of the plasma 17-OHCS to ACTH was not altered by Nilevar therapy for 40 to 80 days. K.L. had only a slight rise in the plasma 17-OHCS prior to therapy and a normal response after 40 days of Nilevar. In patient F.G., the control levels of plasma 17-OHCS were normal prior to and after therapy; however, the levels of 17-OHCS were elevated after ACTH. This increased response of the plasma 17-OHCS levels was unaltered by Nilevar therapy for 80 days.

It is well known that cortisone and its derivatives will suppress the adrenal cortex and its ability to respond to ACTH, as measured by the plasma 17-OHCS, and will produce adrenal atrophy. On the other hand, testosterone propionate and 17α-methyl-19-nortestosterone (unpublished) do not alter control plasma 17-OHCS levels. Similarly, these studies indicate that adrenocortical function, as evaluated by plasma 17-OHCS levels and response to ACTH, was unaltered by Nilevar given orally over a prolonged period of time.

Conclusions. In 5 subjects receiving clinically effective oral doses of Nilevar, there was no alteration in adrenocortical function as measured by plasma 17-OHCS levels before and after intravenous ACTH.

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Studies on Copper Metabolism. XXVI. Plasma Copper in Patients with Tropical Sprue.* (24117)

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Although increased concentration of copper in plasma has been observed in a wide variety of clinical disorders(1), hypocupremia has been observed in relatively few conditions. It has been observed consistently in newborn infants(2); it is the usual finding in hepatolenticular degeneration (Wilson's disease)(3); and it has been observed frequently in the nephrotic syndrome(4). In addition, hypocupremia has been recorded in an occasional patient with hypochromic anemia(5,6, 7), idiopathic hypoproteinemia(8,9), kwashiorkor(6), and celiac disease(6,10). The causes of hypocupremia were discussed recently and a classification presented(7).

Because of the finding of hypocupremia in 2 patients with "non-tropical" sprue and severe microcytic hypochromic anemia(9), a study of plasma copper in patients with tropical sprue and megaloblastic anemia was undertaken. The results of this investigation are here reported. Observations on 6 patients with megaloblastic anemia of pregnancy are also presented.

Materials and methods. Blood samples were obtained from 29 Puerto Rican subjects with sprue in relapse. The diagnosis of sprue was based on clinical findings of chronic diarrhea, flatulence, weight loss, weakness and glossitis; macrocytic anemia with typical megaloblastic morphology in bone marrow; and laboratory evidence of intestinal malabsorption. The average hemoglobin value for the group was 5.5 g % (1.2 to 10.9 g %). Malabsorption was demonstrated for at least 2 test substances, usually xylose, Vit. A, or butter(11). In addition, steatorrhea was demonstrated by a modified fat balance technic in all 21 subjects on whom such studies were

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TABLE I. Summary of Data.

Condition	Plasma copper, μg % No. subjects	Mean ± S.D. (range)	α_2 globulin, % of total proteins No. subjects	Mean ± S.D. (range)
Normal	228	116 ± 14 (68–161)	19	11.8 ± 3.5
Sprue, relapse	29	87 ± 33 (19–157)	29	6.8 ± 2.0
" , remission	27	114 ± 33 (24–186)	14	10.0 ± 3.3
Megaloblastic anemia of pregnancy	6	159 (105–242)	3	10.6 (6.5–16.0)

done(12). Blood samples were also obtained from 27 patients during remission of their illness following at least 3 months of therapy with folic acid or Vit. B_{12}. These subjects were no longer anemic but had varying degrees of persistent malabsorption, attributable presumably either to severity or duration of previous digestive tract disease. Observations were made on specimens of plasma from 6 patients with megaloblastic anemia of pregnancy. In all 6 patients the hemoglobin was less than 9.5 g% and megaloblastic changes were present in the bone marrow. Malabsorption and steatorrhea were not present. Plasma copper was determined by the method of Gubler, *et al.*(13). Values in normal subjects have been reported(4,14). Filter paper electrophoresis of serum proteins was performed on specimens from normal subjects and patients with sprue. Electrophoretic components were estimated by means of a Spinco "Analytrol" instrument. Total serum protein measurements were not done.

Results. The mean plasma copper concentration (± 1 S.D.) of the 29 patients with untreated sprue was 87 ± 33 μg %, as compared with the normal mean of 116 ± 14 μg % (Table I). The difference between the means of the 2 groups is highly significant ($t = 4.5$; $P = <0.001$). Values in 18 (62%) of patients were less than 88 μg %, the lower limit of normal (–2 S.D.). Values greater than 144 μg % were observed in only 3 (10%) patients, 2 of whom were postpartum.

No correlation was observed between copper values and clinical severity or duration of the disease or severity of the anemia. Values were normal in a number of apparently severe and long standing cases of sprue, while in several clinically mild cases values were low. There was no significant difference between the sexes. Five of the 12 females were postpartum by 2 months or less. In 3 plasma copper was low (75, 87 and 87 μg %) while in 2 the values were slightly elevated.

Mean plasma copper concentration of the 27 patients with treated sprue was normal (114 ± 33 μg %). Values were less than 88 μg % in 2 of the patients (24 and 63 μg %), and in 2 others the values were above the upper limit of normal (156 and 186 μg %).

Plasma copper concentration was normal in 3 of the patients with megaloblastic anemia of pregnancy and was increased in the remaining 3.

Four patients with sprue were given 1 mg of copper, as copper acetate, intravenously daily for 10 days. One patient (B) had received no therapy prior to copper; one (C) was given a single oral dose of 5 mg of folic acid 7 days before; one (A) was given 15 mg of folic acid 10 days before; and one (D) had received 5 mg of folic acid daily for 5 months but had failed to respond hematologically to this medication.

In none of the patients was a hematologic response observed following administration of copper (Table II). In 2 of the patients copper therapy failed to increase concentration of copper in the plasma. In one (C) there was a modest increase. In the fourth patient (D) administration of copper was followed by

TABLE II. Response to Administration of Copper.

Patient	Before copper — Hb, g %	Retics., %	Plasma copper, μg %	After copper — Hb, g %	Retics., max %	Plasma copper, μg %
A	6	1	87	6	4	81
B	4	1	85	4	1	85
C	9	5	59	8	2	80
D	10		57	8		122

prompt and sustained increase in concentration of plasma copper to normal.

There was a significant reduction in the α_2 globulin fraction of plasma proteins of patients with untreated sprue as compared with that of normal subjects ($t = 57$; $P = <0.001$) or of treated patients ($t = 3.6$; $P = <0.001$). Simultaneous determinations of plasma copper and α_2 globulin were made in 40 patients. A significant degree of correlation between plasma copper concentration and α_2 globulin level was not observed ($r = +0.2$; $P = <0.2$).

Discussion. The present observations indicate that hypocupremia occurs in patients with tropical sprue and macrocytic anemia as well as in patients with non-tropical sprue accompanied by hypochromic anemia, as reported previously(9). The occurrence of hypocupremia in 62% of patients with untreated tropical sprue is in contrast to findings in 23 patients with pernicious anemia in relapse(1, 15). In this group, plasma copper values less than 88 μg % were observed in only 2 patients.

Three possible mechanisms may be invoked to explain the hypocupremia in sprue: (1) a reduced dietary intake of copper; (2) reduced absorption of copper by the intestine; or (3) impaired ceruloplasmin synthesis as a result of protein deficiency(7).

The first of these possible explanations seems unlikely since the daily dietary copper requirement of the adult is low and copper is abundantly supplied in natural foods(16). Copper deficiency due to a reduced dietary intake of copper is extremely rare in human subjects(7,16). Furthermore, if the hypocupremia in sprue were secondary to either a dietary deficiency or malabsorption of copper, it would be expected that parenteral administration of copper would be followed by a rapid return of the plasma copper concentration to normal. This did not occur in 3 of the 4 patients given copper.

About 95% of the copper in normal plasma is present in the form of ceruloplasmin, an α_2 globulin. In protein-deficient animals(17) and in human subjects under certain conditions(7), hypocupremia may result from inability to synthesize the protein portion (apoceruloplasmin) of the ceruloplasmin molecule. Since malabsorption of proteins, hypoproteinemia and reduction in the proportion of α_2 globulin in the plasma are all features observed in patients with sprue, it would seem reasonable to assume that in those patients in whom no rise in plasma copper followed administration of copper, the hypocupremia was secondary to deficiency of plasma protein, presumably due to impaired protein synthesis. Failure to observe a correlation between per cent of plasma α_2 globulin and plasma copper can probably be attributed to our failure to measure total serum protein concentration, thus making it impossible to calculate concentration of α_2 globulins in g %. In many conditions in human subjects, a high degree of correlation between concentration of α_2 globulin and plasma copper has been observed(18).

In one of the 4 patients given copper intravenously, a prompt, substantial and sustained increase in plasma copper occurred following intravenous administration of copper. In this patient, α_2 globulins constituted 11.6% of the total proteins, a normal value. Therefore, in this patient, malabsorption of copper may have been the explanation for the hypocupremia.

The observation of hypercupremia in 3 patients with megaloblastic anemia of pregnancy is in keeping with the hypercupremia which accompanies normal pregnancy(2). Four of the 6 patients with megaloblastic anemia of pregnancy were studied only in the early postpartum period. Plasma copper values in 3 of these were within normal limits. It was shown previously that the hypercupremia of pregnancy decreases rapidly during the post-partum period(2).

Summary. 1. Plasma copper was determined in 29 patients with sprue in relapse, 27 patients with sprue in remission, and 6 patients with megaloblastic anemia of pregnancy. 2. Mean plasma copper concentration (± 1 S.D.) in patients with sprue in relapse was 87 ± 33 μg %; in treated patients, 114 ± 33; and in patients with megaloblastic anemia of pregnancy, 159 (105 – 242). 3. It is suggested that hypocupremia in sprue may frequently be due primarily to an inability to

synthesize the protein portion of ceruloplasmin. In a few patients malabsorption of copper may be a contributing factor.

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Observations on Blood Flow During Spontaneously Occurring Traube-Hering Waves. (24118)

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Rhythmic fluctuations in blood pressure which are slower than the respiratory rate and on which respiratory and cardiac waves are superimposed are commonly designated by the names of several or all of the authors describing them in the latter part of the last century; Traube(1), Hering(2), and Mayer(3). These investigators agreed that the waves in blood pressure were probably due to rhythmic changes in peripheral resistance secondary to rhythmic impulses conveyed from the central nervous system *via* the sympathetic nerves. Hering, further, felt on the basis of his studies that the respiratory center was the source of the rhythmic impulses which acted on the vasomotor center by way of its connections with the latter. More recently evidence has been reported indicating that chemo- and baro-receptors may be the ultimate starting point of the rhythmic impulses(6,7). Much evidence has since accumulated to support the view that rhythmic alterations in peripheral resistance account for blood pressure fluctuations. Thus it has been shown that the diameter of arteries in the ear of rabbits and dogs fluctuate rhythmically in time but opposite in direction to the rhythmic changes in arterial pressure(4). Blood flow as estimated by the hot-wire anemometer technic fluctuates similarly when measured in the leg muscles of the cat(5). Recent studies in humans using plethysmograph technics have shown similar findings and, moreover, indicate that the Traube-Hering waves are commonly seen in normal, unanesthetized subjects(8-11). Direct measurements of blood flow during the