When used in combination with streptomycin the furan derivative showed only a slight degree of potentiation (chemotherapeutic effectiveness of 13.1 as against 9.6 + 1.2 or 10.8), while the sulfone showed a high degree of potentiation. The chemotherapeutic effectiveness of combined therapy with streptomycin and the sulfone was 20.6 as against 9.6 + 2.9 or 12.5, the sum of the effects of the two drugs. It should be noted that the chemotherapeutic effectiveness of sulfone-streptomycin combined therapy was somewhat greater than that of the double dose of streptomycin.

*Comments and conclusions.* The favorable results reported by Shpanir for the benzyl furamide were based on experiments in mice. Though the mouse test is currently in use in several laboratories for screening of compounds for possible antitubercular activity we are not impressed with it as a satisfactory test object(8). It is possible that the present results are at variance with those of Shpanir on account of species differences.

N-Benzyl-2-furamide has no appreciable activity in experimental tuberculosis in guinea pigs. So far the sulfones alone, next to streptomycin, have been demonstrated to have a definitely suppressive effect on this disease.

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## Oral Treatment of Pernicious Anemia with Swine Duodenal Mucosa and Vitamin $B_{12}$. (17746)

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Since the initial report by West(1) there has been ample evidence that the parenteral administration of as little as 1-2 $\mu$g of vitamin $B_{12}$ daily to pernicious anemia patients in relapse is followed by reticulocytosis, rise in hemoglobin and erythrocytes, and clinical remission(2-6). The minimal effective oral daily dose lies between 75 and 150 $\mu$g(7,8). However, the oral administration of gastric juice from a normal person with 5 to 10 $\mu$g of vitamin $B_{12}$ results in satisfactory hematologic and clinical response(9,10). More recently Bethell has shown that the ingestion of an extract of desiccated swine duodenal mucosa and 5 $\mu$g of vitamin $B_{12}$ daily will induce a similar reaction(11). It is the purpose of this report to present additional data confirming this latter observation.

Two patients with typical Addisonian pernicious anemia in relapse were treated with daily oral doses of 2 g of an aqueous extract of swine duodenal mucosa and 10 $\mu$g of vita-

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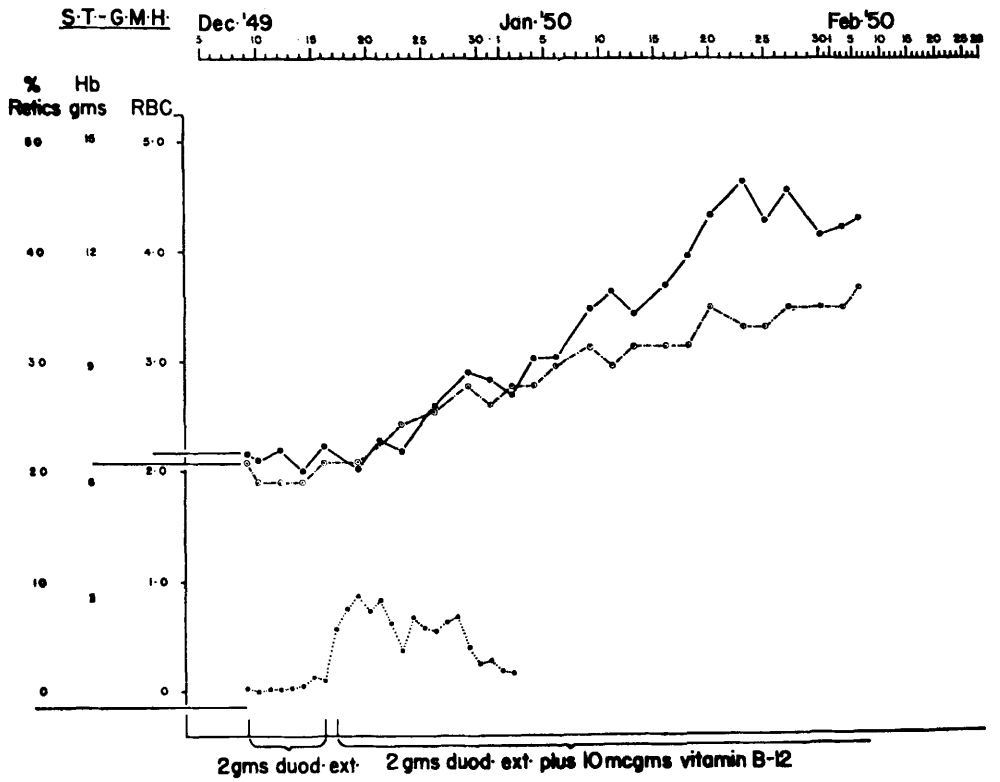


FIG. 1.

Hematologic data on patient, I.S., treated with oral daily doses of 2 g of swine duodenal mucosa and 10 $\mu$g of vit. $B_{12}$.

min $B_{12}$ (Rubramin).* The mucosal extract was given daily for one week before the vitamin $B_{12}$ was added in order to insure against any activity in the extract when administered alone. Previous studies have already demonstrated that daily oral doses of vitamin $B_{12}$ below 75 $\mu$g are ineffective in the treatment of pernicious anemia(7,8). Both cases showed hyperchromic macrocytic anemia, histamine fast achlorhydria, and megaloblastic bone marrow. X-ray examinations of the gastro-intestinal tract, urinalyses and blood chemistry determinations were all normal. In one patient there was evidence of an old vascular accident of the left internal capsule. The other person was senile and a satisfactory evaluation of the neurologic status could not be made.

* The materials used in this study were supplied by Dr. Geoffrey Rake of the Squibb Institute for Medical Research, New Brunswick, N.J.

I. S., male, age 83 years, was admitted to the hospital because of weakness and pallor. He was a known case of pernicious anemia treated years ago with ingestion of liver extract but stopped therapy of his own accord. At the time of the present admission he was completely disoriented so that a reliable history and neurologic survey was not possible. Physical examination disclosed marked pallor and an icteric tint. Liver was felt 2 cm below the right costal border. Knee and ankle jerks were sluggish. The initial blood count was hemoglobin 6.5 g, erythrocytes 2.15 million/cu mm and leukocytes 4450/cu mm. He received 2 g of desiccated duodenal mucosa extract daily for one week. The clinical condition deteriorated slightly and the hematologic status was unchanged. Ten $\mu$g of vitamin $B_{12}$ were added to the mucosal extract and given orally, daily, thereafter. The hemoglobin, red blood cell and reticulocyte values are shown in Fig. 1. A suboptimal reticulocyte

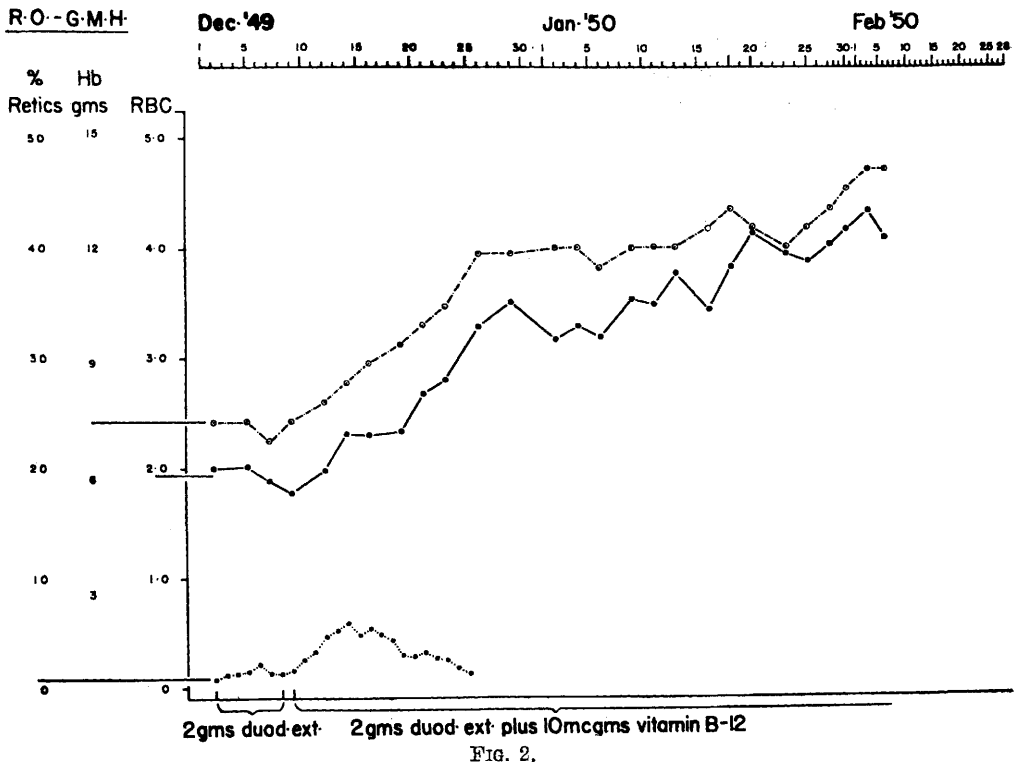


FIG. 2.

Hematologic data on patient, I.R., treated with oral daily doses of of 2 g of swine duodenal mucosa and 10 $\mu$g of vit. $B_{12}$.

response with a peak of 8.6% was observed on the 3rd to 5th days after the combined therapy was started. Clinical improvement was slow. The mental deterioration did not change. At the end of 8 weeks of treatment the hemoglobin reached 11.0 g and the erythrocytes 4.28 million per cu mm.

I. R., female, age 71 years, was admitted to the hospital because of weakness and spells of unconsciousness. She was observed at another institution for 3 months but no diagnosis was reached. Her appetite was poor and she lost 4 pounds during the past 2 months. She had difficulty in walking but never experienced any paresthesias. Physical examination disclosed the liver edge palpable at the costal margin. Slight pitting oedema of the legs was present. Positive neurologic findings were compatible with those following a vascular accident involving the left internal capsule. The initial hemoglobin was 7.5 g, erythrocytes 2.00 million/cu mm, and leukocytes 3800/cu mm. She was given 2 g of desiccated hog duodenum mucosa daily for one week with no signs of hematologic change. Thereafter, 10 $\mu$g of vitamin $B_{12}$ were added to this daily dose. A suboptimal reticulocyte response of 5.9% was observed on the 5th day (Fig. 2). Clinically there was slow subjective improvement. The hemoglobin rose to 13.5 g and erythrocytes to 4.15/cu mm after 2 months of treatment. The neurologic status remained unchanged.

*Discussion.* The nature of intrinsic factor which is present in normal human gastric juice and in the mucosa of the stomach and duodenum of swine is at present under investigation. Agren and Waldenstrom have shown that a highly purified amino polypeptidase isolated from the pyloric mucosa of swine, incubated with fresh liver, and administered to patients with pernicious anemia in relapse, induced a satisfactory hematologic and clinical remission(12). More recently it has been observed that the simultaneous oral administration of subminimal doses of pteroyl

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glutamic acid and vitamin $B_{12}$ to cases of pernicious anemia in relapse results in an excellent hematologic and clinical response(13).

Vit. $B_{12}$ and at least one other growth factor are present in the mucosa of the stomach of the pig(11,14). No attempt was made to determine the vit. $B_{12}$ activity of the extract used in the present study. However, since there was no response to the ingestion of this material after one week, followed by hematologic and clinical improvement when it was combined with 10 $\mu$g of vit. $B_{12}$, it would appear that there was not enough present for therapeutic efficacy when administered alone.

*Conclusion.* The oral administration of an extract of swine duodenal mucosa and subminimal doses of vitamin $B_{12}$ to patients with pernicious anemia in relapse is followed by a suboptimal reticulocyte response and satisfactory hematologic and clinical improvement.

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## Experimental Pulmonary Edema. III. Hypoglycemia, a Cause of Pulmonary Edema.* (17747)

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During a study of long continued hypoglycemia in the rat(1) it was found that death from respiratory failure always ensued and there was marked edema of the lungs. Some time before death the pulmonary pathology was evidenced by the oozing of blood-tinged serous fluid from the nostrils of the comatose animals. This recalled the edema of rats after an overdose of epinephrine(2,3) and the possibility occurred to us that the effect of insulin was, at least in part, an overproduction of epinephrine resulting from the hypoglycemia. At the time we were able to demonstrate measurable concentrations of epinephrine by bioassay in the blood of rats with insulin shock. Removal of the adrenal medullas with sufficient time allowed for regeneration of the cortical tissue prior to insulin treatment failed to prevent the development of the pulmonary pathology in most rats. We have now studied the hypoglycemia lung edema further with special reference to the effect on it of an adrenergic blocking agent.

*Experimental.* The rat (Slonaker strain(4)) groups were made up of equal numbers of both sexes within a weight range of 40 g. To produce a hypoglycemia the rats were fasted for 24 hours and given 2 units of regular and 2 units of protamine insulin (u-40)† per 100 g body weight by subcutaneous injection. One group had been adrenalectomized the preceding day and another group had their adrenals demedullated the week before. After they succumbed to the hypoglycemia the lungs were removed and weighed. Our data are summarized in Table I.

*Discussion.* Prior adrenalectomy (Grp. 2) reduced the degree of pulmonary edema as measured both by inspection and lung weight but this may have been due to the naturally poor condition of the animals when tested. However demedullation of the adrenals (Grp. 3) from which the animals had completely recovered reduced the degree of edema of the lung just as much. It seems probable then that hypersecretion of the adrenal medulla due to hypoglycemia definitely contributes to the occurrence and extent of pulmonary

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