Treatment of Pernicious Anemia with Crystalline Vitamin $B_{12b}$

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Following the isolation of crystalline vitamin $B_{12}$ in 1948, physico-chemical studies demonstrated the presence of other biologically effective compounds in this group. Vitamin $B_{12b}$ or vitamin $B_{12s}$ (which are probably identical) is a slow moving component in chromatographic studies and may be converted from vitamin $B_{12}$ by sodium bisulfite, hydrogenation or exposure to light. It further differs from vitamin $B_{12}$ in the absence of the cyanide radical, and may be changed to it by treatment with potassium cyanide. Vitamin $B_{12s}$ is discolored and its microbiologic activity destroyed by exposure to an excess of vitamin C or some of its salts; vitamin $B_{12}$ is only slowly degraded under similar circumstances.

Clinical trials by Lichtman and his co-workers concerned the treatment of 5 patients with pernicious anemia in relapse using intramuscular injections of 1.0, 1.5 and 2.0 $\mu g.$ of vitamin $B_{12b}$, daily. These patients were observed for a period of three weeks. Clinical improvement, including regression of neurologic symptoms and glossitis, was noted. Increase of leukocytes and reduction in hypersegmentation of polymorphonuclear leukocytes was reported. The reticulocyte peak was higher than anticipated in one case (1.0 $\mu g.$ per day), satisfactory in a second case (1.0 $\mu g.$ per day), and less than the expected level in the remaining three patients (1.0, 1.5 and 2.0 $\mu g.$ per day). The rate of erythrocyte regeneration was satisfactory during the observed period (three weeks). Spies and his co-workers reported 4 patients with pernicious anemia in relapse treated with vitamin $B_{12b}$. The details of 1 case were presented. This person received one intramuscular injection of 10.0 $\mu g.$ of vitamin $B_{12b}$. Reticulocytosis with rise in hemoglobin and red blood cells ensued. Observations of this case were made for fourteen days. Schilling and his associates administered 1.0 $\mu g.$, 2.0 $\mu g.$ and 4.0 $\mu g.$ of vitamin $B_{12b}$ ($B_{12s}$) intramuscularly, daily, for thirteen to sixteen days to 5, 1 and 1 patients with pernicious anemia in relapse, respectively. The reticulocyte response was satisfactory in only 1 patient receiving 1.0 $\mu g.$ per day. Each of the persons treated with 2.0 or 4.0 $\mu g.$ per day showed an optimal reticulocyte peak. Clinical improvement with increase in erythrocytes was observed in all instances. In a second period, 3 of the patients previously treated with 1.0 $\mu g.$ of vitamin $B_{12b}$ received 1.0 $\mu g.$ of vitamin $B_{12}$ intramuscularly, daily, for nine to thirteen days. A small secondary reticulocytosis was noted in 1 case.

From the foregoing data it is evident that vitamin $B_{12b}$, administered intra-
muscularly daily to patients with pernicious anemia in relapse, will induce a remission in clinical symptoms, reticulocyte response and increase in hemoglobin and red blood cells. In none of these studies were the patients treated long enough to determine complete efficacy of therapy. The present investigation was undertaken to determine the optimal dose of crystalline vitamin $B_{12}$ necessary for complete hematologic and clinical remission in 9 patients with pernicious anemia in relapse. Each case showed hyperchromic macrocytic anemia, histamine-fast achlorhydria and megaloblastic bone marrow. Roentgen examinations of the gastrointestinal tract, urinalyses and blood chemistry determinations disclosed no abnormalities. The dose of vitamin $B_{12}$ ranged from 1.0 to 4.0 $\mu$g., intramuscularly, daily. Hemoglobin and red blood cell determinations were made three times a week, leukocyte counts once a week and reticulocyte estimations daily. All of the patients came from the same economic level so that differences in diet and nutrition were not major factors.

**Case Reports**

**Case M. M.**

M. M., white female, age 55, a known case of pernicious anemia, was admitted to the hospital because of weakness and edema of legs of one month's duration. She failed to attend clinic and received no treatment for about five months. Except for moderate edema of the legs, physical examination disclosed no significant changes. Initial blood count showed hemoglobin 9.5 Gm. per 100 ml., red blood cells 2.58 million per cu. mm., and leukocytes 3,250 per cu. mm. She received 1.0 $\mu$g. of vitamin $B_{12}$, intramuscularly, daily for ten days, and thereafter 1.5 $\mu$g. at weekly intervals. A maximal reticulocyte response of 4.5 per cent was noted on the sixth day. The patient reported an increase in strength within 48 hours. Edema of ankles decreased rapidly and was completely dissipated in seven days. Her appetite was increased and a sense of well-being prevailed after the third day of treatment. The maximal blood count of hemoglobin 13.5 Gm. per 100 ml., red blood cells 4.38 million per cu. mm., and leukocytes 7200 per cu. mm. was attained one month after specific therapy was instituted. After this date, the patient again failed to return for further care. No neurologic changes were observed.

**Case F. N.**

F. N., white male, age 51, was admitted to the hospital with the chief complaints of weakness, pallor, anorexia, paraesthesias of hands and feet and difficulty in walking of three months' duration. Physical examination was unremarkable except for apparent pallor. Neurologic survey showed absent knee and ankle jerks, loss of position and vibratory senses in lower extremities and strongly positive Romberg sign bilaterally. Initial blood count was hemoglobin 6.0 Gm. per 100 ml., erythrocytes 1.90 million per cu. mm. and leukocytes 5200 per cu. mm. (fig. 1). He was treated with 1.0 $\mu$g. of vitamin $B_{12}$, intramuscularly, daily for ten days. His appetite was improved on the sixth day of treatment. Weakness prevailed for ten to fourteen days. A reticulocyte peak of 22.3 per cent was reached on the ninth day. On the eleventh and twenty-first days he received 10.0 $\mu$g. of vitamin $B_{12}$. Following the first of these injections a slight secondary response (up to 10.0 per cent) was observed. No rise was noted after the second of these larger doses. Thereafter, he was treated with 15.0 $\mu$g. of vitamin $B_{12}$, intramuscularly, every two weeks. The maximal hemoglobin levels of 13.0 Gm. per 100 ml., and red blood cell count of 4.70 million per cu. mm. were reached three months after treatment was begun. Leukocytes ranged between 4600 and 6900 per cu. mm. Satisfactory clinical improvement was attained only after three to four months, and the central nervous system changes were never reversed.
Case J. G.

J. G., white male, age 62 years, was admitted to the hospital with the chief complaints of weakness, fatigue, vertigo, exertional dyspnea, and paraesthesias in the upper and lower extremities. Physical examination disclosed an icteric tint to the sclerae and skin. Liver was felt 3 cm. below the right costal margin. Slight edema over the ankles and legs was present. Neurologic changes included absence of vibratory sense in both lower extremities up to the iliac crests, diminution of position sense in toes, bilateral positive Romberg sign and loss of ankle jerks. Initial blood examination showed hemoglobin 7.0 Gm. per 100 ml., red blood cells 1.40 million per cu. mm. and leukocytes 2100 per cu. mm. (fig. 2). He was treated with 1.0 μg. of vitamin B₁₂₇, intramuscularly, daily, for ten days and thereafter at the rate of 1.0 μg. a day at ten to fifteen day intervals for two months. Improvement in appetite and sense of well-being were observed within 72 hours. Subjective complaints referable to the nervous system disappeared in one week. A peak reticulocyte count of 24.1 per cent was noted on the ninth day. Hemoglobin and erythrocytes reached 12.0 Gm. per 100 ml. and 3.50 million per cu. mm., respectively, in about five weeks and remained at this level for one month. The dose of vitamin B₁₂₇ was raised to 15.0 μg., intramuscularly, weekly. This induced a further increase in hemoglobin to 14.5 Gm. per 100 ml. and erythrocytes to 4.16 million per cu. mm., at which level these values remained stationary. Subsequent increase in dosage to 22.5 μg. of vitamin B₁₂₇ intramuscularly, weekly, was followed by a rise in hemoglobin and red blood cells to normal levels in one month. No fall in hematologic values was observed during the next six weeks of observation. Throughout this entire period the neurologic status was unchanged, but the patient appeared otherwise well.

Case C. W.

C. W., white male, age 52, was admitted to the hospital with the chief complaints of anorexia, weakness, dyspnea, precordial pain and edema of the lower extremities for the past two months. Physical examination disclosed yellowish tint to the sclerae and skin, liver

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**Fig. 1.**—F. N., patient with pernicious anemia in relapse treated with 1.0 μg. of vitamin B₁₂₇, intramuscularly, daily. Reticulocyte response was suboptimal during the first ten day period. Secondary reticulocytosis noted after 10.0 μg. dose. Complete hematologic and clinical remissions were attained after three months. Spinal cord changes were unaltered.
edge palpable 2.0 cm. below the right costal border, and edema of the ankles. Neurologic status was normal. Initial blood count revealed hemoglobin 5.0 Gm. per 100 ml., erythrocytes 1.30 million per cu. mm. and leukocytes 3000 per cu. mm. (fig. 3). He was treated with injections of 1.0 µg. of vitamin B₁₂₅ intramuscularly, daily, for ten days, and then at the rate of 1.0 µg. a day at intervals of ten to fourteen days for a period of seven weeks. During the time when he received 1.0 µg. a day, a peak reticulocyte response up to 25.4 per cent was noted on the eighth day. A slight increase in hemoglobin and erythrocytes was observed. Clinical response was minimal. Secondary reticulocytoses were noted after the first and second injections of 10.0 µg. of vitamin B₁₂₅, which were administered on the eleventh and twenty-first days. The rise in hemoglobin and red blood cells was slow, and a plateau of 10.5 Gm. per 100 ml. and 2.80 million per cu. mm., respectively, was maintained during this period of observation. Leukocytes remained at or below 5000 per cu. mm. His clinical condition was only moderately improved. Accordingly, he was treated with 2.0 µg. of vitamin B₁₂₅ intramuscularly, daily, for fourteen days and subsequently with 15 µg. weekly for five weeks. No significant reticulocyte response was evoked. Hemoglobin and red blood cells rose slowly to 12.5 Gm. per 100 ml. and 4.0 million per cu. mm., respectively, and remained at this level for two to three weeks. Leukocytes hovered at or below the 5000 per cu. mm. mark. The patient’s clinical status was only moderately improved. The weekly dose of vitamin B₁₂₅ was increased to 30.0 µg. for nine weeks. Leukopenia persisted and hemoglobin and red blood cells rose to 14.5 Gm. per 100 ml. and 4.60 million per cu. mm., respectively. Clinically, the patient was improved. Following the institution of 60.0 µg. doses of vitamin B₁₂₅ intramuscularly, bi-weekly, leukocytes increased to 7000 per cu. mm., hemoglobin 16.0 Gm. per 100 ml., and red blood cells 5.30 million per cu. mm. Subjectively, the patient was entirely well.

Case J. F.

J. F., white male, age 64, was a known case of pernicious anemia who received no treatment for three years. He returned to the clinic because of weakness and inability to walk.

**Fig. 2.**—J. G., patient with pernicious anemia in relapse, treated with the equivalent of 1.0, 2.0 and 3.0 µg. of vitamin B₁₂₅, intramuscularly. Complete hematologic remission was not attained until the latter dose was administered. Clinical remission satisfactory but spinal cord changes were unaltered.
Physical examination was negative. Neurologic survey revealed absence of vibratory sense in both lower extremities up to the iliac crests. No other abnormalities were observed. Blood examinations showed hemoglobin 9.0 Gm. per 100 ml., red blood cells 2.58 million per cu. mm. and leukocytes 4500 per cu. mm. He was treated with 7.5 µg. of vitamin B₁₂₁₂₁₂₁₂ intramuscularly, weekly, for three weeks, followed by 15.0 µg. every two weeks for six weeks. He reported improvement in appetite and general well-being within 48 hours. At this time pretibial edema was observed which lasted for about ten days. A peak reticulocyte response of 15.2 per cent was noted on the sixth day. Seven weeks after the beginning of therapy the blood count was hemoglobin 13.5 Gm. per 100 ml., erythrocytes 4.20 million per cu. mm., and leukocytes 6750 per cu. mm. This level of hemoglobin and red blood cells was attained five weeks earlier with no evidence of further improvement. In addition, there were signs of further nervous system deterioration: ataxia, bilateral positive Romberg signs and loss of position sense in both feet, in addition to absence of vibratory sense noted in both lower extremities on admission to the hospital. The dose of vitamin B₁₂₁₂₁₂ was increased to 15.0 µg. intramuscularly, weekly. Hemoglobin and red blood cells rose to 14.0 Gm. per 100 ml., and 5.03 million per cu. mm., respectively, in six weeks. The patient's gait improved but was still ataxic. Neurologic status remained unchanged. The dose of vitamin B₁₂₁₂ was increased to 45.0 µg. every two weeks, but the abnormalities of the nervous system persisted. Subsequent treatment with 30.0 µg. of vitamin B₁₂ or 15 units of liver extract, intramuscularly, weekly, during the following eighteen months, were ineffective in reversing the spinal cord changes. Hematologic status has remained normal. At present he is receiving 30.0 µg. of vitamin B₁₂ intramuscularly every two weeks.

Case S. W.

S. W., Negro male, age 60, was admitted to the hospital because of anorexia, nausea, dyspnea, weakness and paraesthesias of feet, of one month's duration. Physical examination
disclosed atrophy of the papillae of the tongue and icteric tint to the sclerae. Neurologic status was not remarkable other than absence of ankle jerks bilaterally. Initial blood count showed hemoglobin 7.5 Gm. per 100 ml., erythrocytes 1.30 million per cu. mm., and leukocytes 3200 per cu. mm. (fig. 4). He received 7.5 µg. of vitamin B₁₂ intravenously. Clinical improvement was noted on the fifth day, with increase in appetite, strength and sense of well-being. A reticulocyte peak of 13.7 per cent was attained on the seventh day. No significant change was observed in the number of erythrocytes or leukocytes. He received another intravenous injection of 7.5 µg. of vitamin B₁₂. This resulted in further clinical improvement. A secondary reticulocytosis up to 11.9 per cent occurred six days later. Hemoglobin, red blood cells and leukocytes gradually rose and reached a plateau of 10.0 Gm. per 100 ml., 2.30 million per cu. mm. and 5,000 per cu. mm. after one month. The clinical course remained stationary. He was then treated with 1.5 µg. of vitamin B₁₂ intramuscularly, daily, for twelve days, and thereafter with 15.0 µg. every ten days for eighteen weeks. Subsequent treatment consisted of intramuscular injections of 30 µg. of vitamin B₁₂ every twenty days for six months. Clinical improvement was rapid during the period of daily treatment with 1.5 µg. The reticulocyte peak was 3.9 per cent on the ninth day of treatment. A secondary small peak of 2.6 per cent was observed after the first injection of 15.0 µg. administered after ten days' treatment with 1.5 µg. daily. Normal blood levels were not attained until after five months of treatment. Neurologic changes were unaltered.

Case J. M.

J. M., white female, age 76, was admitted to the hospital with the chief complaints of weakness of six weeks' duration and faintness for the past week. Physical examination disclosed a lemon-yellow tint to the sclerae and skin and atrophy of the papillae of the tongue. Vibratory sense was absent at the left ankle. Initial blood count was hemoglobin 8.0 Gm. per 100 ml., erythrocytes 2.35 million per cu. mm. and leukocytes 3200 per cu. mm. (fig. 5). She was treated with 2.0 µg. of vitamin B₁₂ intramuscularly, daily, for twelve days and then with 15.0 µg. at weekly intervals for about four months. The patient reported an increase
FIG. 5.—J. M., patient with pernicious anemia in relapse, treated with 2.0 mcg. of vitamin B₁₂₇, intramuscularly, daily. A better than anticipated reticulocyte response was observed. Clinical and hematologic remissions were satisfactory. Neurologic status was unaltered.

FIG. 6.—K. B., patient with pernicious anemia in relapse, treated with 2.0 mcg. of vitamin B₁₂₇, intramuscularly, daily. Clinical and hematologic remissions were satisfactory. Neurologic status was unaltered.

in appetite on the third day of treatment with improvement in sense of well-being and return of strength. A reticulocyte peak of 27.0 per cent was observed on the eighth day. The blood count reached normal levels about nine weeks after treatment was begun. There was no change in neurologic status.
Case K. B.

K. B., white female, age 74, was admitted to the hospital because of weakness, pallor and purpura. She was confused, noisy, irrational and uncooperative. A coherent history was not obtainable. Physical examination revealed icterus of sclerae and skin and scattered areas of purpura. Liver was felt 3.0 cm. below the right costal border. Spleen was barely palpable. Slight pretibial edema was present. All deep tendon reflexes were hyperactive. Babinski sign was positive bilaterally. Initial blood examination showed hemoglobin 3.5 Gm. per 100 ml., erythrocytes 1.40 million per cu. mm. and leuкоocytes 1560 per cu. mm. (fig. 6). She was treated with 2.0 μg. of vitamin B₁₂₃, intramuscularly, daily, for twelve days, followed by 15.0 μg. weekly for three months. The sensorium cleared within 48 hours. No new purpuric areas were noted after 72 hours. At the same time her appetite visibly improved and she felt stronger. A peak reticulocyte response of 24.5 per cent was observed on the eighth day of treatment. Normal blood levels were attained in two months. Neurologic status remained unchanged.

Case L. S.

L. S., white male, age 75, a known case of pernicious anemia, returned to the hospital for treatment after a lapse of about three months during which time no specific therapy was received. He had advanced subacute combined degeneration of the cord for many years, but recently noted parasthesias of the upper and lower extremities. Physical examination was not remarkable. Neurologic survey revealed active tendon reflexes in arms and legs. Vibration sense was absent in both lower extremities up to and including the levels of the iliac crests. Position sense of toes was absent. Babinski reaction was not elicited. Bilateral Romberg sign was noted. Initial blood count showed hemoglobin 12.5 Gm. per 100 ml., erythrocytes 3.88 million per cu. mm. and leuκocytes 5000 per cu. mm. He was treated with 15.0 μg. of vitamin B₁₂₃, intramuscularly, weekly for six months. No reticulocyte response was evoked. Hemoglobin and red blood cells reached normal levels in five weeks and were unchanged during the period of observation. Parasthesias of extremities decreased. Maximal improvement was attained in one month, at which time symptoms in hands and fingers were minimal and strikingly decreased in feet and toes. Return of position sense of right toe was observed in six weeks.

Discussion

A summary of the hematologic data and salient clinical features is presented in table 1. It is clear that the daily administration of 1.0 μg. of vitamin B₁₂₃ or its equivalent when administered in weekly or biweekly doses is inadequate for optimal hematologic and clinical remission. Patient M. M. was not followed for a long enough period of time to evaluate therapy at this dose level but the reticulocyte response did not reach the anticipated value. The rate of erythrocyte regeneration was satisfactory up to the time of her last visit to the clinic, but unfortunately she failed to return and the question of complete hematologic remission remains in doubt. Clinical symptomatology was distinctly improved. That the reticulocyte response in patient F. N. was not maximal during the ten day period when he received 1.0 μg. of vitamin B₁₂₃ a day is evident from the secondary reticulocyte response provoked after the 10.0 μg. dose administered on the eleventh day. Normal hematologic values were not reached until after three months of treatment. Relief of clinical symptoms was slow and no improvement of spinal cord disease was observed.

Patient J. G. showed an early remission of symptoms, including those referable to the nervous system, while receiving 1.0 μg. of vitamin B₁₂₃, daily, or its equivalent, at intervals of ten to fourteen days. However, the hematologic response was
### CRYSSTALLINE VITAMIN B₁₂ IN PERNICIOUS ANEMIA

#### Table 1—Hematologic Data and Clinical Features of Cases Discussed

<table>
<thead>
<tr>
<th>Patient</th>
<th>B₄m dose µg</th>
<th>Initial Hgb. Gm./100 ml</th>
<th>Final Hgb. Gm./100 ml</th>
<th>Initial RBC X₁₀⁶ per cu. mm</th>
<th>Final RBC X₁₀⁶ per cu. mm</th>
<th>Retic. % peak/day</th>
<th>Days of observation</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. M.</td>
<td>1.0/day</td>
<td>9.5</td>
<td>13.5</td>
<td>2.58</td>
<td>4.38</td>
<td>4.5/6</td>
<td>35</td>
<td>Satisfactory clinical and hematologic response. Patient failed to report for continued treatment.</td>
</tr>
<tr>
<td>F. N.</td>
<td>1.0/day</td>
<td>6.0</td>
<td>7.5</td>
<td>1.80</td>
<td>1.90</td>
<td>22.3/9</td>
<td>10</td>
<td>Clinical improvement.</td>
</tr>
<tr>
<td></td>
<td>10.0/10 days</td>
<td>9.9</td>
<td>3.10</td>
<td>10.0/4</td>
<td></td>
<td></td>
<td>10</td>
<td>Secondary reticulocytopsis on 4th day after 10.0 µg. dose. Clinical improvement but neurologic status unchanged.</td>
</tr>
<tr>
<td></td>
<td>10.0/10 days</td>
<td>13.0</td>
<td>4.70</td>
<td></td>
<td></td>
<td></td>
<td>210</td>
<td>Satisfactory hematologic and clinical remission with no improvement in neurologic disease.</td>
</tr>
<tr>
<td></td>
<td>15.0/2 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. G.</td>
<td>1.0/day</td>
<td>7.0</td>
<td>12.0</td>
<td>1.40</td>
<td>3.50</td>
<td>24.4/9</td>
<td>65</td>
<td>Clinical improvement without complete hematologic remission.</td>
</tr>
<tr>
<td></td>
<td>10.0/10 days</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Hematologic remission incomplete.</td>
</tr>
<tr>
<td></td>
<td>12.0/12 days</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>15.0/2 weeks</td>
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</tr>
<tr>
<td></td>
<td>15.0/week</td>
<td>14.5</td>
<td>4.16</td>
<td></td>
<td></td>
<td></td>
<td>37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.5/week</td>
<td>15.5</td>
<td>5.04</td>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td>Complete hematologic remission in one month which has been sustained.</td>
</tr>
<tr>
<td>C. W.</td>
<td>1.0/day</td>
<td>5.0</td>
<td>6.0</td>
<td>1.30</td>
<td>1.80</td>
<td>25.4/8</td>
<td>10</td>
<td>Clinical relapse maintained.</td>
</tr>
<tr>
<td></td>
<td>10.0/10 days</td>
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<td></td>
<td>Slight clinical improvement. Secondary reticulocytopsis observed.</td>
</tr>
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<td></td>
<td>10.0/10 days</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>No significant clinical or hematologic improvement. Tertiary reticulocyte response to 10.0 µg. dose.</td>
</tr>
<tr>
<td></td>
<td>15.0/15 days</td>
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<td></td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0/day</td>
<td>10.5</td>
<td>2.60</td>
<td>None</td>
<td></td>
<td></td>
<td>35</td>
<td>Moderate but incomplete clinical improvement.</td>
</tr>
<tr>
<td></td>
<td>15.0/week</td>
<td>12.5</td>
<td>4.00</td>
<td>2.0/10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.0/week</td>
<td>14.5</td>
<td>4.60</td>
<td></td>
<td></td>
<td></td>
<td>63</td>
<td>Further clinical improvement.</td>
</tr>
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</table>
again incomplete and maximal blood values were subnormal after sixty-five days. Normal hematologic indices were not attained until the equivalent of 3.0 \( \mu g \) daily of vitamin \( B_{12} \) were administered. No improvement in objective signs of combined system disease was demonstrable. A similar experience was observed in patient C. W. He failed to show any clinical remission after ten days of treatment with 1.0 \( \mu g \) of vitamin \( B_{12} \), daily, even though a suboptimal reticulocyte response of 25.4 per cent was observed on the eighth day and a slight rise in hemoglobin and red blood cells was noted. Clinical improvement following administration of 10.0 \( \mu g \) on the eleventh and twenty-first days was not remarkable. Secondary and tertiary reticulocyte peaks were observed and hematologic indices
were improved. Satisfactory clinical and hematologic remissions were not attainment until the dose of vitamin B\textsubscript{12b} was increased to the equivalent of 4.0 \mu g. a day at weekly or bi-weekly intervals. It is also noteworthy that the leukocytes did not rise above 5000 per cu. mm. consistently until this dosage level was used.

Patient J. F. showed a better than anticipated reticulocyte response when treated with 7.5 \mu g. of vitamin B\textsubscript{12b} weekly or 15.0 \mu g. every two weeks. However, on this regimen, he failed to reach normal hematologic levels after fifty-five days and signs and symptoms of progressive spinal cord changes were observed. When the dose of vitamin B\textsubscript{12b} was increased to 15.0 \mu g. a week the blood count rose to normal but no reversal of neurologic disease followed. Subsequent treatment with 30.0 \mu g. of vitamin B\textsubscript{12} or 15 units of liver extract, weekly, had no effect on the spinal cord changes. Patient S. W. showed a poor clinical response following intravenous administration of 7.5 \mu g. of vitamin B\textsubscript{12b}, this dose being repeated a week later. Reticulocyte response after the first injection was suboptimal and a secondary response was elicited after the second treatment. When a plateau of hemoglobin and erythrocyte levels was reached the patient was treated with 1.5 \mu g. of vitamin B\textsubscript{12b}, intramuscularly, daily, and then with this equivalent dose at ten to twenty day intervals. Reticulocyte response during the first ten day period was suboptimal and a secondary response was found after injection of 15.0 \mu g. on the eleventh day. Clinical remission was slow and normal hematologic indices were not attained until after five months.

The 3 patients treated initially with 2.0 \mu g. of vitamin B\textsubscript{12b} daily, or 15.0 \mu g. weekly, showed the usual satisfactory hematologic and clinical remissions seen with adequate doses of liver extract or vitamin B\textsubscript{12}. Although the reticulocyte response in patient K. B. was not optimal the rate of increase of red blood cells was satisfactory and no secondary response was observed after the administration of 15.0 \mu g. on the eleventh day. Patient J. M. showed a better than anticipated reticulocyte rise. Since the hemoglobin and red blood cell values of patient L. S. were 12.5 Gm. per 100 ml. and 3.85 million per cu. mm., respectively, a reticulocyte rise was not expected. However, hematologic remission ensued following treatment with 15.0 \mu g. per week. Regression of signs and symptoms referable to spinal cord changes were reported.

It appears, therefore, that the optimal intramuscular dose of vitamin B\textsubscript{12b} is at least 2.0 \mu g. daily in order to induce a satisfactory hematologic and clinical remission. It is likely, but not certain, that patient M. M. would have attained normal blood levels. It is impossible to state whether patient F. N. would have shown regression of neurologic disease if treated with larger doses of vitamin B\textsubscript{12b}, vitamin B\textsubscript{12} or liver extract. The hematologic response was not optimal. The other 4 patients receiving the equivalent of 1.0 or 1.5 \mu g. of vitamin B\textsubscript{12b} daily, showed poor hematologic and clinical response and required 2.0 to 4.0 \mu g. a day to attain satisfactory clinical remissions. Whether they would have all responded maximally if the initial dose was 2.0 \mu g. a day is uncertain.

Since it has been shown that 2.0 \mu g. of crystalline vitamin B\textsubscript{12b}, daily, intramuscularly, will induce complete clinical and hematologic remissions it appears likely that it is slightly inferior to vitamin B\textsubscript{12} as an anti-anemia factor.
CONCLUSIONS

1. Six patients with pernicious anemia in relapse were treated with 1.0 µg. of vitamin B₁₂ in intramuscularly, daily, for 35 to 210 days. Clinical and hematologic remissions were unsatisfactory in all instances. In 4 cases the dose was increased to 2.0 to 4.0 µg. a day in order to attain optimal results.

2. Three other patients were treated with 2.0 µg. of vitamin B₁₂ intramuscularly, daily, for 90 to 190 days. Satisfactory clinical and hematologic remissions were observed.

3. Crystalline vitamin B₁₂ is probably less potent as an anti-anemia agent than crystalline vitamin B₁₂.

REFERENCES


Treatment of Pernicious Anemia with Crystalline Vitamin B\textsubscript{12b}

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