

## RECENT DEVELOPMENTS IN THE FIELD OF HEMATOLOGY.

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Progress in both the fundamental and clinical phases of hematology during recent years has been phenomenal. The complexity of bone marrow has been greatly simplified, and the mystery, which for so many decades, surrounded the spleen has become less enigmatic. Both spleen and marrow bear an intimate relationship to each other, and, in turn, to the vital economy of the body as a whole. In the detailed knowledge now available, we have the key to the solution of a whole host of human diseases, some hitherto unrecognized, and, therefore, uncontrolled. Moreover, some of the basic mechanisms are now revealed, whereby new syndromes or combinations of disease syndromes may be detected early, and direct rational measures of control instituted promptly with confidence and with dramatic clinical results.

The most recent significant clinical application of basic information, accumulated from a wide variety of sources through the past ten years of intensive chemical and biological investigations, is that involving so-called folic acid, a derivative of the vitamin B complex. There are five designations which have been somewhat indiscriminately applied to this "group" of compounds: vitamin B<sub>c</sub> (essential to growth and hemoglobinogenesis in young chicks), vitamin M (essential to hematopoiesis in monkeys), *Lactobacillus casei* factor (essential to the growth of these milk-souring bacteria), folic acid (derived from the "foliage" of spinach), and eluate factor (chemical procedure in processing liver, yeast and other natural sources). A conjugate of B<sub>c</sub> has been isolated from yeast, having a more complex molecular structure 2.8 times that of the simpler B<sub>c</sub> obtained originally from liver. Typical vitamin B<sub>c</sub> may be obtained from the "conjugate" on enzyme digestion.

The culminating climax of these fascinating studies came last August (1945) with the announcement by Angier and associates of the chemical synthesis of a compound, recently revealed as pteroylglutamic acid, and ultraviolet and infrared absorption spectra, crystalline structure and *biologic activity* identical with *L. casei* factor isolated in pure form from liver by Stoksted and Manning (1938). The importance of this discovery cannot well be overemphasized or overstated. The "yield" of this biologically essential molecule from natural sources, such as liver, is exceedingly small, 0.1 ounce from one ton of beef liver, so that to have it available in relatively unlimited quantities the synthetic chemist has immeasurably enhanced its effective application both clinically and in further biologic exploration.

Studies in this field were begun in this laboratory in 1940, with Drs. Woolpert, Henry Wilson, Samuel Saslaw and associates in the Department of Medicine and Bacteriology. Rhesus monkeys were used on experimental dietary regimes and it was determined that without "folic acid-containing concentrates" a gradual pan-marrow hypoplasia developed. Langston and associates had previously shown that diets of the Goldberger, black-tongue type were inadequate, and that liver or yeast contained a common essential for normal hematopoiesis in the monkey, "vitamin M." Granulocytopenia occurred in 100 per cent of our dietary deficient monkeys, anemia in approximately 50 per cent. Folic acid concentrate was found to be invariably effective in relieving the granulocytopenia at once, within 24 hours, in our monkeys, and, in those animals showing also anemia, a reticulocyte response was elicited followed by red cell and hemoglobin regeneration entirely comparable to the anti-anemic response to liver extract. Blood thrombocytes also returned to normal.

The translation and transference of the animal results to clinical patients was begun in the summer of 1943 in Birmingham, Alabama, in association with Dr. Tom Spies. Patients chronically deficient in many dietary essentials, more particularly the vitamin B complex, were selected, who showed clinically, frequently recurring oral ulcers, associated with a leucopenia hematologically. Folic acid was then given under controlled conditions, and both clinical and hematologic improvement was noted. Later the synthetic molecule was substituted for the natural source with similar results.

With the availability of larger quantities of synthetic folic acid (pteroylglutamic acid) in the early fall of 1945, Spies extended the use of this material to the macrocytic anemias in and around Birmingham with spectacular responses. Darby and Jones reported from Nashville the response of macrocytic anemia in non-tropical spure, and Moore and associates in St. Louis and our own group here, comprising Henry Wilson and Claude Starr Wright, found equally spectacular results in Addisonian pernicious anemia and the macrocytic anemia of pregnancy. Spies then showed that the macrocytic anemia of tropical sprue in Cuba responds promptly. Furthermore, it has been established that those patients sensitive to liver and liver extract may receive folic acid synthetic with impunity and with the maintenance of complete clinical and hematologic remissions. It remains to be proved whether the neurological changes, associated with pernicious anemia in many patients, will remain permanently under control with folic acid.

There is good reason to believe at the present time that pteroylglutamic acid is not the active principle in liver nor is it the extrinsic factor of Castle. The exact and precise role of this extremely interesting and important molecule in the complex chemistry of hematopoiesis remains to be determined, but a new and fascinating chapter is being written in fundamental biological mechanisms and a new and potent therapeutic agent has been made available for the relief of a large number of human sufferers.