Proc. Natl. Acad. Sci. USA
Vol. 79, pp. 7494–7498, December 1982
Medical Sciences

Response of vitamin B-6 deficiency and the carpal tunnel syndrome to pyridoxine

(neuropathy/nutrition/vitamin supplementation/diet)

JOHN M. ELLIS*, KARL FOLKERS†, MOISE LEVY‡, SATOSHI SHIZUKUISHI†, JAN LEWANDOWSKI§, SATOSHI NISHII†, H. A. SCHUBERT‡, AND RICHARD ULRICH¶

*103 West 20th Street, Mt. Pleasant, Texas 75455; †Institute for Biomedical Research, The University of Texas, Austin, Texas 78712; ‡Temple, Texas 76501; ¶1020 East Idel Street, Tyler, Texas 75701; and §University of Texas Health Center, Tyler, Texas 78701

Contributed by Karl Folkers, April 15, 1982

ABSTRACT **The specific activities and percentage deficiencies of the glutamic oxaloacetic transaminase of erythrocytes (EGOT) were determined for patients with carpal tunnel syndrome (CTS) diagnosed by clinical examination and electrical conduction data; the EGOT data revealed a severe deficiency of vitamin B-6. After double-blind treatment with pyridoxine and placebo, two physicians identified those receiving pyridoxine (clinically improved) and those receiving placebo (did not improve) without error, $P < 0.0078$. Correcting a deficiency of the coenzyme at receptors of existing molecules of the apoenzyme appears to take place within days; correction of the deficiency in the number of molecules of the transaminase takes place over 10–12 weeks. The clinical response, appraised by the diminution of the symptoms of CTS, was correlated only with the restored levels of the transaminase which presumably results from a translational long-term increase in the number of molecules of EGOT by a mechanism activated by correcting a deficiency of pyridoxal 5′-phosphate. Apparent K_m values of EGOT were identical for groups of patients with CTS and others without CTS but with identical specific activities, indicating that CTS is a primary deficiency of vitamin B-6 rather than one of a dependency state. Clinical improvement of the syndrome with pyridoxine therapy may frequently obviate hand surgery.**

Folkers and co-workers (1, 2) initiated a study to detect and quantitate human deficiencies of vitamin B-6 by the determination of the specific activities and percentage deficiencies of the glutamic oxaloacetic transaminase of erythrocytes (EGOT). Ellis *et al.* (3) reported that a deficiency of vitamin B-6 existed in patients who had the carpal tunnel syndrome (CTS). Ellis *et al.* extended the EGOT data to show a severe deficiency of vitamin B-6 in 10 patients (4) and 11 more patients (5). Comprehensive biochemical (6) and clinical studies (7), including cross-over treatment, with pyridoxine and placebo were conducted on the exemplary 22nd patient with CTS. For all patients receiving therapy with pyridoxine, the B-6 deficiency was corrected and the neurological syndrome was alleviated.

Becker and Granger (8) described CTS as a "common clinical entity," often associated with rheumatoid arthritis, obesity, myxedema, diabetes, pregnancy, and other conditions. "Rheumatic" conditions associated with this syndrome have included "tennis elbow," Dupuytren contracture, deQuervain disease, "trigger fingers," bursitis, and periarthritis of the shoulder.

From data on 1,215 patients with CTS at the Mayo Clinic between 1930 and 1960, Yamaguchi *et al.* (9) made the astounding observation that some patients had had the symptoms for up to 40 years. About 85% were more than 40 years old; 459 were surgically treated; 318 had associated systemic disease; 237 had other rheumatic conditions; only 660 appeared to have only CTS. The most common clinical findings were paresthesias, thenar muscle weakness and atrophy (which we now believe may result from many years of a severe deficiency of vitamin B-6), and positive Phalen and Tinel signs.

When the compression of the median nerve in the carpal tunnel exists for many years, there may be a permanent sensory and motor loss. The synovium is involved, and the symptoms appear to result from tenosynovitis. Phalen (10) and Maxwell *et al.* (11) reviewed diseases associated with CTS. Tobin (12) and Sabour and Fadel (13) observed the syndrome in connection with pregnancy and use of the "pill." Morelli and Sala (14) stated "the treatment . . . clearly must be surgical." Dolenc and Trontelj (15) asserted "microsurgery is a method of choice in the treatment of pressure neuropathies." Treatment by local injection or systemic administration of corticosteroids has been used. Surgery has been widely practiced, providing relief (16), often erratically, of limited duration, and no relief for up to 20% of those so treated.

For our 23rd to 29th patients, the EGOT data revealed a severe deficiency of vitamin B-6, and they were treated, in double-blind fashion, with pyridoxine and a placebo. Patients on placebo were treated with pyridoxine on a cross-over basis. The double-blind assessment was successful. The results are described herein.

DESIGN OF THE DOUBLE-BLIND TRIAL AND METHODS

A large population of patients exists in which symptoms of the fingers or hands or both are present. Some have evidence of entrapment of the median nerve; others have symptoms in the region of the ulnar nerve, with or without evidence of entrapment of the median nerve. Some patients may reveal no evidence of a rheumatoid disease, and the expression "idiopathic carpal tunnel syndrome" describes their condition. Seven such patients were chosen for this double-blind trial. Patients were excluded if they had a history of myxedema, amyloidosis, acromegaly, rheumatoid arthritis, cerebral or myocardial infarction, degenerative joint disease of the cervical spine, alcoholism, or other systemic conditions that may be associated with CTS.

Three blood samples were taken on successive days for determination of basal specific activities (SAs) and the percentage deficiencies of EGOT (1, 2). SA was more important for patient selection than was percentage deficiency. Values of SA in the range 0.20 to 0.25 (4–7) guided biochemical selection of patients.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U. S. C. §1734 solely to indicate this fact.

Abbreviations: EGOT, glutamic oxaloacetic acid transaminase of erythrocytes; CTS, carpal tunnel syndrome; SA, specific activity; PIP, proximal interphalangeal.

Clinically, these patients were examined and graded in terms of 14 signs and symptoms (Table 1). The severity of symptoms was indicated by an increasing score of 1 through 5. Stiffness of the proximal interphalangeal (PIP) joints of the index fingers was measured with a goniometer. The strength of pinch between the distal phalanges of the thumbs and index fingers was measured in pounds with a Preston pinch gauge. Pinch levels of 12 and 6 pounds (5.4 and 2.7 kg) for adult males and females, respectively, are considered normal. Nerve electrical conduction studies were made on five patients for diagnosis; E.H. and T.G. were unavailable.

Patients were accepted when they gave informed consent. Tablets of 50 mg of pyridoxine hydrochloride and of a placebo were coded. The physicians did not know how many patients received pyridoxine and how many received placebo nor which patients received pyridoxine or placebo.

After *ca.* 12 weeks of double-blind treatment, and before the biochemical data were revealed, at least two physicians declared whether a patient was on pyridoxine or placebo.

EXPERIMENTAL PROTOCOL

E.H. Black male; age, 58 yr; height, 185 cm; weight, 75 kg. For the past 3 yr this patient had experienced increasing bilateral nocturnal numbness and tingling in his hands. Morning stiffness and a severe incoordination of finger movements prevented use of a razor or buttoning of clothes. Pain on abduction and rotation of arms at the shoulders was severe. Examination revealed stiffness of fingers at interphalangeal joints and hypoesthesia of the tips of the right thumb and index and long fingers. There was no angular stomatitis of the mouth or unusual color of the tongue and mucous membranes. Control and subsequent relevant data are shown in Table 2. On day 11, E.H. was entered in the double-blind trial. On day 79, declaration of "placebo" was made, which was correct. The EGOT data showed no change, in agreement with this declaration. On day 83, treatment with pyridoxine hydrochloride, 100 mg daily, was started for the cross-over study. During days 111–161, EGOT data showed no deficiency of vitamin B-6. During days 328–330, EGOT data showed mild deficiency, due to failure of the patient to take the pyridoxine daily.

T.G. Caucasian male; age, 47 yr; height, 185 cm; weight, 86 kg. For 6 months this patient had had pain in his hands, elbows, arms, and shoulders and nocturnal numbness and tingling in the hands causing loss of sleep. The interphalangeal joints of the fingers were painful to pressure and flexion. There was morning swelling and stiffness of fingers, with weakness of handgrip. Examination revealed a positive Phalen sign of the CTS bilaterally, slight swelling of soft tissues of the fingers, incomplete flexion of fingers at interphalangeal joints, and bilateral weakness of pinch between the thumb and index finger (Table 2). On day 13, T.G. was entered in the double-blind trial. The subsequent data are shown in Table 1. On day 89, a declaration of "pyridoxine" was made, which was correct. T.G. had been taking pyridoxine (100 mg daily) regularly. The higher basal SA values compared to E.H. (0.9 vs. 0.7) resulted from the higher temperature (25°C vs. 20°C) used in the determination of activity. The EGOT data for days 283–284 show that T.G. was taking pyridoxine irregularly prior to these tests.

A.C. Latin American male; age, 61 yr; height, 170 cm; weight, 61 kg. The patient had had wide distribution of pain and tenderness in his arms, leg, hands, and feet, morning stiffness in his fingers, and incoordination of finger movements for 2 yr.

Table 1. Scores of the symptoms and signs in patients during control, double-blind trial, and cross-over trial

Pat.	Age, yr	Duration of disease, yr	Regimen* Rx	Regimen* Day	Scores for symptoms and signs† A	B	C	D	E	F	G	H	I	J	K	L	M	N	Total score‡
E.H.	58	3	Con.	1	5	5	5	5	5	3	5	5	5	5	5	3	2	3	61
			Pl	73	5	5	5	5	5	3	5	5	5	5	5	3	2	3	61
			B-6	77	0	1	0	2	2	0	0	0	0	0	2	1	0	0	8
T.G.	47	0.5	Con.	1	5	5	4	4	4	4	0	3	5	3	0	5	0	1	43
			B-6	76	0	1	1	0	1	1	0	0	0	0	0	1	0	0	5
W.R.	45	8	Con.	1	2	5	5	5	4	4	5	5	5	5	5	3	4	5	62
			Pl	54	2	5	5	5	4	4	5	5	5	5	5	3	4	5	62
			B-6	83	0	3	3	3	1	0	0	1	0	1	2	1	2	0	17
A.C.	61	2	Con.	1	5	5	5	5	5	3	2	5	5	4	4	3	0	0	51
			B-6	100	1	2	1	2	1	0	0	1	0	0	1	0	0	0	9
F.C.	66	1.5	Con.	1	5	5	5	4	4	5	4	0	0	3	4	3	0	0	42
			Pl	84	5	5	5	4	4	5	4	0	0	3	4	3	0	0	42
			B-6	84	1	1	2	2	2	1	1	0	0	1	2	2	0	0	15
A.L.	77	10	Con.	1	3	5	4	3	2	2	5	4	4	3	4	2	5	0	46
			Pl	80	3	5	4	3	2	2	5	4	4	3	4	2	5	0	46
			B-6	76	1	1	1	1	1	0	4	1	0	1	4	1	1	0	17
B.M.	43	0.25	Con.	1	5	1	5	4	3	3	5	2	5	0	1	0	4	1	39
			B-6	84	0	0	2	0	0	0	1	0	0	0	0	0	1	0	4

* Con., control; Pl, placebo; B-6, vitamin B-6; when two entries follow Con., the second is the cross-over trial.

† Scores are based on increasing severity from 1 to 5. Symptoms and signs: A, paresthesia of hands; B, morning stiffness of fingers; C, impaired finger flexion, PIP joints; D, weakness in hands; E, pain in hands; F, fluctuating edema in hands; G, impaired sensation in fingers; H, impaired coordination in finger function; I, tenderness over carpal tunnel with Tinel or Phalen signs; J, dropping of objects; K, pain in shoulder; L, pain in elbow; M, painful abduction/medial rotation of thumb at metacarpophalangeal joint; N, "sleep paralysis."

‡ Mean values (±SD): control, 49 ± 9; placebo, 53 ± 10; vitamin B-6, 11 ± 6 (for difference from control, $P < 0.001$).

Table 2. Summary of biochemical and physical measurements

	EGOT				Physical					
					Goniometer, degrees				Pinch, lb	
Patient	Period, days	*n*	SA	Deficiency, %	Period, days	*n*	Right	Left	Right	Left
E.H.	1–12	6	0.18 ± 0.03	36 ± 10	1–12	6	91 ± 10	97 ± 2	4.2 ± 1.3	6.3 ± 1.8
	78–80	3	0.20 ± 0.03	38 ± 7	78–80	6	91 ± 1	90 ± 1§	6.3 ± 1.7*	7.5 ± 1.1
					99–114	5	95 ± 1	94 ± 4	7.9 ± 1.5‡	8.4 ± 1.1*
	111–113	3	0.70 ± 0.06§	−5 ± 3§						
					123–160	6	105 ± 5	106 ± 2§	10.0 ± 1.6§	10.4 ± 1.4†
	159–161	3	0.70 ± 0.05§	1 ± 1§						
	328–330	3	0.53 ± 0.01§	8 ± 2‡						
T.G.	1–4	4	0.23 ± 0.03	18 ± 7	1–13	5	89 ± 2	90 ± 1	8.5 ± 1.5	8.0 ± 1.7
					41–89	9	96 ± 6*	97 ± 3§	15.8 ± 2.6§	15.8 ± 3.0§
	87–89	3	0.94 ± 0.02§	−2 ± 2‡						
	283–284	3	0.58 ± 0.01	12 ± 5 (20°C)	283–288	4	104 ± 2§	101 ± 3§	19.8 ± 1.3§	18.4 ± 2.5§
A.C.	1–8	5	0.30 ± 0.02	14 ± 1	7–9	3	90 ± 2	84 ± 2	1.5 ± 0.5	1.0 ± 0.5
	83–118	4	0.95 ± 0.14§	4 ± 8						
					118	3	90 ± 2	93 ± 1‡	4.0 ± 1.0†	5.0 ± 1.0‡
W.R.	1–41	3	0.36 ± 0.05	27 ± 3	0–42	4	30 ± 2	37 ± 6	4.0 ± 1.2	4.9 ± 2.4
	74–136	3	0.27 ± 0.07	20 ± 2*						
					82–135	3	31 ± 16	37 ± 1	5.7 ± 0.8	6.8 ± 1.6
					184–403	6	42 ± 8†	48 ± 10	8.2 ± 3.4*	7.9 ± 2.3
	403–438	6	0.47 ± 0.08	10 ± 7‡						
					436–439	3	91 ± 5§	91 ± 4§	18.5 ± 3.0§	15.5 ± 1.8§
F.C.	1–42	3	0.42 ± 0.03	10 ± 8	1–42	3	87 ± 1	64 ± 1	11.2 ± 1.0	11.5 ± 0.5
	74–134	2	0.33 ± 0.02*	5 ± 14						
					92–136	2	87 ± 1	64 ± 1	11.5 ± 0.1	11.6 ± 0.1
	287–288	2	0.83 ± 0.14§	2 ± 2	287–288	2	87 ± 1	64 ± 1	11.5 ± 0.7	11.8 ± 0.4
A.L.	1–8	2	0.46 ± 0.01	18 ± 4	1–25	2	87 ± 1	88 ± 1	10.6 ± 0.1	11.1 ± 0.1
	40–100	2	0.36 ± 0.06	17 ± 2	39–100	2	97 ± 1‡	99 ± 1‡	10.3 ± 1.8	11.3 ± 0.4
	143–144	2	0.98 ± 0.02§	−4 ± 1§	143–144	2	97 ± 1‡	99 ± 1‡	10.3 ± 1.8	11.3 ± 0.4
	388	1	0.66 (20°C)	−2	388	1	102	103	12.0	12.0
B.M.	1–3	3	0.25 ± 0.01	37 ± 4	1–13	5	87 ± 3	91 ± 5	8.7 ± 1.6	18.3 ± 2.5
	56–125	15	0.45 ± 0.04	9 ± 11	51–122	10	97 ± 3§	98 ± 3‡	18.8 ± 4.2§	23.2 ± 1.7§

Results are shown as mean (± SD). *n*, number of measurements. *P* values for difference from control (first entry line for each patient) are indicated as follows: no symbol, not significant; * $P < 0.05$; † $P < 0.02$; ‡ $P < 0.01$; § $P < 0.001$.

His sleep frequently was interrupted by severe nocturnal paresthesia in his hands and pain in his shoulders. Examination revealed exquisite tenderness to pressure on all fingers and advanced bilateral stiffness of his index fingers at the interphalangeal joints. There was marked tenderness to pressure and palpation of soft tissues at the volar aspects of both wrists at the carpal tunnels and a marked weakness of pinch and handgrip (Table 2). On day 13, he was entered in the double-blind trial. On day 118, a declaration of "pyridoxine" was made, which was correct. A.C. had taken pyridoxine (100 mg daily) regularly; the EGOT values (determined at 25°C) were normal.

W.R. Causasian male; age, 45 yr; height, 178 cm; weight, 77 kg. For 8 yr this patient had experienced severe nocturnal paresthesia in both hands and pain in his shoulders and all extremities. These conditions persisted unabated, along with incoordination and weakness of handgrip which had been prodromal for an insidious, progressive, and crippling stiffness of the fingers, particularly the index. Examination revealed remarkable loss of flexion of his fingers with associated bilateral reduction of pinch by the thumb and index finger. There was hypoesthesia of the tips of all fingers. The Phalen sign of CTS was positive bilaterally. Various laboratory studies gave negative results. Biopsy of the triceps muscle for electron microscopy revealed "ultrastructural characteristics not diagnostic for a specific condition." The control EGOT data were determined at 25°C (Table 2). On day 43, W.R. was entered in the double-blind trial. On day 136, a declaration of "placebo" was made, which was correct. Then, W.R. was started on pyridoxine treatment, 100 mg daily. After 9–10 months of pyridoxine therapy, the EGOT data suggested irregular compliance.

F.C. Caucasian male; age, 66 yr; height, 180 cm; weight, 77 kg. For 18 months this patient had experienced increasing bilateral stiffness of fingers and hands, numbness and tingling along the ulnar nerves, and elbow pain. Shoulder pain accompanied abduction and rotation of the arms at the shoulders, and it radiated toward the base of the neck posteriorly. Examination revealed stiffness and impaired finger flexion at the interphalangeal joints and slight swelling of the soft tissues of the fingers and hands. The control EGOT data were determined at 25°C (Table 2). On day 42, he was entered in the double-blind trial.

On day 136, a declaration of "placebo" was made, which was correct. This patient then began therapy with pyridoxine, 100 mg daily, on day 136. The EGOT data for days 287–288 showed correction of the vitamin B-6 deficiency and compliance with the pyridoxine regimen.

A.L. Caucasian male; age, 77 yr; height, 183 cm; weight, 98 kg. The patient had been experiencing, for 10 yr, increasing stiffness and pain in his hands and fingers and moderate paresthesia upon awakening or when the hands were at rest. Abduction and rotation of arms caused pain at the shoulders. Flexion and rotation of thumbs caused pain deep in the thenar muscles bilaterally and pain in the metacarpophalangeal joints of the thumbs. Examination revealed severe stiffness of the hands, impaired flexion of the fingers, moderate enlargement of interphalangeal joints of the fingers, and failure of abduction and flexion of the thumbs at the metacarpophalangeal joints. After control data were obtained (Table 2), A.L. was entered in the double-blind trial on day 25. On day 99, a declaration of "placebo" was made, which was correct. EGOT assays were run at 25°C. Then, A.L. was started on pyridoxine therapy, 100 mg daily. The EGOT data during days 143–388 showed correction of the vitamin B-6 deficiency and an excellent compliance.

B.M. Black male; age, 43 yr; height, 178 cm; weight, 102 kg. B.M. had had severe nocturnal numbness and tingling paresthesia in the right hand for 3 months with increasing stiffness and swelling in the fingers (right hand), weakness of grip, marked hypoesthesia of the thumb and fingers, and incomplete flexion of all fingers. The thumbs could not be rotated so that tips pressed the palms at the base of the little fingers. Control data are shown in Table 2. On day 20, B.M. was entered into the double blind-trial. On day 129, a declaration of "pyridoxine" was made, which was correct. The dosage of pyridoxine, beginning on day 20, was 150 mg daily. The EGOT data during days 56–128 show the disappearance of a deficiency of pyridoxal phosphate but the SA was low, indicating irregular use of the pyridoxine.

RESULTS

Seven patients who had the symptoms and signs of idiopathic CTS were selected clinically. They had some or all of the 14 symptoms and signs in Table 1, and they ranged from 43 to 77 yr in age. The duration of symptoms was from 3 months to 10 yr. Paresthesia (A) and stiffness of fingers (B) were particularly prominent.

The mean basal SA of EGOT (assays at 20°C) was 0.30 ± 0.07 and the mean deficiency of enzymatic activity was 22% ± 9%. These values agree with the mean basal SA values (0.27 ± 0.06 and 27 ± 0.13) and the mean deficiencies (26.8% ± 3.4% and 21.4% ± 10.0%) for previous groups of 10 and 11 patients, respectively (4, 5).

All seven patients had a significant deficiency of vitamin B-6. All seven had the typical CTS. The control EGOT data were made available to the physicians for patient selection. At the end of *ca.* 12 weeks, the physicians redetermined the clinical status of the patients and made a declaration as to whether a patient was being treated with pyridoxine or with a placebo. The commitments were correct. For this binomial distribution, $P < 0.0078$. Decoding revealed that four of the patients had received placebo and three had received pyridoxine. The four patients who had initially received the placebo were then treated with pyridoxine. The results of the open cross-over were as follows.

E.H., who had had symptoms for 3 yr, showed a complete biochemical response during days 111–113, a response ($P < 0.01$) of the pinch of the right hand during days 99–114, and a complete response ($P < 0.001$–0.01) by goniometer and pinch for both hands during days 123–160.

W.R., who had had symptoms for 8 yr, complied with the regimen only partially, as revealed by an incomplete biochemical response during days 403–438, but during this period there was a complete response ($P < 0.001$) by both goniometer and pinch for both hands. During days 48–267, only the right hand improved ($P < 0.02$–0.05).

F.C., who had had symptoms for 18 months, showed a complete biochemical response during days 187–288, but there were no differences between the measurements by the goniometer and for pinch for either hand in comparison with the control data. However, the score of symptoms had decreased from 42 to 15 (Table 1).

A.L., who had symptoms for 10 yr, showed compliance by the EGOT data during days 143–144, and the measurements by goniometer showed significant improvement ($P < 0.01$) for both hands. The pinch values were unchanged even up to day 388.

For their declarations, the physicians were primarily guided by the objective measurements with the goniometer and the Preston pinch gauge. The scores in Table 1 include the subjective opinions of the patients on the presence and severity or the absence of such signs and symptoms and are less reliable than the objective measurements. The mean value of the total scores is 49 ± 9 ($n = 7$). The mean value of the total scores of those patients who received a placebo during the double-blind trial is 53 ± 10 ($n = 4$), a difference not statistically significant. The mean value of the scores for the three patients taking pyridoxine during the double-blind trial and for the four patients taking pyridoxine during the cross-over is 11 ± 6 ($n = 7$). The difference between the mean values of the scores for control and the combined trials with pyridoxine is significant ($P < 0.001$).

The electromyographic data on five patients, obtained by two electrophysiologists, are in Table 3. These data are in agreement with the clinical diagnosis of CTS for two patients, A.L. and M.B. Phalen (10) cautioned "One must remember, however, the carpal tunnel syndrome may be present with no evidence of electromyographic abnormalities." Melvin *et al.* (19) reported on the diagnostic specificity of motor and sensory conduction variables in the CTS and stated that "distal sensory latent periods were the most sensitive electrodiagnostic

Table 3. Control electrical conduction data

	Patient				
Measurement*	A.L.	W.R.	F.C.	A.C.	B.M.
MMDL, sec					
Right	9.0	3.3	3.4	3.8	4.4
Left	4.1	3.7	3.9	3.2	3.7
MSDL, sec					
Right	—	3.2	3.2	3.2	—
Left	4.2	3.2	3.2	2.9	3.2
RSDL, sec					
Right	—	3.5	3.8	—	
Left	—	3.4	3.5	—	
MM, m/sec					
Right	41.0	55.3	54.3	58.1	
Left	47.5	55.2	52.3	58.6	
UM, m/sec					
Right	60.7	55.8	50.6	62.0	
Left	51.4	57.6	55.4	58.5	

* MMDL, median motor distal latency (normal, <5 msec); MSDL, median sensory distal latency (normal, <4 msec); RSDL, radial sensory distal latency (normal, <4 msec); MM, median motor (normal, >45 m/sec); UM, ulnar motor (normal, >47 m/sec).

measurements for ascertaining the presence of carpal tunnel syndrome."

DISCUSSION

Biochemical. The EGOT data on the patients in the double-blind and cross-over trials agree with the data on the previous 22 patients (4–7). There has never been an exception to the association of this entrapment syndrome with a deficiency of vitamin B-6. A low SA (<0.20–0.25) for EGOT is diagnostic of the severity of vitamin B-6 deficiency and of CTS. SA is more diagnostic than is the percentage deficiency although both values have significance. The increase in SA from <0.20–0.25 to *ca.* 0.7 over *ca.* 10–12 weeks is unambiguously associated with clinical improvement. The differential enzymic analysis of EGOT is so precise that it may also show compliance or negligence on the part of a patient in taking pyridoxine.

The increase in SA and the decrease in the symptoms were seldom decisive in *ca.* 6 weeks but were decisive in 10–12 weeks. This difference in time shows that the increase in the number of molecules of the transaminase is a long-term change and is presumably based upon mechanisms of translational increase in the number of molecules of EGOT. These mechanisms are activated by therapeutically correcting the deficiency of pyridoxal 5′-phosphate.

Merely correcting the deficiency of the coenzyme (pyridoxal 5′-phosphate) at the vacant receptors of the existing molecules of the apoenzyme appears to take place within days, but this correction has not been found to be associated with clinical improvement. The correction of a deficiency in the number of molecules of the transaminase, over 10–12 weeks, is associated with clinical improvement. Individuals may live for years with limited deficiencies of vitamin B-6, but when the deficiency becomes sufficiently severe, paresthesia, stiffness, pain, etc. may be felt by the individual and reveal the presence of CTS to a physician. As the symptoms become unbearable, patients accept recommended orthopedic surgery of the hands.

There are two categories of vitamin deficiencies. A primary deficiency is caused by an inadequate level of the vitamin in the diet. A dependency state is caused by a biochemical abnormality due to a genetic defect. Homocystinuria (20) is said to be a dependency state of vitamin B-6. Dependency states are controlled by higher doses than those required for a primary deficiency. Our study (6, 7) of patient 22, which showed that his CTS and vitamin B-6 deficiency were significantly improved, but not completely, by 2 mg of pyridoxine daily, the recommended daily allowance, indicated that the CTS is a primary deficiency. Shizukuishi *et al.* (22) compared the apparent K_m values in the EGOT assays for a group of eight patients with a severe CTS and for a group of eight students; the mean SA values for the groups were identical; no significant difference was found for the apparent K_ms.

Solomon and Hillman (23) studied the regulation of the metabolism of vitamin B-6 in human erythrocytes. The full induction of enzyme activity reflected the gradual replacement of circulating erythrocytes by newly formed cells with higher enzyme levels.

Clinical. The hand symptoms in patients with CTS are prominent because: (*i*) the physical use of hands accentuates symptoms; (*ii*) hands are important to human functions; and (*iii*) the symptoms are visible.

It is remarkable that patients having had such symptoms for years can show significant improvement on therapy with pyridoxine. W.R., who was 45 yr old, had had severe symptoms for 8 yr, but treatment with pyridoxine improved ($P < 0.001$) his hand performance by objective measurements. When, in the double-blind and cross-over trials, W.R. and A.L. had been treated with pyridoxine for 12 weeks, the strength and coordination of the thenar muscles improved so that the tip of the thumb could be lifted and rotated medially to press the palm at the base of the little finger. A.L. had experienced increasing stiffness in hands for 10 yr, but the improvement after therapy with pyridoxine was unambiguous and pronounced. Before treatment with pyridoxine, E.H. and A.C. could not hold a razor for shaving. Weakness and incoordination of finger movements prevented buttoning and unbuttoning of clothing or normal use of a knife and fork. Frequently, the thumb and index and long fingers could not be opposed for writing with a pen or pencil.

If muscle atrophy in the hands were not prominent, as for E.H., T.G., A.C., W.R., and B.M., the strength of pinch after therapy with pyridoxine was about tripled. The PIP joints of fingers before therapy with pyridoxine were invariably painful on forced flexion. Hypoesthesia of the median nerve distribution was common. F.C. had severe hypoesthesia of the ulnar distribution; during the cross-over trial on pyridoxine, he appeared to improve subjectively but objective measurements were negative. The electrical conduction studies indicated severe changes in ulnar nerves.

Appreciation is expressed to the Robert A. Welch Foundation for their support of this research.

1. Kishi, H., Kishi, T., Williams, R. H. & Folkers, K. (1975) *Res. Commun. Chem. Pathol. Pharmacol.* **12**, 557–569.
2. Kishi, H. & Folkers, K. (1976) *J. Nutr. Sci. Vitaminol.* **22**, 225–234.
3. Ellis, J. M., Kishi, T., Azuma, J. & Folkers, K. (1976) *IRCS Med. Sci.* **4**, 193.
4. Ellis, J. M., Kishi, T., Azuma, J. & Folkers, K. (1976) *Res. Commun. Chem. Pathol. Pharmacol.* **13**, 743–757.
5. Ellis, J. M., Azuma, J., Watanabe, T., Folkers, K., Lowell, J. R., Hurst, G. A., Ahn, C. H., Shuford, E. H., Jr., & Ulrich, R. F. (1977) *Res. Commun. Chem. Pathol. Pharmacol.* **17**, 165–177.
6. Folkers, K., Ellis, J., Watanabe, T., Saji, S. & Kaji, M. (1976) *Proc. Natl. Acad. Sci. USA* **75**, 3410–3412.
7. Ellis, J., Folkers, K., Watanabe, T., Kaji, M., Saji, S., Caldwell, J. W., Temple, C. A. & Wood, F. S. (1979) *Am. J. Clin. Nutr.* **32**, 2040–2046.
8. Becker, G. E. & Granger, C. V. (1972) *Conn. Med.* **36**, 206–215.
9. Yamaguchi, D. M., Lipscomb, P. R. & Soule, E. H. (1965) *Minn. Med.* **48**, 22–23.
10. Phalen, G. S. (1972) *Clin. Orthop. Relat. Res.* **83**, 29–40.
11. Maxwell, J. A., Clough, C. A., Reckling, F. W. & Kelly, C. R. (1973) *J. Kans. Med. Soc.* **74**, 190–193.
12. Tobin, S. M. (1967) *Am. J. Obstet. Gynecol.* **97**, 496–498.
13. Sabour, D. M. & Fadel, H. E. (1970) *Am. J. Obstet. Gynecol.* **107**, 1265–1267.
14. Morelli, E. & Sala, E. (1978) *Muscle Nerve* **1**, 509–510.
15. Dolenc, V. & Trontelj, V. J. (1978) *Muscle Nerve* **1**, 510–511.
16. Garland, H., Langworth, E. P., Taverner, D. & Clark, J. (1964) *Lancet*, 1129–1130.
17. Azuma, J., Kishi, T., Williams, R. H. & Folkers, K. (1976) *Res. Commun. Chem. Pathol. Pharmacol.* **14**, 343–378.
18. Ellis, J., Azuma, J., Watanabe, T., Folkers, K., Lowell, J., Hurst, G. A., Ahn, C. H., Shuford, E. H., Jr., & Ulrich, R. F. (1977) *Res. Commun. Chem. Pathol. Pharmacol.* **17**, 165–178.
19. Melvin, J. L., Johnson, E. W. & Duran, R. (1968) *Arch. Phys. Med.* **49**, 502.
20. Barber, G. W. & Speath, G. L. (1967) *Lancet* **i**, 337.
21. Rosenberg, L. E., Lilljeqvist, A.-Ch. & Hsia, Y. E. (1968) *Science* **162**, 805–807.
22. Shizukuishi, S., Nishii, S., Ellis, J. & Folkers, K. (1980) *Biochem. Biophys. Res. Commun.* **95**, 1126–1130.
23. Solomon, L. R. & Hillman, R. S. (1979) *Am. J. Clin. Nutr.* **32**, 1824–1831.