THE RELATION OF THERAPY IN PERNICIOUS ANEMIA TO CHANGES IN THE NERVOUS SYSTEM. EARLY AND LATE RESULTS IN A SERIES OF CASES OBSERVED FOR PERIODS OF NOT LESS THAN TEN YEARS, AND EARLY RESULTS OF TREATMENT WITH FOLIC ACID

By Frank H. Bettell, M.D., and Cyrus C. Sturgis, M.D.

THE FREQUENT occurrence of nervous system involvement in pernicious anemia, the characteristic localization of the lesions in the spinal cord, and the extension of the process before specific treatment became available, suggested to early observers a common cause of, or a cause and effect relationship between, the hematologic and neurologic manifestations of this disease. However, the absence of combined system degeneration or even peripheral neuropathy in many cases of pernicious anemia and the complete dissociation of the severity of the neurologic and hematologic features are not satisfactorily explained by these concepts. With the general acceptance of Castle’s hypothesis of a conditioned metabolic deficiency as the basic mechanism responsible for the pernicious anemia syndrome the view was often expressed that the changes in the hematopoietic and nervous systems resulted from distinct deficiencies which, in turn, probably depended upon a primary defect in gastric function. Evidence for the existence of such separate deficiencies was difficult to obtain because of the lack of exact information pertaining to any of the metabolic factors involved.

When effective treatment of pernicious anemia was introduced by Minot and Murphy, the importance of evaluating the new therapy in the control of combined system degeneration was at once recognized. Over the past two decades many clinical reports bearing on this problem have been published, and an extensive review of the literature is not pertinent to the present communication. The diversity of results and conflict of opinions which characterized the earlier experiences with liver and stomach therapy have been largely explained as due to differences in the conditions of observation and in the amount and potency of the medications employed and the modes of their administration. It is now the consensus of most observers that with individualized optimal therapy the progress of disease of the spinal cord can be arrested in every patient with pernicious anemia unless serious complications are present; that the probability of improvement of the neurologic status and the extent of the benefit which may be expected are inversely related to the duration of the process at the time of institution of therapy; that the period during which improvement may be anticipated is largely limited to the first few months after commencement of intensive treatment.

The regular administration by the intramuscular route of potent liver extract in doses adjusted to the needs of the individual, controlled by periodic clinical and hematologic evaluation, is almost a guarantee against further nervous system
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damage. Such an ideal therapeutic regimen, however, is not employed in the actual management of many cases of pernicious anemia. Particularly is this true of those patients who live at a distance from their physicians, those who change physicians, and those who are seriously influenced by economic considerations. It therefore becomes important to evaluate the results of therapy over a long period of time in a series of cases presenting varied manifestations of the disease and differing with respect to type and amount of therapy received. It is well recognized that patients with previously active neuropathies who discontinue treatment, or those whose therapy becomes so inadequate as to permit development of pronounced anemia, almost invariably suffer reactivation of their neurologic process. It is also true, although less commonly observed, that patients without previous evidence of nervous system involvement may acquire neurologic manifestations after omission or gross inadequacy of anti-pernicious anemia therapy. It may not be so easy, however, to demonstrate a close relationship in all cases between the progress of disease of the nervous system and continued or recurrent suboptimal therapy, as evidenced by relatively slight disturbances of erythrocyte values.

The 70 patients comprising the first series to be reported have all been under observation at the Simpson Memorial Institute for ten years or longer. When seen initially they were in hematologic relapse and had received no effective antianemia therapy for at least several months prior to their first examination. Fifty-eight of the patients were previously undiagnosed and untreated. The diagnosis was established by the clinical and hematologic features characteristic of pernicious anemia, by the absence of other demonstrable conditions associated with macrocytic anemia, by the invariable presence of histamine refractory achlorhydria, and by the therapeutic response in every instance to the administration of potent antiperinicious anemia medication. The neurologic status was evaluated and the cases were classified on the basis of objective as well as subjective evidence of involvement of the peripheral nerves and posterior columns, or of the posterior and lateral columns, of the spinal cord. Although the distinction between evidence of peripheral neuropathy, posterior column disease only, and combined system degeneration is useful as an indication of the severity of the process and in the interpretation of therapeutic results, such a separation is by no means an exact one. The extent of the process in each patient was graded primarily on the basis of peripheral nerve and posterior column involvement as one plus to four plus, indicating, in order of increasing severity: 1 plus, diminution of vibratory sense and altered reflexes in the lower extremities with paresthesia, but without significant disability; 2 plus, loss of vibratory sense and impairment of sense of motion and position in the distal portions of the lower extremities, with mild ataxia; 3 plus, complete loss of vibratory sense in the lower extremities with moderate to severe ataxia; 4 plus, ataxic or spastic paraplegia with inability to stand unassisted, sometimes associated with sphincter disturbances. Evidences of improvement were likewise graded arbitrarily on a plus basis, according to which 4 plus signifies complete disappearance of all subjective and objective manifestations. Evaluation of degrees of improvement less than complete recovery is dependent upon the
The extent of the pre-existing disease and so cannot be defined in terms applicable to all patients. In general, improvement of 3 plus indicates freedom from serious disability with persistence of some paresthesia, and with slight to moderate ataxia in patients who had had the more severe forms of neural involvement. Much of the improvement of these patients may be attributed to recovery from peripheral neuropathy, with education of new muscle groups and adaptation to altered proprioceptive pathways playing important parts. However, the greatly superior results of therapy in patients, often with extensive disease, whose neurologic manifestations were of short duration, suggests that in the early stages of spinal cord involvement, nerve recovery may occur.

The demonstration of unequivocal peripheral nerve changes in pernicious anemia explains the transient and fluctuating paresthesias which occur so frequently in this condition. Peripheral neuritis is probably always present during the active periods of combined system disease and it may occur in the absence of convincing evidence of spinal cord involvement. Patients whose sole neurologic complaint was variable paresthesia or tenderness in the extremities without demonstrable deep sensory disturbances were not considered to suffer from significant disease of the nervous system. Evidence of some degree of cerebral involvement was fairly common among the members of this series. Yet the multiplicity of factors which may have contributed to the production of mental changes in these patients, including anemia, malnutrition, and degenerative vascular disease, and the difficulties involved in comparative measurements on a group of advancing age, render the precise consideration of the mental status of doubtful significance in the evaluation of long-term therapeutic results.

Several types of therapy were employed in the initial management of these patients. Some of them were among the first cases of pernicious anemia to receive the benefits of the liver diet. A considerable number were seen before parenteral liver extracts became available. During the years there has been a tendency to substitute refined and concentrated preparations of liver extract for the cruder less potent parenteral extracts and for oral products. Nevertheless, a number of patients, largely for reasons of personal choice, have continued to take oral liver extract or desiccated stomach or the cruder parenteral liver extracts. It thus becomes possible to compare the effects of different kinds of therapy with respect both to initial responses and to the neurologic status after a long period of time. Moreover, the information afforded by this analysis may be used in the evaluation of results obtained with new types of antianemia medication. In this connection, a small series of patients treated with folic acid will be reported with particular reference to changes in the nervous system.

Of the 70 cases under observation for ten years or longer, there were 45 males and 25 females, giving percentages, respectively, of 64.3 and 35.7. This is a somewhat higher proportion of males than is found in our entire series of over 1,000 cases of pernicious anemia seen at the Simpson Memorial Institute, in which the percentage of males is approximately 55. The average age of the patients at the time of diagnosis of their disease was 53.8 years, and the age distribution for the two sexes was approximately the same. The youngest member of the series was 35 and the oldest
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was 68. The lower age range of these patients as compared to that generally reported for pernicious anemia is, of course, explained by the fact that they were all followed for at least ten years after the diagnosis was made. The average length of the observation period in the case of the males was 13.4 years and for the females was 13.3 years.

Objective manifestations of disease of the nervous system were present in 67.1 per cent of the patients in this group. Serious disability on a neurogenic basis was present in 15.7 per cent, but only 4 patients, or 5.7 per cent, were unable to stand or walk without assistance. It should be pointed out that the low incidence of extremely severe central nervous system disease in this series may be accounted for by the fact that the commonest causes of death in pernicious anemia are the complications of spinal cord involvement. It is of interest, however, that, in some cases, such fatal complications may be prevented for an apparently indefinite period, even though serious disability has been present for a relatively long time before treatment is instituted. Although the incidence of neuropathy is approximately the same for the men and women of this series, the latter tended to have manifestations of more severe involvement when first seen (table 1). Nevertheless, the differences are not sufficiently great and the number of cases is too small to warrant separate consideration of the sexes with respect to the long term course of their disease.

The changes in the neurologic status may be correlated with the duration of symptoms referable to the nervous system before institution of therapy (table 2) and with the type of treatment given (table 3). Of special significance for the purposes of this study is the correlation of the long term results with the adequacy of therapy (table 4).

Improvement in the neurologic status was essentially limited, in all cases, to the first year of treatment, and in fact most functional recovery took place during the

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Total, both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (+)</td>
<td>14</td>
</tr>
<tr>
<td>Slight (+)</td>
<td>10</td>
</tr>
<tr>
<td>Moderate (+++)</td>
<td>17</td>
</tr>
<tr>
<td>Severe (+++)</td>
<td>3</td>
</tr>
<tr>
<td>Very severe (+++)</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
</tr>
</tbody>
</table>
TABLE 2.—The Maximum Extent of Clinical Improvement in Neurologic Manifestations During Period of Adequate Therapy Related to the Duration of Neurologic Symptoms Before Treatment Was Begun

<table>
<thead>
<tr>
<th>Degree of improvement</th>
<th>Number of cases</th>
<th>Symptons present for less than 3 months</th>
<th>Symptoms present for 3 to 12 months</th>
<th>Symptoms present for longer than 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extent of neuropathy</td>
<td>+ to ++</td>
<td>+++ to ++++</td>
<td>+ to ++</td>
</tr>
<tr>
<td>None (o)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Slight (+)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Moderate (+++)</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Marked (+++)</td>
<td>11</td>
<td>2</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Complete recovery (++++)</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

TABLE 3.—The Maximum Extent of Clinical Improvement in Neurologic Manifestations Related to the Type of Therapy Employed During Period in Which Improvement Occurred

<table>
<thead>
<tr>
<th>Degree of improvement</th>
<th>Number of cases</th>
<th>Desiccated stomach</th>
<th>Oral whole liver and liver extract</th>
<th>Parenteral crude liver extract</th>
<th>Parenteral refined liver extract</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extent of neuropathy</td>
<td>+ to ++</td>
<td>+++ to ++++</td>
<td>+ to ++</td>
<td>+++ to ++++</td>
</tr>
<tr>
<td>None (o)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Slight (+)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Moderate (+++)</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Marked (+++)</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Complete recovery (++++)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TABLE 4.—The Neurologic Status After not Less than Ten Years of Observation and Therapy, The Long Term Results Related to the Initial Severity of the Neuropathy and the Adequacy of Treatment as Measured by the Maintenance of Normal Hematologic Values

<table>
<thead>
<tr>
<th>Extent of neuropathy</th>
<th>Number of cases</th>
<th>Optimal therapy</th>
<th>Suboptimal therapy without definite relapses</th>
<th>Clinical and hematologic relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P.D.</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Slight and Moderate</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Severe and very severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

P.D. signifies neurologic manifestations progressed in severity or developed during observation.
0 signifies neurologic status remained essentially unchanged.
— signifies absence of neuropathy; hence, no room for improvement in the disease process.
first six months. The results are about equal for the different types of therapy employed, including desiccated stomach, whole cooked liver or oral liver extract, and parenteral crude liver extract, usually given intravenously (table 3). Because the more refined and concentrated liver extracts were not available when most of the patients were first seen, only 2 cases treated initially with such preparations are included in this series. However, for the past decade, refined liver extract given intramuscularly has been employed in the management of most of our new cases of pernicious anemia, and the results have been fully equal to those obtained with oral preparations and parenterally administered crude extracts. Some of these cases have been included in previous reports. 9 No patients who received optimal therapy, regardless of type, suffered exacerbation of their neurologic manifestations.

In this series, there was no apparent difference over a long period of time, with respect to changes in the neurologic status, between those patients who received the recommended amount of therapy and whose blood values were consistently within normal limits, and those in whom treatment was irregular or was inadequate as judged by variations in erythrocyte count or morphology (table 4). In neither group was development of nervous system disease observed in patients who presented no manifestations of neurologic involvement when therapy was first instituted. The incidence and degree of improvement was about the same in the two groups. However, these observations require comment, and the conclusion that irregular or suboptimal therapy provides a safeguard against development of nervous system disease is not justifiable. In the first place, all of the patients received intensive initial therapy with apparent complete arrest of spinal cord degeneration. In the second, the fact that these patients returned frequently over a period of many years is evidence that they were cognizant of the importance of adequate follow-up examination and treatment, even though they at times neglected it. Recurrence of paresthesia or of mild symptoms of anemia was a warning to them to resume active therapy. In the third place, the severity of the neurologic process in the two groups is not comparable. Of the 11 patients with evidences of extensive spinal cord involvement, 10 are included in the optimal therapy group, justifying the inference that irregular or inadequate treatment seriously affects the chances for long time survival of patients with severe nervous system disease. On the other hand, it is worthy of note that no patients in the inadequately treated group with the milder degrees of involvement showed more than transient exacerbations of their neurologic manifestations.

The patients in this series who suffered definite hematologic relapse, as indicated by an erythrocyte count of less than 3,000,000 per cu. mm. with macrocytosis did not fare as badly as might have been expected. Eleven of this group were free of evidence of neural involvement when first seen, and only 4 of these developed neurologic manifestations during subsequent relapses. In each instance the lesion was classified as moderately severe (++) and was arrested with good functional improvement when intensive therapy was resumed. Of 8 patients presenting symptoms and signs of mild or moderate degree, only one suffered irreversible progression of spinal cord damage during hematologic relapse. Here also, it should be
emphasized that the relapses suffered by these patients were generally of short duration, that the series includes only those patients who were willing and able to return, and that no patient with pre-existing severe central nervous system disease who suffered hematologic relapse has been followed for as long as ten years.

**EXPERIENCES WITH FOLIC ACID**

Since January, 1946, 15 patients with pernicious anemia have been treated with synthetic folic acid (pteroylglutamic acid) for sufficiently long periods to permit an evaluation of the early therapeutic results obtained with this material and a comparison of the results with those secured with other forms of treatment. Nine members of the group were males, 6, or 40 per cent, were without evidence of neuropathy, 5 had previously been under treatment for pernicious anemia, but only 1 had normal blood values at the time folic acid treatment was begun. The 6 patients without nervous system disease have all maintained normal blood values for one year or longer, while receiving 5 mg. of folic acid by mouth daily, and none have developed neurologic manifestations.*

**REPORT OF CASES**

One patient (H. W.), a man of 64, had paresthesias of the extremities, diminished knee and ankle jerks and impaired vibratory sense in the lower extremities when folic acid, 10 mg. orally each day, was started during hematologic relapse. Within three months, coincident with restoration of blood values to normal, paresthesias had disappeared, and the patient had no complaints. A woman (T. K.), aged 69, had evidences of presumptive peripheral nerve and posterior column involvement with slight ataxia and impairment of sense of motion and position when the diagnosis of pernicious anemia was first made during hematologic relapse. On folic acid, 10 mg. daily by mouth, there was significant functional and symptomatic improvement of moderate degree observed over a period of eight months. A man (C. N.), aged 76, had moderate involvement of the nervous system when first seen in 1938. He was treated with refined liver extract by intramuscular injection with marked (+ + +) improvement in his neurologic status. In April, 1946, his blood values were slightly abnormal, presumably due to too long intervals between treatments, and therapy was changed to folic acid, 10 mg. daily by mouth, later reduced to 5 mg. There was no reactivation of the neurologic process at the time of institution of folic acid therapy, and none has occurred over a period of fourteen months. A woman (E. C.), 70 years old, was found to have pernicious anemia in 1938, with a moderately severe neural lesion. While under treatment with desiccated stomach, there was marked (+ + +) improvement in the neurologic manifestations. In May, 1946, treatment was changed to folic acid, 10 mg. orally each day. After six months, there was no exacerbation of the neurologic process, but the erythrocyte level had declined to 3,600,000 per cu. mm. with a mean corpuscular volume of 105 cubic microns. Desiccated stomach, 10 Gm. daily, was substituted for the folic acid and the blood values were rapidly restored to normal.

The 4 remaining patients with pernicious anemia in our folic acid treated series may be said to have had unsatisfactory results with respect to their neurologic status. In 2 of these, the adverse changes were slight and may have been equivocal, or the dosage, for these individuals, may have been too small. A physician (W. F.) was first found to have pernicious anemia in April 1946 and was treated initially with folic acid, 15 mg. daily by intramuscular injection. His erythrocyte count was 1,600,000 per cu. mm., and the maximum reticulocyte percentage, reached on the eighth day, was 15.6. He had troublesome paresthesia, especially in the toes, mild ataxia, impaired vibratory sense distal to the mid-tibias, and swaying in the Romberg position. After one month on the parenteral 15 mg. dosage, the patient felt much stronger, his appetite had improved, and he had gained weight, but there was no change in his neurogenic symp-

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* Since this report was submitted, one of the patients developed severe paraplegia while receiving 10 mg. of folic acid daily.
The erythrocyte count was 4,300,000 per cu. mm., and slight macrocytosis was still present. At this time the dosage of folic acid was reduced to 5 mg. orally each day. Two months later the neurologic manifestations and the blood values were unchanged. He was then given refined liver extract, 15 units intramuscularly, every three weeks, together with the daily oral dose of folic acid, 5 mg. All neurogenic symptoms, except occasional slight tingling in the toes, disappeared within two months' time, and the blood values have been entirely normal for one year. A woman (B. C.), aged 51, was first seen and diagnosed as pernicious anemia in September, 1946. Anemia was minimal, the erythrocyte count being 3,900,000, but characteristic morphologic changes were present, and achlorhydria persisted after histamine injection. There were manifestations of active, moderately severe, neurologic disease, chiefly paresthesia, ataxia, and deep sensory disturbances. Folic acid orally, 10 mg. daily, was given for two months. There was no change in the blood values, and the patient stated that numbness and tingling had become more severe, although there was no demonstrable alteration in the neurologic signs. Folic acid was discontinued, and refined liver extract, 15 units, was given intramuscularly, at first twice and later once weekly. The blood values were entirely normal, and there was a moderate degree of relief of neurogenic symptoms one month later.

In the other 2 remaining cases, there can be no doubt that spinal cord disease progressed actively while the patients were receiving reasonably large doses of folic acid. One of these (J. N.) a man of 51 years, was found to have histamine refractory achlorhydria and atrophic gastritis by gastroscopic examination four years before the diagnosis of pernicious anemia was made. At the earlier examination his complaints were limited to gastrointestinal disturbances, he had no glossitis, no anemia, and no symptoms referable to the nervous system. In April 1946 he was admitted to another hospital where the diagnosis of pernicious anemia was made. Symptoms of increasing fatigability, paresthesia of the hands and feet, and ataxia had been present for about six months. Shortly before his admission, he developed pronounced mental changes characterized by depression, feelings of guilt, and religious preoccupation. Details of the hematologic and neurologic examinations at the time of admission are not available, but it is known that the anemia was of moderate degree with an erythrocyte count of approximately 3,000,000 per cu. mm. The patient was able to walk unassisted, and there were no sphincter disturbances. He received one or two injections of liver extract, and then was treated exclusively with folic acid, 20 mg. by mouth daily. There was symptomatic improvement with clarification of the mental status, and he was discharged after about one month in the hospital, in May, 1946. He continued to take folic acid in the above dosage at home, and the fact that he actually received the medication is attested by his wife who is an entirely reliable person, well known to us. On June 14, 1946, he was first seen in the outpatient department of the Simpson Memorial Institute. He walked alone, but with considerable ataxia, was oriented and responsive, and had no specific complaints other than paresthesia. His erythrocyte count was 3,400,000 per cu. mm., hemoglobin 11.9 grams per 100 cc., and hematocrit 35 per cent. He was advised to continue taking folic acid, 20 mg. daily. On the morning of June 20 he was unable to leave his bed, and during the next two days he rapidly developed the signs of extremely severe spastic ataxic paraplegia with loss of sphincter control. On June 22 he was admitted to the Simpson Memorial Institute. Knee and ankle jerks were not obtained. Plantar stimulation gave an extensor response bilaterally. Vibratory sense was completely lost over the bones of the lower extremities and the crests of the ilium. Sense of motion and position of the toes was absent. The patient was unable to bear any weight on his legs and had no sense of floor resistance. Folic acid was discontinued, and refined liver extract, 15 units, was given daily by intramuscular injection. This dosage was continued until August 5, when it was reduced to 15 units, three times a week, until December 12, when it was changed to 15 units twice weekly. Improvement of the neurologic status was slow but definite. After six weeks he was able to use a walking device, and sphincter control had returned. In four months he could get about with crutches, and nine months after the institution of liver extract therapy he discarded the crutches for canes. At that time, March, 1947, the knee and ankle jerks had returned, the Babinski sign was no longer obtained, and vibratory sense was present, although diminished as far distal as the mid-tibiae. Hematologic values were restored to normal within a few weeks after beginning liver therapy.

The last case to be reported is that of a man (S. K.) of 55 years who was admitted to our service on July 11, 1946. His earliest symptom was impaired sense of taste (?olfactory disturbance) and anorexia which developed eleven months before his admission. One month later he first noted numbness and tingling of the extremities and difficulty in walking. His symptoms were very slowly progressive, and he
continued with his occupation as a merchant until his hospital admission. The initial red blood cell count was 3,600,000 per cu. mm., hemoglobin 11.2 grams per 100 cc., hematocrit 36 per cent. Histamine refractory achlorhydria was present. The gait was ataxic, Romberg and Babinski signs were present, knee and ankle jerks were hyperactive bilaterally, vibratory sense was impaired to absent over the lower extremities, and sense of motion and position of the toes was disturbed but not completely lost. A diagnosis of pernicious anemia with moderately advanced posterolateral column degeneration was made, and the patient was treated with folic acid, 10 mg. intramuscularly daily. After ten days the oral route was substituted for the intramuscular mode of administration. The patient was discharged on July 28 and walked out of the hospital unassisted. He returned eleven days later, on August 9, unable to stand or walk alone and with complete loss of vibration and position sense in the lower extremities. The erythrocyte count at this time was 3,900,000 per cu. mm., hemoglobin 14.6 grams per 100 cc., hematocrit 39 per cent. In place of folic acid he was given refined liver extract, 15 units intramuscularly daily for one week, then 15 units three times a week. He returned four weeks later, on September 9, showing some improvement, but unable to walk without assistance. At his next visit, after another interval of four weeks, he walked alone with the aid of a cane. On June 17, 1947, after ten months of liver extract therapy, he felt quite well and walked with only a slightly hesitant gait. Vibratory sense was apparently normal over the right lower extremity, but was diminished, although nowhere absent, over the left. There was return of sense of motion and position of the toes.

**Discussion**

Experience in the management of cases of pernicious anemia during the early period of their treatment and over a number of years indicates that administration of sufficient amounts of desiccated stomach, whole liver, oral liver extract, and crude or refined liver extracts by parenteral routes, if accompanied by a hematologic response, will invariably lead to the arrest of the neurologic degenerative process and will usually be followed by a significant degree of symptomatic and functional improvement. Furthermore, if adequate treatment, as judged by consistently normal erythrocyte values, is taken continuously, exacerbation of nervous system disease will not occur. Even if treatment is irregular and suboptimal, provided there are no long periods of relapse, patients with less severe degrees of neurologic involvement will rarely suffer irreversible progression of their neural lesion. These statements are apparently not valid in the case of folic acid therapy. The occurrence and progression of combined system degeneration in patients with pernicious anemia under treatment with folic acid was first reported by Vilter, Vilter and Spies and by Meyer. The phenomenon has also been noted by Heinle and Welsh and by Hall and Watkins. In some of the cases reported, the activity of the process was not arrested when the dosage of folic acid was increased many times.

The failure of folic acid to control spinal cord disease in some cases may be taken as evidence that this vitamin corrects only a specific deficiency responsible for the hematopoietic disturbances occurring in pernicious anemia. This hypothesis, however, does not satisfactorily explain two types of observations which have been made by ourselves, as well as by others; namely, first, the fact that not all patients with pernicious anemia, in the absence of important complications, respond to folic acid by restoration of fully normal hematologic values, even when large doses of the vitamin are given by both oral and parenteral routes, and second, some patients experience definite relief of neurogenic symptoms while receiving folic acid. This improvement may be due primarily or entirely to peripheral nerve
recovery, but even so it may be said that such patients, over a period of many
months, show no evidence of progress of nervous system involvement.

The fairly uniform and predictable results of liver and stomach therapy in perni-
cious anemia and the variability of the responses of persons with this disease to
administration of synthetic folic acid suggest that there is in pernicious anemia a
widespread metabolic defect in which a number of interrelated factors or processes
are involved, one of these being the ability to convert the naturally occurring con-
jugated form of folic acid to the free vitamin. However, defective utilization
of folic acid is not the only cause either of the hematopoietic or the neural distur-
bances. It appears, with some supportive evidence, that among the therapeutic
properties of stomach and liver is included a corrective effect on the disordered
metabolism of folic acid which is responsible, in part, for the manifestations of
pernicious anemia.

SUMMARY AND CONCLUSIONS

Seventy patients with pernicious anemia have been observed for periods of not
less than ten years. The clinical course in these cases has been analyzed
with particular reference to changes in the neurologic status.

Most of the patients, whether treated with oral preparations of stomach or liver,
or parenteral crude or refined liver extracts, showed significant improvement of
their neurologic manifestations. The period of improvement was limited, essen-
tially, to the first year of therapy.

Thirty-six members of the series received treatment regularly and were
maintained consistently in complete hematologic remission. Fifteen of the pa-
tients did not adhere to an optimal therapeutic regimen, and their blood values
were frequently abnormal, although definite relapses did not occur. In the former
group there were no instances of development or progression of neural lesions. In
the latter such adverse changes as did occur were transient and reversible on re-
sumption of adequate therapy. Nineteen patients in the series suffered clinical
and hematologic relapses after their initial response to intensive therapy. The end
results in this group were not so favorable, but nevertheless serious progression of
spinal cord involvement was rarely observed. The apparent infrequent occurrence
of pronounced changes is attributed to the short duration of the relapses and to the
relatively mild degree of nervous system involvement present when the diagnosis of
pernicious anemia was made. It may be assumed that patients with more extensive
neural disease who suffered relapses, progressed to a fatal termination.

The observations reported in no way justify the conclusion that irregular or sub-
optimal therapy is without serious risk. They are presented in order to indicate
what the long-term clinical results may be in the case of patients with pernicious
anemia, who frequently fail to adhere to an ideal therapeutic regimen.

The early results of treatment with synthetic folic acid, as observed in a series of
15 patients, indicate that both the hematologic and neurologic response to this
form of therapy is much less predictable than is the case with stomach or liver pre-
parations. It is suggested that disturbance of folic acid metabolism is not the sole
cause of either the hematologic or the neurologic manifestations of pernicious
anemia, but that inability to utilize folic acid effectively may play a part in the development of both myeloid and neural abnormalities.

REFERENCES


THE RELATION OF THERAPY IN PERNICIOUS ANEMIA TO CHANGES IN THE NERVOUS SYSTEM. EARLY AND LATE RESULTS IN A SERIES OF CASES OBSERVED FOR PERIODS OF NOT LESS THAN TEN YEARS, AND EARLY RESULTS OF TREATMENT WITH FOLIC ACID

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