The Treatment of Pernicious Anemia with Massive Parenteral Doses of Vitamin B₁₂

By Edward H. Reisner, Jr. M.D. and Leo Weiner, M.D.

FOLLOWING THE ISOLATION of vitamin B₁₂ the possibility was created for the use of doses of antianemic principle much larger than any previously employed in the treatment of pernicious anemia. The expectation was legitimate that the use of single massive injections of vitamin B₁₂ might produce prolonged hematologic remissions, and that regular use of such doses might bring about further improvement in stabilized cases of combined system disease. The following studies were undertaken to investigate these two points.

METHODS

Fourteen patients with proven pernicious anemia in relapse were treated with single intramuscular doses of 1000 µg. of crystalline vitamin B₁₂. Complete hematologic remission resulted in all but 1 case. The patients were then followed without further treatment until they showed evidence of hematologic relapse.

Seven patients with combined system disease that had shown no change after months to years of conventional therapy, during which time satisfactory hematologic remission had been maintained, were treated with weekly injections of 1000 µg. of vitamin B₁₂ for periods of from four to thirteen weeks.

In some of the patients in both groups urinary and spinal fluid levels of B₁₂ were assayed chemically by J. C. Rickards and G. E. Boxer of the Research Laboratories of Merck & Co., Rahway, N. J.¹

RESULTS

Table 1 shows the duration of remissions obtained following single 1000 µg. injections of vitamin B₁₂. They ranged from three to seven months. Four patients were lost from follow up four, six, eight and nine months after treatment, at which time they were still in remission. Two patients showed slight polycythemia with red blood counts in excess of 6,000,000. In one of these patients the red blood count has remained high and he may have developed a true polycythemia as has been reported in some other instances.¹² The other subsequently relapsed. In one patient the injection had no apparent effect on the blood count and was followed in two months by an exacerbation of cord disease.

Table 2 shows the effect of weekly 1000 µg. doses of B₁₂ on the course of combined system disease in 7 patients. All of these patients except 1 had had the disease under regular conventional treatment for two years or more, and were felt to have become stabilized on that therapy. One patient, who had only had symptoms for six months, voluntarily discontinued treatment after four weeks.

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¹ The vitamin B₁₂ used in these studies was supplied by Merck & Co., Inc., Rahway, N. J. Chemical determinations of vitamin B₁₂ levels in the urine were done by J. C. Rickards and G. E. Boxer from the Research Laboratories of Merck & Co.

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because she thought that the liver injections she had been used to, made her feel better. During the period of observation there was no objective improvement detected, although we feel that the time of observation was too short to warrant further conclusions. In 1 patient treated for 13 weeks there was a steady and gradual improvement in strength, balance, position sense and gait, but no change in vibratory sense or deep tendon reflexes. This improvement continued after the patient was returned to conventional therapy and we felt that some of it,

Table 1—Duration of Remission in Pernicious Anemia following 1000 µg. of
Vitamin B₁₂ Parenterally

<table>
<thead>
<tr>
<th>Time to Relapse</th>
<th>No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mos.</td>
<td>3</td>
<td>Four patients had not relapsed at the time of their last visit</td>
</tr>
<tr>
<td>4 mos.</td>
<td>1</td>
<td>4, 6, 8, and 9 months respectively after treatment.</td>
</tr>
<tr>
<td>5 mos.</td>
<td>2</td>
<td>Two showed counts in excess of 6,000,000.</td>
</tr>
<tr>
<td>6 mos.</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>7 mos.</td>
<td>1</td>
<td>In 1 patient the injection was followed by no complete remission and an exacerbation of cord disease within two months.</td>
</tr>
<tr>
<td>No remission</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Table 2—Effects of 1000 µg. of Parenteral Vitamin B₁₂ per week on Chronic Cord Disease

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Weeks of Treatment</th>
<th>Improvement Graded 0-4 (N means normal originally)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O. D.</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>S.</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>R.</td>
<td>6</td>
<td>X</td>
</tr>
<tr>
<td>S. G.</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>D. R.</td>
<td>4</td>
<td>X</td>
</tr>
<tr>
<td>L. D.</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>J. G.</td>
<td>13</td>
<td>2</td>
</tr>
</tbody>
</table>

All patients had been previously treated with adequate amounts of liver extract or vitamin B₁₂ and were relatively stabilized neurologically.

at least, was due to the fact that she was no longer treating herself as a bedridden invalid (as she had for the preceding year) but was making a constant effort to keep mobilized and ambulatory. In a second case who had symptoms of combined sclerosis for four years, treated with massive doses for nine weeks there was moderate improvement of balance and gait, evident after the first two weeks and not progressive. The other 4 patients showed no objective evidence of improvement after periods of treatment of ten, six, ten and seven weeks, respectively. They had combined system disease for approximately four, four, six and two years, respectively.

In 2 patients spinal fluid levels were obtained following a single injection and seven daily injections of 1000 µg. of B₁₂, respectively. The results as determined
by microbiologic assay (L. leishmanii) are shown in table 3. They show a much higher level after repeated injections.

In 4 patients with pernicious anemia in relapse and 1 patient with acute leukemia, urinary excretion of vitamin B₁₂ for 48 hours following a single massive injection was determined by chemical assay. The results (table 4) indicate from 51 to 98 per cent of the dose excreted in that time.

**Table 3—Spinal Fluid Levels before and after Massive Dose Vitamin B₁₂ Therapy, Intramuscularly**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose</th>
<th>Spinal Fluid level of B₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. K.</td>
<td>1000 μg.</td>
<td>0.08 μg/ml. before treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25 μg/ml. 24 hrs. after treatment</td>
</tr>
<tr>
<td>J. F.</td>
<td>1000 μg. daily</td>
<td>0.033 μg/ml. before treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.7 μg/ml. after seven days.</td>
</tr>
</tbody>
</table>

**Table 4—Urinary Excretion of Vitamin B₁₂ in 48 Hours following Single Large Injections**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (μg.)</th>
<th>Urinary B-12 (μg.)</th>
<th>% Excreted</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. J.</td>
<td>500</td>
<td>488</td>
<td>97</td>
</tr>
<tr>
<td>J. H.</td>
<td>500</td>
<td>255</td>
<td>51</td>
</tr>
<tr>
<td>J. M.</td>
<td>200</td>
<td>197</td>
<td>98</td>
</tr>
<tr>
<td>A. S.</td>
<td>100</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>H. C.</td>
<td>1000</td>
<td>810</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>740</td>
<td>74</td>
</tr>
</tbody>
</table>

**Discussion**

It is well known that pernicious anemia patients vary greatly in the time to hematologic relapse following the discontinuation of therapy. This may be due to variations in the capacity of the body organs to store vitamin B₁₂, or perhaps to the degree to which the remission may be maintained by extrinsic sources of vitamin B₁₂ and folic acid derived from food and intra-intestinal synthesis.

The question naturally arises, how much of the large doses was retained by these pernicious anemia patients. Conley et al.³ found that parenteral doses of B₁₂ larger than 25 μg. were excreted in the urine, the amount rising rapidly with increasing doses. Plasma levels of B₁₂ as high as 130 μg/ml. immediately following the injection of 1000 μg. of the vitamin, declined to less than 10 μg/ml. in 4 to 6 hours, coincidentally with a rapid rise of B₁₂ levels in the urine. Chesterman, Cuthbertson and Pegler⁴ proposed the formula $E = D - 1.2D^{0.89}$ to express the relation between the amount excreted (E) and the parenterally administered dose (D). Sokoloff, Sanneman and Beard⁵ found similar results and indicated that while doses of 42.2 μg. were largely retained, larger doses up to 211 μg. showed up to 68 per cent excretion.

In several of our patients in relapse urinary assays of B₁₂ were made prior to and following the injection of doses ranging from 100 to 1000 μg. of B₁₂. The excretion pattern varied from one individual to the next but the amount of B₁₂ recovered in 48 hours following injection ranged from 51 to 98 per cent of the
injected dose. It appears that the capacity of the body to take up and hold
vitamin B₁₂ is limited and that amounts in excess of a threshold value between
25 and 40 µg. are quantitatively excreted. In contrast to other body tissues, the
brain takes up B₁₂ more slowly but shows a steady increment in the amount
stored with continued injections. Table 3 shows that in one patient the spinal
fluid level of B₁₂ rose from 0.08 µg. per ml. to 0.25 µg. per ml. in 24 hours following
a single injection of 1000 µg., and in another patient receiving 1000 µg. of B₁₂
every day the spinal fluid levels rose from 0.033 µg. per ml. before treatment to
2.7 µg. per ml. at the end of one week.

The failure to observe prolonged remissions in many of the patients receiving
single large doses of B₁₂ is not surprising, since in fact, the dose retained was of a
magnitude comparable to more conventional therapeutic doses. It would appear,
therefore, that vitamin B₁₂ in doses of more than 50 µg. at a time is probably
wasted.

It is even more difficult to evaluate the effect of massive dose therapy in chronic
combined system disease of the spinal cord. As Hall⁷ has pointed out, the mood
and activity of the patient influence the rehabilitation of these patients to a
large degree. If a patient who has been more or less neglected, sedentary and
bed-ridden, is suddenly given a new treatment, with frequent questioning about
improvement and regular neurologic examination he will often feel stronger and
walk better, even though the treatment itself is innocuous. One cannot conclude
that additional benefits are derived from a new treatment until it is certain that
optimum benefits have been gained from the old. The longer the period of ob-
observation the more valid the conclusions may be. These principles apply equally
to any chronic neurologic disorder, and especially so to a disease like multiple
sclerosis, the course of which is often marked by spontaneous remissions.

Several reports have been published of cases of combined dorso-lateral sclero-
sis,⁸ multiple sclerosis,⁹ chronic peripheral neuropathies and tabes dorsalis¹⁰
alleged to have responded to massive doses of vitamin B₁₂. Other reports have
been conflicting.¹¹⁻¹³

On the basis of our observations we are sceptical of the positive reports, for
the reason that it appears highly unlikely that more than a small fraction of the
injected massive dose is retained and, therefore, similar results might logically
be expected from vigorous treatment employing conventional amounts of B₁₂.
We feel that more than 30 to 50 µg. of vitamin B₁₂, intramuscularly two or three
times a week is not warranted in the treatment of chronic cord disease.

The preceding statements apply to the chronic neuropathy of pernicious
anemia. There have lately appeared some claims of the efficacy of massive dose
vitamin B₁₂ therapy in alleviating pain in painful neuritis of nutritional origin,¹⁴
osteoarthritis pain¹⁵ and trigeminal neuralgia.¹⁷ Pain is, of course, a subjective
sensation that can be readily influenced by suggestion, and this may account for
some of the reported results. However, one of us (E.R.) has just seen a remarkable
improvement in a previously intractable case of sciatica secondary to arthritis
receiving daily doses of 1000 µg. of B₁₂ intramuscularly. In a few days the sciatic
nerve was no longer tender to pressure and the patient was free of sciatic root
pain, although the joint pain due to arthritis was unchanged. One can only con-
clude that in such a case B₁₂ was acting in a fashion different from that in which
it acts in chronic combined system disease, and in such cases further exploration
of the use of massive dose vitamin B₁₂ therapy is probably warranted. The question may be asked whether prior to excretion of the massive dose transient high levels of B₁₂ might be obtained in the spinal fluid which would be helpful to the patient. Our limited study in 2 cases (table 3) suggests that such is not the case, better levels being obtained with regular continued doses.

**CONCLUSIONS**

These studies indicate that massive single injections of vitamin B₁₂ cannot be substituted for more frequent regular injection of smaller doses in the treatment of pernicious anemia, without the danger of relapse and the aggravation of central nervous system disease. Furthermore, there is no evidence to indicate that a greater degree of improvement follows the regular weekly injections of massive doses of vitamin B₁₂ to patients with chronic combined system disease than occurs with regular conventional doses. This is probably because amounts of B₁₂ above a threshold value of 25 to 50 μg. by injection, are rapidly and quantitatively excreted in the urine.

**REFERENCES**

7. **CHOW, B. F.**: Personal communication.
The Treatment of Pernicious Anemia with Massive Parenteral Doses of Vitamin B₁₂

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