ABSTRACTS

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ABSTRACTS OF SPECIAL INTEREST


These three papers describe blood group serologic findings in a total of nine patients aged 57 to 85, seven of whom had cancer. All were of group A1 (one of genotype A1A2) but possessed a weakly reacting B-like antigen on the red cells. Evidence is presented to show that this antigen probably develops as an acquired character. The red cells of these patients were agglutinated by some but not all anti-B sera, but in no case by the apparently normal anti-B in their own sera. The strength of the agglutination reaction varied considerably from patient to patient. The reaction was strongly inhibited by saliva from B and AB secretors but not by saliva from O and A secretors or nonsecretors. None of the patients was found to secrete B substance. In the case described by Marsh et al., blood taken three days after death showed that the genotype was unchanged but that the reaction of the postmortem cells to anti-B was almost negative. These authors describe a technic by which a B antigen can be produced in vitro in group A1 cells.—R. M. H.


The enlargement of this month's abstract section was made possible by a kind contribution from Burroughs-Wellcome and Company, Tuckahoe, N. Y.
The authors have published (Rev. HématoL. 1958, p. 148) a previous case of acute leukemia with a double red cell population: A1 cells and cells with characteristics similar to group O. In the present case, 80 per cent of the cells were normal group A1, and 20 per cent behaved like "weak A," although they were only feebly agglutinated by anti-H. The significance of this fact is discussed. An embryonic chimera cannot be possible genetically without accepting a mutation in one of the parental gametes. An acquired somatic modification would seem to be more acceptable, as the patient had been found to be group A several years previously. Four "weak A" phenotypes (two A3 and two Am) in other patients with acute leukemia would also be consistent with the latter possibility. One of the type Am was seen in a patient whose mother was group A1B; without accepting a mutation in the maternal gamete, the serologic properties of the patient's red cells cannot be explained genetically. It is suggested that in some cases of acute leukemia a somatic mutation of the A gene occurs affecting all or some of the red cells depending on the extent of invasion of the hematopoietic system.—G. M.


Serial chromosome studies on the sternal marrow cells of a case of acute leukemia showed a modal chromosome number of 48, later changing to 47 together with abnormalities of chromosome form, after seven months' treatment with steroids. No chromosomal abnormality was found in skin biopsy material. Marrow obtained immediately after death from a lumbar vertebra, which had been irradiated 5 days previously, contained fewer cells in mitosis than did the sternal marrow obtained at the same time and had a modal chromosome number of 49, as against 47 in the sternal marrow cells. Chromosomal abnormalities were found in the bone marrow cells of 3 of 4 other cases of acute leukemia but in none of five cases of chronic myeloid leukemia, one of chronic lymphatic leukemia and two of myelomatosis. These important findings are discussed in relation to the pathogenesis of leukemias and the natural history and treatment of acute leukemia. The authors suggest that the observed chromosomal changes in acute leukemia may be the consequences of a more subtle genetic change which initiates the leukemic process.—R. M. H.


An apparently female child aged 16 months, the offspring of a normal male and a known carrier of hemophilia, suffered from a severe bleeding disorder and was found to have an antihemophilic globulin level of 0.1 per cent, as compared with 25 per cent and 35 per cent in female carriers in the same family. Nuclear sex determination on blood films and skin showed a male pattern, and chromosome studies showed a probable XY chromosomal constitution.—R. M. H.


A study was made of certain metabolic changes that occurred in guinea pig polymorphonuclear leukocytes during the ingestion of inert particles. The changes observed included an increased lactate production and an increased oxygen uptake. During phagocytosis a much greater fraction of glucose converted to lactate seemed to be metabolized by the direct oxidative pathway than under resting conditions. Interference with glycolysis by iodoacetate and fluoride inhibited phagocytosis. The authors suggest that, contrary to previous belief, phagocytosis does require a specific expenditure of energy on the part of the phagocytizing cell.—T. E. B.
ERITHROPOIESIS


Multiple intravenous injections of detoxified human and bovine sera into rabbits resulted in inhibition of maturation of bone marrow elements and occasionally in suppression of hematopoiesis. In animals deprived of 46 per cent of their bone marrow this effect was exaggerated. Heated sera had no such effect. The above results can be explained by: (a) effect of antigen-antibody reaction, (b) "toxic" effect of foreign protein or (c) by the presence in the serum of specific factors concerned with the regulatory mechanism of hematopoiesis. The authors favor the last explanation.—W. J. M.


It was shown in earlier experiments that the resection of major peripheral nerves is followed by anemia and trophic disturbances in the albino rat. Bilateral adrenalectomy prevents both the anemia and the trophic disturbances as well. Investigations into the mechanism of this phenomenon are in process. Preliminary experiments suggest that the absence of glycocorticoids is mainly responsible for the prevention of the trophic disturbances and anemia.—S. R. H.


Hypophysectomy has induced an anemia in every animal investigated, including the human. The present authors have claimed that hypothyroidism, hypoadrenalism and a lack of growth hormone are all involved in the hematologic changes found in hypophysectomized rats. They have also indicated that these effects, particularly those involving erythropoiesis, are not due to specific effects of these hormones on marrow erythroid elements but rather to their general influence on metabolism. If this theory is correct, hypophysectomized animals are anemic because of a decreased need for oxygen, and various hormone therapies prevent, or eliminate, this anemia by increasing the oxygen need of the tissues. Experimental evidence obtained from studies of female rats 3 to 4 months of age supports this view.—O. P. J.


Rabbits starved for 5 days were found to have low plasma iron turnover and low iron utilization. Rats starved for 5 days were found to have low 20 hour utilization of iron and high liver utilization. Extracts of boiled plasma from phenylhydrazine-treated rabbits increased iron turnover and utilization in starved recipient rabbits and produced an increase in 20 hour iron utilization accompanied by a drop in liver iron utilization in starved rats. An erythropoietically active, nondialyzable material was isolated by alcohol fractionation from urine of anemic rabbits. The material resembled a mucoprotein and was shown to contain 10 per cent carbohydrate.—A. E.

A condition resembling glomerulonephritis was produced in mice by irradiation of the kidneys. Progressive anemia accompanied the development of uremia only if all the kidney tissue was irradiated; if \( \frac{1}{3} \) to \( \frac{1}{4} \) of one kidney was shielded, uremia occurred without a fall in hemoglobin. Mice subjected to total irradiation of the kidneys developed a reticulocytosis following the injection of serum from bled normal mice, or of a protein-free ultrafiltrate of such serum. Nephrectomized mice failed to develop reticulocytosis after bleeding. These and other related findings are presented as evidence that the kidney produces an erythropoietic principle, and that the anemia of renal failure is independent of the excretory function of the kidneys. It is suggested that the production of an erythropoietic principle from the kidneys may be related to certain changes observed in the granules of the juxtaglomerular cells. Insufficient experimental details are given in this preliminary report to enable the conclusions to be properly evaluated.—R. M. H.


Uremic patients were found to be able to conjugate potentially toxic phenols in a normal manner. Free phenol and cresol were not elevated, and it was believed unlikely that the high levels of conjugated phenols were of pathogenetic importance in the anemia of chronic renal disease.—A. E.


Plasma from rats treated with cobalt for 26 days was shown to increase the reticulocyte counts of hypophysectomized recipient rats. The increase in reticulocytes was significantly higher than those observed after administration of normal plasma, but slightly lower than observed after administration of plasma from bled rats.—A. E.


The total uptake of radioactive iron in the bone marrow was determined directly in normal rats, rabbits and monkeys by isolating the skeleton and measuring its activity. In man it was measured indirectly by assuming that \( \frac{1}{8} \) of an injected dose of radioactive iron is incorporated into marrow cells. The uptake was then compared with the uptake in a small bone marrow aliquot and the total number of bone marrow cells were estimated from these values and from the number of cells in the aliquot specimen. The total nucleated marrow cells Kg. \( \times 10^8 \) was found to range from 12 in rabbits to 34 in monkeys, with man and rats having an average of 18.—A. E.


Mitochondria prepared from rabbit bone marrow or rat liver were added to hemolysates of washed chicken erythrocytes. Study of this system suggests that mitochondria take part in three steps of porphyrin and heme biosynthesis. (1) In the formation of delta-aminolevulinic acid from glycine and active succinate the presence of uninjured mitochondria in the hematopoietic tissue is essential. (2) Mitochondria participate in some steps in the synthesis of protoporphyrin from delta-aminolevulinic acid. Not only are intact mitochondria from bone marrow, erythrocyte, liver and mesenteric lymph nodes active, but also disrupted mitochondria or the aqueous extracts of acetone powders of mitochondria are active. (3) Mitochondria appear to participate in the incorporation of iron into the porphyrin ring in the formation of heme.—G. W. J. III.
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If hemoglobin, hemin, coproporphyrin and bile pigments, with the exception of stercobilinogen and stercobilin, are exposed to hydrogen peroxide, a colorless compound termed pentdyopent is formed. This is changed to pentdyopent when treated with potassium hydroxide and dithionite. Pentdyopent has a maximum absorption of 525 m and takes its name from this figure. The pentdyopent reaction is a group reaction not obtained with monopyrroles but given by many pyrromethenes and oxypyrromethenes. Paper electrophoretic study suggested that the propentdyopent obtained from hemoglobin, hemin, bilirubin, urobilin, icteric urine and normal bile moved in two well delineated fractions. Similarly in paper chromatography, propentdyopent gave rise to two spots with good separation.—G. W. J. III.


Rabbits were injected intravenously with 2000 mg of saccharated iron oxide. One week afterwards approximately 1700 mg were recovered from various organs, the bulk (1250) coming from the liver. The hemosiderin and ferritin fractions were equal. After six months, the total liver iron increased to 1500 mg. There was also a decrease of the iron content of the spleen, bone marrow and the kidneys. The increase of the liver iron was associated with a proportionally greater increase of hemosiderin and a corresponding reduction of ferritin. These observations indicate that the time factor is important in the considerations of ultimate iron distribution after overloading.—W. J. M.


Small doses of propylthiouracil had no marked effect upon the iron uptake by the rat bone marrow, but the uptake in the spleen and the liver increased significantly. After prolonged treatment with larger doses, the iron uptake of the red cells was decreased.—C. W.


In this study the blood loss of patients with hookworm infestation of the bowel was measured in two ways. In some the red cells were labelled in vivo by injections of 10 to 20 μc. of Fe59 bound to plasma, and in others red cells were labeled in vitro with 100 μc. Cr51 and reinjected into the blood stream. Stools were then collected over long periods and measured for radioactivity. It was found that the maximum daily blood loss in patients infested with 1,500 Necator Americanus amounted to about 30 ml, and average daily losses over a period of 40 days before deworming amounted to about 12 ml. The blood loss in patients with between 1000 and 1500 worms was of the same order. Although a proportion of the iron released in the bowel is reabsorbed by the body, it was felt that the losses from severe hookworm infestation were enough to cause a negative iron balance. This would be especially true in tropical countries, in which such losses occur against a background of poor iron intake.—T. H. B.


Carbon14-labeled porphobilinogen was prepared by treating rabbits with allyl-isopropyl-acetyl-carbamide for 10 days, then giving subcutaneously 160 μc. of glycine-2-C14 in 5
divided doses. From the pooled urines, crystalline porphobilinogen was isolated with a specific activity of 6300 count/mm per milligram. It was added to the sterile nutrient media used in the biosynthesis of vitamin B_{12}. The results revealed the biosynthesis of the porphyrin-like moiety of vitamin B_{12} is along the same primary pathway as that of other naturally occurring porphyrins. The point of divergence beyond porphobilinogen remains to be determined, but it appears unlikely that uro- or coproporphyrin is involved, as this would require partial degradation—that is, removal of the delta-methylene bridge to provide the curious double bond carbon linkage in the porphyrin-like moiety of B_{12}. Although B_{12} is essential to normal erythropoiesis and resembles the heme compounds, there is at present no evidence that vitamin B_{12} deficiency is associated with diminished porphyrin or bile pigment formation.—G. W. J. III.


Vitamin B_{12} in normal rat sera samples ranged from 322 to 736 (mean value 496) μg./ml. The vitamin exists chiefly bound to alpha-2 globulin. With the addition of 1.5 mg. or more of vitamin B_{12} to 1 ml. of serum in vitro, the mean concentration of the bound vitamin increased from about 0.4 μg./ml. to a maximum of about 0.8 μg./ml. of serum. With increasing additions of the vitamin to serum, up to 1.5 μg./ml., the vitamin is recoverable in the alpha-2 and beta globulin fractions. A close parallelism was observed between the concentration of the bound vitamin in the whole serum and in the alpha-2 globulin and between free vitamin concentration and the beta globulin-bound vitamin. With large additions of the vitamin, there was a rapid increase in the vitamin concentration of the gamma globulin fraction. In gamma globulin the vitamin existed in the free state.—J. B. C.

ABSORPTION OF VITAMIN B_{12} IN PERNICIOUS ANAEMIA. DEFECTIVE ABSORPTION INDUCED BY PROLONGED ORAL TREATMENT. M. Schwartz, P. Lous and E. Meulengracht. From Bispebjerg Hospital, Copenhagen, Denmark. Lancet ii:1200-1204, 1958.

The use of Schilling’s technic confirms that the absorption of vitamin B_{12} in the presence of hog intrinsic factor (I.F.) becomes blocked in patients with pernicious anemia previously treated with preparations of vitamin B_{12} plus hog pyloric mucosa. This blockage develops within 6 to 12 months of starting treatment. No such blockage occurs in patients treated either with parenteral vitamin B_{12} or with crude stomach preparations without added vitamin B_{12}. The blockage can be overcome by binding the Co^60 vitamin B_{12} to human I.F. but not by the administration of human I.F. after the vitamin B_{12} is already bound to hog I.F. In some cases the presence of great excess of hog I.F. also overcomes the blockage. No blockage occurs in these patients when human fundus mucosa or rat gastric juice is administered with the Co^60 vitamin B_{12} instead of hog pyloric mucosa. It is concluded that the blocking mechanism is directed against vitamin B_{12} bound to hog pyloric mucosa. The findings support the concept that blockage is the result of an immune reaction against the species-specific intrinsic factor.—R. M. H.


The distribution of radioactivity in the small intestine was measured in 4 patients at laparotomy 3 hours after the oral administration of vitamin B_{12}. At this time, little or no radioactivity was demonstrable in the blood, but all was in the distal half or two-thirds of the small intestine. All four patients absorbed normal amounts of vitamin B_{12}, with a normal pattern of plasma radioactivity, reaching a peak 8 to 12 hours after the oral dose. Investigations on patients who had undergone resection or short-circuiting of the ileum showed that the absorption of radioactive vitamin B_{12} was invariably impaired,
and was unaffected by intrinsic factor or by previous treatment with chlortetracycline. Resection of the jejunum or of the terminal 1 foot of the ileum did not interfere with vitamin $B_{12}$ absorption. These observations demonstrate convincingly that vitamin $B_{12}$ is absorbed from the ileum in man. It is suggested that the ileum may contain a specific receptor mechanism for vitamin $B_{12}$ absorption.—R. M. H.

**INFLUENCE OF CALCIUM IONS ON VITAMIN $B_{12}$ ABSORPTION IN STEATORRHOEA AND PERNICIOUS ANAEMIA.** R. Grässbeck, I. Kantero and M. Siurala. From the Fourth and First Medical and Children’s Clinic, University of Helsinki, Finland. Lancet i:234, 1959.

The oral administration of calcium lactate increased the absorption of vitamin $B_{12}$ in 4 of 6 cases of steatorrhea, as measured by the Schilling technic. No such effect was produced in 6 cases of pernicious anemia. It is suggested that a deficiency of free calcium ions in the intestine may be one cause of deficient vitamin $B_{12}$ absorption in steatorrhea.—R. M. H.


Large amounts (400 to 1,400 mg.) of an impure preparation of pig intrinsic factor (IF) are shown to inhibit the absorption of vitamin $B_{12}$ in normal human subjects. This inhibitory effect is not abolished by heating, which destroys the IF activity but not the vitamin $B_{12}$-binding capacity of the preparation. It is concluded that the inhibition may be due either to oversaturation of an intestinal acceptor mechanism or to the presence of contaminating $B_{12}$-binding material without IF activity, or to both.—R. M. H.


D-Sorbitol in daily doses of 3 to 12 Gm. failed to enhance the absorption of vitamin $B_{12}$ administered orally to normal subjects and geriatric patients, as measured by serial estimations of serum vitamin $B_{12}$.—R. M. H.


It was shown in the authors’ previous work that chicks kept on a diet containing imbalanced quantities of ascorbic and folic acid in proportion to other water-soluble vitamins developed anemia and degenerative changes in the liver. In the present study the effect of antibiotics on metabolism of these two vitamins was investigated. Studies were conducted on chicks kept on diets of varying composition. The feedings consisted of basal diet (cereals, devitaminized casein, vitamin $B_{12}$ and fat-soluble vitamins) supplemented by sets of water-soluble vitamins. There were 3 sets of vitamins supplementing the basal diet: water-soluble vitamins, lacking both ascorbic and folic acid, or lacking only one of these two vitamins. Some diets were supplemented by streptomycin and aureomycin; others of the same composition were not supplemented by antibiotics. As compared with the un-supplemented diets, the diets supplemented by antibiotics prevented the symptoms of anemia and hepatic degeneration. Also the ascorbic acid levels in the livers of chicks kept on diets supplemented with antibiotics were higher than in those fed on unsupplemented diets. Significant improvement was found only in the ascorbic acid-deficient group: changes in the folic acid-deficient group were probably coincidental. On the basis of presented results the authors conclude that streptomycin and aureomycin, when simultaneously added to the diet, stimulate the synthesis of ascorbic acid.—E. K.

Patients with low serum vitamin B₁₂ levels (pernicious anemia, adult celiac disease and regional ileitis) had significantly lower resting plasma ascorbic acid levels than did normal controls, and showed an increased rate of clearance of injected sodium ascorbate from the plasma. Following vitamin B₁₂ therapy, the ascorbic acid metabolism was restored to normal in pernicious anemia, partially corrected in adult celiac disease, and unaffected in regional ileitis. The effect in the first two groups was masked in those patients receiving a diet containing either an excess or a gross deficiency of ascorbic acid. In regional ileitis, the low plasma ascorbic acid levels were correlated with the activity of the disease, as indicated by the seromucoid level. The abnormality of ascorbic acid metabolism was greater in 15 vitamin B₁₂-deficient cases with megaloblastic anemia than in 8 cases with low serum vitamin B₁₂ but normoblastic marrows.—R. M. H.


Five of 10 patients with pernicious anemia in relapse excreted less than the normal amount of folic acid within 24 hours after the intramuscular injection of 5 mg. This evidence of unsaturation was abolished by 1 to 3 further injections of 5 mg. folic acid. Following treatment with vitamin B₁₂, a reduction of excretion of injected folic acid and citrovorum factor occurred. This reduction was maximal in 8 of 10 patients after the reticulocyte peak had occurred; the authors are therefore reluctant to attribute it to a change in the nature or rate of hemopoiesis, although it clearly denotes a temporarily increased demand for the pteroylglutamate complex.—R. M. H.


Twenty-two cases of pernicious anemia in relapse were treated with oral vitamin B₁₂ in daily doses of 20 to 500 μg. for periods varying from 15 days to 50 months. All those treated with 500 μg. daily showed prompt hematologic responses, and had serum vitamin B₁₂ levels within the normal range by the 10th day of treatment. The responses of those receiving 20 to 200 μg. daily were variable, and only 1 of 7 patients in this group had a normal serum vitamin B₁₂ level 15 days after starting treatment. Nine patients receiving 100 to 500 μg. daily maintained normal serum vitamin B₁₂ levels for periods up to 26 months, but 3 patients receiving 50 μg. daily failed to do so. After initial parenteral therapy, serum vitamin B₁₂ levels were maintained as well in a group of 20 patients receiving 100 μg. oral vitamin B₁₂ daily as in 15 patients receiving 100 μg. B₁₂ parenterally every month. It is emphasized that trials of extraneous sources of intrinsic factor in the treatment of pernicious anemia should include controls with vitamin B₁₂ alone.—R. M. H.


No advantage was found in raising the monthly intramuscular maintenance dose of vitamin B₁₂ above 100 μg. Over a two year period, 71 patients were maintained as effectively on a daily oral dose of 100 μg. vitamin B₁₂, as judged by hemoglobin and red cell levels, as were 84 patients on a monthly intramuscular dose of 100 μg. At the end of the period, serum vitamin B₁₂ levels performed on a small number of patients showed no significant difference between the two groups.—R. M. H.

TREATMENT OF PERNICIOUS ANEMIA BY ORAL ADMINISTRATION OF VITAMIN B₁₂ WITHOUT ADDED INTRINSIC FACTOR. E. A. Brody, S. Estren and L. R. Wasserman. From the De-

Complete hematologic and clinical remissions were induced and maintained in 11 of 14 patients with pernicious anemia, 2 patients with total gastrectomy, and 1 patient with malabsorption syndrome treated with oral doses of 50 μg. of vitamin B₁₂ thrice daily for periods of 2 to 34 months. Serum vitamin B₁₂ levels in the majority of patients remained borderline or subnormal, reflecting probable inadequate tissue stores, manifested by rapid relapse after discontinuance of therapy in 1 case. Similar long-term results have been obtained by British workers (J. N. M. Chalmers and N. K. Shinton; E. H. Hemsted and J. Mills; see the two immediately preceding abstracts. Ed.). These studies demonstrate that a majority of patients with vitamin B₁₂ deficiency disease may be maintained on oral treatment with large daily doses of vitamin B₁₂ alone, provided they religiously take their medication and are very closely followed from both the hematologic and neurologic points of view. Such therapy is not uniformly reliable, even under these circumstances; it is expensive in terms of both medication and the close supervision required, and in the general practice of medicine it is poor treatment compared to intramuscular injection of vitamin B₁₂ in doses of 150 μg. every 3 weeks or 500 to 1000 μg. once a month. These studies add to the evidence that a small aliquot of large doses of vitamin B₁₂ may be absorbed in the absence of intrinsic factor, possibly by diffusion across the intestinal wall.—V. H.


Of a total of 3199 women delivered in the hospital during a 15 month period, 474 with a hemoglobin of 65 per cent (9.6 Gm. per 100 ml.) or less, at or after the 32nd week of pregnancy, were investigated by sternal puncture, blood counts and serum iron estimations. Ninety of these had megaloblastic marrows and all responded to treatment with folic acid; 28 of the 90 were diagnosed during the puerperium. A general clinical and hematologic survey of the megaloblastic group is given. The more severe the anemia, the more likely was it to be megaloblastic. A brief dietary history showed that 42 per cent of women with megaloblastic anemia had an inadequate diet, as compared with 12 per cent of patients with normoblastic anemias and 4 per cent of healthy pregnant women; the greatest difference was in meat intake. The fecal fat content was estimated in 24 of the cases of megaloblastic anemia, and showed impaired fat absorption in 4 of these.—R. M. H.


This paper reports the case of a 16 year old boy who developed megaloblastic anemia while being treated with primidone and phenytoin. Laboratory investigations showed a normal serum concentration of vitamin B₁₂ and normal radioactive vitamin B₁₂ absorption. There was an optimal hematologic response to folic acid therapy. This is the 33rd reported case of megaloblastic anemia associated with anticonvulsant therapy. The main features of previously reported cases are summarized. Certain features common to the majority of these cases suggest that a folic acid deficiency or a derangement of folic acid metabolism is responsible for the megaloblastic anemia. All 20 patients treated with folic acid responded optimally. Eight patients are reported to have responded to vitamin B₁₂ one to liver extract and 4 to a combination of folic acid and vitamin B₁₂. It is suggested that the anticonvulsant drugs have an antifolic acid action which is too mild to produce megaloblastic anemia in the majority of epileptics unless 1 or more co-factors operate. A suboptimal folic acid intake is postulated as the main co-factor in at least 5 of the 20 cases in which there was a response to folic acid and perhaps also in some of the cases.
in which a response has been reported to vitamin B₁₂. In one case repeated hemorrhage, in another pregnancy and in a third case a possible latent steatorrhea are postulated as additional co-factors.—G. C. de G.

PERNICIOUS ANAEMIA IN THE SOUTH AFRICAN BANTU. J. Metz, R. Cassel and S. M. Lewis.

True Addisonian pernicious anemia has been regarded as extremely rare in the Bantu. However, the authors were able to find 11 examples of the disease from 3 hospitals over a period of 2½ years. In only six subjects was it possible to do serum vitamin B₁₂ levels, but in these the results were uniformly low. In 9 of the cases little or no Co⁶⁰ B₁₂ was excreted in the urine after its oral administration, whereas the results were within normal limits when the radioactive B₁₂ was given with an "intrinsic factor" concentrate. One case died shortly after admission, and at autopsy the gastric mucosa showed typical histologic features. The remaining cases responded promptly to specific therapy.—T. H. B.

THYMIDINE IN MEGALOBLASTIC ANAEMIA. G. H. Spray and L. J. Witts.

Five patients with Addisonian pernicious anemia in relapse and one with nutritional megaloblastic anemia were treated by intramuscular injection of thymidine. One patient with pernicious anemia showed a slight hemopoietic response after receiving 250 mg daily for 10 days, but doses of 500 mg daily for 8 to 14 days were completely without effect in all the other patients, who subsequently responded promptly to treatment with vitamin B₁₂ and folic acid, respectively.—R. M. H.

STIMULATION OF HEMOPOIESIS IN SUBLETHALLY IRRADIATED RATS. L. Fárdi, Zs. Btage, B. Horváth and E. Kertész.

The authors investigated the effect of folic acid, vitamin B₁₂, and atabrine treatment on the hemopoiesis of irradiated rats. B₁₂ was ineffective. Folic acid treatment elicited reticulocytosis, and the atabrine treatment a significant rise in the leukocyte count and an increased rate of myelopoiesis as compared to the untreated irradiated controls.—S. R. H.

HEMOSTASIS

THE INFLUENCE OF DEFECTIVE PROTHROMBIN CONVERSION ON SERUM AND PLASMA ANTITHROMBIN III ACTIVITY. Basil A. Bradlow.

Raised serum antithrombin levels are present after coumarin type anticoagulant administration and also in cases of severe thrombocytopenia, hemophilia and Christmas disease associated with poor prothrombin consumption. In the latter group the raised serum antithrombin can be lowered by increasing prothrombin conversion in vitro with brain thromboplastin. Brain thromboplastin has only a slight effect on the serum antithrombin in the "dicoumarol" group and in normals. The raised serum antithrombin level in these cases, therefore, appears to be a function of defective prothrombin conversion, either due to deficiency of prothrombin and factor III, or to defects in the first stage of blood coagulation. The raised serum antithrombin levels reported in liver disease might be due to the coagulation defects present in some cases. Serum antithrombin levels only reflect residual antithrombin activity after the thrombin produced during clotting has been inactivated.—T. H. B.
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Reported methods of antithrombin III assay are reviewed and compared, and the results of an experimental study of the problem are presented. Thrombin-defibrinated plasma (DFP) appears to be the most suitable assay material for clinical studies. Serum antithrombin levels are lower than the corresponding DFP levels. If whole plasma is used, antithrombin I is also estimated. The optimal thrombin concentration suggested yields a clotting time of about 10 seconds. The amount of thrombin inactivated by DFP is directly proportional to the volume of DFP within stated limits after incubation at 37°C and pH 7.35 for 10 minutes or less. After longer incubation times this proportionality no longer holds. Fibrinogen is used as a substrate material in these studies. A rapid method of antithrombin assay suitable for routine clinical use is described. The assay results are expressed as the percentage of thrombin solution inactivated by 0.2 ml. test material in 10 minutes at 37°C and pH 7.35. In normals the mean antithrombin level by this method is 51.5 (S.D. 4.7). The mean percentage error of the method is 4.8 per cent.—T. H. B.


Normal dogs, hemophilic dogs, dogs on dicumarol medication and dogs with chloroform-induced liver dysfunction were injected intravenously with thromboplastin. Normal dogs developed a characteristic reaction consisting of neuromuscular and cardiorespiratory disturbances, thrombocytopenia, hypothrombinemia, hypofibrinogenemia and a depression of AHF activity in the plasma. These responses were diminished or abolished in dogs with hypocoagulable blood. These findings suggest that the hemorrhagic states in conditions associated with circulating thromboplastic tissue products result from widespread intravascular coagulation and concomitant consumption of many clotting factors.—W. J. M.


A greater fall in the “Stypven time” of three subjects after a fatty meal was observed when the Russell viper venom and calcium chloride were added simultaneously than when the test plasma was incubated with venom for one minute before recalcifying. It was found that venom has a lipolytic action on the phosphatide fraction of plasma, liberating substantial quantities of fatty acids and lysophosphatides during 1 minute’s incubation; more fatty acids are liberated from lipemic than from fasting plasma. Lysophosphatides prepared by the action of stypven on egg-phosphatides were found to prolong the Stypven time of both fasting and lipemic plasma, the latter to a greater extent. It is concluded that the accelerating effect of lipemia on the Stypven time is partly masked by the inhibitory effect of lysophosphatides produced during incubation of the plasma and venom; venom and calcium chloride are therefore better added simultaneously. With the use of this “instantaneous” method, a positive correlation was found between the fall in Stypven time and the degree of lipemia after a fatty meal, irrespective of the type of fat given. —R. M. H.


This critical review of the literature is divided into a consideration of the effects of fatty meals on blood coagulation and a longer section on the effects of adding fatty substances to plasma in vitro, with particular reference to ethanolamine phosphatide. The author repeatedly emphasizes that no conclusions should be drawn from these observations about the possible significance of fats in the pathogenesis of thrombosis until a connection
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between blood coagulation in vitro and thrombosis is established. The issue of the British Medical Bulletin in which this paper appears is devoted to the "Metabolism of Lipids," and also includes, among others, articles on "Removal of lipids from the blood stream" by J. E. French, B. Morris and D. S. Robinson, and "The effect of dietary fats on the blood lipids and their relation to ischaemic heart disease" by B. Bronte-Stewart.—R. M. H.


A patient with severe angina pectoris who did not respond to the usual therapy was treated with leeches. Following the application of nine leeches over the heart area, pain and other symptoms subsided. There was little local bleeding after the leeches had fallen off but during the next few days the patient coughed up blood, had a hemorrhage from the ear, and his stools contained blood. This was accompanied by a transient acute thrombocytopenia (14,800 platelets/cu.mm.) with a very poor clot formation and clot retraction. Though the anticoagulant action of hirudin is well recognized, the physician is advised to watch for other possible hemorrhagic complications which may occur in the course of treatment with leeches.—J. J. B.


In view of the frequent occurrence of thrombophlebitis and endarteritis in the course of virus influenza, clotting times and prothrombin times of patients suffering from the disease were estimated. In most patients clotting times were shortened and prothrombin times prolonged. The latter did not return to normal for three to four weeks after recovery. It is advised that patients suffering from virus influenza who present those clotting abnormalities should receive anticoagulant therapy as a prophylactic measure, particularly if they also present some degree of arteriosclerosis.—J. J. B.


Artificial phlebothrombosis was produced in rabbits' ear veins by ligation of the veins and injection of sodium salicylate. Following the production of thrombi, dicumarol therapy was instituted either at once or 7 or 14 days later and continued for 14 days. The veins were examined histologically after the conclusion of therapy. Nearly all of them contained well organized thrombi which presented the usual thrombus structure. Dicumarol was found to possess no thrombolytic activity.—J. J. B.


Experiments on the isolated rat uterus show that the release of plasma kinin by contact with glass occurs in two stages: an inactive plasma precursor ("component A") is converted to the active "contact factor," which in turn interacts with another substance ("component B") to release plasma kinin. No "contact factor" was found when plasma from a case of Hageman trait was exposed to glass. Hageman factor appears to be identical with "component A," and to be necessary both for the initiation of blood coagulation and the release of plasma kinin. "Contact factor" reacts with plasma thromboplastin antecedent (PTA) to produce clot-promoting activity, and with "component B" to release plasma kinin. "Component B" is distinct from PTA. Further studies of the details of these two reaction sequences show that they run a closely parallel course, both "component B" and
PTA being quantitatively consumed before Hageman factor ("component A"). The possible physiologic significance of these "plasma foreign surface reactions" is discussed. Many other details of these reactions are considered in this closely reasoned paper, which deserves careful study.—R. M. H.


In 4 cases of thrombopathy (Naegeli), 1 case of Willebrand-Jürgens disease and 2 cases of thrombocytopenia, the thromboplastin generation test with the patients' platelets and the heparin tolerance test were performed, as well as the usual coagulation tests. The discrepancy of the results obtained by means of the two tests suggested that the antiheparin and the thromboplastic factor of platelets should be not considered identical, as suggested by some investigators.—P. d. N.


The fate of P32-tagged platelets was studied in rats. A marked concentration of radioactivity was found in reticuloendothelial tissues, and especially in the spleen.—P. d. N.


Platelet suspensions stored at 4 C. were studied as to their ability to promote clot retraction and their thromboplastic activity (recalcification time, prothrombin consumption test, thromboplastin generation test). The clot retraction-promoting activity was lost early in storage, but thromboplastic function remained unimpaired. The platelet suspensions were stored for 21 days, and their concentration was 500,000 platelets per cubic millimeter.—P. d. N.


Injection of streptokinase with the second injection of bacterial endotoxins prevented development of renal thrombi and bilateral cortical necrosis of the generalized Schwartzman phenomenon in rabbits. When given with the first injection of endotoxins, the streptokinase greatly reduced the number of thrombi in the lungs and liver. When given after 24 hours, it had no effect.—W. J. M.

A METHOD OF PREPARING FIBRINOGEN TAGGED WITH RADIOACTIVE IODINE. W. E. Clement and G. P. McNicol. From the University Department of Medicine, Royal Infirmary, Glasgow, and the Regional Physics Department, Glasgow, Scotland. Lancet ii:1212, 1958.

A short preliminary communication describing a simple method of tagging fibrinogen: 89 to 94 per cent of the radioactivity was found in the clot after the addition of thrombin.—R. M. H.

LEUKOCYTES


Dogs were injected subcutaneously with Se75Cl4, and their leukocytes were isolated 24
hours later. Some of the injected selenium appeared to have been incorporated into the leukocytes. The author suggests that, due to the chemical similarity of selenium and sulfur, selenium can be converted to one or more of the selenium analogs of the naturally occurring sulfur amino acids and thereby prevent the normal utilization of the sulfur-containing amino acids.—T. E. B.


Precipitates were formed between water-soluble extracts of normal or leukemic granulocytes and similar extracts of other human blood cells, with the use of the Ouchterlony double gel diffusion method. No reaction occurred between extracts of granulocytes and untreated human sera, but sera which had been dialyzed against saline produced a precipitate with granulocyte extract. The nature of the precipitate is not considered in this article, and the physiologic significance of this reaction is unknown.—R. M. H.


A method is described which results in 20 per cent recovery of leucocytes from whole blood, with a leucocyte-erythrocyte ratio of more than 1800 in the final suspension. Leucocytes prepared in this way are shown to preserve their viability and antigenicity. An adaptation of the method for titrating sera for leucocyte antibodies is also described. This has the advantages that it is sensitive and simple to carry out, the end point is easy to determine, and spontaneous clumping of cells does not occur.—R. M. H.


More than 3000 blood sera were examined by means of an agglutination method using leukocytes from a panel of 20 leukemic patients. In the sera from 412 blood donors no leukoagglutinating antibodies were found. Positive results were obtained in 3 of 61 pregnant women. Positive results were also found in 91 of 474 patients, predominantly with blood diseases. When comparing these positive sera with the 20 different leucocyte types the percentage of positives with compatible erythrocytes was 19 to 76, with erythrocytic incompatibility 34 to 95. Thus it is recommended that only leukocytes from erythrocyte-compatible systems be used for the performance of agglutination tests. As there are apparently multiple antigenic groups of leukocytes, it is necessary to examine leukoagglutinins of blood sera against a series of leukocytes from different persons. Leukemic leukocytes from patients with lymphatic leukemia are less suitable than those from patients with myeloid leukemia.—L. D.


The authors describe a female patient with anemia who was given 43 transfusions and developed serious febrile reactions. Incompatibility of donor leukocytes was established, and transfusions of plasma deprived of buffy coat or washed erythrocytes were well tolerated. Antibodies against leukocytes and also against erythrocytes and platelets were demonstrated. Leukocyte incompatibility is found relatively often in patients who have received more than 10 transfusions, and is associated with antibodies against leukocytes. Transfusion of blood with a lower number of leukocytes is recommended in cases in which those reactions are of a more severe character.—L. D.

The author discusses the existence of 5 possible mechanisms involved in neutropenia. Those are: depression of marrow granulopoiesis, excessive circulatory polymorphonuclear destruction either by lysis or R.E.S. phagocytosis, hypersplenism, abnormal retention of polymorphs in normal reservoirs, accumulative migration into the intestine or into other sites of inflammatory reaction. The part played by the various mechanisms is difficult to evaluate with available methods. Cytologic studies of bone marrow do not give always a clear answer. Three different pictures may be found: aplasia of the neutrophil series, maturation arrest with predominance of young forms, or a normal balance of immature and mature forms with normal or even increased total numbers. The first has long been accepted as indicating a basic failure of granulopoiesis, the second as evidence of a maturation arrest presumably due to the absence of some essential factor, and the third as implying a failure in the release of mature polymorphs. It is now established that excessive destruction and probably extravascular migration may be accompanied by any of the three marrow patterns. It is possible to get a more direct measure of marrow insufficiency by taking into account the granulocyte/erythroblast ratio, with erythropoiesis assessed from red cell survival studies and the total volume of circulating red cells. A diagnosis of neutropenia due to excessive destruction of adult polymorphs requires in vitro evidence of lysis, agglutination or an increased fragility of the polymorphs. No indirect evidence of leukocyte destruction, such as an increased blood concentration of substances released from the destroyed cells is now available. Survival time studies of leukocytes cannot answer this problem, if it is accepted that the time in the circulation represents only about one-hundredth of the life of the white cells. The clinical importance of neutropenias due to peripheral polymorph destruction, whether or not due to antibodies, is still very limited. Clinical and experimental evidence suggests that the spleen plays some part in the release of granulocytes from the marrow; in hypersplenism this release would be inhibited. A splenic factor necessary for maturation has not been demonstrated. Phagocytosis by a large spleen can produce a picture suggestive of lack of maturation which has for long been accepted as the strongest argument in favor of some hormonal action by the spleen on granulopoiesis. It is still impossible to gauge any possible clinical significance of neutropenias due to progressive sequestration in the marrow, lung, spleen or other extravascular reservoirs. The adrenaline test reflects to a small extent the importance of such reservoirs and may indicate the extent of pathologic retention in such sites. Marrow granulopoiesis is presumably stimulated by certain substances, and others may regulate or inhibit the rate of escape of adult cells. It is possible that neutropenias may be due to an excess of one or lack of another of such substances.—G. M.


NEGATIVE L.E. CELL PHENOMENON IN TRUE SYSTEMIC LUPUS ERYTHEMATOSUS. P. Formijne and F. van Soeren. From the Department of Internal Medicine, University of Amsterdam, Holland. Lancet ii:1206–1207, 1958.
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A typical case of systemic lupus erythematosus, confirmed at autopsy, is described, in which the L.E. cell phenomenon was consistently negative. The patient's serum was anti-complementary, and the L.E. cell phenomenon became positive on the addition of excess human or fresh guinea pig complement. These and other observations lead to the conclusion that free complement is required for the L.E. cell phenomenon.—R. M. H.


By means of Coon's fluorescent antibody technic, it was shown that the nuclei of leukocytes and skin epithelium adsorb globulin when exposed to serum from patients with disseminated lupus erythematosus (D.L.E.). Nuclei of cells from normal subjects showed greater affinity for the specific globulin than did those taken from patients with D.L.E. No evidence of in vivo adsorption of globulin to nuclei from D.L.E. patients was found.—R. M. H.


The production rate of DNA-P32-labeled lymphocytes in the thoracic duct of dogs has been studied, and their rate of appearance in the peripheral blood has been followed. Lymphocytes develop rapidly, enter the blood stream quickly, but spend a relatively short time in the intravascular compartment. When autologous thoracic duct lymphocytes were labeled in vitro and then reinjected, radioactivity appeared almost immediately in the bone marrow.—T. E. B.

LEUKAEMIA


Synthetic indican was given intravenously to RFH mice. Twenty-two and one-half per cent of them developed leukemia after injection of a total dose of 100 mg. Leukemoid reactions were seen in an additional 30 per cent of the mice. The induced leukemia was of the myelocytic type. Spontaneous leukemia in the RFH-strain occurs only in 0.2 per cent and is not of the myelocytic type.—H. M.


The case records of 679 British servicemen who developed leukemia were compared with those of two control series from the same source as to the incidence of various factors alleged to be leukemogenic. The control series consisted of 813 cases of all diseases and injuries and 554 cases of neoplasms other than the reticuloses. Associations were found between leukemia and irradiation and between leukemia and the rheumatic diseases. No association could be demonstrated between the incidence of leukemia and any of the following factors: fractures, other injuries, antibiotics, chronic sepsis or acute infections. The evidence relating the use of sulpha drugs to the incidence of acute leukemia was inconclusive. The validity of the evidence is discussed in relation to the limitations imposed by the retrospective use of case notes.—R. M. H.

The author has studied the records of 204 children under 10 years of age who have died from leukemia in Victoria in the past decade. It is asserted that this number constitutes the “vast majority” of all children dying from leukemia during this period. To the parents of these 204 children was sent a questionnaire about radiologic examination of the abdomen during pregnancy; satisfactory details were secured about 171 of these children. Of the 171 mothers, 12 had had an x-ray examination during pregnancy, an incidence of 7 per cent. Four of the mothers had one film each, six had had two films each, and only two had undergone an x-ray pelvimetry involving many films. In the 10 years under consideration, an average of 20 children under the age of 10 died of leukemia each year, and approximately only one of these 20 had had an x-ray examination prior to delivery. G. C. de G.


Chromatographic studies of the amino acids in the serum of two cases of erythroleukemia revealed a peptide giving a purple spot above alanine. This peptide was also found in the serum of three cases of myelogenous leukemia, but could not be demonstrated in the serum of 50 healthy adults or in serum from 8 cases of pernicious anemia. In addition, 5 other peptides were found in some of the cases of leukemia, but not consistently. The authors do not mention whether the cases of myelogenous leukemia were acute or chronic, and the cases of erythroleukemia are not described.—C. W.

**IMMEDIATE EFFECT OF THIOIODOHYROACETIC ACID ON OXYGEN CONSUMPTION OF MYELOID LEUKAEMIC LEUCOCYTES IN VITRO. W. D. Alexander and S. K. Bisset.** From the Clinical Chemotherapeutic Research Unit of the Medical Research Council, and the Department of Biochemistry, Western Infirmary, Glasgow, Scotland. Lancet ii:1265, 1958.

The oxygen consumption of myeloid leukemic leukocytes in vitro was significantly increased by the addition of 1-3:5:3′-triiodothyroacetic acid (triac) at concentrations between 10 and 35 mg. per 100 ml. Over the same range of concentrations of triac, lymphatic leukemic leukocytes showed no significant response.—R. M. H.


The study of leukocytic zinc in leukemias has indicated that its level is inversely proportional to the percentage of immature cells in the blood. The zinc content of the immature cells in leukemic syndromes should be, therefore, considerably lower than in mature cells.—P. d. N.


In 5 leukemic children, the urinary 17-corticosteroids were studied by means of a chromatographic technic. An increase of androstanolone and of dehydroepiandrosterone was observed in some cases, whereas in other cases inconstant variations in andosterone, ethiocolanolone, 11-hydroxyandrostosterone and 11-hydroxyethiocolanolone were demonstrable. After treatment with prednisone, a constant diminution of all steroid fractions was observed, except 11-hydroxyethiocolanolone and 11-hydroxyandrostosterone.—P. d. N.

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A histochemical method for estimating leukocytic alkaline phosphatase was applied to smears of blood of normals and patients with myeloproliferative diseases. The efficiency with which the test discriminated between the leukemic and nonleukemic persons varied with the white blood cell count. The risk of misdiagnosing nonleukemia as leukemia was 17 per cent when the WBC was 7500 or less. It diminished to 10 per cent for the WBC range 7,600 to 15,000, to 1 per cent for the range 15,000 to 30,000 and vanished (0 per cent) in counts above 30,000.—W. J. M.


Fifty-eight cases belonging to the "chronic" myeloproliferative syndrome were examined cytochemically for the alkaline phosphatase content of the mature neutrophils. All patients with polycythemia vera had high levels of the enzyme. The majority of the myeloid metaplasia cases also showed high levels, but a few patients had low normal or lower than normal values. The enzyme was virtually absent in the cells of chronic granulocytic leukemia. Therapy had no effect on the alkaline phosphatase levels in polycythemia vera and in myeloid metaplasia, but in several of the patients with chronic granulocytic leukemia who developed prolonged remissions, the enzyme levels returned to normal.—W. J. M.


In West Germany there were 1356 registered deaths in 1948 and 2716 in 1956 from leukemia. The death rate per 10,000 population was as follows: 1948: men 0.35, women 0.24; 1956: men 0.62, women 0.48. In 1948 the death rate among women was 33 per cent lower in women than men, but in 1956 it was only 21 per cent lower. The author feels that this increased incidence of leukemia cannot be attributed to radioactive fallout.—H. M.


At the age of 40 years, a woman presented cervical adenopathy and 1 year later inguinal adenopathy. Both disappeared with radiotherapy. At the age of 53, there was loss of weight and weakness. Meanwhile abdominal enlargement developed. Exploratory laparotomy showed a large inoperable mesenteric tumor mass, which histologically proved to be a giant follicular lymphosarcoma. After further radiotherapy the patient lived normally for 6 years. Then pains returned and loss of weight and fever set in. Multiple myeloma was diagnosed both clinically and at autopsy. Autopsy also showed a mesenteric retroperitoneal tumor at the place where 6 years before the giant follicular lymphosarcoma had been found. This turned out to be a reticulolymphosarcoma and partly polymorphocellular. In the author’s opinion this tumor was the result of Brill-Symmers’ disease. They discuss the possibility that the same type of transformation taking place in the bone marrow led to myeloma.—J. G.

MISCELLANEOUS


Probably the erythrocytes from patients with paroxysmal nocturnal hemoglobinuria undergo hemolysis only in the presence of the properdin system. Normal erythrocytes
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contain substances which are capable of absorbing properdin in vitro and which can be isolated from the stroma in a water-soluble form. By extraction from normal erythrocytes (or the stroma) with phenol-water it is possible to prepare a water-soluble substance which not only absorbs properdin but is highly pyrogenic in rabbits. The minimum pyrogenic dose of this substance is approximately 0.4 μg./Kg.—H. M.


The height of the counting chamber is several times higher than the diameter of the erythrocytes. This is the reason that two or more erythrocytes, settling down in the chamber, and lying one over the other, cannot be differentiated. In the author’s opinion, the counting chambers should have a height of 50 μ or less instead of 100 μ, as is now usual. The dilution in the pipettes should be increased to 1:400 (minimum 1:300) instead of 1:100 or 1:200 and the areas which are counted should be 4 times greater.—H. M.

EFFECT OF CHLORPROMAZINE ON ANTIBODY FORMATION. L. Kocsir, T. Szilágyi, O. Veress and A. Bán. From the Institute of Pathophysiology and 1st Department of Medicine, Medical University, Debrecen. Acta physiol.Hung. 14:103–166, 1958.

After treatment with chlorpromazine for 3 to 4 months the level of specific agglutinins to typhoid-0 vaccine has been found significantly higher in the serum of the treated rabbits than in the untreated controls. As a result of treatment the leukocyte count decreased by 20 to 30 per cent. The erythrocyte count remained unchanged. Toxic changes in bone marrow and peripheral blood occurred in one animal only. Total serum protein did not change during treatment, but the amount of beta and gamma globulins increased by 20 to 40 per cent.—S. R. H.


Cortisone and ACTH were found to be of benefit in experimental benzol intoxication. The maturation and defective production of the bone marrow cells were corrected, and the degree of peripheral pancytopenia was reduced.—P. d. N.


Recent investigations in the field of immunochemistry have related the virus-neutralizing, bacteriocidal and parasitocidal activity of normal serum to the complement-properdin system. Other investigations have been concerned with a possible relationship of this system to neoplastic disease. In the present investigation, normal serum factors appear to destroy atypical cells and cancer cells, while sparing relatively normal cells. Horse, guinea pig, rat and rabbit sera showed no toxic effect on these cells under the same experimental conditions. The cytotoxicity was shown to be heat-labile and unrelated to the properdin system. The toxic factors resembled C3, C4, and possibly C2 in their behavior toward heat, and the various conventional procedures for inactivation of complement. Perhaps they are nonspecific factors in serum concerned with the natural resistance to cancer.—O. P. J.
