
The findings of the present study, when combined with those of previous studies, support the following concept of binding of vitamin B₁₂ by serum or plasma in vitro. There are primary binders of B₁₂ which preferentially take B₁₂ when small amounts are added and combine firmly with it. They include two already identified substances, TC I and TC II, which are of the seromucoid fraction of plasma. At concentrations of added B₁₂ of the order of 1.0 mg./ml of plasma, these proteins become saturated and secondary binders become important. The latter are relatively unimportant at lower concentrations of B₁₂; they are weak binders of B₁₂; they cannot be saturated by concentrations used to date and are not seromucoids.


The vitamin B₁₂ binding capacities of transcobalamin I and II were evaluated in plasma from patients with diseases known to affect the plasma binding. In CML in relapse, the capacity of TC II was very much diminished or absent. The capacity of TC I was very much increased. There was a lesser degree of both abnormalities during remission and in AML. There was either diminished or absent binding to TC II in PA, but the capacity of TC I was not altered.


The frequency of chromosome aberrations in the lymphocytes of 36 hematologically normal women who had received radiation therapy for cervical carcinoma was measured. The decrease with time in the frequency of cells with acentric fragments, of cells with a single dicentric, and of quasidiploid cells can each be represented by a single exponential with an average lifetime, respectively, of 530 ± 64 days, 788 ± 98 days, and 5.55 ± 1.23 × 10² days. Aneuploid cells fall into two classes: One contains no chromosomes with structural aberrations and shows a stable frequency of about 5.8 per cent; the other contains chromosomes with structural aberrations and is eliminated at the same rate as cells with acentric chromosome fragments. The distribution of dicentrics among the lymphocytes at the end of the radiation therapy period is similar to that shown by a population of lymphocytes exposed in vitro to a single dose of about 300 rads.


Tritium-labeled folic acid was given intravenously to normal male volunteers
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and the nature of the folate compounds appearing in the urine was studied by column chromatography and microbiological assay.

Three peaks of activity were obtained and these were due to (a) N 10-formyl folate and p-amino-benzoylglutamate, (b) N 5-methyl-tetrahydrofolate, and (c) pteroylglutamic acid. Peaks (a) and (c) were tritium-labeled, but peak (b) containing 5-methyltetrahydrofolate was not tritium-labeled.

It was concluded that between one-quarter to one-third of the folic acid activity in urine following a small parenteral dose was due to 5-methyl-tetrahydrofolate, but that this arose by displacement from the tissue (presumably liver) and not from the administered dose of folic acid.

Heath, C. W., Jr.: Cytogenetic observations in vitamin B₁₂ and folate deficiency. First submitted July 19, 1965; accepted for publication Oct. 25, 1965.

Direct marrow cytogenetic preparations were examined in 14 cases of anemia associated with deficiency in vitamin B₁₂ and/or folate. Seven cases showed distinct alterations in chromosome structure consisting of increased chromosome breakage, incomplete chromosome contraction and centromere spreading. These abnormalities were not present after vitamin replacement and were generally less distinct in cases with major medical complications or with only mild megaloblastic changes. No distinct aberrations in chromosome number or karyotype were found. The cytogenetic changes observed seem compatible with current concepts of megaloblastic cell division and with the role of folate and vitamin B₁₂ in DNA metabolism.


The cytogenetic and morphologic abnormalities arising in the bone marrow following therapy with 1-D-arabinofuranosylcytosine hydrochloride (cytosine arabinoside) were studied with 10 patients with various solid neoplasms. A 5-day course of daily, rapid administration of the drug was employed at a dose of 150–200 mg./M² body surface area. Within 24 hours there was a high incidence of chromosomal aberrations in both granulocytic and erythroid marrow cells. These aberrations consisted of chromatid breaks, erosions, despiralization, precocious separation of the chromatids at the centromeric region, and extensive fragmentation. Prominent morphologic abnormalities were seen in nondividing cells of the erythroid series, but were absent from the granulocytic precursors. Following cessation of cytosine arabinoside therapy the morphologic and cytogenetic abnormalities rapidly returned to normal. These features were discussed in relation to the known pharmacology of cytosine arabinoside.


Perl's test for iron (Prussian blue) has been performed on duodenal and jejunal specimens obtained by the Crosby capsule from healthy persons, as
well as from patients affected with congenital hemochromatosis or acquired hemosiderosis (transfusion type). The small intestine was biopsied after an 18-hour fast.

As far as normal human beings are concerned, no hemosiderin was found in the epithelial cells of duodenum or jejunum, nor in the tunica propria of duodenum. On the other hand, the tunica propria of a number of jejunal villi showed siderotic macrophages which seemed to be storing or moving iron from the tips of the villi into the gut lumen.

In hemosiderosis, iron granulations were never found in the columnar epithelium, whereas siderotic macrophages, storing or removing iron, were much more numerous and iron-positive than in the normal, and these macrophages were not only in the tunica propria of jejunum, but also in that of the duodenum.

In hemochromatosis, the columnar epithelium of some duodenal villi had iron-containing granules, and many villi had siderotic macrophages in the tunica propria. These macrophages were not confined to the tips of villi, but were randomly distributed in the tunica propria. Furthermore, no macrophages appeared to be traversing the columnar epithelium or outside it.


Split products of fibrinogen and fibrin are found in the sera of patients with defibrination syndrome and/or fibrinolysis. They may result from spontaneous (primary) fibrinolysis or from lysis of intravascular fibrin deposits.

The split products can be detected by several immunologic methods. Both immunodiffusion and immunoelectrophoresis in agar gel show abnormal bands in high titer pathologic serum samples (usually more than 12 μg./ml.). One of the lines present on immunodiffusion is closer to the point of application than is the other. The position of the closer band might result from the presence of small amounts of fibrinogen-sized molecules or from moderate amounts of partially polymerized or digested fibrin. A precipitin test in a capillary tube offers a simple and sensitive method for demonstrating split products; immediate precipitin occurs with high-titer products but lesser amounts may require up to 18 hours of incubation. The Fi test, agglutination of antibody-coated latex particles, is simple, rapid, moderately sensitive and commercially available, but it sometimes yields false positive results. The precipitin or Fi test on thrombin-treated blood, plasma or serum may be positive when split products are present in high titer, can be read immediately and thus provide a rapid bedside test.

Neither the precipitin nor the Fi test is as sensitive as the tanned red cell hemagglutination inhibition immunoassay (TRCHII) for the quantitation of fibrinogen and its split products. This test is sensitive to 2.0–5.0 μg./ml. of fibrinogen or split products and much more reliable than the other methods. For example, 13 of 22 samples with up to 24 μg.-ml. of split products yielded negative results with the Fi test and positive results with TRCHII.

Because defective and incomplete coagulation may coexist with fibrinolysis
in these clinical syndromes, an excess of thrombin must be added to remove thrombin clottable fibrinogen to establish the presence of nonclottable split products.

It was necessary to demonstrate split products to diagnose occult fibrinolysis; thrombin-treated normal serum was found to contain up to 2.0-5.0 μg/ml. of split products.

Up to 768 μg./ml. split products was detected in serum from patients with reduced fibrinogen with associated primary fibrinolysis (idiopathic, hepatic disease), induced fibrinolysis (streptokinase, urokinase) or in defibrination syndrome with secondary fibrinolysis (metastatic cancer, abruptio placentae, diffuse allergic vasculitis). In other patients with secondary fibrinolysis, up to 96 μg./ml. was occasionally encountered during and following obstetrical delivery of normal or dead fetus, in pulmonary embolism, myocardial infarction and rheumatoid arthritis.

The actual quantity of split products was of greatest value in assessing clinical progress. Heparin in patients with defibrination syndrome, for example, was associated with a rise in plasma fibrinogen and a fall in the concentration of split products. The data indicate that trace amounts of fibrinolytic split products may occur in normal serum. Larger amounts are found both in primary and secondary fibrinolysis, which are relatively common disorders.


When radioactive B₁₂ was added to normal serum, it was bound predominantly to beta globulin. Deficient binding was observed in the serum of ten patients with untreated pernicious anemia. Treatment of these patients with B₁₂ restored the beta globulin B₁₂ binding capacity toward normal.

In one of the five patients there was virtually no beta globulin binding of added B₁₂ before treatment. This patient exhibited a malabsorptive pattern Schilling test when first seen. Treatment with B₁₂ was attended by an increase of beta globulin binding capacity, and by return of the ability to absorb oral B₁₂ when given with intrinsic factor. It is possible that these two abnormalities are related in that the beta globulin may have an important role in the absorption and transport of B₁₂.


Three patients with different obscure hematologic disorders are presented. All 3 patients had abnormalities of chromosome number confined to marrow cells. Case 1 is a 23-year-old man with aplastic anemia; most of his bone marrow cells contained 45 chromosomes, with one missing from group C. Case 2 is a 62-year-old man who died of idiopathic sideroachrestic anemia; most of his bone marrow cells contained 47 chromosomes with an extra C group chromosome which appeared to be an autosome. Case 3 is a 59-year-old woman with idiopathic thrombocytopenia; while the majority of her bone
marrow cells contained 46 chromosomes, a stable minority cell line had 48 chromosomes.

Although many of the reported patients with myelodysplastic-myeloproliferative disorders have normal chromosomes, 5 cases with some chromosomal aberration, previously reported by others, are summarized. None of these patients had clinical evidence of leukemia. In 4 of the patients, the chromosomal anomaly involved a chromosome in group C, which is the group in which aneuploidy occurred in all 3 of our patients.

It is postulated that a stable, aneuploid stem line does not, of itself, produce neoplasia, but rather that this alteration of the genome may provide a more favorable milieu for the action of some transforming agent. Because of the frequent occurrence of C group abnormalities in these cases of marrow disorders, it is further postulated that genes on one or more C chromosomes might be responsible for hemostatic control of hemopoiesis, and that a change in genetic balance involving a C group chromosome(s) coupled with a transforming agent might result in leukemia in a greater proportion of individuals than aneuploidy of some other chromosomal group.


Leukocytes and platelets labeled by the atabrine fluorescent technic have been demonstrated in the maternal circulation from one-half to 4 hours following intraperitoneal transfusion of the fetus in utero. The peak concentration of labeled cells was observed 2 hours after transfusion. The fetomaternal transfer of cells has been demonstrated in cases of erythroblastosis fetalis. It is not known whether this occurs in normal fetuses and the mechanism is not understood.


1. Data are presented which demonstrate that progressive antithrombin activity results from the interaction of three factors: antithrombin, an antithrombin inhibitor and a platelet factor. In plasma, the antithrombin is held inactive by combination with inhibitor so that no free antithrombic activity is present. When platelets are disrupted in clotting, the platelet factor made available binds the inhibitor, releasing antithrombin to react with thrombin.

2. Antithrombin was isolated from plasma in the 70–75 per cent ammonium sulfate fraction. It was relatively heat stable at 56–57 C. for 15 minutes and was not soluble in perchloric acid.

3. Inhibitor was isolated from plasma in the 30–50 per cent ammonium sulfate fraction. It was inactivated at 56–57 C. for 15 minutes. It was soluble in perchloric acid in which it was purified by a factor of 300.

4. Platelet factor was present in the sedimentable fragments of platelets.


1. A case of promyelocytic-myelocytic leukemia is reported as the terminal
phase of chronic granulocytic leukemia. We believe that this is the first such case reported.

2. The terminal phase of this case is compared with acute promyelocytic-myelocytic leukemia; the course and laboratory data appear almost identical.

3. The nature of the abnormal granules in the promyelocytoid-myelocytoid cells and their relation to the fibrinogenopenia incite speculation.


A fetal hemoglobin variant, designated hemoglobin F,Im,t, was found in the cord blood sample of a healthy, term, Negro infant. The variant, comprising about 15 per cent of the total cord blood hemoglobin, diminished concomitantly with hemoglobin F, and it was barely detectable in the blood when the infant was 4 months old. The hemolysates of the parents and two siblings resolved into the usual adult pattern, but a trace amount of a fraction similar to hemoglobin F,Im,t was present in the father's hemolysates, and not in the mother's.

The ultra-violet absorption spectrum indicates that hemoglobin F,Im,t contains γ polypeptide chains, and immunologic studies reveal the presence of both α and γ chains. In hybridization tests the alteration appears in the γ chain.

Peptide chromatograms of hemoglobin F,Im,t indicated the presence of α and γ chains, but failed to reveal an abnormality. Amino acid analyses suggest that there may be a substitution of an alanyl for a glutamyl residue.