HEMOSTASIS—HEMOPHILIA

THROMBIN FORMATION AND YIELD IN SHED BLOOD IN RELATION TO THROMBOPLASTINS AND PROTHROMBOPLASTINS. P. Fantl. From the Baker Medical Research Institute and Clinical Research Unit, Alfred Hospital, Melbourne, Australia. Australian J. Exper. Biol. 32: 853-866, 1954.

This paper describes a new technic which has been used to study factors which influence the rate of formation of the plasma thromboplastin complex. In an earlier report the author showed the effect of procatechol in depressing antithrombin activity in the assay of prothrombin. Because it does not adversely influence the rate of thromboplastin formation this substance is now made use of in determination of the rate and yield of thrombin formed during spontaneous coagulation in diluted blood. It is therefore possible to use this as an index of thromboplastin formation. Factors shown to accelerate the rate of thrombin formation are: thromboplastins, brain suspensions, suspension of blood vessels, tissue juice contamination in capillary blood specimens, and also long contact with a glass surface by the specimen before testing. Delay in thrombin formation and reduction in the yield of thrombin resulted from decrease in platelets and from decrease in plasma thromboplastin precursors. The technic described has been used to determine the normal rate of thrombin formation under standard conditions. When delay occurs, as in patients with deficiency of a thromboplastin precursor, the correcting effect by the addition of known factors can be determined. By this means it is shown that normal blood contains at least a fourfold excess of thromboplastin precursors.—G.C.deG.


This paper discusses the investigation of 43 male bleeders, 37 with hemophilia and 6 with Christmas disease. The authors designate antihemophilic globulin as alpha-prothromboplastin and Christmas factor (PTC) as beta-prothromboplastin. In addition to the more common tests, the coagulation properties were determined by the rate of formation and the amount of thrombin formed in diluted blood in the presence of pyrocatechol, which acts as a thrombin stabilizer. The deficiencies of thromboplastin components could be corrected by the addition of blood or the appropriate blood products in vitro, and the degree of the deficiency of each patient's blood could be determined by the amounts required.

Variations from complete absence to minor deficiencies of alpha-prothromboplastin were observed, whereas only complete absence of beta-prothromboplastin was encountered.
Normally the rate of formation of thrombin is faster in capillary blood than in venous blood, owing to contamination by tissue thromboplastin in the former. However, in cases of complete alpha-prothromboplastic deficiency, venous blood and capillary blood give identical results. On the other hand, in cases of complete beta-prothromboplastin deficiency, only properly collected specimens of venous blood give reliable results, whereas capillary blood may produce erroneously short thrombin clotting times. Apparently patients with complete beta-prothromboplastin deficiency have enough tissue thromboplastin to mask the results in capillary blood. These observations suggest that the labile alpha-prothromboplastin may be the precursor of the blood thromboplastin complex, and the beta-factor an essential co-factor for rapid thromboplastin formation. Experiments have been presented which indicate the catalytic nature of the blood thromboplastin complex. Normal blood has at least a fourfold excess of the thromboplastin components. A bleeding tendency is therefore expected to occur below a level of 25 per cent of the normal plasma concentration. Whole blood clotting time and the rate of thrombin formation were constant in one patient; an identical degree of deficiency was present in the blood of affected male relatives.

In-vivo studies show that for satisfactory hemostasis, far greater amounts of the missing factor have to be given intravenously than is suggested from the in-vitro results. This would indicate that the rate of destruction of the plasma thromboplastin component is greater than that of other blood proteins, or that the transfused alpha-prothromboplastin or beta-prothromboplastin circulates through a space two to three times the blood volume. A comparison between the laboratory data and clinical findings shows that in general there is some parallelism between the clinical severity of the hemorrhagic tendency in a pedigree and the degree of blood deficiency. However, this is by no means absolute. It was noticed in contrast to the constancy of laboratory findings that the clinical manifestations varied greatly. This, of course, would indicate that, in addition to the blood deficiency, other factors, presumably of vascular nature, play an important part in the clinical manifestations.—G.C.deG.


From a systematic analysis of blood-clotting defect in 35 patients affected by a constitutional hemorrhagic diathesis with the characteristics of hemophilia, the authors were led to discriminate between: hemophilia A: 26 cases; hemophilia B: 5 cases; hemophilia A' or A attenuated: 2 cases. To complete the clinical and biological features of the disease there are to be added those constitutional hemorrhagic diatheses due to lack of factor A in women and to deficiency of factor A associated with another disturbance in hemostasis. The characteristics of hemophilia A' are defined: less frequent and less serious hemorrhages in all hemophiliacs of the same family, subnormal or normal clotting time, concentration in factor A markedly reduced, but far superior to that of plasma of hemophilia A.

The titer of factor B in normal plasma is far superior to that of factor A. Fresh normal plasma contains indeed as much as 20 to 40 times the amount of factor B necessary to ensure normal utilization of prothrombin “in vitro” against 2 or 3 times for factor A. Factor B transfused to a hemophilic B has a survival of 2 to 3 weeks, whereas factor A lasts from a few hours to 24 hours at most. Such facts explain the previously mentioned differences in the response to transfusions in hemophiliacs A and B.—J.D.


The newly described factor X, according to Koller, is assumed to be similar to the Plasma Thromboplastin Antecedent (P.T.A. of Rosenthal). In addition to its congenital deficiencies in hemophilic syndromes, a decrease was also observed in obstructive jaundice and in the newborn. By using the Thromboplastin Generation Test it was possible to ascertain a decrease of factor IX (P.T.C., Christmas factor) during treatment with diemarol and allied compounds. Further experiments suggested that some still unknown ac-
CELERATORS OF THE THROMBOPLASTIN FORMATION ARE PRESENT IN SERUM, IN ADDITION TO PLATELET THROMBOPLASTIN FACTOR (PLATELET FACTOR 4, THROMBOPLASTINASE, SEEGERS' PLATELET FACTOR 3), CALCIUM, FACTOR IX AND FACTOR X.—P.D.N.


Experiments on the thromboplastin generation test in various conditions lead to the assumption that PTA (Plasma Thromboplastin Antecedent) and the newly described factor X are identical. This new thromboplastin factor was decreased, in the author's researches, in cord blood, in the newborns during the first ten days after birth, and during the treatment with dicumarine derivatives.—P.D.N.


A 20 year old male had a bleeding disorder. The platelets were normal, as were the two-stage prothrombin activity and the test for Factor V. There was a prolonged one-stage prothrombin time and deficiency of Factor VII, and thromboplastic generation was fully corrected by normal serum but unchanged by normal plasma. Clot retraction was impaired. There was no evidence of liver disease, and it was concluded that there was a combination of Christmas disease and Factor VII deficiency. Treatment was with compatible 10 day old serum given intravenously. As far as possible the patient's family was studied. Deficiency of Factor VII was found in relatives of both sexes including the patient's mother, and some of the males had Christmas disease as well. The critical hemorrhagic level of Factor VII appeared to be less than 40 per cent of normal, and the tendency to bleed in this family seemed to be determined by deficiency of Christmas factor.—R.H.G.


Patients maintained on phenindione for over 30 days showed a prolonged glass clotting time, with delayed prothrombin consumption and thromboplastin generation. Using the plasma of a patient with PTC deficiency, the PTC content of plasma from patients on anticoagulants was tested by the prothrombin consumption and thromboplastin generation tests. Six patients out of 14 (including one on Dicumarol) gave plasmas which failed to correct the prothrombin consumption test and 3 out of 7, the thromboplastin generation test for PTC deficient plasma. The authors conclude that the PTC deficiency is related to the length of time the patient has received the anticoagulant, although their data indicate it is not a consistent finding in long term anticoagulant therapy.—L.B.J.


Blood flow in the arterioles of the bulbar conjunctiva of 280 patients was examined using a stereohinocular microscope. Results were tabulated as answers to a series of questions regarding aggregates present—position, composition, size, properties, etc.—and regarding vessel walls—size, permeability, hemorrhage, etc. In the 75 patients with myocardial infarction, erythrocyte aggregates were found which produced intermittent embolization of arterioles. These were not found in the control group. The prothrombin concentration was found to have an inconstant relation to the fluidity of the blood. In the presence of prothrombin concentrations between 10 and 30 per cent, erythrocyte aggregates were present which seriously reduced linear velocity of blood flow or plugged arterioles.—L.B.J.
MEGALOBLASTIC ANEMIA


Two important papers giving evidence for the conclusion that the formula for vitamin B₁₂ is as follows:

R. H. G.


Estimates of the absorption of radio-tagged B₁₂ have provided a much needed simple means for the assay of intrinsic factor. Several techniques have been employed but it would seem that the determination of urinary radioactivity, following the oral administration of Co⁶⁰ labeled B₁₂ and the use of "flushing" doses of nonlabeled B₁₂ intramuscularly is the most simple and convenient of these.

The technic employed was the oral administration of 2 µg. of radioactive B₁₂ which contained 0.5 µc of Co⁶⁰, which was followed immediately by the intramuscular injection of one mg. of vitamin B₁₂. On the second day one mg. of nonradioactive B₁₂ was again injected intramuscularly and on the third day, a second oral dose of radioactive B₁₂ was given orally and one mg. of vitamin B₁₂ injected intramuscularly. On each of the subsequent three days one mg. B₁₂ was injected. Each 24 hour urine sample was collected separately over the 6 day period of time and its radioactivity determined.

In this technic errors are avoided from the delayed excretion of orally administered radioactive B₁₂ in the normal individual and in the patient with pernicious anemia to whom intrinsic factor preparations are concurrently given. In this same study, it was found that pretreatment with large doses of intramuscular B₁₂ caused a decrease in the urinary excretion of orally administered labeled B₁₂. The values obtained for urinary excretions of
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radioactive vitamin B₁₂ in 35 patients with pernicious anemia and in 22 normal subjects are in accord with previously published data.—W.N.J.


The use of radioactive vitamin B₁₂ in the investigation of Castle's intrinsic factor has sufficed because of the scarcity of Pernicious anemia patients and then only a limited amount of Co⁶⁰ may be given to any one subject. Although laboratory animals, such as the pig, might prove suitable, the practical difficulties of maintenance and collection of feces would be considerable. For this reason the rat was chosen. After they had been cured of Bartonella infection, some were kept in isolation as controls and others were gastrectomized. Only the glandular part of the stomach was removed, together with the proximal first centimeter of the duodenum. A measured dose of vitamin B₁₂ labeled with Co⁶⁰ was given by mouth, and the amount of radioactivity subsequently excreted in the feces was measured. Normal rats excreted 66.5 per cent of orally administered vitamin B₁₂, while gastrectomized rats excreted 93.8 per cent because they had lost their ability to absorb it. However, absorption was almost restored to normal when gastrectomized rats were given extract of rat stomach along with the vitamin, as indicated by the excretion of 69.5 per cent of the dose. The results obtained with a filtrate of pig pyloric juice were inconsistent.—O.P.J.

ROLE OF FOLIC ACID AND VITAMIN B₁₂ IN TRANSMETHYLATIONS. PART I. FORMATION OF CREATINE IN VITRO AND IN VIVO. P. Fatterpaker, U. Marfatia and A. Sreenivasan.

Deficiency of either folic acid or vitamin B₁₂ or both led to a diminution in creatine formation and excretion. The effect was especially seen in vitro synthesis; in vivo it was less pronounced in the urine and least in skeletal muscle. On the administration of large doses of folic acid or vitamin B₁₂ to the deficient animals there was rapid improvement in the impaired creatine metabolism. In contrast, addition of folic acid or vitamin B₁₂ did not activate in vitro the creatine-forming enzymes in the deficient systems.—J.B.C.

VITAMIN B₁₂ AND FATTY LIVERS IN Pancreatic Duct Ligated Rats. J. C. Sachdev.

Fatty livers were produced in experimental rats by ligation of the pancreatic duct. Vitamin B₁₂ failed to prevent fatty livers in these rats in spite of their being fed on a diet rich in precursors of homocystine.—J.B.C.

RED BLOOD CELL DIAMETERS IN WET AND DRY PREPARATIONS. G. Larsen.

Red cell diameter distribution curves from cases of untreated pernicious anemia are highly abnormal when measurements are carried out on dried smears. These characteristic curves, however, can not be demonstrated when blood cells suspended in plasma are measured on a nonwettable surface. The author suggests that the abnormal diameter distribution curves in dry preparations in pernicious anemia are caused by the presence of macrocytes, which, because they are different from normocytes in water content and adhesiveness, behave differently when placed on a glass slide and dried.—M.S.

CONTRIBUTION TO THE MORPHOLOGY OF MEGALOBLASTIC ANEMIA. F. Hřmanský.
From the 1st Medical Clinic, Charles University, Praha. Čas. lék. čes. 84: 78-83, 1955.

From the analysis of 185 bone marrow examinations in megaloblastic anemias, the conclusion is drawn that both the megaloblast and normoblast series are derived from a com-
mon stem cell, the proerythroblast. According to the degree of deficiency of the antimegaloblastic factors, normoblasts, intermediate forms as well as megaloblasts may develop from this stem cell. Even in the later stages of development, transformation of the cell of one series to that of the other is possible, as long as the cells are able to divide. In some instances, the possibility of a direct development of megaloblasts from reticular cells must be admitted. In using special staining, an increased presence of both intercellular and intracellular iron could be proved, especially in megaloblasts; in the periphery, siderocytes were found rather frequently. The occurrence of megaloblasts in nonmegaloblastic anemias deserves attention; in a case of hereditary spherocytosis, a striking megaloblastosis of the bone marrow could be observed during the inhibitory crisis. Therefore, morphologic criteria as well as the whole clinical picture must simultaneously be evaluated in the diagnosis of megaloblastic anemias.—M.V.


Two further cases are reported of megaloblastic anemia following the administration of phenytoin and phenobarbitone. In one instance these had been given for at least eighteen months, in the other for four years. There was free hydrochloric acid in the gastric contents in both cases, and no clinical evidence of intestinal malabsorption, although this was not investigated. There was a hematologic response to folic acid therapy after cyanocobalamin injections had been tried without success.—R.H.G.


A description is given of three further cases of megaloblastic anemia occurring in patients receiving phenytoin sodium. Test meals showed the presence of free hydrochloric acid in two cases: the third was not investigated for this. One patient seemed to respond to cyanocobalamin therapy.—R.H.G.


To check up the diagnosis of pernicious anemia, 664 persons living in the region of Prague were re-examined. In 210 patients, this diagnosis was found to be incorrect; because of the incompleteness of the anamnestic data, 28 patients could not be included in these statistics.

In 426 patients, who were found to suffer from pernicious anemia, there were 117 males (27%) and 309 females. In 108 patients (25%), the family history showed an occurrence of malignant tumors; cancer of the stomach occurred in the family of 47 patients, diabetes in 28 families, thyreopathy in 40 families. Familial occurrence of pernicious anemia was noted in 14 patients (3.3%). In the case histories, thyreopathy was present in 20 patients, diabetes in 8 patients and premature greying in 120 patients. Atrophic glossitis was found in 91 patients, advanced neuroanemic symptoms in 13 patients. Pernicious anemia was found to be most frequent between the age of 60 and 70 years.—M.V.


Malnutrition often depends more on the type of crops grown in the patient’s neighborhood than on monetary wealth. Taboos are important causes of malnutrition in some regions. In 45 pregnant Nigerian women with malnutrition, the liver was palpable in 30 instances and the spleen in 32. Hematologic investigations were done in 40 of these women. The anemia was macrocytic in 11, normocytic in 19, and microcytic in 10. The M.C.H.C. was usually normal. The marrow was usually macronormoblastic, but was megaloblasic in two. The sickle cell trait was found in six cases. Schumm’s test indicated hemolysis in
21. The anemia was refractory to treatment with iron, folic acid, liver extract or vitamin B₁₂, but responded to casein supplements.

A liver biopsy was done in 42 patients, and the liver showed fatty infiltration. The liver damage was similar to that found in children with protein malnutrition and to that produced in animals by feeding them on diets low in protein and adequate in carbohydrate or fat. The plasma albumin was reduced and the globulin increased. In 10 cases the diet was investigated and found to contain a mean daily protein content of 36.4 Gm., with 1300 Calories. It is concluded that anemia in pregnant women in Nigeria is probably associated with protein malnutrition and liver damage.

In 9 children with protein malnutrition the liver was palpable in 7. Hematologic investigations were done in 6. The anemia was usually normocytic with a normochromic marrow; no megaloblasts were found. The plasma albumin was low and globulin high. The α and γ globulin were the fractions increased; the increase in the former is believed due to malaria and in the latter to liver damage. Liver biopsies showed similar results to those in the pregnant women. Similar findings occurred in older children and adults. The macronormoblastic anemia in all groups is believed to be associated with chronic protein malnutrition and liver damage.—R.H.G.


Hemoglobin levels were estimated in over 1,000 women in Karachi. The feces were examined microscopically in over 1,000 men and women. Hospital outpatients and those obviously ill were excluded. The hemoglobin level was very definitely related to the social status and anemia was most prevalent between 15 and 30 years. A hemoglobin level of less than 80 per cent was present in 75 per cent of those in the artisan class. Among European females in Pakistan, too, the value was less than 80 per cent in nearly three quarters of those examined.—R.H.G.


A 50 year old Bantu woman complained of leg weakness. She had ataxia, loss of vibration and position sense, a positive Romberg's sign, and absent ankle jerks. The plantar responses could not be elicited. The blood levels were hemoglobin 4.7 Gm. per 100 ml., PCV 14%, MCHC 33% (red cell count and MCV not given). There was histamine-fast achlorhydria and a megaloblastic marrow. A gastric biopsy showed atrophic mucosa. Folic acid therapy gave a hematologic response, but the neurologic condition deteriorated, and improved with cyanocobalamin therapy. It was considered that this was a case of pernicious anemia.—R.H.G.


Megaloblastic anemias in Africans can be classified into two groups. One responds to 200,000 units of penicillin by mouth, or 400,000 units intramuscularly, daily for 6 to 12 days, or to a single dose of 80 μg. of cyanocobalamin by mouth. The other group does not respond to these, but to folic acid by mouth. An account is given of seven cases further investigated by serum vitamin B₁₂ measurements (Euglena assay) and by measurement of the excretion of radioactive vitamin B₁₂.

In the cases that respond to cyanocobalamin or penicillin the serum vitamin B₁₂ level is low before treatment, the excretion of labeled vitamin B₁₂ after penicillin therapy is 35-55%, and there is free acid in the gastric juice after histamine. The authors believe that the antibiotic destroys microorganisms in the gut that compete with the body for vitamin B₁₂. (In this report only two such cases are recorded and the outputs of radioactive vitamin B₁₂ were 42% and 52%.)
In the cases that respond to folic acid the serum vitamin B₁₂ level is normal or high, and there is free hydrochloric acid in the gastric juice. The excretion of labelled vitamin B₁₂ was 44-56% (after penicillin and folic acid treatment) in the four cases recorded. The seventh patient had a low serum vitamin B₁₂ level and evidence of subacute combined degeneration. There was histamine-fast achlorhydria but no evidence of gastric atrophy on gastroscopy. There was some response to penicillin by injection and a good response to 80 μg of cyanocobalamin by mouth. The authors consider that this patient, who excreted 78% of the dose of radioactive vitamin B₁₂, had pernicious anaemia with some intrinsic factor remaining.—R.H.G.


From the many pregnant women admitted for treatment of anaemia over a period of 18 months, 30 were investigated in detail. Most Southern Nigerians are very poor and of necessity vegetarians. The author states the criteria used as evidence of a deficiency of “hemopoietic liver principle” were the presence in marrow or peripheral blood of giant stab cells or metamyelocytes or giant multisegmented polymorphs or the presence in the marrow of Ehrlich megaloblasts or intermediate megaloblasts (Dacie and White’s terminology). Twenty patients had such evidence of a deficiency of ‘hemopoietic liver principle’, and of these 15 had macrocytic anaemia. Thirteen patients were treated with cyanocobalamin injections, and there seems to have been a response in most instances but the patients would not remain in hospital or attend as outpatients. The author comments on the lack of response to folic acid of pregnancy anemias in African women, but appears to have given folic acid only to one of these patients, a particularly complex case.—R.H.G.


Four women with megaloblastic anemia were investigated during pregnancy and five after delivery. None showed a definite response to cyanocobalamin therapy except that one in the puerperium had an optimal response which may however have been a spontaneous remission. The dose given was 2000 μg. Achlorhydria was present in two patients, but their uropepsinogen excretion was within normal limits. Gastric biopsy did not show gastric atrophy in any. The absorption of labeled vitamin B₁₂ was normal, as was fat absorption. The serum vitamin B₁₂ level was normal in four patients and in the lower range of normal in a fifth. An absolute deficiency of folic acid cannot be excluded, but the anaemia seems more likely to be due to resistance to the action of hemopoietic factors than to deficiency.—R.H.G.


Serum and urinary concentrations of vitamin B₁₂ in 14 normal Indians were estimated microbiologically using Euglena gracilis var bacillaris as the test organism. In serum, mean values for the total and combined vitamin B₁₂ were 295 (range 98 to 600) and 243 (range 88 to 527) μg. per ml. respectively. In urine the mean value for the total vitamin B₁₂ concentration was 74 (range 10 to 156) μg. per ml.—J.B.C.


Mean values for total and combined concentrations of vitamin B₁₂ in serum in 6 cases of nutritional macrocytic anaemia, estimated microbiologically with Euglena gracilis var bacillaris as the test organism, were respectively 75 (range 20 to 170) and 72 (range 20 to

Theoretically, human vitamin B₁₂ deficiency could possibly occur as the result of an inadequate intake of the vitamin. In this study of 11 individuals who subsisted for a period of years on a diet devoid of animal protein, it was found that the vitamin B₁₂ serum levels averaged 111 μg. per ml. as compared to normal values of 200-320 μg. These patients had normal hemoglobin concentrations, plasma iron levels, leukocyte counts and reticulocyte counts. The symptoms encountered in these patients were those of sore tongue, paresthesia, amenorrhea and pain in the back. The theory that the symptoms observed might be due to a chronic toxicity resultant from vitamin B₁₂ deficiency is presented, but evidence to support the theory is inadequate.—W.N.J.


The study was of 29 Indian and Chinese labourers and artisans with nutritional megaloblastic anaemia. Of these, 11 had low serum vitamin B₁₂ levels (Engelena assay). After a 5 mg. injected dose of pteroylglutamic acid, the urinary output of folic acid was low in 8 instances. After the patients had been saturated by injections of folate, the output after a 5 mg. oral test dose of pteroylglutamic acid was low in 11 instances. The low value after the oral dose presumably indicates malabsorption, but the urine was collected for only six hours. There was a close correlation between the serum vitamin B₁₂ level and the urinary excretion of folic acid after the subcutaneous loading dose: when the serum vitamin B₁₂ level was low, the excretion of folic acid was low also.—R.H.G.

VITAMIN B₁₂ CONCENTRATION OF SERUM IN MONKEYS. C. R. Das Gupta, J. B. Chatterjea, S. K. Ghosh and D. K. Banerjee. From the Department of Haematology, School of Tropical Medicine, Calcutta, India. Bulletin Calcutta School of Tropical Medicine 3: 148.

Mean values of free and total vitamin B₁₂ in 6 healthy monkeys (M. rhesus) estimated microbiologically with Engelena gracilis as the test organism were 29 and 57 μg. per ml. respectively. Free vitamin B₁₂ on an average constituted 50% of total vitamin B₁₂. Both the free and total vitamin B₁₂ contents of monkey serum were thus lower than the corresponding human values; the ratio of free to total vitamin B₁₂ in monkey serum was, however, considerably higher.—J.B.C.


Vitamin B₁₂ in the dosage of 20 to 25 μg. daily, administered orally for a period of 14 to 15 weeks to undernourished Indian children, subsisting on restricted or adequate vegetarian diet, failed to produce any significant growth response or nitrogen retention.—J.B.C.


Fundus oculi was examined in 46 cases consisting of 9 cases of nutritional macrocytic anaemia, 20 cases of iron-deficiency anaemia and 17 cases of dimorphic anaemia. Normal ap-
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Appearance was seen in 11 cases. Common changes in others were pallor of the optic disc (24 cases), varying degree of venous engorgement (24 cases), retinal exudate (13 cases), retinal edema (6 cases) and retinal hemorrhage (5 cases). Retinal changes were commonest in nutritional macrocytic anemia and least in iron-deficiency anemia. The eye changes were reversible and usually cleared up with the improvement of blood picture following antianemic therapy.—J.R.C.

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G. Donati and V. Prato: Acquired hemolytic anemia associated with intermittent purpura. G. Russo: Goats’ milk anemia in three cases of Kwashiorkor in Italy.


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