sponse validates not only the diagnosis, but also the treatment, which is otherwise safe and inexpensive.

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Emmanuel Andrès and colleagues[1] state that the classic treatment for deficiency of vitamin B_{12} is injections of crystalline vitamin B_{12} and that an oral treatment has "recently" been devised. However, oral treatment of pernicious anemia was described in 1926 by George Minot and William Murphy.[2] Indeed, in 1934, they (along with George Whipple) received the Nobel Prize for this work. Not until 1948 did Karl Folkers and his coworkers at Merck succeed in purifying crystalline vitamin B_{12}.[3]

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In a recent review, Emmanuel Andrès and colleagues[1] recommend parenteral or oral administration of cobalamin as the treatment of choice for food-cobalamin malabsorption syndrome. The authors mention hypochlorhydria as a factor in this problem but do not recommend hydrochloric acid (HCl) and pepsin therapy as a potential treatment.

In a study of 5 patients with hypochlorhydria, all of the patients had decreased urinary excretion of protein-bound cobalamin.[2] After receiving supplemental HCl, pepsin, gastric intrinsic factor or some combination of these, 4 of the 5 patients showed improvement in protein-bound cobalamin absorption. Another study examined the effect of water, cranberry juice (pH 2.5–2.6) or a 0.1N HCl solution (pH 1.2) on the absorption of protein-bound cobalamin in 3 groups of elderly subjects: healthy individuals, subjects pretreated with omeprazole to simulate the hypochlorhydria of atrophic gastritis and patients with diagnosed atrophic gastritis.[3] Administration of diluted HCl increased the absorption of protein-bound cobalamin in all 3 groups, and this difference was statistically significant for both the omeprazole-treated and healthy subjects ($p < 0.001$). The authors noted that this improvement might have been the result of the acid's ability to augment the release of cobalamin from protein.

Maintaining adequate gastric pH ensures a sufficient sterilizing barrier against enteric pathogens, allows for proper absorption of micronutrients, preserves normal intestinal permeability and prevents hypergastrinemia.[4,5] High gastric pH (as occurs in atrophic gastritis) is also associated with the development of gastric malignant tumours;[6] therefore, maintaining adequate gastric pH might be a preventive measure. Supplemental HCl has been shown to reduce (acidify) gastric pH in subjects with simulated hypochlorhydria.[7] The method of administration has been described by several investigators.[5,8-10] Patients usually start with one 5- to 10-grain (325- to 650-mg) capsule of betaine or glutamic acid hydrochloride with each meal; pepsin is sometimes added to these capsules to improve absorption. Patients are instructed to increase the dosage by one 5- to 10-grain capsule with each meal, sometimes working up to 60–80 grains with every meal. Patients are advised against this therapy if they are also receiving nonsteroidal anti-inflammatory medications or corticosteroids, if they have active peptic ulcer disease, if they have abdominal pain, or if they experience abdominal pain or burning with this treatment. Patients are also instructed to use fewer capsules with smaller meals and more capsules at larger meals.

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[One of the authors responds:]

We agree with Joel Ray and David Cole regarding the relative practical value of serum total homocysteine and methylmalonic acid in elderly patients with suspected cobalamin deficiency. Although testing for serum holotranscobalamin is not routinely available in many countries, we believe that it may be appropriate in future as a routine clinical test for cobalamin deficiency. However, to date, a consensus on the definition for cobalamin deficiency, especially among elderly patients, has not been achieved.[1] Thus, in our experience, serum total homocysteine is currently a helpful, inexpensive indicator of true (tissue) cobalamin deficiency, as suggested in our article.[2]

We agree with Peter Wetterberg's comments on oral cobalamin. However, the usefulness of oral cobalamin therapy has only recently been documented, starting in 1995, with studies that meet the criteria of evidence-based medicine.[3-6]

We read with great interest Jonathan Prousky's comments, although we have no experience with the therapies he describes. Nevertheless, we believe that this information indirectly supports the concept of food-cobalamin malabsorption.[7]

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Short ACTH stimulation test for adrenal reserves of cortisol, not adrenal function

The classical description of Addison's disease in a 15-year-old girl[1] is a timely reminder of this well-known but uncommon disorder. In their description of the investigative work-up and discussion, Chantelle Barnard and associates[1] imply that the short adrenocorticotropin hormone (ACTH) stimulation test is diagnostic of primary adrenal insufficiency. This is a common misapprehension.

In the test, an intravenous (or intramuscular) injection of 250 µg of synthetic ACTH (tetracosactrin) results in release of preformed cortisol from adrenal stores, which is measured in the serum 30 (and/or 60) minutes later and compared with the baseline concentration. An abnormal response (a serum cortisol peak below 550 nmol/L or an increment of less than 200 nmol/L from baseline or both) identifies adrenal insufficiency but cannot distinguish Addison's disease (primary adrenal failure) from secondary hypoadrenalism. In pituitary disease (ACTH deficiency), for instance, the result of the test may be abnormal because of reduced stores of cortisol, even though the adrenal glands themselves have normal biosynthetic and secretory func-

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