REVIEW ARTICLE

Juvenile Selective Vitamin B$_{12}$ Malabsorption: 50 Years After Its Description—10 Years of Genetic Testing

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ABSTRACT: Fifty years have passed since the description of juvenile selective malabsorption of cobalamin (Cbl). Quality of life improvements have dramatically reduced the incidence of parasite-induced or nutritional Cbl deficiency. Consequently, inherited defects have become a leading cause of Cbl deficiency in children, which is not always expressed as anemia. Unfortunately, the gold standard for clinical diagnosis, the Schilling test, has increasingly become unavailable, and replacement tests are only in their infancy. Genetic testing is complicated by genetic heterogeneity and differential diagnosis. This review documents the history, research, and advances in genetics that have elucidated the causes of juvenile Cbl malabsorption. Genetic research has unearthed many cases in the past decade, mostly in Europe and North America, often among immigrants from the Middle East or North Africa. Lack of suitable clinical testing potentially leaves many patients inadequately diagnosed. The consequences of suboptimal Cbl levels for neurological development are well documented. By raising awareness, we wish to push for fast track development of better clinical tools and suitable genetic testing. Clinical awareness must include attention to ethnicity, a sensitive topic but effective for fast diagnosis. The treatment with monthly parenteral Cbl for life offers a simple and cost-effective solution once proper diagnosis is made. (*Pediatr Res* 70: 222–228, 2011)

Vitamin B$_{12}$ (Cobalamin) Deficiency

In the Western world, lack of vitamin B$_{12}$ alias cobalamin (Cbl) is usually because of malabsorption of this nutrient. In the following we focus on selective malabsorption, where the malabsorption affects in principle only one nutrient, Cbl. At least two such hereditary conditions are known. Recessive mutations in the gene *GIF* (OMIM#609342), coding for the synthesis of gastric intrinsic factor (IF), cause IF deficiency (IFD; OMIM#261000). Biallelic mutations in *CUBN* (OMIM#602997) or *AMN* (OMIM#605779), encoding the receptor for the Cbl-IF complex in the ileum, cause Imerslund-Gräsbeck syndrome (IGS; OMIM#261100).

Sometimes Cbl malabsorption is more-or-less selective, *e.g.* in general malabsorption because of gluten intolerance or tropical sprue (1), intestinal blind loops and diverticulitis with a Cbl-consuming bacterial flora (2), in pancreatic insufficiency and in poor gastric function. Inability to liberate Cbl from food is common in older adults (3). Finally, the fish tapeworm inhibits Cbl absorption by competing for the vitamin (4).

The classical manifestation of Cbl deficiency is macrocytic-megaloblastic anemia and combined degeneration of the spinal cord, but often the neurological symptoms are not observed until sought for (2,5,6). Absence of blood abnormalities may be due to high intake of folate but treatment of Cbl deficiency with folate may mask and worsen the neurological manifestations (2,5). During recent years, infertility, cardiovascular disease (homocysteine induced), and osteoporosis have been advanced as new and often the only clinical long-term signs of mild deficiency (7,8). In persons elder than 65 y, about 12% have Cbl deficiency defined with biochemical parameters (9). One cause may be failure to release food-bound Cbl with increasing age (10).

Long ago, the vitamin A or fat load test (11) revealed that Cbl deficiency in itself induces general malabsorption which also includes Cbl (Ref. 12; Fig. 1) and other nutrients (5). Apparently, the enterocytes suffer from the deficiency. The misleading failure in IF deficiency (pernicious anemia or IFD) to respond to the administration of IF in the Schilling absorption test (13) is probably also a manifestation of enterocytic malfunction. The realization that Cbl deficiency caused general malabsorption led to the finding of several new cases of IGS (14). Thus, Cbl deficiency (*e.g.* because of poor diet) causes reduced Cbl absorption, thereby producing a vicious circle.

Discovery and History of Imerslund-Gräsbeck Syndrome

This condition was described simultaneously in Norway by the pediatrician Imerslund (15) and in Finland (16). Many
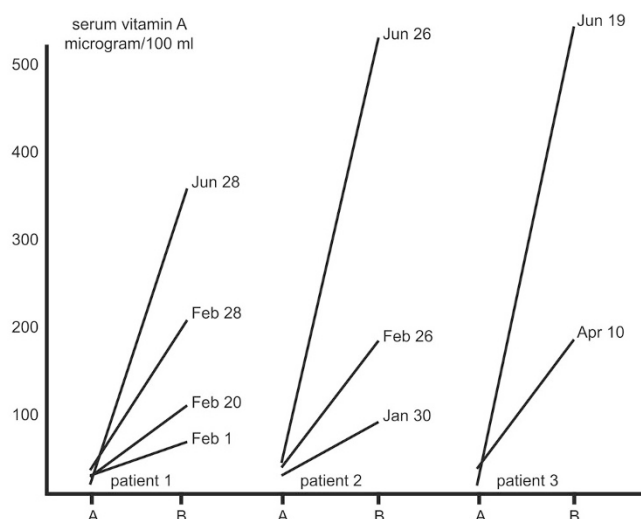
Abbreviations: **Cbl,** cobalamin (vitamin B$_{12}$); **CNCbl,** cyanocobalamin; **CUB,** complement C1r/C1s, Uegf, Bmp1; **IF,** intrinsic factor; **IFD,** intrinsic factor deficiency; **IGS,** Imerslund-Gräsbeck syndrome; **TC,** transcobalamin (also called transcobalamin 2)

Figure 1. Vitamin A load test during parenteral treatment with Cbl. Gradual increase in the vitamin A (fat) load test values over time in 3 patients with pernicious anemia, after parenteral treatment with Cbl. A = basal value and B = value after oral loading dose. Adapted from Gräsbeck R, Nord Med 68:1232–1234. Copyright © 1962 Nordisk Medicin, with permission.

names have been used for the condition. The most commonly used name is Imerslund-Gräsbeck syndrome (IGS) (17).

The first case was an 11-y-old boy. Since the age of 2 y, he had been investigated and treated for megaloblastic anemia and proteinuria at irregular intervals. R.G. was consulted to elucidate the condition. It was found to be due to poor absorption of practically only Cbl. The case was reported at a pediatric congress in 1958 (18). At this early stage, it was already assumed that the error was located in the ileal acceptor (receptor) for vitamin B$_{12}$ and that something similar affected the kidney tubules known to have many properties in common with the intestine (18,19).

The next Finnish case was found under circumstances that could be called serendipity: a student nurse in the ward where R.G. was a resident presented with identical symptoms. This strongly suggested that the two patients had the same disease or syndrome. That the condition was hereditary was suggested by the fact that the parents of the female patient were double cousins.

The two cases were thoroughly examined using up-to-date methods available to investigate Cbl deficiency because of the current research on tapeworm anemia in the department. Kidney biopsies were also performed. Suspecting that the condition represented a hitherto unknown disease entity a manuscript was drawn up. Just before its submission, it was discovered that Imerslund in Norway had collected similar cases and was preparing her dissertation. This confirmed that the syndrome existed, and we published the article (16) where the title indicated the pathogenesis "selective vitamin B$_{12}$ malabsorption." The possible common origin of the intestinal and renal tubular conditions was also pointed out.

Imerslund's (15) dissertation describing 10 cases in 6 families demonstrated that the syndrome existed; that the condition was hereditary, autosomal, and recessive; that functioning IF was secreted; and that the patients did not respond to IF (gastric juice) given together with Cbl by mouth. Despite

proteinuria, kidney function was and remained good. In addition, Imerslund found anomalies in the urinary tract (double ureters and horseshoe kidney). Such findings have not been made by others. Broch, who has continued Imerslund's work in Norway, has not found such new cases either (Ref. 20 and personal communication). Combinations with other anomalies seem to be fortuitous (21).

Imerslund's dissertation did not pass "probably because too few laboratory investigations had been made" (Seip letter to Gräsbeck in 1994), which apparently means that few attempts at elucidating the pathogenetic mechanism had been made. Thus, it was not certain that the Finnish and Norwegian patients suffered from the same condition. However, using radioactive Cbl and other techniques, Imerslund and Bjørnstad (22) later made the same observations that had been made on the Finnish patients.

These first concrete observations were preceded by reports which may represent the same disease, but at the time of their publication radioactive Cbl absorption and other tests did not exist. The case reported by Najman and Brausil (23) is usually quoted. These authors suggested that their case was because of low secretion of IF. Moreover, until recently there was little awareness that an absent or inactive IF could imitate IGS (24).

Following the first reports, Lamy *et al*. (25) quickly reported four similar cases from France. In 1967, we were aware of 47 cases (14). At present, >300 have been published worldwide, but in many cases the diagnosis may be uncertain and some represent cases of IFD (24). In 2006, there were 27 cases from 19 families in Finland and 19 cases from 15 families in Norway (17). Today, most new cases have appeared in the Middle East, and in Europe and North America about 50% of newly diagnosed cases are detected among recent immigrants from North Africa and the Middle East (Tanner, unpublished results). In Finland and Norway, the estimated prevalence is 1:200,000 (17) but worldwide prevalence is hard to estimate. Most recently, a case from Thailand was confirmed genetically (Tanner, unpublished results).

Patient age at diagnosis varies from a few months to puberty. The patients present with diffuse symptoms such as failure to grow and thrive, pallor and fatigue, and recurrent respiratory and gastrointestinal infections. Laboratory investigations usually reveal anemia, low serum Cbl and/or proteinuria. In most cases, the neurological signs appear mild, but exceptions exist. An IGS case compound-heterozygous for two *AMN* mutations showed severe psychiatric instability (26). Only high-dose parenteral Cbl of 1 mg biweekly prevented behavioral relapses, whereas hematological symptoms were cured by a standard dose of 1 mg/mo. The conclusion was that the Cbl receptor may play a role at the blood-brain barrier (26). Nevertheless, Cbl deficiency may express itself only in the results of laboratory tests or after a meticulous search for clinical symptoms. Especially when the relatives of confirmed cases are examined, new cases may be discovered. Interesting possibilities are that children with monosymptomatic "benign" proteinuria or behavioral disturbances may suffer from undiagnosed IGS; therefore assay of serum Cbl of such patients seems advisable.

The combination of megaloblastic anemia and proteinuria attracted both discoverers of the syndrome. However, two of Imerslund's original cases lacked proteinuria and in 1967 two of our 19 patients lacked proteinuria (14). In a study of 13 Finnish patients (27), only 3 clearly excreted increased amounts of total protein, including albumin and smaller amounts of transferrin, light immunoglobulin chains, and alpha$_1$ and beta$_2$ microglobulins. Three cases excreted only modest amounts of protein and the rest had barely increased excretion levels. One explanation for the finding of more nonproteinuric patients may be that the diagnosis was based on mutational analysis, which may reveal clinically less conspicuous patients among relatives of typical patients.

Imerslund died in 1987 and her patients have been supervised since then by Broch (20). He and others, including ourselves have performed kidney biopsies on untreated and treated patients (14,28–30). In untreated patients, weak signs of membranous glomerulonephritis were observed in light microscopy. In electron microscopy, mild signs of glomerulopathy of mesangioproliferative type, increased mesangial matrix, thickening of the basal membrane, and mesangial deposits were detected. Some patients have been biopsied before and after the correction of the deficiency state, and after treatment the pathological kidney findings have usually disappeared (14). Broch recently reported to R.G. that the oldest Norwegian patient died in an accident. He had been biopsied before treatment and electron microscopic changes had been observed, but they were absent in the specimens taken at autopsy. Evidently, the changes have been because of the Cbl deficiency, which affects all cells in the body, enterocytes included. But the proteinuria persists after Cbl treatment and is probably because of the malfunction of the receptor in the kidney (31). There is general agreement that kidney function does not worsen in treated patients, some of which have been observed for more than 50 y.

Intestinal biopsies were performed at an early date and showed no pathology (14,32). Considerable efforts were expended to elucidate the structure of the Cbl-IF receptor in the ileum and its defect in IGS. For instance, it was demonstrated that the binding to the receptor required calcium ions (33,34) and later that the receptor contained two subunits (31,35). The receptor has therefore been called cubam (*cubi*lin and *am*nionless) (31). Decreased urinary excretion of the receptor was found in the Finnish patients, whereas some Arab patients could even excrete increased amounts (36,37). Those patients were probably incorrectly diagnosed and suffered from lack of IF. The overall conclusion was that the disease had subsets, apparently because of different genetic errors (37). Then it was reported that the kidney receptor was identical with the intestinal one and also bound ligands other than Cbl-IF (38,39). That the receptor had several ligands was philosophically satisfying, because it seemed "luxurious" that evolution has produced one special membrane receptor for each substrate. It seems more likely that membrane transport mechanisms are variants on the same theme (40). The detailed structure of the receptor was recently described and excellently illustrated by Nielsen and Christensen (41) and Andersen *et al.* (42). The similarity of the kidney and ileal receptors is striking, but the

two may not be completely identical. The kidney receptor mediates the reabsorption of many proteins. Uptake of nonhuman proteins in the intestine would probably elicit an immune response and be an undesirable property perhaps removed during evolution. Incidentally, porcine IF causes an immune response when given by mouth to patients (43).

The Genetic Errors

In the early 1990s, at the instigation of Albert de la Chapelle a search began to reveal the genetic error causing IGS. The error in Finnish patients was localized by linkage analysis to the short arm of chromosome 10 (44). However, attempts to identify the responsible gene failed at first. Instead, Moestrup *et al.* (45) cloned the gene for the intestinal Cbl receptor. They also demonstrated that the gene was localized to the locus in chromosome 10 affected by IGS (46) and the following year, mutations in the *CUBN* gene in the affected Finnish families were published (47).

The *CUBN* encoded protein named cubilin was found in membrane transport systems in the intestine, kidney, and yolk sack. It is a multiligand receptor with a molecular weight of about 460 kD when glycosylated, and it was found to be identical to the intestinal and kidney Cbl receptors. Cubilin has a peculiar structure with three domains: a 110 amino acid *N*-terminal stretch, followed by a cluster of 8 epidermal growth factor (EGF) regions followed by 27 CUB domains, CUB being an abbreviation for three proteins: complement components C1r/C1s, Uegf, and Bone morphogenic protein-1. The name cubilin is because of its high content of CUB domains. Although lacking a membrane anchor, cubilin adheres to the cell membrane by being bound to several transmembrane partners (41).

Linkage analysis of Imerslund's cases indicated that the affected locus mapped to chromosome 14 and not 10 (as first thought), but the critical interval did not contain any obvious candidate gene. Assuming that the affected gene was expressed in the same tissues as *CUBN*, the tissue expression patterns of all genes were compared with *CUBN*. Amnionless (*AMN*), essential for gastrulation in mice (48), was the top ranking candidate (49). However, previous reports showed that biallelic inactivation of *AMN* was lethal in mice (48) and that posed conceptual problems. Nevertheless, several different recessive mutations and functional assays ultimately demonstrated that *AMN* was indeed the sought after second gene causing IGS (49,50). Consequently, the Finnish and Imerslund's Norwegian cases were because of the mutations in different genes, an example of genetic heterogeneity: one phenotype—several genes.

So far, most Norwegian patients had mutations in the *AMN* gene and most Finnish patients had mutations in the *CUBN* gene but exceptions occur (Tanner, unpublished results). Cases reported from the rest of the world have had mutations in either gene (Ref. 50 and Tanner, unpublished results). The Scandinavian cases are apparently typical instances of enrichment by founder effects. In the Mediterranean region, where numerous cases have been found, rare mutations in both the *CUBN* and *AMN* genes are exposed by a high degree of

consanguinity (50). However, in some cases no errors in either gene were detected. These cases were finally found to be due to mutations in the gene *GIF*, coding for the gastric IF after a third linkage study pinpointed its locus (24). Some of those cases had been considered to suffer from IGS because of the failure of IF to increase the absorption of radioactive Cbl in the Schilling test; this failure was apparently caused by the deficiency state of the enterocytes, leading to a mistaken diagnosis.

IGS has also been observed in dogs, first in giant schnauzers (51,52). The observed cases were mapped to a region orthologous to human chromosome 14 (53). So far, two different mutations were described in the canine *AMN* gene, and the phenotype is similar to that observed in humans (54). That outcome is in contrast to defects in the mouse. One of us has created *Amn* knock-in mice with three human IGS mutations (Tanner, unpublished results). The highly conserved sequences of human and mouse permitted the identical recreation of the human IGS mutations in the mouse. Two of these mutations (*AMN* c.14delG; G5fs and *AMN* c.683_730del48; Q228_L243del16; 50) are apparently lethal—analogous to the knock-out mouse (48)—because we have never observed any homozygous pups among over 100 offspring. Conversely, the Norwegian missense mutation *AMN* c.122C>T; T41I (49) is clearly viable in the homozygous mouse (Tanner, unpublished observations).

Congenital IFD

Lack of IF may be either acquired or congenital. The classic acquired case is pernicious anemia, which is caused by atrophy of the gastric mucosa with loss of secretory function (2,5). This has long been considered to be due to autoimmune destruction of the mucosa, but today it is known that *Helicobacter* infection may be involved (55). Many cases have antibodies against IF, thus removing the last traces of IF secreted and their presence strongly supports the diagnosis of pernicious anemia. The disease is essentially one of old people, but it occurs occasionally in children. We have ourselves described a 10-y-old girl with this disease (14) and Chanarin (2) mentions several pediatric cases.

Congenital IF deficiency (IFD) has been known since at least 1937 (56). The gastric IF gene *GIF* had long been postulated to be implicated in IFD (57), and the defect was expected "to reflect the usual spectrum of nonsense and missense changes" (58). In 2004, the first *GIF* mutation was described (59), and a larger series of cases was identified by linkage analysis (24). The clinical picture and laboratory findings do not differ from that of other juvenile Cbl deficiencies, with one exception: If the Schilling test result is low, there may be an increase if the oral radio-Cbl dose is accompanied by IF. Moreover, the patient's gastric juice may lack IF activity. Patients with IGS do not respond to IF in the Schilling test and their gastric juice contains IF. Such tests are therefore able to distinguish between the two conditions, however, a recent problem is the unavailability of radio-Cbl needed for the Schilling test (10). Immunoassay of IF is less reliable as biologically inactive (mutant) IF may still be

immunoreactive. Finally, the patient may fail to respond to IF owing to the deficiency state of the enterocyte. This is probably why we detected several cases of mutations in the *GIF* gene among patients initially thought to suffer from IGS (24). It might be noteworthy that patients suffering from juvenile Cbl malabsorption with roots in Western Sub-Saharan Africa thus far carried a single founder mutation in *GIF* that may simplify diagnostic testing (60).

Practical Suggestions

Clinical picture and laboratory tests. IGS, IFD, and other conditions are subgroups of Cbl deficiency. Therefore, before performing the tests discussed below, the presence of Cbl deficiency must be established or strongly suspected. In adults, the classical clinical symptoms are typical macrocytic anemia and neuropsychiatric signs. The tongue is often sore, and lack of gastric secretion is observed. In babies, the first signs are failure to thrive and respiratory and gastrointestinal infections but the symptoms seen in adults may also be observed when sought for. The bone marrow is typical for megaloblastic anemia. The anemia is strongly responsive to Cbl injections; there is reticulocytosis and rise in the concentration of blood cells and Hb. Such a reaction strongly indicates that Cbl deficiency was present, thus allowing diagnosis *ex juvantibus*. This is still a useful procedure, especially as absorption tests may suggest general malabsorption during the deficiency state. Preferably, such tests should be performed after abolishment of the deficiency. However, many adults with Cbl deficiency do not exhibit a classical clinical picture, and indications of Cbl deficiency are found only by laboratory tests, such as observing low concentrations of Cbl and high concentrations of methylmalonate or homocysteine in the serum. None of these tests have turned out to be the "gold standard," although sensitive, they are not specific for any particular type of Cbl deficiency. At present, measuring transcobalamin (TC)-bound (active) Cbl in serum (holo-TC) seems to be accepted as the best indictor of Cbl deficiency (61,62). The finding of proteinuria should steer the thoughts to IGS. As discussed, one may also suspect that cases of monosymptomatic benign proteinuria might be due to IGS. Nutritional lack of Cbl is frequent in developing countries. In some Western countries, Cbl deficiency is common in Vegans and abusers of nitrous oxide (which destroys the Cbl coenzymes) and especially in their nursing babies. However, most cases of Cbl deficiency are caused by poor absorption from the gastrointestinal tract, and in Europe and North America IGS and IFD today seem to be the most common causes of juvenile Cbl deficiency. Radioactive Cbl absorption tests therefore have played an important role in the diagnosis of Cbl deficiency diseases. Unfortunately, the Schilling test has almost disappeared (10).

A new nonradioactive Cbl absorption test may replace the Schilling test (63). It is based on the observation that cyano-Cbl (CNCbl) passes the intestine and enters the blood unchanged where it appears bound to TC. The patient is given three doses of CNCbl for 1 d and the TC-bound vitamin is measured. The TC-bound CNCbl then reflects Cbl absorption.

At present, there is little experience of using this test. However, nonradioactive tests should be the future, for example by modernizing the assay for the Cbl-IF receptor in the urine (36,37) for diagnosis of IGS. It was shown long ago that there is IF in the urine (64), so IFD might also be diagnosed by a urinary assay.

Family History

As in other hereditary conditions, the appearance of similar cases in relatives strongly suggests that the patient has a familial condition. This is also the case if the parents are closely related. An ethnic background with roots in the Mediterranean region should also lead to the suspicion of IGS (50).

Mutational Analysis

Definite diagnosis of IGS and IFD are achieved by demonstrating biallelic mutations in one of the genes coding for the two subcomponents of the Cbl-IF receptor, *CUBN* or *AMN* (47,49,50), or the gene coding for gastric IF, *GIF* (24,60). Unfortunately, there is currently no single genetic test that distinguishes IGS and IFD from other Cbl deficiencies. Genetic testing is certainly the "gold standard" for clinical confirmation but genetic heterogeneity combined with the low frequency have kept commercial providers from offering genetic testing services. The screening task is daunting, as the three genes contain 87 exons covering >320 kb of genomic sequence. The coding sequences exceed 10 kb and there are >100 polymorphisms that complicate the analysis. One of us (S.M.T.) recently completed the accrual of 150 cases or sibships with suspected IGS or IFD for genetic research. However, our experience is that genetic testing is warranted only after careful clinical workup has excluded other, mostly acquired causes of deficiency (see below). Once alternative diagnoses are excluded, genetic testing is advisable because it might clarify the cause of the deficiency and demonstrate that life-long parenteral Cbl treatment is required. In addition, diagnostic results permit family counseling to prevent yet undiagnosed cases to go unnoticed. Until the lack of commercial genetic testing is resolved, we recommend that DNA samples of affected and unaffected family members are banked, so that genetic testing may resume quickly when the testing situation changes.

Diagnosis by Exclusion

This is the way the original cases of Gräsbeck *et al.* (16) were diagnosed. Actually, Table 1 in that article can still serve as a check list of tests to be performed. After the establishment of Cbl deficiency, Cbl absorption should be studied, traditionally with the Schilling test or possibly with the new CNCbl test (63). If the result is low, indicating poor Cbl absorption, the test is repeated by adding IF to the oral Cbl dose. If the absorption clearly increases, IF deficiency is most likely present. Whether this is because of classical pernicious anemia or IFD must then be elucidated, *e.g.* by testing for antibodies against IF or parietal cells, measuring hydrochloric acid, pepsin, and IF in gastric juice, or examining the gastric mucosa by gastroscopy. If the patient does not respond to IF, receptor malabsorption must be suspected, whether general or selective can be elucidated using a variety of absorption tests, blood tests indicating celiac disease, endoscopy, and examining biopsy specimens.

As stated above, the absorptive capacity of the enterocytes suffers from Cbl deficiency and the recovery may take a long time. However, after the establishment of the Cbl deficiency and replenishment of the Cbl stores by several Cbl injections, there is no hurry in establishing the exact cause of poor Cbl absorption, perhaps with the exception of intestinal blind loops, strictures and other conditions which need surgical treatment, or the presence of tapeworm and exclusion of Veganism and abuse of laughing gas in nursing mothers. As the performance of numerous tests is both expensive and time-consuming, and some informative tests are nowadays unavailable, it is advisable to keep treating the patients, especially babies, as long as health is achieved and maintained. Attempts to establish a final diagnosis can be postponed until the necessary tests become available or the patient wishes to get a more definite diagnosis.

Treatment

After reports that CNCbl may have side effects such as muscular pains following injection, worsening of tobacco amblyopia and possibly neurological conditions (65,66), hydroxocobalamin has partially replaced CNCbl in the therapy of Cbl deficiency in Europe, at least in parenteral treatment. CNCbl remains in use in the United States. (67). Oral treatment with milligram tablets has been satisfactory in pernicious anemia, but it was observed that IGS patients absorbed less of such megadoses than pernicious anemia patients (14). In adolescents and adults, we therefore suggest monthly intramuscular injections of 1 mg of hydroxocobalamin as maintenance treatment. To abolish the deficiency state, daily injections may be given for 7–10 d. Less may be given to babies, but large doses seem to have no negative side effects. One of the two original patients of R.G. reported that he had received 1 mg injections every 3 wk for over 50 y without any side effects. This routine results in fairly high serum concentrations of Cbl. Because the patients feel well long after cessation of therapy, they are tempted to stop therapy altogether. This should be strongly discouraged, especially as brain damage may ensue, notably in children (26).

Final Remarks

The clarification of the two hereditary conditions IGS and IFD has provided novel insight into cellular transport systems. The once surprising fact that the small Cbl molecule needs to attach to a big molecule (IF) to be absorbed has led to a greater understanding of intestinal absorption mechanisms. The detection of the underlying genes, whose products transport not only Cbl but many different substrates, have shed light on both intestinal and kidney function and pathology. Unfortunately, practical clinical diagnosis of these conditions has not kept pace with the corresponding development in the basic sciences. This problem is shared with other rare hereditary

conditions. However, efficient maintenance treatment of both IGS and IFD results in perfect health, a gratifying result for the doctor, the patient, and the family.

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