PROGNOSIS IN THE NEUROLOGIC MANIFESTATIONS OF PERNICIOUS ANEMIA

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FOLLOWING the introduction of liver therapy for pernicious anemia in 1926, the curability of the neurologic manifestations of this disease became a matter of intense interest and large series of patients with acute, chronic and residual neurologic defects were treated with lightly cooked liver and oral liver extracts. It was found that while this treatment restored satisfactory blood levels and reversed the atrophic and inflammatory lingual changes the neurologic benefit was far less conspicuous. Some investigators concluded that liver therapy resulted in no neurologic improvement beyond that due to the correction of the anemia and betterment of the patient's general condition, and that progressive disability might occur in some cases in spite of treatment. The most optimistic observers were of the opinion that adequate treatment arrested the progression of the disease and that some degree of functional improvement might occur when treatment was begun reasonably early.

In recent years the general outlook regarding the neurologic prognosis in pernicious anemia has been altered by several factors. For one, the diagnosis is now made earlier in the illness and the neurologic disease is less advanced when treatment is begun. Concentrated liver extracts for parenteral use, although refined and tested only to give the maximal hematologic response, have abolished the uncertainties of oral types of therapy, and optimal treatment is now possible in all cases. The demonstration of unequivocal degenerative changes in peripheral nerves removed by biopsy has finally substantiated the many suggestions that peripheral neuropathy rather than spinal cord degeneration is actually responsible for many of the typical neurologic signs and symptoms. The great recuperative power of the peripheral nerves indicates, of course, a far greater potential curability. Finally, the isolation of new vitamins in the B group has permitted experiments bearing on the problems of diagnosis and therapy. While the common crystalline vitamin B components have failed to be of direct value in the treatment of any of the clinical manifestations of pernicious anemia, each new one isolated has to be evaluated as a possible substitute or adjunct to standard therapy.

The present report is based on a study of 20 recent patients with the neurologic manifestations of pernicious anemia whom we were able to follow with frequently repeated examinations from the start of treatment of pernicious anemia in relapse until maximum neurologic recovery had occurred. Somewhat less than one half of all our new patients were judged to have significant neurologic disease. Those chosen for study appeared to be typical of the large number of patients with this
disease treated and followed at the Simpson Memorial Institute over a period of years. It will be apparent from the discussion to follow that the neurologic manifestations of pernicious anemia should be carefully evaluated both for diagnosis and for prognosis and not merely receive the banal designation postero-lateral sclerosis or "cord" degeneration. Four types of disturbed neurologic function actually occur in pernicious anemia: (1) cerebral, (2) olfactory, (3) peripheral nerve and posterior columns of the spinal cord, and (4) lateral columns of the spinal cord. The incidence of the different types of neurologic disturbance in the group of patients studied is given in Table 1.

1. Cerebral Symptoms. The cerebral symptoms of pernicious anemia are those of the so-called organic brain syndrome, loss of memory, diminished intellectual capacity, confusion, etc. Psychoses with delusions and hallucinations may occur but the symptoms often suggest senility, except perhaps for an unduly rapid onset. The appearance of these symptoms in combination with other manifestations of pernicious anemia and their response to treatment are illustrated by the following 2 case histories.

S. D., a 61 year old telegraph linesman, had been healthy and worked regularly until 4 months before he was seen, when pronounced loss of memory, confusion, and slow difficult speech became apparent. A few weeks later numbness and tingling of his feet and legs as high as the knees and of his hands developed. His gait became unsteady and he was forced to quit work. His general condition became progressively worse and finally he could walk only with the support of others. Physical examination showed a cooperative but confused male, well developed and well nourished. His tongue was not coated but was normal in color and showed only slight flattening of the papillae at the lingual margins. He was unable to walk except by holding on to the furniture. In the Romberg position standing with the heels together and eyes closed he could not stand without falling. The tendon reflexes were normally symmetrically active except for the ankle jerks which were absent. The vibratory sense was diminished at the pelvis, absent at the knees and below. Motion and position sensibilities were greatly impaired in the lower legs. The plantar response was normally extensor.

He was first seen by a neurologist who insisted that the diagnosis was senility and then by an internist whose major diagnosis was generalized arteriosclerosis. He was referred for a blood examination which showed the RBC to be 3.3 million, WBC 8100, hemoglobin 13.1 Gm. per 100 cc., hematocrit 38 per cent, and the mean cell volume 115 cu. microns. The appearance of the stained cells and the differential white cell count were not definitely abnormal. A presumptive diagnosis of pernicious anemia was made and he was started on intramuscular injections of purified liver extract. In one month's time the RBC had risen to 4.4 million, the hemoglobin to 14.5 Gm. and the macrocytosis had disappeared. The diagnosis of pernicious anemia was considered as established. After 7 weeks of treatment the patient believed that slight neurologic improvement had occurred but the neurologic examination showed little change.

He was examined again at the end of 5 months of treatment when he appeared definitely more alert and no longer confused. His family had noted the improvement in his mental status, also, and thought that he was again completely normal. He was able to walk steadily and with rapid progression without support, and in the Romberg position he could stand with only moderate swaying. The tendon reflexes
were normal. The perception of vibration had returned to normal at the pelvis, but was diminished at the knees and absent at the ankles. Motion and position senses in the lower legs were not demonstrably impaired. The Babinski signs were still inconstantly present. One year after the start of treatment he was able to return to work as a telegraph linesman.

L. M., a 54 year old minister, had enjoyed good health until about one year previously when he began to faint occasionally in the pulpit while preaching and people began to note that his sermons were rambling and less coherent. His memory deteriorated and on several occasions he awakened his wife in the middle of the night to be reassured that he had attended meetings and performed marriage ceremonies that he had promised. He became absent-minded, ignored traffic lights, and was given several police summons for speeding. His family physician advised him to obtain a number of diagnostic studies at a local hospital and later several psychiatric interviews but these led to no recommendations for treatment. Two to 3 months after the onset of the mental symptoms numbness and tingling appeared in his extremities and in a few more weeks his gait became staggering and somewhat slapping. Word circulated in the community that he was suffering from an incurable and progressive disease, presumably tabes dorsalis, and the moral virtue of his first wife was questioned. It became impossible for him to officiate at some of the church services such as communion without stumbling and falling and his bishop advised him to take several weeks' vacation. The rest was of no benefit and he was then given a permanent retirement with pension. His disability progressed until one week before his hospital admission he became entirely unable to walk. He was very confused and sometimes suspicious and antagonistic. On the day before admission to the hospital urinary retention developed. It was later learned that he had had the abrupt onset of complete sexual impotence early in his illness.

Examination on admission showed that he was well developed and well nourished. He was cooperative but appeared markedly depressed and emotionally labile. He could converse with good articulation and vocabulary although he was moderately disoriented, often confused and incoherent. There was no lingual abnormality. His bladder was palpable midway to the umbilicus. On neurologic examination he was unable to stand without holding on to stationary objects. He could move his legs only uncertainly and with visual guiding. The tendon reflexes were absent at the knees and ankles. The cutaneous sensibilities were blunted over both feet. The vibratory sense was diminished at the wrists, absent at the pelvis and below. Motion and position senses were absent in the lower extremities and on heel to shin testing there was a wild ataxia. There was no ankle clonus. The plantar responses were extensor.

The blood examination showed the red cell count to be 3.9 million, hemoglobin 15.7 Gm. per 100 cc., WBC 3,050, hematocrit 46 per cent, and the average cell volume 118 cu. microns. The morphology of the red cells in the stained films and the differential white cell count were not abnormal. There was no free hydrochloric acid in the gastric contents after the subcutaneous injection of histamine. Both the blood and spinal fluid gave negative serologic tests for syphilis.

For days while diagnostic studies were being completed he was given daily intramuscular injections of a mixture of crystalline vitamin B components containing 50 mg. of thiamine chloride, 10 mg. riboflavin, 5 mg. pyridoxine, 50 mg. calcium pantothenate, and 250 mg. nicotinamide. His mental symptoms and neurologic status remained unchanged. He was then started on injections of purified liver extract, 15 units daily, which after discharge home was reduced to 30 units per week. He soon became stronger and after 3 weeks of treatment he was able to walk about the ward holding on to furniture. He returned home and in 2 months' time was able to take a daily walk of 2 miles using a cane.

He was examined again at the end of 5 months' treatment. A tendency toward depression remained but his intellectual interests had returned and he was spending much of his time reading and composing sermons. He was able to walk with rapid progression without conspicuous unsteadiness. He was able to stand in the Romberg position with only slight swaying. The patellar reflexes had returned but the achilles reflexes were still absent. There was no impairment of the cutaneous sensibilities. The heel to knee test was well performed. The vibratory sense was absent at the pelvis and below and the plantar
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responses were inconstantly extensor. There were no urinary complaints and a cystometric examination was entirely normal except for a slightly delayed sense of fill and a somewhat low intravesical pressure.

One year after the beginning of treatment he and his wife believed that his intellectual ability and interests had completely returned to normal. He had not resumed work apparently because of residual doubts concerning the nature of his illness in the minds of his parishioners. Examination showed that his gait was still slightly unsteady and there was some swaying in the Romberg position. Both the patellar and achilles reflexes had become moderately hyperactive. There was no ankle clonus. The vibratory sense was still absent at the pelvis and below, and the plantar responses were still inconstantly extensor.

2. Olfactory Symptoms. A second type of neurologic disturbance occurring in patients with pernicious anemia involves the olfactory sense. While occasionally a nearly complete anosmia develops, the commonest symptom is perversion or loss of "taste" for food, especially for protein foods such as meat and eggs. This alteration occurs independently of atrophic and inflammatory changes of the lingual mucosa. A typical case history follows.

J. D. R., a 55 year old physician, had noted for some 6 months anorexia, undue fatigue, and showers of tingling in his extremities. He was accustomed to having for lunch a chicken salad sandwich at a hotel noted for the excellence of its cuisine. The sandwiches began to taste putrid to him and he sent a number back to the kitchen before he became aware that other people continued to eat them with enjoyment. Soon antiseptics and other chemicals in his office lost their characteristic odors and often smelled like coffee. In a few more weeks numbness, tingling, and cold feelings were continually present in his hands and feet. After some speculative diagnoses had been offered a red blood cell count of 3.8 million with a macrocytosis of 106 cu. microns, and gastric achlorhydria following the injection of histamine were discovered. The appearance of his tongue was not definitely abnormal. The only objective neurologic abnormality concerned the vibratory sense which was diminished at the knees. After one month of intramuscular liver therapy the blood values were normal, his appetite was excellent, his olfactory symptoms had disappeared and his vibratory sense was no longer impaired.

3. Peripheral Nerve and Posterior Column Disease. The commonest and in most cases the earliest type of neurologic disorder in patients with pernicious anemia we now attribute to involvement first of the peripheral nerves and secondarily of the posterior columns of the spinal cord. The symptoms and signs often mimic exactly those of neuritic diseases of different etiology and include muscle weakness with tender and later atrophic muscles, and paresthesias such as numbness, tingling, "cold" feelings, etc., with impairment of the cutaneous sensibilities distally in the extremities. A characteristic finding of the greatest value in differentiating the neurologic abnormalities of pernicious anemia from those of other diseases is the early and severe impairment of the sensibilities of vibration, motion and position. These sensibilities are mediated by the fiber components of the peripheral nerves whose central processes constitute the posterior columns of the spinal cord. The selective involvement of these neurons has been widely interpreted as indicating a primary posterior column degeneration but this idea has never been supported with convincing pathologic studies of both peripheral nerves and spinal cord. There is obviously no clinical means by which impairment of the vibratory, motion and position senses can be distinguished as occurring either peripherally or in the posterior columns of the spinal cord, since but one neuron is involved, except perhaps by the study of the prognosis in different degrees of disease after effective treatment has been instituted.
After neuritic symptoms have appeared distally in the upper extremities there
is little tendency for extension above the wrists and forearms. In the lower ex-
tremities, however, the disturbance ascends sometimes acutely to the level of the
mid-abdomen, or rarely to the level of the mid-thorax, and may simulate a trans-
verse or segmental lesion of the spinal cord. Coincident with this progression dis-
turbed gastro-intestinal or genito-urinary function and in about half of the cases
evidence of disease of the lateral columns of the spinal cord develop.

4. Lateral Column Disease. Involvement of the lateral columns of the spinal cord
in patients with pernicious anemia represents the final stage in the progression of
the neurologic disease and rarely, if ever, appears without adequate warning by
the less serious peripheral nerve symptoms beforehand. Typical clinical evidence
of simple lateral column disease includes the complaints of spastic movements,
stiffness and cramping of the muscles, and the finding of exaggerated tendon
reflexes, clonus and extensor plantar reflexes. The accompanying peripheral nerve
disease in pernicious anemia, however, often modifies this picture to produce a
flaccid paralysis with loss of tendon reflexes in spite of signs of lateral column
involvement. During the course of treatment as peripheral nerve func-
tion is restored the tendon reflexes reappear and may even become exaggerated
with clonus while the abnormal plantar responses persist. The interpretation of
this sequence as representing progression of the neurologic disorder is in error.

5. Intestinal and Bladder Disturbances. A wide variety of gastro-intestinal symp-
toms are encountered in patients with pernicious anemia and among these is a
group that appears to be related to neurologic dysfunction. To be excluded are such
common chronic complaints as vague indigestion, gaseous indigestion, a tendency
toward frequent soft stools, etc., which persist without change in uncomplicated
cases during times of spontaneous or therapeutic remission. Again when the hemo-
globin level falls below about 5 Gm. per 100 cc. most patients develop anorexia
with vomiting. They become able to eat again when the anemia is alleviated by
blood transfusion. Gastric retention has been demonstrated by roentgen study in
such cases. Many patients with no more than a moderately severe anemia develop
during relapse of their disease a profound distaste for food, lack of appetite, a post-
prandial feeling of distressing fullness, etc., which disappears 2 to 4 days after
the beginning of treatment before other notable response to treatment occurs.
The nature of this functional change is obscure.

The gastro-intestinal symptoms which appear to be of neurologic origin occur
caracteristically in patients with the more severe degrees of neuritic disorder,
especially in those with neurogenic bladder paralysis. The earliest and most
persistent symptom is severe constipation often requiring the continual use of
enemas or massive catharsis. Subsequently post-prandial abdominal distention,
cramps, borborygmi and, in long untreated cases, diarrhea with sphincter weak-
ness develop. In these patient roentgen study has revealed grossly disturbed small
intestinal function with variable caliber, altered speed of transit, and loss of normal
mucosal pattern. The symptoms do not subside until after several weeks or months
of treatment have been given and neurologic improvement has resulted. With the
improvement in the gastro-intestinal symptoms, although an increased tendency
toward constipation may persist indefinitely, there is also a return to normal in the roentgen appearance of the intestinal tract.

Disturbed genito-urinary function is a well known late result of neurologic disease in patients with pernicious anemia but the details of the functional deficit as related to the general neurologic condition as well as the eventual prognosis have received very little study. The earliest symptom to appear in male patients is usually impotence. Hesitancy, weakness of the urinary stream, and finally urinary retention, dribbling, or overflow incontinence develop later. Most present-day patients do not allow incontinence or obstructive urinary symptoms to persist for more than a short time before seeking adequate treatment. Neurologic examination in these patients invariably shows cutaneous sensory impairment in the lower legs and diminished or absent vibratory sense to the level of the iliac crests. Evidence of lateral column disease may or may not be present. Cystometric examination usually discloses the presence of an atonic bladder paralysis with impaired sense of bladder filling, very low intravesical pressure, increased bladder capacity and variable amounts of residual urine. Mechanical obstructive lesions must be ruled out before a neurogenic etiology can be certain. In some patients with disease of the lateral columns of the spinal cord uninhibited contractions may be recorded on the cystometric curve and the bladder capacity, tone and functional behavior found to be more variable. Too few patients of this type have been carefully evaluated and followed for an accurate prognosis to be possible under all circumstances. Most observers agree that bladder neck and sphincter symptoms may disappear with treatment of the pernicious anemia. Three of our recent patients, one of them a woman, with obstructive urinary symptoms and atonic bladder paralysis of fairly short duration regained normal bladder function as regards both symptoms and cystometric findings after a few weeks or months of liver therapy. The prognosis when the paralysis is of longer duration or when there is severe lateral column disease is undoubtedly less favorable. Urologic measures designed to avoid mechanical damage to the detrusor muscle, urinary tract infection, and bladder neck obstruction are of prime importance during the period of recovery.

Therapy. Uncertainties regarding the possible role of primary or conditioned vitamin B deficiencies in the etiology of the neurologic manifestations of pernicious anemia have often led to the recommendation that crude liver extracts and sometimes vitamin supplements be used in treatment. Recent assays of the vitamin content of various liver extracts have shown, however, that the less refined products are not actually richer proportionately in known vitamin B components and that the absolute amounts present in any case are now of little therapeutic importance. It has been found furthermore that the purified vitamin B fractions have no curative effect on the lingual changes of pernicious anemia and that, with the exception of folic acid, they do not possess antianemic properties in this or in the related macrocytic anemias. Castle and his collaborators conducted experiments in which purified casein, normal human gastric juice, and a mixture of 11 of the isolated members of the vitamin B group were fed simultaneously to patients with pernicious anemia in relapse. No hematologic response was observed.
To investigate the effects of the parenteral administration of some of the crystalline vitamin B substances particularly on the neurologic manifestations of pernicious anemia, 5 suitable patients were given a mixture containing 10-60 mg. of thiamine chloride, 10 mg. of riboflavin, 5 mg. of pyridoxine, 50 mg. of calcium pantothenate, and 250 mg. of nicotinamide, intramuscularly every day over periods of 7 to 10 days. One patient was given 450 mg. of nicotinamide daily by mouth in addition and another patient was given a yeast concentrate containing folic acid during a separate trial period. In no case was there any observable hematologic, lingual, or neurologic improvement. After vitamin B therapy was discontinued a definite response was obtained within a similar period of time with purified liver extract, which contains negligible amounts of the same vitamins. The administration of the vitamin B products before the liver did not appear to accelerate or modify this response in any manner. The observations in one of these cases were as follows.

F. B., a 44 year old printer, had been entirely well until one year previously when he began to note numbness and tingling in his fingers. The paresthesias extended and for 6 to 8 months had been felt in his hands, lower extremities and trunk as high as his waist. For 4 to 5 months all types of food had tasted the same and he acquired a dislike for meat. At times his tongue was sore and noticeably red. He became severely constipated and his appetite vanished. Some hesitancy on urination and complete impotency developed. Over a period of 3 months he took several hundred capsules containing a vitamin B mixture but he steadily became worse. Two months before his hospital admission his gait became staggering and for 2 to 3 weeks he had been unable to walk at all without being supported.

Physical examination showed a well developed and fairly well nourished white male. There was a faintly yellowish cast to his skin. His tongue was pinkish-lemon in color and was entirely devoid of papillae. When standing up he reeled about and could not stand or walk without support on both sides. The cutaneous senses were blunted over the hands and below the knees. There was dependent rubor of the feet which vanished quickly with elevation. The vibratory sense was diminished at the pelvis and nearly absent at the knees and ankles. The heel to shin test was very poorly performed and the motion and position senses were moderately impaired. The tendon reflexes in the upper extremities were normally active but those at the ankles and knees were exaggerated. Sustained ankle clonus and Babinski signs were present bilaterally.

Examination of the peripheral blood showed the red blood cell count to be 2.2 million, WBC 2800, hemoglobin 7.9 Gm. per 100 cc., hematocrit 28 per cent, and average cell volume 127 cu. microns. In the stained blood films the erythrocytes varied greatly in size and in shape, reticulocytes were slightly less than 1 per cent, and the percentage of neutrophils was reduced with many of them having multilobed nuclei. The number of platelets was diminished. A gastric analysis with histamine showed gastric achylia. Roentgen examination of the gastro-intestinal tract revealed no abnormality except a functional disturbance of the small intestine. A cystometric examination was not definitely abnormal.

For experimental purposes he was given over a period of 7 days a yeast concentrate containing folic acid. Daily reticulocyte counts were made and there was no hematologic response, his tongue showed no improvement, the anorexia persisted and his neurologic status remained unchanged. During a second period of 7 days he was given every day by injection 10 mg. of thiamine chloride, 10 mg. of riboflavin, 5 mg. of pyridoxine, 50 mg. of calcium pantothenate, and 250 mg. of nicotinamide. At the end of the second 7 day period there was again no therapeutic response in any regard. The vitamin B therapy was discontinued and daily intramuscular injections of 15 units of purified liver extract begun. At the end of the first week of liver therapy the expected reticulocyte response had occurred, his appetite had improved, and there was visible regeneration of the lingual papillae. The patient thought that there was some improvement neurologically as regards muscular strength and the paresthesias. At the end of 2 weeks the neurologic improvement was undoubted since he was able to walk about holding on to furniture.

At home he continued to take injections of 30 to 45 units of liver extract each week. At the end of 5
months he had returned to full time work. Minor paresthesias persisted about his fingers and toes. His blood values were found to be entirely normal. Neurologic examination showed that he was able to walk with good speed and strength although his gait was somewhat unsteady and stiff. When standing in the Romberg position there was a moderate amount of unsteadiness. The only demonstrable sensory impairment was diminished vibratory sense over the toes. The knee and ankle reflexes were exaggerated but there was no ankle clonus and the plantar responses were flexor. During the next 3 months there was still further neurologic improvement, after which his condition remained stable. At that time his appetite, taste for food, and digestion were again completely normal and only a tendency toward constipation remained. There were no urinary symptoms and his normal sexual potency had returned. Although his legs felt stiff and he found it difficult to walk rapidly, his usual gait appeared nearly normal. There was minimal swaying when he stood in the Romberg position. The remainder of his neurologic examination was as before and he regarded the neurologic residuals as being inconsequential.

In view of the lack of demonstrable therapeutic response of either the lingual, anemic, or neurologic manifestations of pernicious anemia to the administration of the common vitamin B components, and the fact that all these manifestations do respond more or less in parallel with liver therapy, the emphasis in the treatment of those with neurologic disability should certainly be placed on giving the optimal amount of the antianemic liver principle. Although quantitative estimations are obviously difficult in this regard, it seems to be a matter of universal experience that larger amounts of liver should be used in the treatment of those with neurologic complications than are required for a maximal hematologic response. Parenteral therapy is always advisable in these cases. Our standard treatment regimen has been the injection of 30 to 60 units of concentrated liver extract a week until there has been a maximum neurologic recovery. When this has occurred a permanent remission with complete assurance that neurologic relapse will not occur is obtained by the regular injection of about 15 units every 10 to 14 days. We have preferred to use the concentrated liver extracts because of the ease with which the comparatively large unitage may be given and to avoid the discomfort and the danger of inadequate dosage attending the use of the crude extracts. Most of our recent patients have, also, been treated without supplementary yeast or vitamin B products and the rate and degree of neurologic recovery appears to be as satisfactory as when these have been added.

**Prognosis.** It has become evident from following the course of recovery of patients with different types and degrees of neurologic disease that a relatively accurate prognosis can generally be given at the start of treatment. As indicated in the individual case histories cited, the over-all improvement in the neurologic status is far greater than generally recognized. Even patients unable to stand or those with nearly complete loss of voluntary control of the lower extremities, especially when this is of acute onset and less than one or two months in duration, may recover to such a degree that only minimal neurologic abnormalities can be detected later. The cerebral or mental symptoms which occur as a part of the neurologic disorder in patients with pernicious anemia appear to be completely curable although 6 to 12 months may be required to accomplish this. Perversion of the olfactory sense and the partial anosmia have likewise been completely cured by liver therapy in from 2 to 4 months in all the patients we have been able to follow.
In the peripheral nerve and associated posterior column disease the degree of recovery depends upon the qualitative defect present, its severity and its duration. The earliest sign of neurologic improvement is the disappearance of muscle tenderness, when this is present, and an increase in muscular strength and motor performance which became apparent as early as one to 2 weeks after the start of treatment. Even muscular weakness and atrophy severe enough to confine patients to bed responds to treatment within a few weeks in those who are not bedridden or severely crippled for other reasons and there is no residual defect. Impairment of the superficial sensibilities with paresthesias of a few weeks’ or months’ duration in which cutaneous anesthesia has not resulted can be expected to clear without residual symptoms other than perhaps slight tingling distally. When complete loss of cutaneous sensibilities has occurred distally in the extremities some degree of permanent sensory blunting with troublesome paresthesias, especially that of tingling, is usual. Of the sensibilities mediated by the posterior columns the vibratory sense, being affected first and most severely, is most likely to be permanently impaired. When the perception of vibration is not completely lost at a given bony prominence a return to normal may be predicted. When a complete loss as high as the pelvis has occurred a permanent defect at least at the level of the knees and below will remain, although this is of little consequence to the individual concerned. In patients with ataxic symptoms up to several weeks in duration the senses of motion and of position will usually improve with treatment until there are no residual signs except perhaps for some unsteadiness when the patient stands in the Romberg position. The loss of tendon reflexes, except at the ankles, is seldom if ever permanent and as they return in patients with lateral column disease exaggerated reflexes with clonus may develop as the end result. Neurologic defects resulting from disease of the lateral columns of the spinal cord carry the poorest prognosis of all. It is not rare, however, for extensor plantar reflexes presumably of short duration to revert to normal after treatment is begun. When symptoms of lateral column disease have been present for longer than one to 2 months the abnormal plantar responses and exaggerated tendon reflexes will almost invariably persist permanently. The functional defect as far as the motor ability of the patient is concerned is not necessarily of great consequence. With vigorous therapy using potent liver extracts the neurologic improvement in pernicious anemia is most rapid after 4 to 6 weeks of treatment and becomes slower after 4 to 6 months. Little if any improvement in the neurologic status can be anticipated after 10 to 12 months. When the response to liver extract is used as a diagnostic test in neurologic disorders of uncertain relationship to pernicious anemia there is no reason to prolong the trial of liver therapy beyond the 4 to 6 month period if definite improvement has not resulted.

The neurologic residuals which remain after a period of intensive treatment as outlined represent degenerative changes for which an effective type of therapy can in all probability never be developed. Prevention of neurologic disability thus depends to an important degree upon the early and accurate diagnosis of pernicious anemia. This unfortunately seems to be a difficult matter for most physicians. More emphasis should be placed on the clinical extremes of the disease, the “ob-
scure'' and the ''atypical'' cases,2,23 and less on anthropologic characteristics of little practical diagnostic significance and on the so-called average or typical features formerly observed in patients succumbing to the disease after several relapses in the days before effective therapy was available.4 The lingual, anemic and neurologic manifestations occur largely independently of each other, and even in individual patients undergoing successive relapses of the disease lingual or anemic changes may predominate on one occasion and neurologic disease on another.8,10,27,31 An early neurologic diagnosis is often possible in patients whose complaints and findings suggest only peripheral neuropathy or organic cerebral changes. Serious neurologic disease may develop before there is notable deterioration of the blood values26 and in these cases the finding of a slightly decreased red cell count with macrocytosis, often overlooked in the work of a routine laboratory, may be of crucial diagnostic significance. In cases where the diagnosis remains in doubt in spite of competent blood study a gastric analysis with histamine should be done and if free hydrochloric acid is found pernicious anemia can be excluded. In patients with achlorhydria the careful observation of the therapeutic response to refined liver extract according to the expectations outlined above is a practical method of proving the diagnosis.

SUMMARY

Four types of disturbed neurologic function occur in pernicious anemia: (1) cerebral, (2) olfactory, (3) peripheral nerve and posterior columns of the spinal cord, and (4) lateral columns of the spinal cord. The neurologic prognosis depends upon the specific type of disability present, its severity, duration, and the adequacy of treatment. With intensive use of highly potent liver extracts intramuscularly the prognosis is far better than generally recognized. Serious neurologic residuals can be avoided if the diagnosis is made reasonably early.

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