LEUKOCYTES AND LEUKOCYTIC DISEASE


The neutrophils were examined in each of 500 routine blood films, stained with Jenner-Giemsa. Chromatin condensation is more striking in the female, but it is easier to recognize the female by a solitary chromatin nodule which becomes separated from the main nuclear lobes in a proportion of the neutrophils. It has to be distinguished from other appendages which occur in both sexes. It has a well-defined, solid, round head, some 1.5 μ in diameter, joined by a single fine chromatin strand to one lobe of the nucleus. No characteristic 'drumsticks' were found when 500 neutrophils were examined in each of 125 male blood films. In each of 125 female blood films, six 'drumsticks' were found on the average in 227 neutrophils, representing approximately 1 to 38 cells, the lowest being 1 to every 6 and the highest 1 to every 98 cells. In a further 250 female films the first 'drumstick' found was, on the average, its the 36th cell examined. A 'racket' structure which differed only by having a pale center was rare and occurred more frequently in the male.

'Drumsticks' occur at any age and are rare in unsegmented cells. It is tempting to think that the chromatin aggregation in the solitary drumstick represents the XX chromosome combination. — R. H. G.


Other workers have shown that in generalized miliary tuberculosis, there is frequently a moderate normochromic anemia with leukopenia and granulocytopenia. Aplastic anemia and also bone marrow infiltration by miliary tuberculosis have been described. In tuberculous splenomegaly, cytopenia has been attributed to hypersplenism; polycythemia has been reported. Leukemoid reactions of the myeloid and lymphatic types have occurred. A description is now given of the hematological changes in four cases of generalized tuberculosis.

1. A 22 year old woman with fever and leuko-erythroblastic anemia with hypoplastic marrow was found at postmortem to have miliary tuberculosis.
2. A 51 year old woman had leuko-erythroblastic anemia, leukopenia and thrombocytopenia. The marrow was hypocellular with an increase in lymphocytes. There was splenic and later glandular enlargement and weight loss. Death was from miliary tuberculosis.
3. A male with fever, anemia and weight loss had hepatic enlargement and a normal marrow, but thrombocytopenia and leukopenia. During life tuberculosis could not be proved but at postmortem it was found to be widespread.
4. A 61 year old woman had fever with enlarged spleen and lymph glands. Anemia was severe, and the platelet count was low. The white cell count was 4,000, lymphocytes being
64 per cent, but in the marrow 98 per cent of cells were lymphocytes. At postmortem there was widespread tuberculosis, but in view of infiltration of the organs by lymphoid cells, co-existing lymphatic leukemia was diagnosed.—R.H.G.

ACUTE MENINGO-ENCEPHALITIS AS A COMPLICATION OF GLANDULAR FEVER. I. M. Librach.

A 19 year old girl with headache, nausea, vomiting and fever was thought to have poliomyelitis. There were no neurological signs apart from slight neck stiffness, and at the time there was no splenic or significant glandular enlargement. The white cell count was 7,200 per cu. mm., with 16 per cent monocytes. The C.S.F. contained 89 cells per cu. mm., all lymphocytes, protein 30 mg. per 100 ml. The Paul-Bunnell test (blood) became progressively more positive. Enlargement of the spleen and lymph glands and a blotchy erythema of the trunk developed. Recovery was rapid.

It is well to consider glandular fever in differential diagnosis of poliomyelitis, including the bulbar type.—R.H.G.

INFECTION MONONECULEOSIS. A REVIEW OF THE CONDITION AS SEEN IN THE ROYAL NAVY.

There appears to have been a great increase of cases of glandular fever in the Royal Navy in recent years. The condition now ranks second only to rubella among the zymotic infections other than the common cold or influenza. This paper consists of a detailed study of the cases seen in the Royal Navy at home during the years 1948 to 1953 inclusive.—R.H.G.

BONE MARROW


Probably the majority of lymphocytes reach the blood indirectly via the lymph stream, and it is likely that they are formed in lymph nodes. Lymphocytes seem to have a viability of several days and might either be filtered out by the bone marrow or eliminated by passing through the intestinal mucous membrane. The latter seems unlikely. In experiments on guinea pigs, the animals were bled to drain the marrow, and a humerus cleaned and the marrow removed. This was placed in serum and the cells uniformly suspended by mechanical shaking. The specific gravity and volume of the marrow was calculated, and absolute differential marrow counts performed. The mean counts per cmm. were erythroid 273,000, myeloid 390,000, lymphocyte 310,000. These and other findings suggest that lymphocytes pass from the blood to the marrow, though the reverse might be the case.

The myeloid reserve in the marrow is about 100 times the number of granulocytes present in the blood, but there is a much smaller reserve of erythroid cells.—R.H.G.


This paper records all cases of toxic anemia and toxic purpura due to T.N.T. that were observed in the United Kingdom during the 1939-45 war. Toxic anemia was first made notifiable in January, 1942. Altogether 24 cases were diagnosed as aplastic anemia due to T.N.T. Of these, 9 recovered and 15 died. The case reports of eight are given in detail, and the others are included in the analysis. A purpuric hemorrhage was often the first sign noticed by the worker. This and pallor should never be disregarded. A worker should be temporarily removed from contact with T.N.T. if his hemoglobin is 70 per cent or less, his white cell count 10,000 per cmm. or more (although leukopenia was usually present in the severe cases), or if the lymphocyte percentage exceeds 35. Monocytosis or reticulocytosis should not be disregarded.

Three of the patients who recovered did not have blood transfusions.—R.H.G.

A 56 year old housewife was given, for bronchitis, about 40 Gm. of chloramphenicol in four months. She developed aplastic anemia with leukopenia and thrombocytopenia. There was no benefit from cortisone therapy, but transfusions caused improvement. A pint of blood from a polycythemic donor drawn into disodium ethylenediamino-tetra-acetate dihydrate (sequestrene) was transfused and menorrhagia promptly ceased. The patient, who has since been maintained on transfusions, appears to be recovering.—R. H. G.


A 58-year-old man was treated for coronary infarction with phenylindanedione. After three weeks he was discharged and told to continue with 112.5 mg. daily. A week later he developed erythema, followed by dysphagia, inflammation of the mouth and pyrexia. The white cell count fell to 3000 per cmm., 90 per cent of the cells being lymphocytes and 10 per cent monocytes. The bone marrow showed granulocytic hypoplasia. There was no response to penicillin or oxytetracycline, but a good response to cortisone. The patient seemed to have recovered, but he suddenly developed cardiac failure and uremia and died. —R. H. G.


A 56 year old male patient took 0.5 Gm. of cinchophen thrice daily for three days and repeated this course twice with three days between each course. He had also taken phenacetin acetylsalicylic acid, caffeine, quinine sulphate, phenobarbitone, theobromine, magnesium chloride, bromide, iodide and fluorid just before symptoms began, and had had cinchophen a year previously without trouble. The current treatment had been for a painful neck.

On the last day of the cinchophen therapy the patient developed a painful left nostril, followed by fever, sore throat, anorexia and pain in the anal region. The white cell count fell to 800 per cu. mm. (2 per cent polymorphs). He was treated with penicillin, aureomycin and pyridoxin, and he recovered.—R. H. G.


The author gives the name “red cell aplasia” to those cases of idiopathic severe normocytic normochronic anemia with decreased or absent red cell precursors demonstrable in the bone marrow but with normal leucocytes and platelets. Observations over a four year period on one such patient are reported. Brief case summaries of 13 cases from the literature are presented. It is interesting that 10 of the 13 cases from the literature were under 4 months of age and 7 of the 13 were under 2 months of age. The usual therapeutic endeavors, including splenectomy, are reported as of no benefit.—W. N. J.

Histologic Study of the Bone Marrow in Normal White Pekin Ducks. G. Crass and R. H. Rigdon. From the Laboratory of Experimental Pathology, University of Texas Medical Branch, Galveston, Texas. Arch. Path. 58: 159-167, 1954.

Bone marrow from 50 normal white Pekin ducks was examined in order to determine the distribution of the various cellular constituents. There is almost a complete reversal in the erythroid-myeloid ratio in the young as compared with the older duck. The granules of the heterophils and eosinophils change their shape from round to oval to elliptical during the process of maturation. This change was not observed in the basophils.—O. P. J.

Anemia Produced by Chloramphenicol (Chloromycetin) in the Duck. R. H. Rigdon, G. Crass, and N. Martin. From Laboratory of Experimental Pathology, University of Texas Medical Branch, Galveston, Texas. Arch. Path. 58: 85-93, 1954.

There are frequent references in clinical medicine to the occurrence of injury to the hematopoietic system following the therapeutic use of chloramphenicol. The majority of
cases have shown the characteristics of an aplastic anemia. Preliminary observations in the duck indicated that an anemia would follow the oral administration of chloramphenicol. Further studies on the changes in the number of erythrocytes within the peripheral blood and in the erythroid and myeloid cells within the bone marrow confirmed this. Anemia apparently results from the effect of this antibiotic on the erythroid cells in the marrow resulting in a rapid decrease in the numbers of reticulocytes in the peripheral blood.—O.P.J.


In the wing membrane of the bat Pizonyx vivesi, there are nodular areas which have been described as "glandular masses". On gross examination they appear as thickened and darkened areas located in both wing and interfemoral membranes. They are sites of chronic hemorrhage, inflammation and hemopoiesis, rather than of glandular activity. The primary factor in producing the nodules is extravasation of blood cells which may be due to a weakening of the vessel walls by a mild vitamin C deficiency or to a greater stress placed on vessels at the intersections of muscle and elastic fiber bundles. Hemopoiesis in the nodules is thought to be centered in one or some combination of the following cells: extravasated or ameboid lymphoid cells, reverted endothelial cells of occluded or isolated capillary segments, reverted connective tissue cells of fibroblastic potentialities and appearance. Leukocytes and erythrocytes are found in these areas. Eosinophils and neutrophils were most numerous. Mast cells were rare. All cells were common in the connective tissue within the nodular areas and outside of them, especially along blood vessels.—O.P.J.

PIGMENT METABOLISM


A 54 year old man with a four year history of intermittent dark urine suffered from bullous skin eruptions on the back of his hands and fingers for about a year. The blistering did not appear to be particularly related to exposure to sunlight, but mechanical trauma to the skin seemed to favor the occurrence of blisters. Abdominal and neurological symptoms were absent. Urine and feces contained large amounts of porphyrins, but porphobilinogen was not detected in the urine.

This patient exhibited the symptoms typical of the condition which is usually designated as porphyria cutanea tarda. Recently a number of similar cases has been described both in this country and abroad. Although the authors state that delayed lightsensitive porphyria is "not familial" this point appears to require further studies, particularly in view of recent reports of large porphyria families discovered in South Africa.—R.S.


The author has reviewed the effect of a variety of compounds upon porphyrin metabolism and excretion in man and experimental animals. The more recent pertinent literature has been adequately considered, but reference has been omitted to some of the important earlier studies, e.g., Stokvis, Kast and Weiss. The review will be of real help to anyone working in the field of porphyrin metabolism.—R.S.


This method is a modification of the procedure described by Grinstein in 1947.—R.S.
ABSTRACTS

SOME STUDIES OF NATURE AND CLINICAL SIGNIFICANCE OF Porphobilinogen. C. J. Watson, with the Technical Assistance of Violet Hawkins and Irene Bossenmaier. From the Department of Medicine, University of Minnesota Medical School and Hospital, Minneapolis, Minn. Arch. Int. Med. 85: 643-657, 1954.

In the first part of the paper, in vitro studies are reported and discussed, relating to the conversion of porphobilinogen and other porphyrin precursors to uroporphyrins. The second part deals with the clinical significance of porphobilinogenuria. In intermittent acute porphyria, porphobilinogen has been found in the urine of all 89 patients studied by the author. Occasional cases have been observed where porphobilinogen was excreted only during episodes of acute abdominal pain or nervous system affections. In conditions other than acute porphyria, porphobilinogenuria is very uncommon. In the course of 15 years, the author has found significant urinary porphobilinogen excretion in 11 cases which could not well be classified as porphyria. These fell into 3 categories: neoplastic diseases, severe liver disease, and nervous system diseases.

Although porphobilinogenuria does not appear to be strictly pathognomonic of acute porphyria, in patients exhibiting abdominal symptoms, nervous system disturbances or psychic manifestations, the demonstration in the urine of a chloroform-insoluble Ehrlich aldehyde compound is of greatest diagnostic significance.—R. S.


The uroporphyrin content of urine from 7 normal individuals was estimated, employing an extraction method and subsequent spectrophotometry. The values obtained ranged from 11 to 40 micrograms per day, as compared to daily coproporphyrin excretion in the same individuals ranging from 50 to 108 micrograms. Possible porphyrin precursors were not included in these values. Although these data suggest the regular occurrence of small amounts of uro type porphyrins in normal urine, the author realizes that isolation and crystallization of this pigment or pigments will be necessary for unequivocal proof.—R. S.


The author has conducted controlled experiments on the conversion of porphyrin precursors to uroporphyrin in the urine of patients with acute (hepatic) porphyria. The best yield of uroporphyrin was obtained by keeping fresh urine for 13 to 15 days in the dark under nitrogen (with chloroform or toluol as bacteriostatic agents), then exposing it for a few days to air. These observations are believed to indicate, that under low oxygen tension, porphobilinogen is converted to uroporphyrinogen, which upon exposure to air, is then oxidized to uroporphyrin. Uroporphyrinogen may be identical with the Ehrlich-negative, nonfluorescing uroporphyrin precursor described by Watson.—R. S.


Dramatic relief of symptoms and decrease in porphyrin and porphobilinogen excretion were observed following intravenous administration of ACTH to a pregnant woman suffering from her first attack of acute porphyria. The onset of abdominal cramps and chest pain had occurred on the day following the ingestion of 10 tablets of 0.3 Gm. quinine sulphate. Symptomatic treatment with codeine, aspirin, and later with 25 mg. progesterone and 30 mg. phenobarbital, "whenever necessary", did not alleviate the acute manifestations.

After establishing the correct diagnosis by urine examination, all medications except demerol were discontinued, before ACTH infusions were started. Within a very few days of intravenous hormone treatment, the patient showed a remarkable improvement and the urinary pyrrole pigment excretion decreased substantially.
The authors concluded that "the dramatic results (were) presumably obtained from the use of ACTH." It should not be overlooked that the withdrawal of the other medications may have played an equally important role.—R.S.

**Fate of Porphobilinogen in the Rat. Relation to Acute Porphyria in Man.** A. Goldberg and C. Rimington. From the Department of Chemical Pathology, University College Hospital Medical School, London, England. Lancet 2: 172-173, 1954.

After parenteral injection, porphobilinogen was rapidly and mainly excreted in the urine, small amounts being excreted in the feces. There occurred in the urine a small but significant rise of coproporphyrin III as well as some uroporphyrin III. Porphobilinogen given enterally was mainly excreted unchanged in the feces. Porphobilinogen was not found in the liver when rats were killed shortly after its enteral or parenteral administration.

Experimental porphyria was produced in a rat with allyl-isopropyl-acetamide within 20 hours of a single dose, the liver then containing a high concentration of porphobilinogen. The findings suggest that extrahepatic porphobilinogen formation in experimental porphyria in the rats is improbable and point to the liver as the site of its formation in that condition. Measurements of renal clearance of porphobilinogen suggest that it is mainly filtered by the glomeruli. The rats had no abnormal symptoms after administration of porphobilinogen.

In acute porphyria in man the rapid elimination of porphobilinogen in an unchanged form would explain the absence of photosensitivity which is caused by an excessive amount of formed porphyrins in the skin. The porphobilinogen content of tissues in acute porphyria in man is similar to that in experimental porphyria in animals.—R.H.G.

**Hemoglobin**


In Britain most hemoglobinometers are standardized by reference to the British Standards Institute Haldane hemoglobin standard, a permanent color standard. Following the investigations of King et al. (Lancet 2: 789, 1947), this standard was valued at 14.8 Gm. per 100 ml. of blood. These workers carried out a large number of blood iron analyses, the results of which were converted into Gm. of hemoglobin per 100 ml. of blood on the assumption that crystalline hemoglobin contains 0.334 per cent of iron. In the present paper it is suggested that the figure of Bernhart and Skeggs (J. Biol. Chem. 147: 19, 1943) should be taken, viz., that hemoglobin contains 0.340 per cent of iron and therefore the hemoglobin standard should be valued at 14.5 Gm. per 100 ml. of blood.

In a subsequent letter (Lancet 2: 332, 1954), E. J. King and I. D. P. Wootton suggest the continuation of the use of present constants until international agreement is reached. —R.H.G.


Using methods described by D. L. Drabkin, the authors prepared solutions of cyanmethemoglobin and accurately measured their hemoglobin concentration. The measurements were confirmed by Drabkin. The solutions, sealed in cuvets, provide stable and accurate hemoglobin standards which have been made available to all clinical laboratories of the U. S. Armed Forces.

The authors emphasize that the possession of an accurate standard does not, of itself, guarantee accurate hemoglobinometry. Instructions for the use of the standard include methods for calibration of glassware and instruments. They recommend the cyanmethemoglobin method of hemoglobinometry for use with the standard. The amount of cyanide in the solutions is toxicologically insignificant.—J.H.A.

The S shape of the curve for oxygenation of mammalian hemoglobin implies interaction between the four hemes attached to each hemoglobin molecule. A hemoglobin molecule reacts more readily with oxygen after some of its hemes have been oxygenated. Compounds that react with nitrogenous groups of the protein might be expected to affect the combination of oxygen with hemoglobin. In the present experiments, formaldehyde was chosen because its reactions with amino acids have been explored and their equilibrium constants determined. Merck's reagent-grade formaldehyde was neutralized to pH 7 with NaOH. The neutral solution was diluted and freed of oxygen by evacuation with a water aspirator. A measured amount of this oxygen-free standard solution was injected by hypodermic syringe into a deoxygenated hemoglobin solution in a tonometer. The fluid concentration of formaldehyde in the hemoglobin solution was 0.1M. The results indicate that when formaldehyde is added to solutions of human hemoglobin near pH 7, the oxygen affinity of the hemoglobin increases considerably—more than tenfold. This interaction between hemes of the same hemoglobin molecule decreases. Some of the effect of formaldehyde on the oxygen equilibrium may be due to combination with sulfhydryl groups of the protein, but nitrogenous groups are probably also involved.—O.P.J.


The effect of the addition of various concentrations of 2-ethyl-5-methylbenzimidazole, 2,5-dimethylbenzimidazole and benzimidazole on the in vitro incorporation of N\textsuperscript{15}-labeled glycine into heme by avian erythrocytes was measured. 2-ethyl-5-methylbenzimidazole was found to effect a greater inhibition of N\textsuperscript{15} incorporation into heme in this system than either 2,5-dimethylbenzimidazole or benzimidazole. This same order of inhibition was noted for the multiplication of influenza A or B virus in previously reported experiments.—W.N.J.


Root nodules of leguminous plants contain a hemoprotein with a prosthetic group, indistinguishable from protohemin IX of hemoglobin. In this investigation it was found that soy bean root nodule homogenates were able to incorporate the alpha carbon atom of glycine and the carbon atoms of acetate into hemin. The soy bean root nodules differed from bone marrow in their ability to incorporate glycine and acetate into hemin.—R.H.G.

ERRATUM

In the article by Carrera, Reid, and Kurnick: Differences in Susceptibility of Polymorphonuclear Leukocytes from Several Species to Alteration by Systemic Lupus Erythematosus Serum: Application to a More Sensitive L. E. Phenomenon Test (Blood 8: 1165, 1954), the following footnote, pertaining to Dr. Carrera, was inadvertently omitted: Fellow, American Cancer Society, recommended by the Committee on Growth, National Research Council.