nates. However, both species were able to methylate guanidoacetic acid to form creatine. The low values found in this study for calf liver are of the same magnitude as those reported by Cohen(11) for beef liver. Cohen (12) found that addition of folic acid and glutamic acid did not bring the levels into line with those for the rat.

The choline oxidase activity of calf liver homogenates as compared to rat liver homogenates is shown in Table II. These results indicate that calf liver possesses a much lower choline oxidase activity than rat liver. The low activity of the enzyme would indicate a slow choline turnover similar to that found by Handler(13) for the guinea pig.

Summary. 1. Using a synthetic milk diet, calves receiving 1.2% DL-methionine exhibited no demonstrable choline requirement, as measured by growth and liver ether extract. On a diet supplying 0.8% methionine, fatty livers developed in the absence of choline. 2. A study was made of the ability of calf liver homogenates to methylate homocysteine to form methionine, when betaine served as methyl donor; to methylate guanidoacetic acid, when methionine served as the methyl donor, and to oxidize choline. It was found that while calf liver homogenates would carry out all of these reactions, the activity of the calf liver enzymes was very much less than that of rat liver homogenates.

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Pernicious Anemia. I. Remission by Small Oral Doses of Purified Vitamin B_{12}.* (22306)

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During studies on pernicious anemia, it was found, contrary to previous experience, that partial remission occurred in a patient with pernicious anemia in relapse who received minimal doses of purified vit. B_{12} by mouth. Pernicious anemia is generally considered to be the result of a heredofamilial atrophy of gastric and duodenal mucosa, with absence of "intrinsic factor," a material necessary for absorption of vit. B_{12} from the gastrointestinal tract into the blood stream. Megaloblastic erythropoiesis of pernicious anemia in relapse can be restored to normal by overcoming the deficiency in intrinsic factor by (1) parenteral administration of vit. B_{12}, thus circumventing the abnormal gastrointestinal tract; (2) oral administration of massive doses of vit. B_{12} (1000 to 9000 μg/wk), through a sort of "mass action" effect; or (3) oral administration of vit. B_{12} together with some outside source of intrinsic factor. How-

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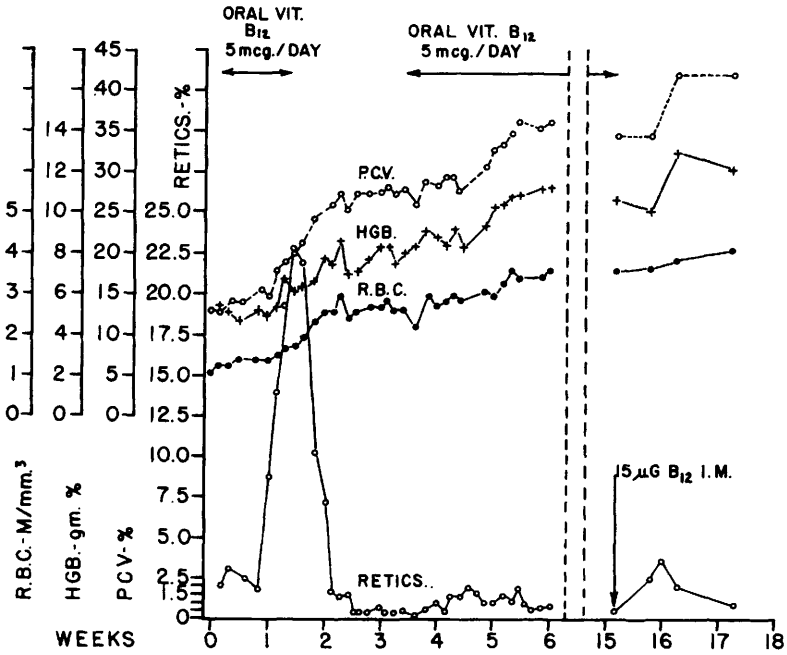

FIG. 1. Case 1a. Pernicious anemia. Submaximal response following oral administration of vit. B_{12}, 5 μg daily.

ever, remissions of pernicious anemia following oral administration of small amounts of vit. B_{12} without intrinsic factor (10 to 250 μg/day) have been reported(1-7). Suboptimal responses have been seen with oral doses of 10 μg(1,2), 15 μg(3), 30 μg(2), and 50 to 250 μg per day(1,4-6); but only rarely have maximal responses to oral vit. B_{12} in doses of 25 to 150 μg/day been noted(1,4,6). In the absence of an outside source of intrinsic factor, remission following oral vit. B_{12} occurred regularly only when massive doses of the material (3000 μg in a single dose) were given (8).

As a result of our experience with one patient (Fig. 1), in whom pronounced reticulocytosis and remission followed oral administration of 5 μg/day of purified vit. B_{12} without added intrinsic factor, similar small doses of vit. B_{12} (5.0 to 16.8 μg/day) were given by the same route to 9 additional patients with pernicious anemia in relapse, and to 1 patient with megaloblastic anemia of obscure etiology. It is our purpose to report the almost regular occurrence of varying degrees of remission under these circumstances.

Methods. Diagnosis of pernicious anemia was established by the presence of macrocytic anemia, histamine-fast achlorhydria, megaloblastic bone marrow, normal gastrointestinal x-ray studies, and absence of steatorrhea. The dose of 5.0 to 16.8 μg of vit. B_{12} was administered by mouth, one to 3 times daily, in tablets or capsules, with no particular relation to meals(6). The vit. B_{12} was obtained from 2 independent sources,†, and was assayed for and found to be free of folic and folinic acids. No intrinsic factor was given in association with oral vit. B_{12}, and the diet, which was free of liver and red meats, was unchanged before and during treatment.

Results. A definite reticulocytosis and hematologic remission of varying degree, with reversion of bone marrow to normoblastic erythropoiesis, occurred in 11 trials in 8 cases of pernicious anemia and in one case of nonpernicious megaloblastic anemia (Table I).

† We are indebted to Dr. Douglas B. Remsen, Squibb Institute for Medical Research, New Brunswick, N. J., and to Dr. Nathaniel S. Ritter, Merck & Co., Rahway, N. J., for generous supplies of these materials.

TABLE I. Remissions in Pernicious Anemia (Cases 1-8) and Non-Pernicious Megaloblastic Anemia (Case 9) on Small Oral Doses of Vit. B_{12}.

Case	B_{12}/day, μg	Initial count: Hgb, g/100 ml	Initial count: Hct, %	Max retics, %/day	Max hemogram: Hgb, g/100 ml	Max hemogram: Hct, %
1 a	5	5.2	13	22.6/ 8	11.4	37
b	10	9.0	27	6.2/ 9	12.6	42
2 a	16.8	5.6	18	9.8/ 3	10.9	37
b	15	8.0	26	9.2/ 8	10.7	36
3	16.8	9.1	27	9.2/ 9	13.3	41
4	15	8.2	26	8.8/20	14	42
5 a	15	8.5	28	9.8/ 9	14.4	43
b	15	9.0	28	8.8/13	14.9	47
6	15	7.6	22	18.0/ 8	11.7	37
7	15	5.4	18	21.0/ 9	10.2	34
8	10	9.3	30	7.4/12	14.1	46
9	10	5.4	17	21.6/15	12.9	46
	Mean*	7.7	23.9	10.7/10	12.6	40.2
	Range*	5.2–9.3	13–28	6.2–22.6/3–20	10.2–14.9	34–47

* Of cases 1-8 only.

Remission was estimated to have been maximal in 3 cases of pernicious anemia and in the one case of non-pernicious megaloblastic anemia, and submaximal in 5 cases of pernicious anemia. Typical responses to oral doses of vit. B_{12} are depicted in Fig. 1-3, and the 9 responsive cases are summarized in Table I. Maximal reticulocytosis usually occurred on 8th or 9th day after initiation of therapy, with a cumulative oral dose of from 35 to 150 μg of vit. B_{12}. Unless parenteral B_{12} was subsequently administered, remission after cessation of therapy usually tended to be short-lived (4 to 6 months), although remissions persisted longer in some patients.

During these observations, 3 patients with pernicious anemia similarly treated failed to show hematologic response (Table II). Case 4 initially showed no hemoglobin response, despite a reticulocytosis, on a dose of 5.6 μg/day, but responded maximally on a dose of 15 μg/day (Table I). Six months later, when again in relapse, this patient failed to show any signs of remission on oral vit B_{12} during

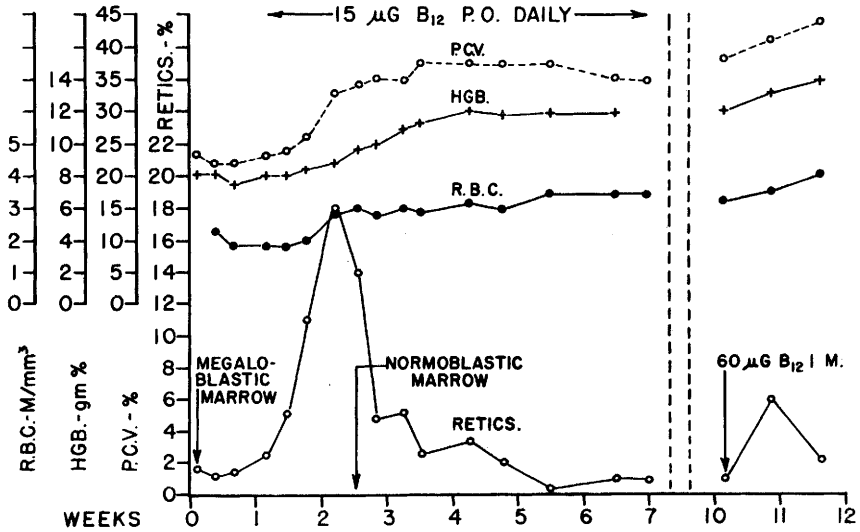

FIG. 2. Case 6. Pernicious anemia. Submaximal response following oral administration of vit. B_{12}, 15 μg daily.

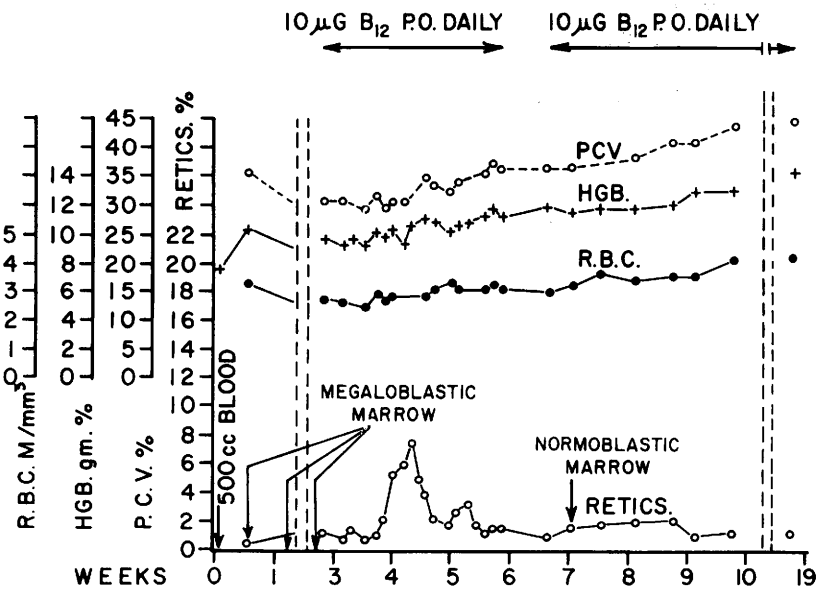

FIG. 3. Case 8. Pernicious anemia. Maximal response following oral administration of vit. B_{12}, 10 μg daily.

successive trials on 5, 10 and 15 μg/day, but at this time he had developed carcinoma of the stomach. Case 7, who showed a remission on the initial oral medication of 15 μg daily (Table I), failed to respond to a similar oral dose following another relapse 9 months later (Table II), whereas parenteral vit. B_{12} was effective. No response to 5 μg of vit. B_{12} was noted in one case of pernicious anemia in relapse (Case 10, Table II), but a larger dose and longer period of observation were not attempted in this patient.

Discussion. If intrinsic factor is indeed necessary for absorption of vit. B_{12}, it appears that some intrinsic factor must have been present in gastric and duodenal mucosa of our patients with pernicious anemia in relapse. Similar conclusions regarding the quantitative rather than qualitative change in gastric secretion in some cases of pernicious anemia were reached by others(9,10), who suggested that the red cell level in pernicious anemia is determined by actual amount of intrinsic factor secreted in the gastric juice.

Since crystalline vit. B_{12} was used in these studies, it is recognized that absorption may have been facilitated by the purified nature of the material, just as ferrous sulfate is absorbed more easily than food iron. This, however, is not a satisfactory explanation in itself, since regular remission with oral use of purified vit. B_{12} has not been reported(1-7).

TABLE II. Cases of Pernicious Anemia Which Failed to Respond to Oral Vit. B_{12}.

Case	B_{12}/day, μg	Initial count — Hgb, g/100 ml	Initial count — Het, %	Max retics, %/day	Max hemogram — Hgb, g/100 ml	Max hemogram — Het, %
4*	5.6	5.3	16.5	6.6/ 8	6.4	20
	5	8.4	27	4.8/18	8.4	27
	10	6.9	27	5.0/ 4	7.2	24
	15	7.0	23	5.4/26	7.0	23
7*	15	6.6	20.5	2.6/16	6.6	20.5
10	5	8.2	25	2.1/ 8	7.4	25
	Mean	7.1	23.2	4.4/13	7.2	23.3
	Range	5.3–8.4	16.5–27	2.1–6.6/4–26	6.4–8.4	20–27

* Same numbers as in Table I.

Although the fasting state may facilitate absorption of vit. B_{12}(6) from the gastrointestinal tract, absorption occurred independent of the fasting state in our patients.

The action of oral preparations containing both intrinsic factor and vit. B_{12} cannot *a priori* be attributed to their intrinsic factor content, since as has been shown above, remission may follow the use of the vit. B_{12} alone.

Studies on vit. B_{12} metabolism in this group of patients are still in progress. Preliminary results in some of these patients suggest that remission occurs without a rise of the serum vit. B_{12} level above relapse levels (less than 20 $\mu\mu$g/ml).

Summary. 1. Hematologic and clinical remissions were induced 11 times in 8 patients with pernicious anemia in relapse, and in 1 patient with non-pernicious megaloblastic anemia, by small oral doses of purified vit. B_{12} without added intrinsic factor. The effective dosage range was 5 to 16.8 μg per day. 2. Unequivocal failure occurred in 1 case of relapsed pernicious anemia. 3. These results further confirm the suggestion that in pernicious anemia there is a quantitative rather than a qualitative change in gastric secretion, and that variations in the amounts of intrinsic factor remaining in pernicious anemia patients may be responsible for varying responses to oral vit. B_{12}. 4. A trial period of vit. B_{12} alone should precede any study with a vit. B_{12} plus intrinsic factor preparation.

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Δ^1-Hydrocortisone: Plasma 17-Hydroxycorticosteroid Concentrations Following Oral and I. V. Administration.* (22307)

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During the past year the Δ^1-steroids have been employed clinically to a considerable extent. These compounds are synthetic derivatives of hydrocortisone and cortisone, differing from the parent steroids by the insertion of a double bond in the 1-2 position of the steroid nucleus. Δ^1-hydrocortisone ($\Delta^{1,4}$-pregnadiene-11β, 17α, 21-triol-3,20-dione) has been produced under various commercial names: metacortandralone, prednisolone, delta-cortef, hydeltra, meticortelone, and sterane.

Clinically, the Δ^1-steroids appear to be 3 to 5 times as effective as the parent compounds(1-3). A similar ratio has been found for glucocorticoid activity (liver glycogen deposition, eosinophil response)(3,4). However, results of *in vitro* studies of anti-inflammatory potency have not been reported. It is possible that the apparent advantages of the Δ-steroids over the parent compounds are attributable to differences in absorption or

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