

showed a greatly reduced but still elevated protein content. The Pandy and Ross-Jones tests were only slightly positive. The cell count was normal.

We have read no reports of spinal fluid examination for heterophile agglutinins in infectious mononucleosis. Serial dilutions beginning with 1:4 concentrations revealed no such agglutinins in our case. Blood and spinal fluid cultures remained sterile.

The chart shows the rapid fall in blood heterophile agglutinins during recovery to an almost insignificant degree just prior to the patient's discharge from the hospital.

Agglutination tests of the patient's serum against *Listerella monocytogenes* were negative. Throat cultures made on the day of admission showed only alpha streptococci. The urine was constantly normal.

#### COMMENT

This case is almost unique among the cases of infectious mononucleosis which showed involvement of the central nervous system, in that there were no signs and almost no cerebrospinal abnormalities (except for 9 cells in one count) pointing to meningeal involvement. Especially striking was the cell protein dissociation in favor of the protein, which speaks against involvement of the meninges. In the majority of the cases reported there was meningeal involvement with a considerable increase in cell content, at least during one phase of the disease, while the protein showed hardly any increase.

Only one case has been reported<sup>6</sup> in which the symptoms (paresis of the left inferior rectus muscle of the eye, highly exaggerated knee jerks, a questionable plantar reflex and entirely normal cerebrospinal fluid) pointed to a purely encephalitic process.

In our case the cerebral involvement was much more extensive. The clinical picture was that of an acute ataxia with outspoken involvement of the cerebellar system.

This is not the place to discuss at any length the question of the localization of the acute ataxia, whether it is produced by the toxi-infectious process of the coordination system (Davidenkoff) or by a circumscribed focus in the hypothalamic region (Margulis). It seems, however, that the pathologic process, whether it is a real "encephalitis," i. e. an inflammatory process, or a "toxic encephalopathy," extends over a rather large area of the brain. In our opinion there cannot be any doubt about the involvement of the cerebellar system. On the other hand there were a number of signs (expressionless face, lack of motor impulse, peculiar kind of somnolence, diffuse perspiration) which make one think of a pathologic process in the gray matter surrounding the third ventricle, the hypothalamic region, so that the possibility of a lethargic encephalitis was considered for a short time.

It is interesting that the lymphadenopathy and palpable spleen, the usual and characteristic signs of infectious mononucleosis, did not appear until the alarming cerebral symptoms were almost gone. We must admit that the diagnosis would have probably been missed except for the laboratory report of positive blood heterophile agglutination, and the case would have been relegated to that wholly unsatisfactory waste-basket category of "aseptic" or "toxic encephalitis." We feel, therefore, that in the presence of acute cerebral symptoms of unknown etiology the heterophile agglutination test should be made.

Several workers have reported isolating *Listerella* in infectious mononucleosis. Schmidt and Nyfeldt were able to obtain cultures of the organism from the spinal

fluid in 4 of 5 cases of the disease, in only 1 of which were cerebral symptoms present. In our case three attempts at obtaining cultures of the organism were unsuccessful.

The spinal fluid in our case was negative for heterophile agglutinins.

#### SUMMARY

1. In a case of infectious mononucleosis the only early symptoms simulated those of encephalitis.
2. The heterophile agglutination determination is of value in cases in which acute cerebral symptoms of unknown etiology are present.

### TREATMENT OF PARALYSIS AGITANS WITH VITAMIN B<sub>6</sub> (PYRIDOXINE HYDROCHLORIDE)

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Pyridoxine hydrochloride, or the vitamin B<sub>6</sub> fraction of the vitamin B complex, was first discovered by György<sup>1</sup> in 1935 and was first prepared synthetically in 1939 by Harris and Folkers.<sup>2</sup> It consists of 2-methyl-3 hydroxy-4, 5-dihydroxy-methyl-pyridine. It was first used clinically by Antopol and Schotland<sup>3</sup> with beneficial results in 6 patients with pseudohypertrophic muscular dystrophy. These authors expressed the belief that the drug, through its pyridine structure, was involved in the enzyme system concerned in muscular metabolism. Jolliffe,<sup>4</sup> believing muscular metabolism to be involved in paralysis agitans, tested the drug in this condition. He reported its use in 15 patients with paralysis agitans, all of whom had severe involvement. All patients received 50 to 100 mg. of pyridoxine hydrochloride intravenously. Four of the 15 patients showed definite objective improvement. The best results occurred in the idiopathic or arteriosclerotic type of the disease.

Since a considerable proportion of the patients visiting the Outpatient Clinic of the University of Minnesota Hospitals suffer from paralysis agitans, the staff naturally was most anxious to obtain and try any new therapeutic agent that might offer possible aid to these unfortunate persons. A group of 15 patients suffering from paralysis agitans were, therefore, selected for intravenous therapy with pyridoxine hydrochloride.

The type of patient, the amount of treatment and the results of the therapy are shown in the accompanying table. Nine obtained only two weeks of treatment at daily intervals; 6 of these received only 50 mg. of pyridoxine hydrochloride; 2 received 50 mg. for one week and 100 mg. during the second week, while 1 received 100 mg. for two weeks, supplemented by 54 grains (3.5 Gm.) of brewers' yeast. Three patients showed definite objective improvement (in cases 1, 10 and 12). Of these, 1 had idiopathic parkinsonism and 1 had postencephalitic involvement, while the condition

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The vitamin B<sub>6</sub> used in these studies was hexabion hydrochloride, furnished by Merck & Co., Inc.

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3. Antopol, William, and Schotland, C. E.: The Use of Vitamin B<sub>6</sub> in Pseudohypertrophic Muscular Dystrophy, *J. A. M. A.* **114**: 1058 (March 23) 1940.

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of the third patient, although she offered no history of any previous illness, suggested postencephalitis, since the age at onset was 39.

Six patients received daily intravenous treatment with pyridoxine hydrochloride for three or more weeks. This treatment was supplemented with the whole vitamin B complex in the form of 54 grains daily of brewers' yeast. In 5 of these patients the illness was idiopathic, while in 1 it was postencephalitic. Three patients, all of whom had idiopathic parkinsonism, showed definite objective improvement. Neither the age of the patient nor the duration of symptoms seemed to have any effect on the treatment. Good results were obtained in persons whose illness had been present for as long as fifteen years, while often no improvement occurred in some whose illness was fairly recent. The most favorable results appeared in the idiopathic type of the disease. This is in agreement with the results reported by Jolliffe.<sup>4</sup> The nature of the improvement varied from patient to patient. In some it consisted of a drastic reduction in the severity of the tremor; in others the tremor was only slightly affected while the rigidity improved, allowing the patient more freedom in movement. All the patients benefiting from the drug reported a definite subjective improvement, consisting of a decreased fatigability, better sleeping and increased appetite. One patient had gross choreiform movements rather than a parkinsonian syndrome. Since the involvement probably was arteriosclerotic and also extrapyramidal, it seemed of interest to attempt therapy with pyridoxine hydrochloride. Her improvement was most striking, suggesting the possibility that this type of therapy may be of benefit in other types of extrapyramidal involvement. A brief report of those patients responding to this therapy will aid in evaluating the results.

#### REPORT OF CASES

CASE 1.—E. C., a woman aged 67, first noticed a definite tremor and rigidity of her hands in 1935. The involvement gradually spread to almost all the muscles of her body, including the muscles of the trunk, producing at first a shuffling gait and mild postural changes and finally an almost complete invalidism, the patient ultimately being confined to a wheel chair. She became weak and for years was able to sit up only for short periods. She had difficulty in sitting up in a car during even a short ride. She had been treated with scopolamine hydrobromide but showed no response to this type of therapy.

Neurologic examination revealed a moderate tremor and extreme rigidity of all limbs. There was complete loss of facial expression and an absence of blinking. The patient was unable to walk or stand without aid. The deep reflexes were reduced but equal. The rest of the examination gave negative results.

She was given daily intravenous injections of 50 mg. of pyridoxine hydrochloride for one week and 100 mg. for the second week. Improvement became apparent after three weeks. Expression rapidly returned to the patient's face. Her tremor became reduced and at times would be completely absent, even under emotional excitement. The rigidity also diminished, so that the patient was soon able to sit up for long periods of time and was also able to walk about the house unassisted. Long rides and even the entertaining of company no longer fatigued the patient.

She has continued to maintain her improvement in spite of two severe gastrointestinal upsets.

CASE 6.—L. S., a man aged 47, a jeweler, in 1935 first became aware of an impairment in speech associated with a generalized bodily weakness. He described this weakness as a general slowing down of all his activities, primarily because of difficulty in using his muscles. Impairment in speech consisted in difficulty in getting words out and a general running together of his words as they came out. The muscular rigidity became more severe, retarding all his voluntary movements. Because

of this difficulty he soon became unable to carry on his work as a jeweler. His writing became impaired and his facies expressionless. Continuation of his illness finally resulted in the patient's complete inability to do any type of work.

The neurologic examination revealed a dysarthria and dysphonia associated with a masklike facies and a generalized muscular rigidity. Tremor was not present. Laboratory tests all gave negative results. The patient was placed on varying doses of scopolamine hydrobromide, which he continued to take for a period of months with no improvement. He was then given two courses of pyridoxine hydrochloride intravenously, separated by a two week interval. The first consisted of 50 mg. of the drug daily for a period of two weeks, the second of 50 mg. daily for one week followed by 100 mg. doses the second week. He was simultaneously given 54 grains of brewers' yeast daily. After the second week of his first course of treatment, the patient began to notice definite improvement in his speech. His voice lost part of its monotonous character and there was a definite ability to phonate better. After three weeks of treatment, his facial expressions became livelier. Improvement continued. The muscular rigidity became so reduced that the patient was able to play ball and perform much of the work which he had been forced to discontinue prior to his treatment. At present he is taking 20 mg. weekly of pyridoxine hydrochloride given orally and has maintained his striking improvement.

CASE 7.—A. G., a man aged 54, first noticed a slight stiffness in his left arm and leg in 1927. This rigidity gradually increased, producing a definite difficulty in gait. Three months after the onset of rigidity a coarse tremor appeared in the left hand and soon extended to the entire extremity but has always remained more or less localized to the left upper extremity. One year later there appeared an involvement of the facial muscles and a slight disturbance in speech. There was no history of any severe infectious process antedating the onset of his present illness.

Neurologic examination revealed a slight masking of the facies and a moderate sialorrhea. There was rigidity involving all extremities, being most noticeable on the left side, with a tremor limited to the left upper extremity. The patient had difficulty in performing both fine and gross movements with his hands. Scopolamine hydrobromide, which he had taken for a number of years, had produced but little improvement. During the past eight or nine years of his illness his condition had been more or less stationary.

He was given daily intravenous injections of pyridoxine hydrochloride, receiving a total of four weeks of treatment with 100 mg. of the medication. At the same time he was given 54 grains of brewers' yeast daily by mouth. After the completion of his treatment, the patient noticed a definite decrease in the tremor of his left upper extremity. His rigidity became reduced, and his impairment in speech completely disappeared. Whereas before the patient was able to walk for only short distances without becoming tired, he could now walk with ease for many blocks. He was given 40 mg. of pyridoxine hydrochloride by mouth weekly and in three months showed no recurrence of the involvement.

CASE 10.—C. S., a woman aged 54, first noticed a tightness of her legs in 1925. One year later there developed a mild tremor of her right hand associated with definite rigidity. This involvement remained localized to the lower limbs until 1938, at which time it spread rapidly to the other extremities. The progress of the illness had been rapid during the past few years, resulting in a slow and shuffling gait and a severe and annoying tremor in her arms. She had continued to walk and travel about unassisted, although she had refused to go out in company because of her condition. More recently a moderate sialorrhea and some scanning of her speech developed. The patient gave no history suggesting any previous involvement of the central nervous system, although her age at onset certainly was suggestive of a postencephalitic involvement.

Examination revealed the characteristic parkinsonian syndrome. The facies was expressionless, and blinking was infrequent. The impairment in speech was noticeable. There was considerable rigidity of all extremities, associated with a rapid,

shuffling gait. A severe tremor was present in the upper limbs and there were beginning contractures of the hands.

She was given a single course of daily intravenous injections of 50 mg. of pyridoxine hydrochloride the first week and 100 mg. the second week. Along with this medication she received 54 grains of brewers' yeast by mouth. After this

was a general slowing up of all her activities, and her gait became shuffling. She found it impossible to do her housework or to carry out her regular activities. At the time of her examination she presented a masklike facies, a staring gaze and a severe tremor and rigidity of all the extremities. She had a definite shuffling gait, walking with small steps and

*Summary of Drug Therapy*

Case No.	Patient	Age	Sex	Type of Paralysis Agitans	Duration of Disease, Years	Severity of Disease	Result of Treatment	Duration of Treatment, Weeks	Type of Medication	Daily Dosage
A. Pyridoxine Hydrochloride Given Intravenously										
1	E. C.	67	♀	Idiopathic	5	Severe	Definitely improved	2	Pyridoxine hydrochloride	50 mg. 1 week 100 mg. 1 week
2	G. F.	65	♂	Idiopathic	2	Moderate	Unimproved	2	Pyridoxine hydrochloride	50 mg.
3	C. M. J.	65	♂	Idiopathic	8	Severe	Unimproved	2	Pyridoxine hydrochloride	50 mg.
4	V. G.	59	♂	Idiopathic	5	Moderate	Unimproved	2	Pyridoxine hydrochloride	50 mg.
5	L. B.	59	♀	Idiopathic	15	Severe	Unimproved	3	Pyridoxine hydrochloride Brewers' yeast	100 mg. 54 grains
6	L. S.	47	♂	Idiopathic	5	Moderate	Definitely improved	4	Pyridoxine hydrochloride Brewers' yeast	50 mg. 3 weeks 100 mg. 1 week 54 grains
7	A. G.	54	♂	Idiopathic	13	Moderate	Moderately improved	4	Pyridoxine hydrochloride Brewers' yeast	100 mg. 54 grains
8	F. Z.	63	♂	Idiopathic	11	Severe	Unimproved	4	Pyridoxine hydrochloride Brewers' yeast	50 mg. 3 weeks 100 mg. 1 week 54 grains
9	I. M.	71	♀	Senile chorea	4	Severe	Definitely improved	3	Pyridoxine hydrochloride Brewers' yeast	50 mg. 1 week 100 mg. 2 weeks 54 grains
10	C. S.	54	♀	?	15	Moderate	Moderately improved	2	Pyridoxine hydrochloride Brewers' yeast	50 mg. 1 week 100 mg. 1 week 54 grains
11	M. F.	58	♀	?	16	Moderate	Unimproved	2	Pyridoxine hydrochloride Brewers' yeast	100 mg. 54 grains
12	G. F.	39	♂	Postencephalitic	4	Moderate	Moderately improved	2	Pyridoxine hydrochloride	50 mg.
13	B. H.	38	♂	Postencephalitic	5	Moderate	Unimproved	2	Pyridoxine hydrochloride	50 mg.
14	G. A.	49	♂	Postencephalitic	18	Severe	Unimproved	3	Pyridoxine hydrochloride Brewers' yeast	50 mg. 1 week 100 mg. 2 weeks 54 grains
15	L. B.	35	♀	Syphilitic	4	Severe	Unimproved	2	Pyridoxine hydrochloride Brewers' yeast	50 mg. 54 grains
B. Pyridine Hydrochloride Given Orally										
16	A. C.	69	♂	Idiopathic	3	Severe	Definite subjective improvement; mild objective improvement	3	Pyridoxine hydrochloride Brewers' yeast	50 mg. 54 grains
17	J. C.	60	♂	Idiopathic	2½	Moderate	Subjective improvement only	3	Pyridoxine hydrochloride	50 mg.
18	J. V.	62	♂	Idiopathic	10	Severe	Unimproved	3	Pyridoxine hydrochloride Brewers' yeast	50 mg. 54 grains
19	A. J.	69	♂	Idiopathic	3	Moderate	Unimproved	3	Pyridoxine hydrochloride Brewers' yeast	50 mg. 54 grains

course of treatment she was given 40 mg. of pyridoxine hydrochloride by mouth weekly.

Improvement began a few weeks after her treatment. The tremor immediately subsided almost to the vanishing point. Her rigidity improved so that she was able to get around much better. Her improvement has been maintained on the oral medication.

CASE 12.—G. F., a woman aged 39, first noticed her illness in 1936, at which time she suffered a mild tremor of the upper extremities. About six months after the onset of the tremor there appeared a definite rigidity of the upper extremities, a noticeable disturbance in speech and severe sialorrhea. There

finding difficulty in raising her extremities. She had been taking scopolamine hydrobromide, amphetamine sulfate and various other types of medication over a period of years, with little alleviation of her symptoms.

She was given daily intravenous injections of 50 mg. of pyridoxine hydrochloride, receiving treatment for two weeks. At the time of the completion of her treatment she showed no definite objective improvement. She was followed for a period of two months. Six weeks after the completion of treatment she began to improve. Her rigidity decreased to the extent that she was able to do her own housework and move about much better. The sialorrhea decreased remarkably, and her

tremor became almost imperceptible. She still has slight difficulty in speech, although this has also improved.

CASE 9.—I. M., a housewife aged 71, had been afflicted for the past twelve years with gross, bizarre, purposeless, involuntary movements which began first in the arms and later spread to the rest of her musculature. For the past three years this involvement had totally incapacitated the patient. Walking had been almost impossible, and she had been unable to care for or feed herself. The patient's mother had been similarly afflicted but not to the degree to which the patient was involved. The patient has one brother, aged 67, who has noted similar mild twitchings during the past few years. The other five siblings are unaffected. She has three daughters who are at present unaffected. The physical examination, aside from the normal evidences of senescence, revealed no abnormalities. The neurologic examination revealed continuous involuntary, irregular movements involving the upper portion of the patient's trunk, arms and head. These choreiform movements also involved, but to a much less extent, the lower extremities, so that walking was difficult and her gait slightly bizarre. Laboratory studies all gave negative results. Fluoroscopic examination of the chest and a 6 foot roentgenogram of the heart gave negative results. The diagnosis in this case was senile chorea.

The patient was given ½ teaspoon (2 cc.) of a concentrated yeast (Anheuser-Busch) twice a day and pyridoxine hydrochloride intravenously daily in 50 mg. doses. The pyridoxine hydrochloride was increased to 100 mg. after the second week. These medications were discontinued after three weeks, and the patient was given 40 mg. of pyridoxine hydrochloride by mouth weekly. After the first few injections of the drug her condition showed improvement, which continued during the treatment. After three weeks the patient was walking unassisted and with ease, and her gait showed no observable abnormality. She was now able to write her own name. She could feed herself, but only with considerable difficulty. The choreiform movements were greatly reduced, and the patient could now sit quietly in a chair, whereas previously she had presented rather a bizarre picture. Subjectively the patient felt stronger. This manifested itself in an improved appetite and more restful sleeping.

#### COMMENT

Fifteen patients suffering from paralysis agitans were treated intravenously with pyridoxine hydrochloride, supplemented in most cases by the oral administration of brewers' yeast. The patients received 50 to 100 mg. of the intravenous medication at daily intervals for from two to four weeks. Nine patients had idiopathic or arteriosclerotic parkinsonism, and of these 4 were improved. One of these patients had senile chorea rather than true parkinsonism. This patient showed a most striking improvement, suggesting the possibility that therapy with pyridoxine hydrochloride may be of benefit in other types of extrapyramidal involvement. Of the remaining 6 patients, 2 showed improvement. In the latter group 3 had postencephalitic paralysis agitans and 1 the syphilitic form. In the remaining 2 patients the etiologic factors producing paralysis agitans were undetermined.

Four patients suffering from arteriosclerotic or idiopathic paralysis were treated orally with 50 mg. of pyridoxine hydrochloride daily for three weeks supplemented by 54 grains of brewers' yeast. Two of these patients insisted that improvement had occurred but in only 1 was there any objective benefit in the form of an observable decrease in the tremor and rigidity.

The small number of patients and the inadequate dosage do not allow any definite conclusions; however, the results with the oral medication are suggestive and have encouraged me to undertake further investigations with this method of administering pyridoxine hydrochloride, or vitamin B<sub>6</sub>.

## THE CEREBROSPINAL FLUID IN DELIRIUM TREMENS

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Drainage of the cerebrospinal fluid by means of spinal puncture as a therapeutic measure in delirium tremens was introduced by Steinebach<sup>1</sup> in 1915. In that same year Hoppe<sup>2</sup> introduced this procedure in the United States; since then the treatment has become highly popular. Although it is now generally assumed that an increase in intracranial pressure occurs in delirium tremens and that drainage of the cerebrospinal fluid will relieve that tension, few data in support of this hypothesis can be found in the literature.

In a series of 18 cases, Steinebach found 14 patients (75 per cent) to have an increased pressure of the cerebrospinal fluid. However, this conclusion was based on his interpretation of any pressure above 150 mm. of water as abnormally increased, which criterion is not in accord with that generally employed in this country, in which the upper limit of normal is usually considered to be 180 mm. of water.<sup>3</sup> All the pressures observed in his cases were not recorded by Steinebach and hence cannot be reevaluated. With no substantiating data, Hoppe also concluded that the pressure of the cerebrospinal fluid is "always increased in delirium tremens."<sup>2</sup> Similar conclusions without supporting data were made by Goldsmith<sup>4</sup> from studies on patients with alcoholic deliriums and other acute alcoholic psychoses, in which he claimed that in 48 per cent of his cases the cerebrospinal fluid "came out under considerable pressure." Likewise, Levinson<sup>5</sup> stated that in delirium tremens the "cerebrospinal fluid pressure is greatly increased, running as a rule from 150 to 300 mm. of water," but gave no data to support his conclusion. In a similar manner other authors,<sup>6</sup> in discussing the treatment of delirium tremens, have expressed the belief that an increase in intracranial pressure occurs, even though ample demonstration of such a phenomenon is still lacking.

The only study on delirium tremens which cast some doubt on the aforementioned general conclusion was that of Thomas, Semrad and Schwab.<sup>7</sup> These authors reported 40 cases of delirium tremens in 20 of which spinal puncture and drainage were done. In only 12 of their cases were readings of pressure reliable, but in all 12 the pressures of the cerebrospinal fluid were normal. In view of the small number of cases involved, these authors could not definitely negate the concept so generally accepted by others.

In view of the preceding reports, a review of the results obtained from examinations of the cerebrospinal fluid of patients with delirium tremens who were treated

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