobalamin deficiency and in 3 with normal mentation.

Computerized cranial tomography showed bilateral mild-to-moderate diffuse cerebral atrophy in 3 patients (aged 69 to 76 years) with mental impairment attributed to cobalamin deficiency and in 1 72-year-old with normal mentation.

The cerebrospinal fluid was normal in 14 patients.

Hematologic findings

The first hematologic data obtained in each episode are summarized in Table 7. The hematocrit was normal in more than a quarter of the episodes, even though in each instance except 1 the patients complained of neurologic symptoms at the time blood tests were done. Only 19% were severely anemic (hematocrit < 20%). In approximately one-fourth of the episodes, the erythrocyte mean cell volume (MCV) was normal. In 22 episodes (16.3%), both the hematocrit and MCV were normal. When the MCV was increased the macrocytosis was often marked (MCV > 110 fl). The white blood cell and platelet counts were normal in the great majority of patients (Table 7). Of 139 episodes from which blood smear readings were available, hypersegmented neutrophils (with or without macro-ovalocytes) were noted in 137 (98.6%); in 15 instances, however, blood smear morphology was reported as normal by routine hospital laboratories, and minimal neutrophil hypersegmentation was detected

TABLE 6. Neurologic syndromes in 153 episodes of cobalamin deficiency

	Alone	Associated with						Total Number of Occurrences (%)
		M/N	PN	MP	BCD	ON	>1 syndrome	
Myelopathy and/or neuropathy (M/N)	52		29	1	4		3*	89 (40.5)
Peripheral neuropathy (PN)	4	29		14	2		6†	55 (25)
Myelopathy (MP)	4	1	14		4		3*	26 (11.8)
Bilateral cerebral dysfunction (BCD)	1	4	2	4		1	6‡	18 (8.1)
Optic neuropathy (ON)								1 (0.5)
Paresthesias without abnormal neurologic examination	31				1			31 (14.1)

* PN and BCD.
† M/N and BCD, 3 episodes; MP and BCD, 3 episodes.
‡ M/N and PN, 3 episodes; MP and PN, 3 episodes.

TABLE 7. Initial hematologic findings in 153 episodes of cobalamin deficiency

Test	Number of Episodes with Finding/Number Tested (%)
Hematocrit	
Normal*	42/153 (27.4)
Decreased	
≥30%	25/153 (16.3)
20–29%	57/153 (37.3)
<20%	29/153 (19.0)
Mean Cell Volume	
<80 fl	1/135 (0.7)
Normal (80–100 fl)	31/135 (23.0)
101–110 fl	41/135 (30.4)
>110 fl	62/135 (45.9)
White blood cell count	
Normal†	150/153 (98.0)
Decreased	3/153 (2.0)
Platelet count	
Normal‡	140/148 (94.6)
Decreased	8/148 (5.4)

Abbreviation: fl = femtoliters.
* 35–47% in women; 40–52% in men.
† >4000/μl in whites; >3000/μl in blacks.
‡ 150,000–400,000/μl.

only after review of the smear by an experienced hematologist. A bone marrow aspirate was obtained in 78 patients, including 15 with either a normal hematocrit, normal MCV, or both findings, and was read as megaloblastic on blind review by one of the authors in every case.

Serial hematologic studies before the institution of Cbl treatment were available in 13 episodes in which the hematocrit and MCV were normal at the onset of neurologic symptoms. In each instance neurologic complaints continued or worsened while the hematocrit remained normal and unchanged for varying periods. In 7 episodes, the MCV also remained normal and unchanged for 3 to 36 months. In 2 others, the MCV increased but remained in the normal range over 14 months and 7 years of observation. In 3 episodes, the MCV became elevated 2, 4, and 6 years later while the hematocrit was unchanged. In the remaining episode the MCV rose above normal over an 18-month period, after which anemia developed.

Folic acid was given to 4 patients and multivitamins containing folate to another before the diagnosis of cobalamin deficiency was established. Two patients responded hematologically; in 1, neurologic symptoms progressed and in the other appeared for the first time while he was receiving folate. Both patients had a normal hematocrit and 1 had a normal MCV when Cbl deficiency was finally diagnosed. In the other 3 there was no hematologic response and neurologic symptoms apparently increased while under treatment. Two additional patients were taking multivitamins at the time neurologic symptoms appeared but it could not be ascertained whether the preparations contained folic acid.

Serum vitamin concentrations

The serum Cbl level was <200 pg/ml (<150 pmol/L) in all but 2 patients. In 1 of them, the concentration was 235 pg/ml by radioassay; in the other, the serum level was 205 pg/ml by radioassay and 280 pg/ml by microbiologic assay. In 27 episodes, the serum Cbl was only moderately decreased (range, 100–200 pg/ml). Serum folate concentrations were above the upper limit of normal (20 ng/ml) in 29 episodes, low in 7, and normal in the remainder.

Severity of neurologic abnormalities before treatment

Most patients had relatively mild neurologic impairment. In 99 (64.7%) of the 153 episodes, the severity score was 9 or less ("mild" dysfunction); these patients typically had little significant functional disability. In 39 episodes (25.4%), nervous system damage was considered to be "moderate", with severity scores between 10 and 19; these patients were disabled with respect to activities of daily living but remained more or less independent. In 15 episodes (9.8%) with "severe" neurologic impairment, scores were 20 or greater, indicating marked functional disability; they usually required substantial support in activities of daily living.

The assignment of a quantitative severity score to each episode facilitated assessment of the influence of various factors that might affect severity. The extent of nervous system dysfunction was clearly related to the duration of neurologic symptoms before treatment. Thus, the mean severity score (± 1 SD) in episodes preceded by 6 months or less of neurologic symptoms was 8.5 ± 7.7 ($n = 88$), in contrast to 12.0 ± 9.1 in episodes with symptoms of 7 to 12 months' duration ($n = 18$) and 15.3 ± 13.3 in those who had symptoms for more than a year before therapy ($n = 23$) ($p < 0.005$ when the 0–6 and >12 months groups were compared). The quantitative correlation between duration of symptoms and severity was significant ($r = 0.36$, $p < 0.00004$). Similar correlations were noted between severity and the duration of all symptoms (i.e., both neurologic and non-neurologic), although they were slightly less strong.

A less anticipated finding was that the neurologic severity at the time of diagnosis was greater with increasing hematocrit. Thus, the mean severity score in 42 episodes without anemia (mean hematocrit, 40.3 ± 3.3%) was 14.6 ± 11.8, nearly twice that (7.7 ± 6.7, $p < 0.00005$) in the 111 episodes in which anemia was present (mean hematocrit, 24.3

± 7.2%). Mean severity score increased with increasing hematocrit (Fig. 2) and the hematocrit correlated significantly by regression analysis with severity ($r = 0.34$, $p < 0.00004$). Although the duration of neurologic symptoms was longer in nonanemic than anemic patients (24.7 ± 50.9 vs. 8.0 ± 15.5 months, respectively; $p < 0.01$), this did not appear to account for the relation between hematocrit and severity. For example, if only those episodes preceded by neurologic symptoms for 6 months or less were considered (average duration 2.4 ± 2.1 months in anemic patients, 1.9 ± 1.5 months in those without anemia), the mean severity

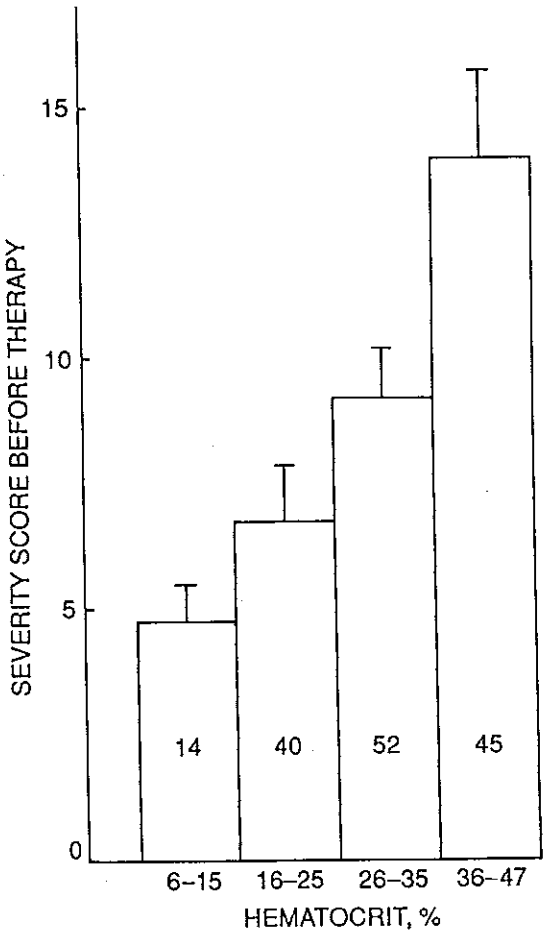

FIG. 2. Mean severity score before treatment associated with different levels of hematocrit in 151 episodes of cobalamin deficiency involving the nervous system. (Hematocrit values were not available for 2 of the 153 episodes in the series.) Bars indicate 1 standard error of the mean and numbers within boxes the number of patients in each group. The mean score in the 36–47% hematocrit group was significantly higher than that of the 6–15% group ($p < 0.005$), the 16–25% group ($p < 0.001$) and the 26–35% group ($p < 0.02$). The mean score of the 26–35% group was also significantly higher than that of the 6–15% group ($p < 0.03$).

in episodes in which the hematocrit was normal remained higher (13.2 ± 9.9 vs 7.3 ± 6.6, $p < 0.005$).

None of a number of other variables showed a significant correlation with severity score, including age, sex, hospital, year of diagnosis, MCV, serum cobalamin ($r = -0.01$) or serum folate ($r = .004$). There was a modest relationship, however, between severity and ethnic background. Severity scores were highest in whites (mean 11.8 ± 9.8, $n = 60$), intermediate in blacks (8.7 ± 8.3, $n = 68$) and lowest in hispanics (6.6 ± 7.5, $n = 24$). The only interethnic difference which was statistically significant was that between whites and hispanics in severity scores ($p < 0.025$). Whites did not differ from hispanics in duration of neurologic symptoms before treatment (16.5 ± 42.6 vs 18.8 ± 28.8 months, respectively), hematocrit (31.3 ± 9.0% vs 27.9 ± 9.6%, $p > 0.1$), age, hospital, MCV, serum Cbl or serum folate.

On multivariate analysis, however, the only remaining variables that significantly affected severity score were duration of symptoms and hematocrit. The contribution of each, as analyzed by "best subset" regression, was approximately equal ($p < 0.001$ for each).

Neurologic abnormalities in recurrent episodes of cobalamin deficiency

In 10 patients, a second episode of cobalamin deficiency associated with neurologic abnormalities occurred after interruption of maintenance therapy with vitamin B_{12}. The 2 episodes were separated by 2 to 16 years (mean, 8.1 years). In 7 patients the neurologic syndrome was the same in the 2 episodes. The severity scores before and after treatment of the initial and recurrent episodes did not differ significantly (data not shown).

Response to cobalamin therapy

Neurologic exacerbations: Four patients experienced exacerbations of neurologic symptoms early after treatment with Cbl was initiated. Two who had paresthesias of the upper extremities before treatment noted dramatic extension of the paresthesias (in 1 case to the thighs and ankles, in the other to the forearms and girdle area) beginning 24 to 48 hours after the first 1 mg injection of cyanocobalamin and persisting for 4 to 6 days. One of them also complained of a worsening of pre-existing numbness of the hands at the same time. These symptoms completely cleared by the end of the first week of treatment and never recurred. A third patient, who had paresthesias of the toes, fingers, and arms prior to therapy, observed spread of the paresthesias to the trunk and legs, new onset of the complaint of paresthesias after neck flexion, and

increasing weakness of the arms during the first 2 months of treatment with 1 mg parenteral doses of cyanocobalamin given once or twice a week. In each instance the worsening of symptoms after Cbl treatment resulted in repeated examinations by neurologists and the speculation that the diagnosis of underlying Cbl deficiency was in error. The only new objective finding noted during the exacerbations was a positive Lhermitte sign in the third patient. A fourth patient had a spastic paraparesis, mild confusion, disorientation only to time and moderate memory impairment before therapy; 72 hours after the first injection of cyanocobalamin, a florid acute psychosis, with visual hallucinations, delirium, total disorientation, and rambling incoherent speech developed, which cleared over 2 to 3 days. After these exacerbations subsided, each patient showed progressive and sustained improvement in the neurologic symptoms and signs originally present as Cbl treatment was continued. (Another patient with megaloblastic anemia due to Cbl deficiency, who had no evidence of a neurologic disorder before therapy and therefore was not included in this series, developed a severe acute psychosis 12 hours after the initiation of treatment, which cleared within 36 hours.)

Neurologic responses: In 32 of the 153 episodes, follow-up data were inadequate to determine whether there was a response to Cbl therapy. Three patients died before or shortly after Cbl therapy was initiated. (In 1, an autopsy showed severe demyelination of the posterior and lateral columns of the spinal cord.) In 27 episodes, no neurologic evaluation after Cbl treatment was available. In 2 there was no response, but follow-up assessment of neurologic status took place after only 2 to 3 months of treatment.

In each of the remaining 121 episodes, a definite response to cobalamin therapy was documented. In 57 (47.1%), there were no remaining neurologic symptoms and the neurologic examination returned to normal (complete response). Eleven of the 18 patients with mental impairment were included in the group with complete responses. In 64 episodes (52.9%), an unequivocal but partial response to Cbl therapy was noted and there were residual abnormalities in the neurologic examination. (Nine patients in the group with an incomplete response in whom the final neurologic evaluation took place less than 3 months after initiation of therapy have been excluded from the subsequent analysis.) The mean duration of observation on cobalamin therapy was 37.6 months. Moderate or severe neurologic residual disability after treatment (severity score $\geq$ 10) was present in only 7 episodes, representing 6.3% of those with known treatment outcome. Of the 112 episodes with known outcome, the severity score was reduced by 50% or greater in 101 (91.0%). The mean severity score after treatment (3.0 ± 5.3) was less than one-third of that before therapy (9.6 ± 8.9, $p < 1 \times 10^{-6}$).

Complete or partial responses occurred in patients with pretreatment severity scores in the mild, moderate or severe range. However, the extent of neurologic involvement after therapy was strongly related to that before treatment. In the 10 episodes in which the pretreatment severity score was 20 or greater a complete response was seen in only 2 and residual neurologic dysfunction was observed in all of the 8 episodes in which the severity score was more than 23 before therapy. After 3 of these episodes the post-treatment severity score remained in the severe range, but in the other 5 residual neurologic impairment was mild or moderate. There was a strong quantitative correlation between pre- and post-therapy severity scores (Fig. 3; $r = 0.76$, $p < 1 \times 10^{-7}$).

The duration of neurologic symptoms before treatment with Cbl therefore also correlated with post-treatment neurologic dysfunction. The mean severity score after treatment was 1.7 ± 2.4 in those episodes preceded by symptoms for 6 months or less, 3.5 ± 8.4 in those with 7 to 12 months of complaints, and 8.4 ± 9.8 in those with symptoms for longer than a year ($p < 0.0001$ for >12 compared with $\leq$6 months). Duration of symptoms correlated quantitatively with post-treatment severity ($r = 0.43$, $p < 1 \times 10^{-6}$).

In addition, the absence of anemia before therapy was predictive of residual neurologic damage. The mean post-treatment severity score after episodes without anemia was 6.0 ± 7.8 compared to 1.7 ± 2.8 in those with a low hematocrit ($p < 0.001$). Pretreatment hematocrit correlated positively with post-treatment severity ($r = 0.37$, $p < 0.0001$). Severity score after treatment did not correlate, however, with ethnic group, sex, age, hospital, MCV, serum Cbl, serum folate, or duration of follow-up after therapy.

Because pretreatment severity score, duration of symptoms, and hematocrit all correlated significantly with post-treatment severity score, a multivariate analysis was performed. On "best subset" analysis, all 3 variables correlated independently with post-treatment severity. The relationship with pretreatment severity was by far the strongest ($t = 10.34$, $p < 1 \times 10^{-7}$); duration of symptoms showed a modest independent correlation ($t = 3.37$, $p < 0.001$) and the correlation of post-treatment severity with hematocrit was only barely significant ($t = 2.00$, $p < 0.05$). As might be expected from the above-mentioned findings, the presence of a complete versus incomplete neurologic response to ther-

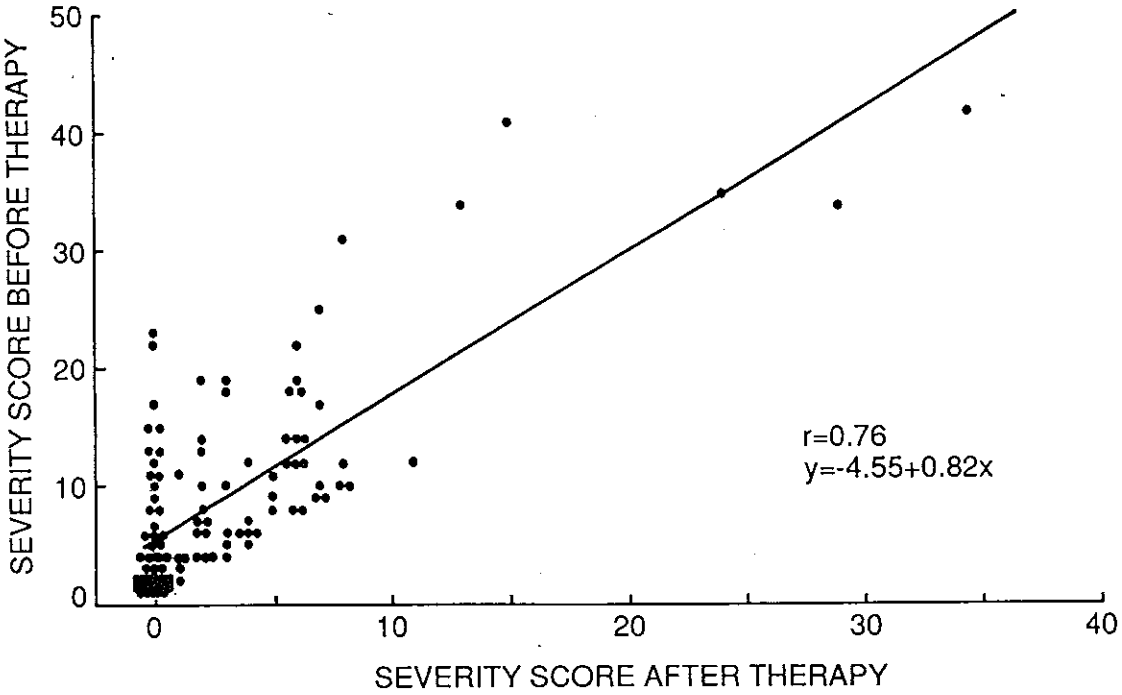

FIG. 3. Relationship between severity score before and after treatment with cyanocobalamin in 112 episodes of deficiency involving the nervous system.

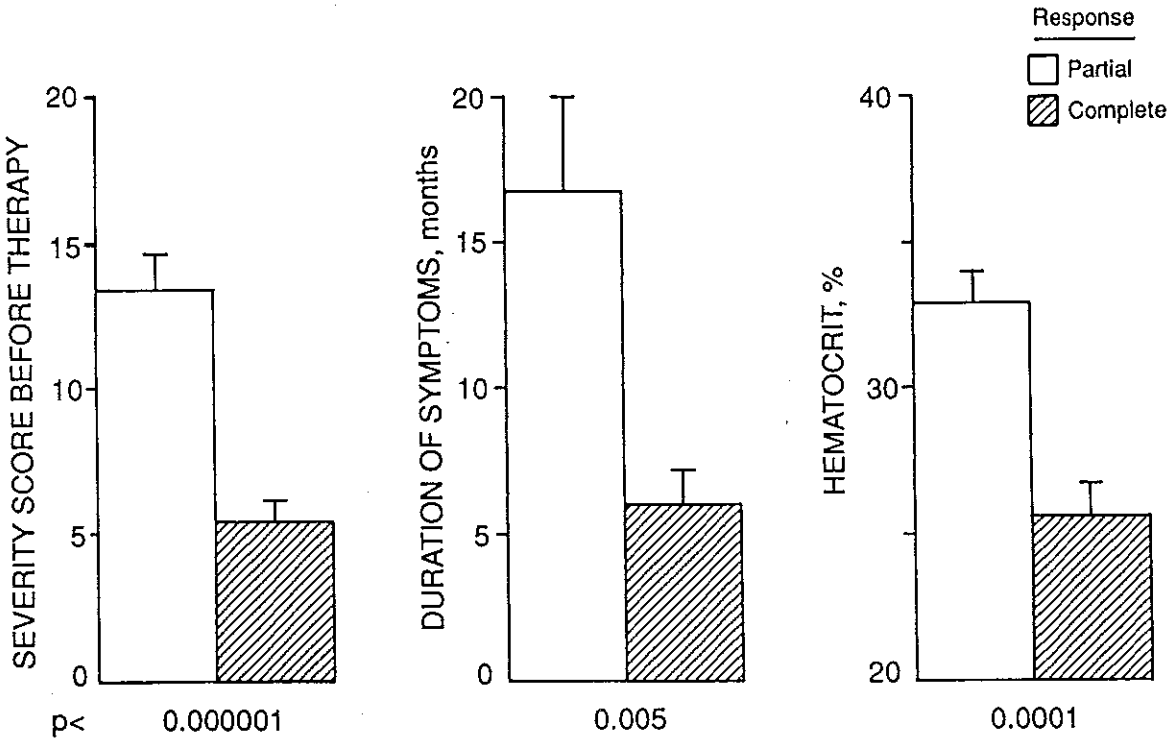

FIG. 4. Mean values for pre-treatment severity score, duration of neurologic symptoms before therapy, and hematocrit in patients who had complete versus partial neurologic responses to cyanocobalamin. Bars indicate 1 standard error of the mean.

apy correlated significantly with each of the 3 variables (Fig. 4).

The percentage of improvement over pre-treatment neurologic status was calculated as another and different way of assessing response to therapy; this was calculated as

$$1 - \frac{\text{post-treatment severity score}}{\text{pre-treatment severity score}} \times 100$$

The mean percent improvement for the entire group of patients was 74.6 ± 28.4% (range, 14.7–100). The duration of neurologic symptoms before treatment, hematocrit, and pretreatment severity score all correlated inversely with percentage of improvement on univariate analysis. After stepwise multivariate analysis, duration of symptoms correlated most strongly with improvement ($p < 0.0003$); hematocrit also correlated significantly ($p < 0.002$) but the relationship with pretreatment severity was no longer significant.

Although there was insufficient documentation for quantitative analysis, the overall *rate* of response to cobalamin therapy and the length of time to maximum improvement was not identical for different abnormalities and syndromes. With the exception of the 3 patients described above in whom paresthesias transiently worsened soon after therapy was begun, this symptom usually responded quickly. Paresthesias frequently began to subside after a few days of treatment and reached maximum improvement within 1 to 3 months, although in some cases no response was noted during the first 4 to 6 weeks. Other neurologic abnormalities usually did not begin to improve until 2 to 4 weeks of treatment and maximum response was usually reached within 6 months, as has been previously reported with liver therapy (28, 88), although continued improvement was documented for at least 12 months in some cases. In 1 patient progressive objective functional improvement in signs of myelopathy was documented beyond the third year of treatment. In all patients some evidence of symptomatic or objective improvement was noted during the first 3 months. Sensory abnormalities often improved earlier than spastic weakness or bladder dysfunction. In the single case of optic nerve impairment, visual acuity was normal within 5 months of treatment. In the patient with 2 episodes in which orthostatic hypotension was the chief complaint, rapid recovery of symptoms and blood pressure responses was documented during the second episode within a week of beginning therapy with Cbl, before any change in the hematocrit occurred; however, treatment of the first episode with Cbl did not correct the orthostatic hypotension for at least 3 weeks.

Hematologic responses: Hematologic data following therapy with parenteral cyanocobalamin were available from 99 of the 111 episodes in which anemia was present. The hematocrit rose after Cbl treatment in 94 patients. The additional administration of iron was necessary for a hematologic response in 3. In the remaining 2 (1 with the anemia of chronic disease attributable to metastatic carcinoma, the other with a hereditary chronic hemolytic anemia) there was no change in the hematocrit after Cbl therapy, although the MCV fell. In the 42 episodes in which the hematocrit was normal before treatment, hematologic follow-up was obtained in 39. The hematocrit rose within the normal range in 25 of the 39 episodes; the increment in hematocrit was substantial (≥5%) in 11. The MCV fell to normal in all 83 episodes associated with an elevated MCV from which follow-up data were available. In those episodes in which the MCV was normal before treatment, the MCV also decreased in 27 of the 29 instances in which cell size was subsequently measured. In 21 of these 29 episodes a marked fall in MCV (≥5 fl) was observed. In only 2 cases, however, was the post-treatment MCV below the lower limit of normal; in other words, in patients with an initially normal MCV, Cbl therapy caused a fall to a lower point within the normal range. The MCV responses in 24 of these episodes have been reported previously (58).

Comparison of patients with and without neurologic dysfunction

Clinical and laboratory data were available from 180 Cbl-deficient patients (187 episodes) in whom no neurologic signs or symptoms were present, for comparison with the 143 patients (153 episodes) in this series. The patients without neurologic involvement differed significantly from those with disorders of the nervous system in a number of respects. In the group lacking neurologic dysfunction, the duration of symptoms before diagnosis was shorter (mean, 7.3 ± 9.1 vs 11.2 ± 14.5 mo, respectively, $p < 0.006$); anemia was more severe (mean hematocrit, 22.5 ± 8.2 vs 28.7 ± 9.4%, $p < 0.0001$); and serum lactate dehydrogenase was higher (1767 ± 2040 vs 1259 ± 1881 U, $p < 0.05$). The MCV tended to be higher in those without neurologic involvement (115.4 ± 10.7 vs 112.6 ± 13.4 fl $p < 0.06$) and the white blood cell count lower (5.0 ± 2.5 vs 5.5 ± 2.6 × 10^3 cells/μl, $p < 0.06$).

In addition, hispanic patients were less frequently represented among those with neurologic disease (24 of 143, or 16.8%) than among those without it (58 of 180, or 32.2%, $\chi^2 = 9.23$, $p < 0.003$). Neurologic dysfunction developed in only 24 (29.3%) of 82 hispanics with Cbl deficiency in

contrast to 56 (52.8%) of 106 whites ($\chi^2 = 9.56$, $p < 0.003$) and 62 of 134 blacks (46.3%) ($\chi^2 = 5.44$, $p < 0.02$). The hispanics also differed from the other 2 groups in that tropical sprue was a frequent underlying cause of Cbl deficiency. If only patients with pernicious anemia were considered, the same trends were seen but the interethnic differences were no longer significant. Involvement of the nervous system occurred in 15 of 37 hispanics with pernicious anemia (40.5%), 49 of 92 whites (53.3%) ($\chi^2 = 1.24$, $p > 0.05$) and 51 of 108 blacks (47.2%) ($\chi^2 = 0.26$). The patients with neurologic involvement did not differ from those lacking it in age, sex, hospital, or the incidence of anorexia, weight loss or glossitis. Serum Cbl was similar in the 2 groups (mean values, 85.5 vs 84.0 pg/ml, respectively).

Discussion

There are certain limitations to the series presented here, including its largely retrospective nature and the fact that many different physicians were involved in the care of the patients. There are a number of advantages, however, including the generally high quality of the neurologic evaluations, the large numbers of patients studied, the high percentage with follow-up after therapy, and the inclusion of every patient with a low serum Cbl seen at 2 institutions serving populations of differing socioeconomic backgrounds over a period of nearly 2 decades. Although a few patients may have been missed, i.e., those who were treated without obtaining a serum Cbl level and some who were deficient although the serum Cbl was normal (59), it is highly likely that most patients with Cbl deficiency of the nervous system seen at the 2 teaching hospitals during the period of study were included, affording a comprehensive view of the clinical picture of this disorder as seen in current practice.

The neurologic manifestations of Cbl deficiency as revealed in this series are in many ways consistent with the findings recorded in early reports (11, 36, 54, 57, 64, 68, 76, 94, 95) and subsequent observations as summarized in several excellent reviews (17, 27, 75, 91). In Addison's (3) classic clinical description of pernicious anemia in 1855, the only neurologic abnormalities were periods of confusion or delirium in terminally ill patients. In 1887 Lichtheim (57) reported 3 patients with anemia, ataxia and paresthesias; autopsy in 1 showed severe degeneration of the spinal cord. Other investigators confirmed the association of motor, sensory, autonomic, and reflex abnormalities with demyelination and axonal destruction in the posterior and lateral columns of the spinal cord. In these early reports vibratory or position sense loss and even diminished reflexes were attributed to spinal cord disease, for which the term "subacute combined degeneration" was introduced (76). Other investigators, by contrast, attributed motor, sensory, and reflex abnormalities to peripheral neuropathy (36, 64, 71). Histologic confirmation has been infrequent (2, 33, 65, 72), and the dispute remains unresolved. Although sensory, motor, and reflex disturbances were the commonest neurologic abnormalities in our patients, the findings were frequently compatible with involvement of peripheral nerve, spinal cord or both, and the classification of "myelopathy and/or neuropathy" was used. Only a small number of patients had unequivocal evidence of exclusive peripheral nerve or spinal cord localization (Table 6). Our observations, therefore, indicate that the long-standing controversy in the literature concerning the relative importance of myelopathy versus peripheral neuropathy in patients with Cbl deficiency cannot be resolved on clinical grounds alone.

Electromyographic studies in the small number of cases reported in the literature have been consistent with axonal or demyelinating neuropathy, a combination of the 2, or neither (28, 47, 52, 60, 62, 63, 65, 71, 86). Subclinical peripheral nerve involvement has also been demonstrated (60). Somatosensory evoked potentials have shown delayed cervical conduction in patients in whom localization of sensory abnormalities was uncertain on clinical grounds as well as in those with definite myelopathy (28, 47, 97). Delayed conduction in visual evoked response testing has been reported in patients with both impaired and unimpaired vision (28, 47, 52, 97). Brainstem auditory evoked responses have been normal in most of the patients studied (28, 52, 63, 97). When followed serially, evoked response studies have shown improvement after Cbl therapy (28, 52, 63). Electromyographic studies in a select group of our patients in whom peripheral nerve disease was suspected usually showed evidence of both axonal and demyelinating neuropathy. For a more complete understanding of the relative contribution of peripheral neuropathy and myelopathy to the pathology of Cbl deficiency, systematic electrophysiologic or detailed histologic studies in a large series of patients will be required.

Previous observations (17, 27, 75, 91) that are confirmed in our series include the predominance of paresthesias and ataxia as initial symptoms (Table 4); the considerable inter-patient variability in signs and symptoms (Tables 4 and 5); the very high incidence of disturbances in sensation on neurologic examination, with defects in vibration perception the most common; the less frequent occurrence of motor abnormalities, with cortical spinal tract

or motor nerve involvement only in advanced cases; the usually symmetric and initially distal involvement of the extremities, most commonly in the lower limbs; the occurrence of cerebral and autonomic disorders in some patients; and the rare occurrence of anosmia, hypoalgusia, optic nerve disease, and orthostatic hypotension. Abnormalities that have been reported in the literature in association with Cbl deficiency but which were not seen in our patients include positional vertigo (61), paralysis of upward gaze (79), downbeat nystagmus (63), coma (41, 51, 73, 93) and (in infants) involuntary movements (41, 45, 93).

Altered mental status, including a wide variety of psychiatric symptoms, has frequently been observed in patients with Cbl deficiency (42, 54, 87, 94, 95, 98), although other causes of abnormal mental function in these often elderly patients have not always been excluded and the response to therapy has frequently not been well documented. In our patients cerebral dysfunction attributed to Cbl deficiency occurred less frequently than in some reports, possibly because we excluded patients in whom Alzheimer's disease, alcohol-related dementia, or other disorders may have been present in addition to lack of Cbl. Mental impairment caused by Cbl deficiency presented as global dementia, a predominantly amnestic syndrome, or psychiatric symptoms, which were the most striking feature in 2 patients. With the exception of 1 patient who could not cooperate adequately for a complete neurologic examination, other neurologic abnormalities were always present in patients with cognitive dysfunction. Mental impairment as the sole manifestation of Cbl deficiency was thus not convincingly established in our patients. When mental impairment occurred, however, it was frequently the most disabling and dominant neurologic abnormality.

The degree of neurologic dysfunction in our patients was generally milder than in many earlier series, although a minority was severely disabled (5, 8, 20, 27, 31, 72, 75). The mean and median duration of symptoms was also shorter (20, 31, 43, 72). Nonetheless, a relationship between duration of symptoms and severity of neurologic involvement before treatment was apparent, as has often been observed by others (10, 20).

A striking finding in this study was the inverse correlation between degree of anemia and extent of neurologic impairment. Not only was anemia significantly more severe in patients lacking nervous system damage, but in those affected neurologically the hematocrit correlated positively with severity of neurologic dysfunction. Many previous observers have noted a lack of correlation between the hematologic and neuropsychiatric manifestations of Cbl deficiency (17, 21, 31, 40, 43, 46, 54, 88, 91). Most large series have included few or no patients who were not anemic; in contrast, the hematocrit was normal in 27% of our cases. Perhaps because of the inclusion of these non-anemic episodes, our findings extend the oft-noted lack of correlation between the extent of anemia and of nervous system damage to indicate that there is an *inverse* relationship, i.e., the higher the hematocrit, the more severe the neurologic disorder. The explanation for this is uncertain. It does not appear to be attributable to an effect of a better folate status on the bone marrow of the less anemic patients (17, 19, 20, 40, 91). In only 2 episodes did the prior administration of folic acid result in a hematologic response that may have been associated with progression of neurologic disease. Furthermore, there was no correlation between serum folate and severity of neurologic damage. In addition, among the black patients, the extent of neurologic involvement did not differ according to the hospital where care was given, even though the socioeconomic status of the black population served by Harlem Hospital has been found to be lower than that of their counterparts at Presbyterian Hospital (81), who might therefore be expected to have greater access to a diet abundant in folate.

Our observations also suggest that the presence of nervous system findings in Cbl-deficient patients is not related to the overall severity of deficiency of the vitamin. Thus, profoundly anemic patients frequently had no neurologic signs or symptoms, as has been noted by previous observers (20, 21, 27, 31, 43), and the mean hematocrit of patients without any evidence of nervous system damage was significantly lower than that in those with neurologic dysfunction, as was also found by Cox (20). Other evidence of severe hematologic compromise, such as higher levels of serum LDH (a reflection [74] of ineffective hematopoiesis), more severe macrocytosis, and lower leukocyte counts, was seen as well in the group that was spared neurologically. In addition, there was no correlation between serum Cbl and the presence or severity of nervous system disease. Neurologic impairment thus does not appear only after anemia as a later stage of deficiency. Rather, in the majority of patients with nervous system disease, neurologic complaints were the initial symptoms, as was observed by Ungley and Suzman (89). The shorter duration of symptoms in patients who had anemia without neurologic dysfunction, which has also been noted by others (20, 68), may not indicate a less extended period of vitamin deficiency, since mild hematologic abnormalities typically are present for years before symptoms related to anemia occur (15, 35, 78, 80). Although comparable impairment of both systems occurs in a minority of patients, in most it is

apparent that either neurologic or hematologic dysfunction predominates.

As mentioned, the presence of a normal hematocrit in more than 25% of the episodes of Cbl deficiency differs from previous large series in the literature, although presentation without anemia was reported as early as the nineteenth century (76), and Greenfield and O'Flynn (33) found that 24% of 45 achlorhydric patients with subacute combined degeneration demonstrated at autopsy between 1929 and 1932 originally presented with little or no anemia. Since then many case reports have appeared drawing attention to patients with predominantly neurologic dysfunction (7, 17, 34, 42, 43, 46, 49, 54, 87, 91, 98).

Based on our large series of such patients, several points other than the frequent presence of advanced disease seem worthy of emphasis. First, the white count, platelet count, serum LDH and serum bilirubin are all typically normal in such patients, since abnormalities of these tests are usually seen only in Cbl deficiency with moderate or severe anemia (17, 58, 84). Second, most nonanemic patients did have hematologic abnormalities, although often subtle. In some, the MCV was clearly elevated; in others, although normal, the MCV fell to a lower point within the normal range after therapy. Hypersegmented neutrophils (often with macro-ovalocytes) were demonstrable on the blood smears of almost all nonanemic patients, although sometimes in small numbers, so that the abnormalities were frequently missed on routine examination by the clinical laboratories of our hospitals.

Third, as emphasized by others (17, 40, 49, 59, 91), the serum Cbl measurement is an extremely useful test in detecting Cbl deficiency in patients with minimal or borderline hematologic abnormalities. However, although the serum Cbl was almost always low in this series, the degree of depression was often not marked, and serum Cbl concentrations in the range of 100 to 200 pg/ml (75–150 pmol/L) were not unusual even though measured (as in this series) by current methods which are free of the technical difficulties noted in some assay techniques of the 1970s (50). Furthermore, in 2 deficient patients, the serum Cbl level was at the lower end of the normal range. These patients did not differ in any apparent respect from the remainder who had low serum values of the vitamin. Such patients may constitute 5% or more of cases of Cbl deficiency (59), and the clinician must be aware that the syndrome of lack of Cbl, with either predominant neurologic or hematologic abnormalities, may occur in the absence of a depressed serum Cbl concentration. We have presented evidence elsewhere that measurement of serum methylmalonic acid and total homocysteine levels are useful in demonstrating the presence of Cbl deficiency in patients with slightly depressed or low normal serum Cbl concentrations and neurologic abnormalities consistent with deficiency (58). Alternatively, a therapeutic trial with vitamin Cbl and subsequent close clinical follow-up is always worthy of consideration in such patients.

Whether genetic or environmental factors determine the predominant organ system failure in a given patient is unclear. The finding that hispanic patients had both a lower incidence and severity of neurologic disease is consistent with either possibility and could also be disease-related, in view of their high incidence of tropical sprue. The concept that Cbl deficiency may predominantly affect either the nervous system or the bone marrow with little or no involvement of the other organ is consistent with other observations. In monkeys, fruit bats and pigs, deficiency of Cbl or its inactivation causes a severe neurologic disorder without any associated hematologic abnormalities (4, 32, 66, 82, 92). In humans, inactivation of Cbl by acute continuous exposure to nitrous oxide for many hours results in cytopenias and megaloblastic bone marrow changes without apparent damage to the nervous system (6), while prolonged low-grade exposure for many months or years causes severe neurologic impairment without anemia (55). The reasons for these differences in organ susceptibility are obscure. Nor is it understood why men predominate among patients who develop optic nerve dysfunction due to Cbl deficiency; 39 (80%) of 49 reported patients with this complication, including our case, were males (1, 9, 12, 26, 29, 30, 37, 42, 48, 49, 53, 56, 69, 70).

A striking feature of our patients was the high degree of responsiveness to Cbl therapy. In nearly half, there was complete resolution of all signs and symptoms, and most of the remainder showed more than 50% improvement over their pretreatment status. Although other observers have emphasized the responsiveness of neurologic symptoms and signs to treatment (10, 44, 75, 88), the extent of reversibility noted in our patients was even greater than in previous series. This is most likely a reflection of the generally shorter duration of symptoms and lesser degree of neurologic damage in our patients. Indeed, the strongest predictors of posttreatment residual damage were pretreatment severity and duration of symptoms (Figs. 3 and 4). Previous workers have noted similar findings, especially with regard to the importance of symptom duration (10, 18, 27, 43, 44, 67, 75, 88, 96).

We would also emphasize that although the effects of various factors such as symptom duration and hematocrit on neurologic impairment were found to be highly significant statistically, tremen-

dous interpatient variability in the severity of neurologic dysfunction before and after treatment was evident (Fig. 3), most of which remains poorly understood.

Many observers have noted that with adequate treatment with vitamin B_{12} (or highly potent liver extract preparations), the neurologic damage never worsens with therapy (10, 17, 18, 43, 44). Our observations are in full agreement with this generalization, as it applies to the long-term effects of treatment. An interesting finding, however, was the apparent exacerbation of the neurologic disorders of 4 patients during the first days or weeks after cyanocobalamin injections were given. These patients were carefully evaluated and closely followed before and after treatment and the transient exacerbations appeared to be real, although we have no explanation for them. None of them received folic acid. Single cases with similar exacerbations have previously been reported (18, 39, 42).

Summary

We reviewed 153 episodes of cobalamin deficiency involving the nervous system that occurred in 143 patients seen over a recent 17-year period at 2 New York City hospitals. Pernicious anemia was the most common underlying cause of the deficiency.

Neurologic complaints, most commonly paresthesias or ataxia, were the first symptoms of Cbl deficiency in most episodes. The median duration of symptoms before diagnosis and treatment with vitamin B_{12} was 4 months, although long delays in diagnosis occurred in some patients. Diminished vibratory sensation and proprioception in the lower extremities were the most common objective findings. A wide variety of neurologic symptoms and signs were encountered, however, including ataxia, loss of cutaneous sensation, muscle weakness, diminished or hyperactive reflexes, spasticity, urinary or fecal incontinence, orthostatic hypotension, loss of vision, dementia, psychoses, and disturbances of mood. Multiple neurologic syndromes were often seen in a single patient.

In 42 (27.4%) of the 153 episodes, the hematocrit was normal, and in 31 (23.0%), the mean corpuscular volume was normal. Neutropenia and thrombocytopenia were unusual even in anemic patients. In nonanemic patients in whom diagnosis was delayed, neurologic progression frequently occurred although the hematocrit remained normal. In 27 episodes, the serum cobalamin concentration was only moderately decreased (in the range of 100–200 pg/ml) and in 2 the serum level was normal.

Neurologic impairment, as assessed by a quantitative severity score, was judged to be mild in 99 episodes, moderate in 39 and severe in 15. Severity of neurologic dysfunction before treatment was clearly related to the duration of symptoms prior to diagnosis. In addition, the hematocrit correlated significantly with severity, independent of the longer duration of symptoms in nonanemic patients.

Four patients experienced transient neurologic exacerbations soon after beginning treatment with cyanocobalamin, with subsequent recovery. Follow-up evaluation was adequate to assess the neurologic response to vitamin B_{12} therapy in 121 episodes. All patients responded, and in 57 (47.1%), recovery was complete, with no remaining symptoms or findings on examination. The severity score was reduced by 50% or greater after treatment in 91% of the episodes. Residual long-term moderate or severe neurologic disability was noted following only 7 (6.3%) episodes.

The extent of neurologic involvement after treatment was strongly related to that before therapy as well as to the duration of symptoms. The percent improvement over baseline neurologic status after treatment was inversely related to duration of symptoms and hematocrit. Some evidence of response was always seen during the first 3 months of treatment.

The 143 patients with nervous system disorders were compared with 180 patients with Cbl deficiency seen during the same period without neurologic manifestations. In the group lacking neurologic dysfunction, anemia was more severe even though the duration of symptoms was shorter. Hispanic patients with Cbl deficiency were less likely to develop nervous system damage than whites or blacks.

We conclude that the neurologic disorders due to Cbl deficiency encountered in current clinical practice are generally less severe than in the past and are highly responsive to therapy, although most patients have some residual abnormalities. Early diagnosis and treatment remain important in preventing permanent damage. Patients without anemia or MCV elevations are commonly seen and tend to have more severe nervous system involvement. The reasons for the predominance of neurologic or hematologic dysfunction in individual patient (or ethnic groups) remain uncertain.

References

1. Adams P, Chalmers TM, Foulds WS, Withey JL. Megaloblastic anaemia and vision. Lancet 2: 229–31, 1967.
2. Adams RD, Kubik CS. Subacute degeneration of the brain in pernicious anemia. N Engl J Med 231: 1–9, 1944.
3. Addison T. On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules. London: Samuel Highley, 1855.

4. Agamanolis DP, Chester EM,Victor M, Kark JA, Hines JD, Harris JW. Neuropathology of experimental vitamin B_{12} deficiency in monkeys. Neurology 26: 905–14, 1976.
5. Ahrens RS. Neurologic aspects of primary anemia. Arch Neurol Psychiatr 28: 92–111, 1932.
6. Amess JAL, Burman JF, Rees GM, Nancekievill DG, Mollin DL. Megaloblastic haemopoiesis in patients receiving nitrous oxide. Lancet 2: 339–42, 1978.
7. Arias IM, Apt L, Pollycove M. Absorption of radioactive vitamin B_{12} in nonanemic patients with combined-system disease. N Engl J Med 253: 1005–10, 1955.
8. Baker BM Jr, Bordley J II, Longcope WT. The effect of liver therapy on the neurologic manifestations of pernicious anemia. Am J Med Sci 184: 1–24, 1932.
9. Baldwin JN, Dalessio DJ. Folic acid therapy and spinal-cord degeneration in pernicious anemia. N Engl J Med 264: 1339–42, 1961.
10. Bethell FH, Sturgis CC. The relation of therapy in pernicious anemia to changes in the nervous system. Early and late results in a series of cases observed for periods of not less than ten years, and early results of treatment with folic acid. Blood 3: 57–67, 1948.
11. Bickel H. Funikulare myelitis mit bulbaren and polyneuritschen symptomen. Arch Psych 53: 1106–17, 1914.
12. Bjorkenheim B. Optic neuropathy caused by vitamin B_{12} deficiency in carriers of the fish tapeworm, *Diphyllobothrium latum*. Lancet 1: 688–90, 1966.
13. BMDP Statistical Software 1981. Dixon WJ, ed. Berkeley: University of California Press, 1981.
14. Butler WM, Taylor HG, Diehl LF. Lhermitte's sign in cobalamin (vitamin B_{12}) deficiency. JAMA 245: 1059, 1981.
15. Carmel R. Macrocytosis, mild anemia, and delay in the diagnosis of pernicious anemia. Arch Intern Med 139: 47–50, 1979.
16. Carmel R. Subtle cobalamin malabsorption in a vegan patient: evolution into classic pernicious anemia with anti-intrinsic factor antibody. Arch Intern Med 142: 2206–07, 1982.
17. Chanarin I. The Megaloblastic Anaemias. 2nd ed. Oxford: Blackwell Scientific Publications, 1979.
18. Conley CL, Green TW, Hartmann RC, Krevans JR. Prolonged treatment of pernicious anemia with vitamin B_{12}. Am J Med 13: 284–93, 1952.
19. Conley CL, Krevans JR. Development of neurologic manifestations of pernicious anemia during multivitamin therapy. N Engl J Med 245: 529–31, 1951.
20. Cox EV. The clinical manifestations of vitamin B_{12} deficiency in Addisonian pernicious anaemia. In: Heinrich HC, ed. Vitamin B_{12} und Intrinsic Factor, 1. Europaisches Symposion, Hamburg. Stuttgart: Enke, pp 590–602, 1962.
21. Davidson LSP, Gulland GL. Pernicious anaemia. London: Kimpton, 1930.
22. Davidson SP. Clinical picture of pernicious anaemia prior to introduction of liver therapy in 1926 and in Edinburgh subsequent to 1944. Br Med J 1: 241–48, 1957.
23. Dawson DW, Sawers AH, Sharma RK. Malabsorption of protein bound vitamin B_{12}. Br Med J 288: 675–78, 1984.
24. Doscherholmen A, Swaim WR. Impaired assimilation of egg Co^{57} vitamin B_{12} in patients with hypochlorhydria and achlorhydria and after gastric resection. Gastroenterology 64: 913–19, 1973.
25. Draper NR, Smith H. Applied Regression Analysis. 2nd ed. New York: Wiley, pp. 303–13, 1981.
26. Enoksson P, Norden A. Vitamin B_{12} deficiency affecting the optic nerve. Acta Med Scand 167: 199–208, 1960.
27. Farquharson RF, Graham D. Liver therapy in the treatment of subacute combined degeneration of the cord. Can Med Assoc J 23: 237–44, 1930.
28. Fine EJ, Soria E, Paroski MW, Petryk D, Thomasula L. The neurophysiological profile of vitamin B_{12} deficiency. Muscle & Nerve 13: 158–64, 1990.
29. Freeman AG, Heaton JM. The aetiology of retrobulbar neuritis in Addisonian pernicious anaemia. Lancet 1: 908–11, 1961.
30. Gleeson MH, Graves PS. Complications of dietary deficiency of vitamin B_{12} in young Caucasians. Postgrad Med J 50: 462–64, 1974.
31. Goldhamer SM, Bethell FH, Isaacs R, Sturgis CC. Occurrence and treatment of neurologic changes in pernicious anemia. JAMA 103: 1663–67, 1934.
32. Green R, van Tonder SV, Oettle GJ, Cole G, Metz J. Neurological changes in fruit bats deficient in vitamin B_{12}. Nature 254: 148–50, 1975.
33. Greenfield JG, O'Flynn E. Subacute combined degeneration and pernicious anaemia. Lancet 2: 62–63, 1933.
34. Gross JS, Weintraub NT, Neufeld RR, Libow LS. Pernicious anemia in the demented patient without anemia or macrocytosis. A case for early recognition. J Am Geriatr Soc 34: 612–14, 1986.
35. Hall CA. Vitamin B_{12} deficiency and early rise in mean corpuscular volume. JAMA 245: 1144–46, 1981.
36. Hamilton AS, Nixon CF. Sensory changes in the subacute combined degeneration of pernicious anemia. Arch Neurol Psych 6: 1–31, 1921.
37. Hamilton HE, Ellis PP, Sheets RF. Visual impairment due to optic neuropathy in pernicious anemia: Report of a case and review of the literature. Blood 14: 378–85, 1959.
38. Hector M, Burton JR. What are the psychiatric manifestations of vitamin B_{12} deficiency? J Am Geriatr Soc 36: 1105–12, 1988.
39. Heinle RW, Welch AD. Folic acid in pernicious anemia. Failure to prevent neurologic relapse. JAMA 133: 739–41, 1947.
40. Herbert V. The megaloblastic anemias. New York: Grune & Stratton, 1959.
41. Higginbottom MC, Sweetman L, Nyhan WL. A syndrome of methylmalonic aciduria, homocystinuria, megaloblastic anemia and neurologic abnormalities in a vitamin B_{12}-deficient breast-fed infant of a strict vegetarian. N Engl J Med 299: 317–23, 1978.
42. Holmes JM. Cerebral manifestations of vitamin B_{12} deficiency. Br Med J 2: 1394–98, 1956.
43. Hyland HH, Farquharson RF. Subacute combined degeneration of the spinal cord in pernicious anemia. Arch Neurol Psychiatr 36: 1166–1205, 1936.
44. Hyland HH, Watts GO, Farquharson RF. The course of subacute combined degeneration of the spinal cord. Can Med Assoc J 65: 295–302, 1951.
45. Jadhav M, Webb JKG, Vaishnava S, Baker SJ. Vitamin B_{12} deficiency in Indian infants: A clinical syndrome. Lancet 2: 903–7, 1962.
46. Jewesbury ECO. Subacute combined degeneration of the cord and achlorhydric peripheral neuropathies without anaemia. Lancet 2: 307–12, 1954.
47. Jones SJ, Yu YL, Rudge P, Kriss A, Gilois C, Hirani N, Nijhawan R, Norman P, Will R. Central and peripheral SEP defects in neurologically symptomatic and asymptomatic subjects with low vitamin B_{12} levels. J Neurol Sci 82: 55–65, 1987.
48. Kassirer JP, Kopelman RI. Searching for a pony. Hosp Pract 23: 17–19, 1988.
49. Killander A. Subacute combined degeneration of the spinal cord. The diagnostic value of serum vitamin B_{12} assay. Acta Med Scandinav 160: 75–84, 1958.
50. Kolhouse JF, Kondo H, Allen NC, Podell E, Allen RH. Cobalamin analogues are present in human plasma and can mask cobalamin deficiency because current radioisotope dilution assays are not specific for true cobalamin. N Engl J Med 299: 785–92, 1978.
51. Kosik KS, Mullins TF, Bradley WG, Tempelis LD, Cretella AJ. Coma and axonal degeneration in vitamin B_{12} deficiency. Arch Neurol 37: 590–92, 1980.
52. Krumholz A, Weiss HD, Goldstein PJ, Harris KC. Evoked responses in vitamin B_{12} deficiency. Ann Neurol 9: 407–9, 1980.
53. Lampert F, Harms K, Bidlingmaier F, Kiefhaber P, Meister P. Pernicious anemia with dermatologic and neurologic involvement in a 10-year-old boy. Monatsschrift für Kinderheilkunde 122: 217–20, 1974.
54. Langdon FW. Nervous and mental manifestations of pre-pernicious anemia. JAMA 45: 1635–38, 1905.
55. Layzer RB. Myeloneuropathy after prolonged exposure to nitrous oxide. Lancet 2: 1227–30, 1978.
56. Lerman S, Feldmahn AL. Centrocecal scotomata as the presenting sign in pernicious anemia. Arch Ophthalmol 65: 381–85, 1961.
57. Lichtheim L. Zur Kermtoriss der Perniciosen anaemie. Munch Med Wschr 34: 300–6, 1887.
58. Lindenbaum J, Healton EB, Savage D, Brust JCM, Garrett TJ, Podell ER, Marcell PD, Stabler SP, Allen RH. Frequency of neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 318: 1720–28, 1988.
59. Lindenbaum J, Savage DG, Stabler SP, Allen RH. Diagnosis of cobalamin deficiency. II. Relative sensitivities of serum cobalamin, methylmalonic acid and total homocysteine concentrations. Am J Hematol 34: 99–107, 1990.
60. Lockner D, Reizenstein P, Wennberg P, Widen L. Peripheral nerve function in pernicious anemia before and after treatment. Acta Haematol 41: 257–63, 1969.
61. Mahmud K, Ripley D, Doscherholmen A. Paroxysmal positional vertigo in vitamin B_{12} deficiency. Arch Otolaryngol 92: 278–80, 1970.
62. Mayer RF. Peripheral nerve function in vitamin B_{12} deficiency. Arch Neurol 13: 355–62, 1965.

63. Mayfrank L, Thoden U. Downbeat nystagmus indicates cerebellar or brainstem lesions in vitamin B_{12} deficiency. J Neurol 233: 145–48.
64. McAlpine D. A review of nervous and mental aspects of pernicious anaemia. Lancet 2: 643–47, 1929.
65. McCombe PA, McLeod JG. The peripheral neuropathy of vitamin B_{12} deficiency. J Neurol Sci 66: 117–26, 1984.
66. Metz J, van der Westhuyzen J. The fruit bat as an experimental model of the neuropathy of cobalamin deficiency. Comp Biochem Physiol 88A: 171–77, 1987.
67. Minot GR, Murphy WP. A diet rich in liver in the treatment of pernicious anemia. JAMA 89: 759–68, 1927.
68. Minot GR. Some aspects of the diagnosis of pernicious anemia. Med Clin North Am 18: 935–44, 1935.
69. Olivarius BDF. Opticusatrofi ved anaemia perniciosa. Nordisk Medicin 65: 157–59, 1961.
70. Olivarius BDF, Jensen L. Retrobulbar neuritis and optic atrophy in pernicious anemia. Acta Ophthalmol 39: 190–97, 1961.
71. Pallis CA, Lewis PD. The Neurology of Gastrointestinal Disease. London: Saunders, pp. 30–97, 1974.
72. Pant SH, Ashbury AK, Richardson EP. The myelopathy of pernicious anemia. A neuropathological reappraisal. Acta Neurol Scand 44 (Suppl 35): 1–36, 1968.
73. Pearson HA, Vinson R, Smith RT. Pernicious anemia with neurologic involvement in childhood. J Ped 65: 334–39, 1964.
74. Pezzimenti JF, Lindenbaum J. Megaloblastic anemia associated with erythroid hypoplasia. Am J Med 53: 748–54, 1972.
75. Rundles RW. Prognosis in the neurologic manifestations of pernicious anemia. Blood 1: 209–19, 1946.
76. Russell JSR. The relationship of some forms of combined degenerations of the spinal cord to one another and to anaemia. Lancet 2: 4–14, 1898.
77. Russell JSR, Batten FE, Collier J. Subacute combined degeneration of the spinal cord. Brain 23: 39–110, 1900.
78. Rustgi RN, Bettigole RE. Nonanemic pernicious anemia. NY State J Med 81: 1739–42, 1981.
79. Sandyk R. Paralysis of upward gaze as a presenting symptom of vitamin B_{12} deficiency. Eur Neurol 23: 198–200, 1984.
80. Savage D, Lindenbaum J. Relapses after interruption of cyanocobalamin therapy in patients with pernicious anemia. Am J Med 74: 765–72, 1983.
81. Savage D, Lindenbaum J, Van Ryzin J, Struening E, Garrett TJ: Race, poverty, and survival in multiple myeloma. Cancer 54: 3085–94, 1984.
82. Scott JM, Dinn JJ, Wilson P, Weir DG. Pathogenesis of subacute combined degeneration: A result of methyl group deficiency. Lancet 2: 334–37, 1981.
83. Spray GH. An improved method for the rapid estimation of vitamin B_{12} in serum. Clin Sci 14: 661–67, 1955.
84. Stabler SP, Allen RH, Savage DG, Lindenbaum J. Clinical spectrum and diagnosis of cobalamin deficiency. Blood 76: 871–881, 1990.
85. Stambolian D, Behrens M: Optic neuropathy associated with vitamin B_{12} deficiency. Am J Ophthalmol 83: 465–68, 1977.
86. Steiner I, Kidron D, Soffer D,Wirguin I, Abramsky O. Sensory peripheral neuropathy of vitamin B_{12} deficiency: a primary demyelinating disease? J Neurol 235: 163–64, 1988.
87. Strachan RW, Henderson JG. Psychiatric syndromes due to avitaminosis B_{12} with normal blood and marrow. Q J Med 34: 303–17, 1965.
88. Ungley CC. Subacute combined degeneration of the cord. I. Response to liver extracts. II. Trials with vitamin B_{12}. Brain 72: 382–427, 1949.
89. Ungley CC, Suzman MM. Subacute combined degeneration of the cord: Symptomatology and effects of liver therapy. Brain 52: 271–94, 1929.
90. Victor M. Polyneuropathy due to nutritional deficiency and alcoholism. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral Neuropathy. 2nd ed. Philadelphia: W.B. Saunders, pp 1899–1939, 1984.
91. Victor M, Lear AA. Subacute combined degeneration of the spinal cord. Am J Med 20: 896–911, 1956.
92. Weir DG, Keating S, Molloy A, McPartlin J, Kennedy S, Blanchflower J, Kennedy DG, Rice D, Scott JM. Methylation deficiency causes vitamin B_{12}-associated neuropathy in the pig. J Neurochem 51: 1949–52, 1988.
93. Wighton MC, Manson JI, Speed I, Robertson E, Chapman E. Brain damage in infancy and dietary vitamin B_{12} deficiency. Med J Aust 2: 1–3, 1979.
94. Woltman HW. The nervous symptoms in pernicious anemia: An analysis of one hundred and fifty cases. Am J Med Sci 157: 400–9, 1919.
95. Woltman HW. The mental changes associated with pernicious anemia. Am J Psych 80: 435–49, 1924.
96. Woltman HW, Heck FJ. Treatment of neurologic changes complicating pernicious anemia. Minnesota Med 24: 653–58, 1941.
97. Zegers de Beyl D, Delecluse F, Verbanck P, Borenstein S, Capel P, Brunko E. Somatosensory conduction in vitamin B_{12} deficiency. Electroenceph Clin Neurophysiol 69: 313–18, 1988.
98. Zucker DK, Livingston RL, Nakra R, Clayton PJ. B_{12} deficiency and psychiatric disorders: Case report and literature review. Biological Psychiatr 16:197–205, 1981.