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... AND NOW B12!

In these crowded days when one therapeutic miracle succeeds another in rapid succession, the appearance of a new substance with almost incredible therapeutic effects inspires but little excitement. Successive triumphs by teams of chemists, often working in commercial laboratories, appear to have left us jaded. The isolation of vitamin B₁₂ in the research laboratories of Merck and Company in this country¹ and almost simultaneously in the Glaxo Laboratories in England² is the most recent case in point. Here is a substance that, when given to a patient suffering from pernicious anemia, results in a maximal reticulocyte response and a near maximal erythrocyte response following a single injection of ⁵ to ¹⁰ thousandths of a milligram (0.00005 Gm.)! Has there ever been in the history of medicine a more potent material, microgram for microgram?²

Folic acid (pteroylglutamic acid) came out of the research laboratories of the Lederle Laboratories. Its history has been told in these columns.³ Folic acid and the folic acid antagonists⁴ will long stand as a monument to Dr. Yellapragada SubbaRow, who initiated work with these materials and carried it along brilliantly.

It is of interest that a bacterium was used as the assay "animal" in testing both these materials. With folic acid, Lactobacillus casei was used; with vitamin B₁₂, it was the L. lactis Dorner.⁵ Successive assays of concentrated and reconcentrated material required a readily available means for assay and this the bacterium supplied, since the necessary growth factor proved to be identical with the liver extract factor required by the human in erythropoiesis.⁶

Search for the factor in liver extract that is responsible for its hematopoietic and neurologic effects has proceeded almost continuously since liver was first found to be effective in the treatment of pernicious anemia. A year after the introduction of liver, Cohn⁷ in 1917 produced a liver extract called "Fraction G"; this was a water soluble material obtained after protein precipitation. From this substance a solution was later prepared for parenteral use, at first in "crude" form containing only 1 or 2 units per cc. of extract, and later in concentrated form containing 10-15 "units" per cc. The concentrated extracts proved to be of greatest value since in a small amount of solution they gave maximal effects with the least local irritation. They were furthermore highly potent in combating and preventing neurologic involvement.

The place of the crude liver extracts in therapy became quite limited, particularly with the advent of folic acid. This latter material, although only partially helpful in typical Addisonian pernicious anemia was of distinct value in other ("atypical") members of the pernicious anemia family, i.e., in sprue, tropical macrocytic anemia, pernicious anemia of pregnancy and megaloblastic anemia of infancy.⁸ Here the response was often better than with liver extract and neurologic involvement did not occur.

The mysterious relationships between folic acid and liver extract, which are as yet by no means solved, will probably become better understood now that chemi-
cally pure vitamin B₁₂ is at hand. At this writing, B₁₂ appears to be the long-awaited liver extract factor. In minute amounts it appears to possess all the effects of liver extract, both hematologically and neurologically. That it acts on the neurologic disturbance would tend to discredit the assumption that the hematologic and the neurologic lesions of pernicious anemia are due to separate deficiencies.

Some of the macrocytic deficiency states may conceivably not be benefited by B₁₂ administration. This may indicate that the pernicious anemia "family" of diseases is composed of a group of different types of deficiency states but characterized by the common denominator of a megaloblastic bone marrow and macrocytic anemia. In one group are those cases primarily benefited by liver extract; the other is composed of cases in which the best effects appear to be obtained with folic acid. It is reasonable to assume that in the latter group the primary deficiency is in folic acid. A working concept for the present (subject to change at a moment's notice) is as follows:

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<th>Pernicious Anemia &quot;Family&quot; (Megaloblastic Bone Marrow with Macrocytic Anemia)</th>
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<tr>
<td>Deficiency in Vitamin B₁₂</td>
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<tr>
<td>Addisonian Pernicious Anemia</td>
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<tr>
<td>Sprue (certain cases)</td>
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It should be noted that the syndromes in which folic acid is most effective include largely those conditions in which free hydrochloric acid is present in the gastric juice. In the presence of complete achlorhydria, as Spies has already postulated, folic acid does not protect against neurologic involvement. Already, there is indication that B₁₂, like liver extract, may be ineffective in the pernicious anemia of pregnancy, whereas folic acid is highly effective. Further investigations will undoubtedly bring a more complete elucidation of the different types of deficiency states with macrocytic anemia.

Although the chemical formula of vitamin B₁₂ has not as yet been announced, it may be presumed that work on this problem as well as on methods for synthesis is going on. In solution, B₁₂ has a purplish hue and the startling discovery has been made by both the Glaxo and Merck Laboratories that this is due to the presence of cobalt. For years, cobalt has been used in the experimental production of polycythemia. The epizootic occurrence of cobalt deficiency in sheep and cattle in Australia, New Zealand, Canada, and even in this country has been reported. Animals so affected have developed anemia, changes in coat, weakness, emaciation, and finally death as the result of the cobalt deficiency. The whole subject of cobalt metabolism and of the activities of this trace element in the human economy is thus thrown wide-open for new vistas of research.

Vitamin B₁₂ may prove to play a prominent role not only in therapeutics but also in the field of animal nutrition. It has been recognized for a considerable period that an unknown substance or substances present in crude materials such as fish meal, cow manure and liver is required for optimum growth of chicks and for
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adquate hatchability of hen's eggs. Recently, the administration of a concentrate of this "animal protein factor" prepared by Stokstad et al. in two cases of pernicious anemia produced a well defined hematopoietic response. More recently, Ott and collaborators demonstrated that crystalline vitamin B₁₂ can replace these crude sources of the "animal protein factor" in promoting chick growth. Thus, B₁₂ may be responsible either wholly or in part for the growth promoting activity of such feed supplements.

The finding of a potent growth factor in cow manure and doubtless in the excreta of other animals harks back to the days of the witches' brew, and to the naive medicine of certain country districts. Perhaps there was something in these old concepts of medical therapy after all!

In this complex modern world where chemists and physicists and mathematicians are constantly at work, one never knows what new complexities lie ahead of us, what new worlds await us in tomorrow's news!

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REFERENCES

9 Betheill, Frank: Personal communication.
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