To better estimate how frequently patients with low serum cobalamin (Cbl) levels in current clinical practice are truly deficient in Cbl and to determine the incidence of atypical or nonclassic presentations of Cbl deficiency, we prospectively studied 300 unselected consecutive patients with serum Cbl concentrations less than 200 pg/mL seen at two medical centers over a 2-year period. Baseline hematologic, neuropsychiatric, and biochemical measurements were obtained, followed by a course of parenteral Cbl therapy and reassessment. A response to Cbl therapy was defined as one or more of the following: (1) an increase in hematocrit of 0.05 or more; (2) a decrease in mean cell volume of 5 fl or more; (3) a clearing of hypersegmented neutrophils and macroovalocytes from the peripheral blood smear; and (4) an unequivocal and prompt improvement of neuropsychiatric abnormalities. Of the 300 patients with serum Cbl levels less than 200 pg/mL, 86 had one or more responses to Cbl therapy and 59 had no response. In 155, insufficient data was available. In the Cbl-responsive patients, normal values were found for the following tests: hematocrit, 44%; mean cell volume ≤100 fl, 36%; white blood cell count, 84%; platelet count, 79%; serum lactic dehydrogenase, 43%; and serum bilirubin, 83%. Peripheral blood smears were nondiagnostic in 6% when reviewed by the investigators, but 33% as reported by routine laboratories. Serum Cbl levels in the 100 to 199 pg/mL range were present in 38%. Neuropsychiatric abnormalities were noted in 28%, often in the absence of anemia, macrocytosis, or both. Serum levels of methylmalonic acid and/or total homocysteine were elevated greater than 3 SDs above the mean for normal subjects in 94% of the Cbl-responsive patients. We conclude that Cbl deficiency should be considered and investigated in patients with unexplained hematologic or neuropsychiatric abnormalities of the kind seen in Cbl deficiency, even if anemia, an elevated mean cell volume, a marked depression of the serum Cbl, or other classic hematologic and biochemical abnormalities are lacking. Levels of serum methylmalonic acid and total homocysteine are useful as ancillary diagnostic tests in the diagnosis of Cbl deficiency.

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MATERIALS AND METHODS

Patients. During the 2-year period between September 1983 and August 1985, there were 7,747 serum samples submitted for assay of Cbl at Harlem Hospital Center and Columbia-Presbyterian Medical Center (New York, NY). The serum Cbl tests were ordered by internists, neurologists, surgeons, and other attending and house staff physicians involved in the care of ward and private patients who were either hospitalized or seen as outpatients. The serum Cbl level was less than 200 pg/mL in a total of 300 samples. In accord with standard practice in our laboratory, all samples in the range of 180 to 220 pg/mL were re assayed a second time. For samples with original values in the 180 to 199 pg/mL range that were below 200 pg/mL on retesting, the lowest of the two values was used. If a sample with an original value of 200 to 220 pg/mL had a value of less than 200 pg/mL on retesting or if a sample with an initial value of 180 to 199

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pg/mL had a value of greater than 200 pg/mL on retesting, they were assayed for a third time. If 2 of the 3 values for these samples were ≥200 pg/mL, the lowest value was used and the patient was included in the study. If 2 of the 3 values were ≥200 pg/mL, the patient was excluded.

Every attempt was made to obtain a full history, physical examination, and laboratory evaluation both before and after therapy with multiple injections of 1,000-μg doses of parenteral Cbl. We defined patients as Cbl-responsive if they had one or more of the following responses to Cbl therapy: (1) an increase in hematocrit of 0.05 or more; (2) a decrease in mean cell volume of 5 fl or more; (3) disappearance of hypersegmented polymorphonuclear leukocytes and macroovalocytes on the peripheral smear; and (4) improvement of neuropsychiatric abnormalities that was unequivocal and prompt examination, and laboratory evaluation both before and after disappearance of hypersegmented polymorphonuclear leukocytes.

We defined patients as Cbl-responsive if they had one or more of the following responses to Cbl therapy: (1) an increase in hematocrit of 0.05 or more; (2) a decrease in mean cell volume of 5 fl or more; (3) disappearance of hypersegmented polymorphonuclear leukocytes and macroovalocytes on the peripheral smear; and (4) improvement of neuropsychiatric abnormalities that was unequivocal and prompt.

### Methods

The interpretations of blood smears by the routine hematology laboratories were noted. In addition, when available, smears were coded and interspersed with those of patients without evidence of Cbl or folate deficiency for blinded review by one of the authors (D.G.S. or J.L.). Hypersegmentation was defined as any six-lobed or more than five five-lobed cells/100 neutrophils. Serum Cbl and folate levels were determined by radioassay using purified intrinsic factor and milk folate binding proteins, respectively (Quan- taphase, Bio-Rad Laboratories, Richmond, CA). Based on a study of 238 healthy adults and 105 patients with proven Cbl deficiency, the manufacturer's stated diagnostic ranges are normal (greater than 200 pg/mL), indeterminate (160 to 200 pg/mL), and deficient (less than 160 pg/mL). The mean (±1 SD) serum Cbl level in 125 healthy normal residents of New York, NY (59 male, 64 female; median age 35.5 years; range 21 to 76 years) as measured in one of the authors' (J.L.) laboratories was 509 ± 176 pg/mL; after log transformation because of skewness of higher values, the calculated normal range based on 2 SDs around the mean was 230 to 990 pg/mL. Within- and between-run coefficients of variation averaged 5.2% and 6.3%, respectively. The laboratory's normal range for the serum folate level is 2.1 to 13.0 ng/mL. Serum methylmalonic acid9,23 and total homocysteine9,23 concentrations were measured by recently developed techniques using capillary-gas chromatography and mass spectrometry.

### RESULTS

**Cbl-responsive patients.** The frequency of the various responses to Cbl therapy in the 86 Cbl-responsive patients are shown in Table 1. There were 43 (50%) patients who had an increase in hematocrit of 0.05 or more, 70 (81%) patients who had a decrease in mean cell volume of 5 fl or more, 41 (48%) patients who cleared hypersegmented polymorphonuclear leukocytes and macroovalocytes from the peripheral blood smear, and 24 (28%) patients who had significant improvement in neuropsychiatric abnormalities. Follow-up blood smears were not available in 17 patients with hypersegmentation. Of the 86 patients in the Cbl-responsive group, 28 (33%) had a single response, 27 (31%) had two, 28 (33%) had three, and 3 (3%) had four responses.

 Diagnostic studies were adequate to determine the etiology of the Cbl deficiency in 78 of the 86 patients. Pernicious anemia, as demonstrated by serial Schilling tests or serum antibodies to intrinsic factor, was established in 53 patients and was considered likely to be present in an additional 7;
16 had malabsorption of Cbl due to other causes (eg, tropical sprue, gastric or ileal resection, jejunal diverticula); and 2 were strict vegetarians. At the time the serum Cbl was found to be decreased, 62 (72%) of the patients had symptoms that appeared to be caused by lack of Cbl.

The hematocrits and mean cell volumes of the 57 women in the Cbl-responsive group are plotted in Fig 1A. The values from only 23 (43%) were in the upper-left quadrant, which contains patients with both anemia and an elevated mean cell volume. Only six (10%) had both marked anemia (hematocrit less than 0.25) and marked macrocytosis (mean cell volume greater than 110 fL). There were 14 (25%) who had an elevated mean cell volume but a normal hematocrit (upper-right quadrant), and five (8%) who were anemic but had a normal mean cell volume (lower-left quadrant). In 15 women (26%), both the hematocrit and mean cell volume were normal (lower-right quadrant).

The data from the 29 men in the Cbl-responsive group, shown in Fig 1B, were similar to those obtained for the women. There were 17 (59%) male patients with anemia and an elevated mean cell volume; in only six (21%) was the hematocrit less than 0.25 and the mean cell volume greater than 110 fL. There were three (10%) males in the normal hematocrit, elevated mean cell volume group and three (10%) with a decreased hematocrit and normal mean cell volume. In six men (21%), both the hematocrit and mean cell volume were normal.

In all of the eight patients (five men and three women) who presented with anemia and a normal mean cell volume, another cause for anemia in addition to lack of Cbl (eg, iron deficiency, gastrointestinal bleeding) was present.

There were 24 patients in whom neuropsychiatric abnormalities responded to Cbl. These patients are indicated by the solid circles in Fig 1. In 7 of the 24, the hematocrit and mean cell volume were both normal; only seven had the combination of a decreased hematocrit and an elevated mean cell volume. Only 1 of the 24 had a hematocrit less than 0.25 and a mean cell volume greater than 110 fL.

The distribution of serum lactic dehydrogenase levels is shown in Fig 2. Only 14 (20%) of the 70 Cbl-responsive
Fig 2. Serum lactic dehydrogenase levels in 70 of the 86 Cbl-responsive patients in whom values were available. The horizontal line represents the mean ± 2 SDs for normal subjects. Solid circles (○) represent patients whose response to Cbl therapy included improvement in neuropsychiatric abnormalities.

patients in whom lactic dehydrogenase levels were available had markedly elevated levels (above 600 U/L). In all of these patients the hematocrit was ≤26%. Normal values were found in 30 (43%) patients, and 26 (37%) had only modest elevations (225 to 600 U/L). Serum lactic dehydrogenase levels were available on 19 of the 24 patients that had a neuropsychiatric response to Cbl therapy, and only one of these patients had a value above 600 U/L.

Serum Cbl levels in the 86 Cbl-responsive patients are presented in Fig 3. In 33 patients (38%), the serum concentration was above 100 pg/mL. Serum levels greater than 100 pg/mL were observed in 10 (42%) of the 24 Cbl-responsive patients who had a neuropsychiatric response to Cbl therapy.

Of the 86 Cbl-responsive patients, there were only two (2.3%) in whom all of the following findings were present: hematocrit less than 0.25, mean cell volume greater than 110 fL, leukopenia, thrombocytopenia, serum lactic dehydrogenase greater than 600 U/L, and serum Cbl less than 100 pg/mL.

Comparison of patient groups. Data concerning the pretreatment hematologic data in the 86 Cbl-responsive patients is summarized in Table 2, together with similar data for the 59 Cbl-responsive patients and the 155 patients whose Cbl response could not be evaluated because of insufficient information. Normal hematologic values were very common in the Cbl-responsive group. Anemia was absent in 44%, 36% did not have a mean cell volume greater than 100 fL, 84% had a normal white blood cell count, and 79% had a normal platelet count. The peripheral blood smear was reported as normal or showing only anisocytosis by the routine laboratories in 33% of the Cbl-responsive patients, although only 6% failed to demonstrate hypersegmented neutrophils and macroovalocytes when the smears were reviewed by the investigators.

None of the hematologic abnormalities could be used to completely distinguish the Cbl-responsive patients from the Cbl-nonresponsive patients. The greatest difference was in the incidence of abnormal peripheral blood smears as reviewed by the investigators. Of the 63 smears available for evaluation from Cbl-responsive patients, 94% were abnormal as compared with only 10% of the 39 smears available from the Cbl-nonresponsive group. Marked anemia (hematocrit

Fig 3. Serum Cbl levels in 86 Cbl-responsive patients. Solid circles (○) represent patients whose response included improvement in neuropsychiatric abnormalities.
less than 0.25) was more frequent in the responsive patients (20%) than in those who did not respond (5%). Marked macrocytosis (mean cell volume greater than 110 fL) was seen much more frequently in the responsive than nonresponsive patients (36% vs 2%, respectively). Nevertheless, moderate anemia (hematocrit greater than 0.25), lack of anemia, moderate macrocytosis (mean cell volume greater than 100 to 110 fL), and lack of macrocytosis (mean cell volume ≤100 fL) were very common in both the Cbl-responsive and Cbl-nonresponsive groups.

Other data concerning the Cbl-responsive and nonresponsive groups are presented in Table 3. No single laboratory test could be relied on to distinguish between the Cbl-responsive and nonresponsive patients. Marked increases in serum lactic dehydrogenase (greater than 600 U/L), an elevated serum folate, the presence of anti-intrinsic factor antibodies, an abnormal Schilling test, and a serum Cbl less than 100 pg/mL occurred more frequently in the Cbl-responsive group. However, these findings were either absent in substantial numbers of the responsive patients, present in some of the nonresponsive patients, or both.

**Serum metabolites.** The values for serum methylmalonic acid and serum total homocysteine of the patients responding to Cbl are illustrated in Fig 4 and of those in the nonresponsive group in Fig 5. The use of the mean ± 3 SDs gives a better separation of responsive and nonresponsive subjects than the mean ± 2 SDs. The data for all three patient groups is summarized at the bottom of Table 3.

Only 5 (6%) of the 86 Cbl-responsive patients did not have a marked elevation (greater than 3 SDs above the mean for normal subjects) of serum methylmalonic acid and/or serum total homocysteine. In 66 (77%) both metabolites were markedly elevated, while eight (9%) had an isolated elevation of methylmalonic acid and seven (8%) an isolated elevation of total homocysteine. The five patients without a marked elevation of either metabolite were all in the group that had only a single response to Cbl therapy (Table 1). The distribution of values for the 24 patients with a neuropsychiatric response to Cbl therapy are indistinguishable from those of the group as a whole. Values for serum methylmalonic acid and total homocysteine obtained after treatment with parenteral cobalamin were available from 55 of the 81 patients with initial elevations of one or both metabolites. In all 55, there was a decrease of methylmalonic acid and/or total homocysteine to normal or to less than 50% of the pretreatment value.

Only 5 (8%) of the 59 patients who did not respond to Cbl had marked elevations of both serum methylmalonic acid and serum total homocysteine. Another eight (14%) had an isolated marked elevation of serum methylmalonic acid while five (8%) had an isolated marked elevation of serum total homocysteine; in 41 (69%) neither metabolite showed a marked elevation. Of the 18 patients in the Cbl-nonresponsive group that had a marked elevation of one or both metabolites, nine had pernicious anemia or Cbl malabsorption; one had hemosiderosis; and another had a Schilling test of 0.25. Only 6 (10%) of the 59 patients who showed no response to Cbl therapy had unexplained elevated values of 1 of the 2 metabolites. None of the six had elevated values of both metabolites. One of them, in whom a Schilling test was not done, had previously had a gastrectomy, and another, who had a normal Schilling test, had a markedly elevated serum gastrin level (1,000 pg/mL).

**Neuropsychiatric signs and symptoms.** Table 4 lists the neuropsychiatric abnormalities and their response to Cbl therapy in the 24 Cbl-responsive patients who had a neuropsychiatric response to Cbl therapy. In all 24 responsive patients, serum methylmalonic acid and/or total homocysteine returned to normal or to less than 50% of the pretreatment value. None of the patients had a neurological or psychiatric disorder that could be attributed to vitamin B12 deficiency.
results of many of the tests listed in Tables 2 and 3 (eg, altered by Cbl therapy. Ataxia, and impaired vibration sense, none of which were associated with disorientation in 2, frank psychosis in 2, and Cbl treatment, even though hematologic responses occurred. Six with neuropsychiatric disorders that did not improve after both groups, and no individual sign or symptom distinguished one from the other. Impaired vibration, touch/pain and symptoms referable to the nervous system were similar in both groups, and no individual sign or symptom distinguished one from the other. Impaired vibration, touch/pain and position senses, and abnormal gait were the most common neurologic signs that responded to Cbl therapy. Paresthesias and ataxia were the most common symptoms that responded, but were also frequently present in the Cbl-nonresponsive group.

In the Cbl-responsive group, in addition to the 24 patients who had neuropsychiatric responses to therapy, there were six with neuropsychiatric disorders that did not improve after Cbl treatment, even though hematologic responses occurred. Memory loss was prominent in 5 of these patients and was associated with disorientation in 2, frank psychosis in 2, and labile affect in 1. The sixth patient had muscle weakness, gait ataxia, and impaired vibration sense, none of which were altered by Cbl therapy.

**Patients with unknown Cbl status.** With respect to the results of many of the tests listed in Tables 2 and 3 (eg, percent with mean cell volume (MCV) elevations, blood smear abnormalities, very low serum Cbl levels, or antibodies to intrinsic factor), the patients with unknown Cbl status resembled those who did not respond to Cbl more than those who did. However, more than half of the unknown Cbl status group had a marked elevation of one or both serum metabolite concentrations (Table 3), and in most instances there was no apparent explanation other than Cbl deficiency for the increased metabolite levels. In 25 patients, the serum folate was decreased. In 15 of them, the serum total homocysteine was markedly elevated but the serum methylmalonic acid was not; in 7 of these 15, hypersegmented neutrophils and macroovalocytes were found on blood smears.

### DISCUSSION

A deficiency of Cbl (vitamin B12) can cause a number of hematologic and neuropsychiatric abnormalities. The former include anemia, an elevated erythrocyte mean cell volume, decreased white blood cell and platelet counts, the presence of hypersegmented neutrophils and macroovalocytes on pe-
The findings of our study indicate that if the serum Cbl is used liberally as a screening test, many patients will be identified who respond to treatment but who lack the florid manifestations of Cbl-deficiency as described in many textbooks. Leading textbooks of internal medicine, hematology, neurology, and family practice teach that the typical patient with Cbl deficiency has an elevated erythrocyte mean cell volume that is usually markedly increased, a moderately decreased white blood cell and platelet and an elevated serum lactate dehydrogenase level that is usually markedly increased. A variety of neuropsychiatric abnormalities may be seen, and it has long been known that they may occur without overt anemia. Nevertheless, their presence in the absence of anemia or macrocytosis is said to occur only occasionally or exceptionally.

Of our 86 Cbl-responsive patients, 44% were not anemic and another 36% had hematocrits above 0.25. The mean cell volume was ≤100 fL in 36% and in the range of greater than 100 to 110 fL in another 28%. The white blood cell and platelet counts were decreased in only 14% and 21% of the patients, respectively, and the lactate dehydrogenase was normal in 43%. Neuropsychiatric abnormalities which responded to Cbl therapy that were present in 24 of our 86

Fig 4. Pretreatment levels of serum methylmalonic acid (A) and serum total homocysteine (B) in 86 Cbl-responsive patients who are defined as described under Materials and Methods. Horizontal lines represent the mean ± 2 or ± 3 SDs from the mean for normal subjects. Solid circles (●) represent patients whose response included an improvement in neuropsychiatric abnormalities.
Cbl-responsive patients, occurred commonly in the absence of anemia (58%), in the absence of a mean cell volume greater than 100 fL (42%), in the absence of at least one of these two findings (71%), or in the absence of both (25%).

Our findings, in the context of careful follow-up examination after therapy (in a large series of patients), therefore confirm and extend the observations of previously published studies that Cbl deficiency frequently presents with "atypical" or subtle hematologic manifestations. Our study almost certainly underestimates the frequency of normal or mildly abnormal hematologic and biochemical findings in Cbl deficiency. Many physicians do not order a serum Cbl level in patients who lack various hematologic and biochemical abnormalities, and therefore such patients would not have been included in our study. Furthermore, our investigation was limited to patients with serum Cbl levels less than 200 pg/mL.

Textbooks are also in almost universal agreement with the concept that the serum Cbl level is not merely low (less than 200 pg/mL) in Cbl deficiency, but is characteristically markedly decreased (less than 100 pg/mL). Our study demonstrates that exceptions to this concept are so common that it cannot be considered valid: 38% of our 86 Cbl-responsive patients had serum Cbl levels in the 100 to 199 pg/mL range, and 10% of the 59 patients in the nonresponsive group had levels less than 100 pg/mL.

Of the 300 consecutive patients with low serum Cbl levels in our study, 86 were clearly Cbl-responsive; a minority of the nonresponders had underlying Cbl malabsorption states such as pernicious anemia; and one or both serum, metabolite concentrations were elevated in approximately half of the 155 patients of unknown Cbl status (Table 3). It is a reasonable estimate, then, that the majority of the 300 patients were deficient in Cbl or had underlying disorders predisposing to the development of clinical evidence of deficiency. Our observations lead us to conclude that the finding of a low serum Cbl must be taken seriously, even in patients with little or no obvious hematologic evidence of deficiency, as has been argued by others and that the diagnosis of Cbl deficiency should be considered and pursued in every patient with unexplained hematologic or neuropsychiatric abnormalities of the kind seen in Cbl deficiency. We believe that the serum Cbl assay should be used as the initial screening test in such patients because of its apparent sensitivity, relatively low cost, and wide availability. However, our findings also indicate that a substantial fraction of patients with low serum Cbl levels will not respond to therapy and also do not have elevations of serum metabolite concentrations. Therefore, it is likely that not infrequently a subnormal serum Cbl level is of little clinical significance. In many patients with low (less than 200 pg/mL) or low normal (200 to 300 pg/mL) levels of serum Cbl, there will be a need for additional diagnostic tests to determine which patients are Cbl-deficient and will benefit from and require lifetime

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Fig 5. Pretreatment levels of serum methylmalonic acid (A) and serum total homocysteine (B) in 59 Cbl-nonresponsive patients who are defined as described under Materials and Methods. Horizontal lines represent the mean ± 2 or ± 3 SDs from the mean for normal subjects. Squares that contain an X represent patients with serum anti-intrinsic factor antibodies, abnormal Schilling tests, or both. The single asterisk denotes a patient with an apparent primary defect of L-methylmalonyl-CoA mutase or adenosyl-Cbl synthesis in whom an isolated marked elevation of methylmalonic acid did not respond to cobalamin therapy. The double asterisk denotes a patient with chronic renal failure and a serum creatinine of 5.9 mg/dL in whom markedly elevated methylmalonic acid and total homocysteine levels did not respond to Cbl therapy. The triple asterisk denotes a patient who 6 weeks previously at another hospital had a hematocrit of 0.20 and a mean cell volume of 135 fL, and had already responded to Cbl therapy with correction of the anemia and a decrease of the mean cell volume to 98 fL before entry into the study.
ried examination of the blood smears by a trained observer is morphologic abnormalities nonetheless often had elevated

tion who did not respond to vitamin therapy and who lacked our observation that patients with underlying Cbl malabsorp-
six-lobed neutrophils were seen per 100 granulocytes by the one third of the Cbl-responsive patients' blood smears were

highly reproducible. An advantage of the measurement of investigators, a finding that could not be expected to be

Cbl and folate deficiency, metabolite elevations decrease in Cbl and folate deficiency, metabolite elevations decrease

which are now available via several national reference laboratories, need not require additional patient visits since

assays can be performed on serum that remains in the laboratory after the serum Cbl is measured. Metabolite

assays can be repeated after 7 to 14 days of therapy to assess therapeutic responsiveness. Recent studies have shown that in Cbl and folate deficiency, metabolite elevations decrease to normal if the appropriate vitamin is used, but remain essentially unchanged if the wrong vitamin is administered even in pharmacologic amounts. The only other ancillary test that performed as well in the identification of Cbl-responsive patients was the detection of neutrophil hypersegmentation and macroovalocytes on blood smear by a trained hematologist. However, it should be emphasized that the morphologic changes were often subtle in patients without anemia, and one third of the Cbl-responsive patients' blood smears were read as normal by our routine hospital laboratories. In several patients who responded to Cbl, only one or two six-lobed neutrophils were seen per 100 granulocytes by the investigators, a finding that could not be expected to be highly reproducible. An advantage of the measurement of serum metabolite concentrations over even a careful unhurried examination of the blood smears by a trained observer is our observation that patients with underlying Cbl malabsorption who did not respond to vitamin therapy and who lacked morphologic abnormalities nonetheless often had elevated metabolite concentrations that returned to normal after treatment.

Based on current information and availability, other choices for such ancillary tests are limited to the following: (1) serum antibodies to intrinsic factor, which is inexpensive and has the advantage of high specificity for pernicious anemia, but will fail to diagnose 40% to 50% of such patients as well as all patients with other causes of Cbl deficiency; (2) the Schilling test, which requires a reliable 24-hour urine collection and additional patient visits to a nuclear medicine facility and will fail to diagnose deficient patients who only malabsorb Cbl from food sources; and (3) a course of multiple parenteral Cbl injections over 8 to 16 weeks followed by clinical and laboratory reevaluation for improvement in initial abnormalities, although the therapeutic trial may need to be continued for up to a year in cases with neuropsychiatric abnormalities. Additional clinical studies will be required to learn more about the comparative value of these approaches or some combination of them.

We presently are studying the utility of performing assays for serum methylmalonic acid, total homocysteine, and anti-intrinsic factor antibodies on all patients with serum Cbl levels less than 300 pg/mL, and in rare patients with values greater than 300 pg/mL where the clinical picture is extremely suggestive of Cbl deficiency. Patients with a marked elevation of one or both metabolites or who have anti-intrinsic factor antibodies are then treated with Cbl and observed for objective responses. Based on our preliminary results obtained over the past several years with this ap-

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### Table 4. Neuropsychiatric Abnormalities in the Cbl-Responsive and Cbl-Nonresponsive Patients

<table>
<thead>
<tr>
<th>Abnormality</th>
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<th>Cbl-Nonresponsive Patients</th>
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*There were six additional patients in the Cbl-responsive group who had neuropsychiatric abnormalities that did not respond to Cbl therapy (see text for details).
proach, we estimate that 90% to 95% of Cbl-deficient patients have serum Cbl levels less than 200 pg/mL, that 5% to 10% have values in the 200 to 300 pg/mL range, and that 0.1% to 1% have values greater than 300 pg/mL.41

At the time of presentation, the 86 patients found to respond to Cbl in the present study often differed strikingly from those described in standard texts. The widespread availability of determinations of the mean cell volume and serum Cbl in current clinical practice has enabled the recognition of more subtle manifestations of the deficiency state. In addition, our attempt to fully evaluate and treat every available patient with a low serum Cbl regardless of preconceived notions has allowed better definition of a much wider spectrum of Cbl deficiency.

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