ABSTRACTS

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PIGMENTS


1. Normal and Pathological Metabolism of Porphyrins. H. M. Muri. From the Medical Unit, St. Mary's Hospital, Paddington, London W 2. (pp. 4-16.)

The author gives a condensed review of the results which have been obtained in recent years with the use of tracer techniques. a-aminolevulinic acid and porphobilinogen are obligatory intermediates in the biosynthesis of all porphyrins and heme. Only protoporphyrin IX can be used for prosthetic groups of chromoproteins, but the pathway, by which protoporphyrin is formed from porphobilinogen is not yet entirely clear. In addition to hemoglobin, hematin and protoporphyrin can also be broken down to bile pigments, but not other porphyrins. Porphyrin biosynthesis can take place in organs other than the bone marrow, e.g. in the liver in porphyria cutanea tarda and in acute porphyria.

2. Patterns of Porphyrin Excretion. J. E. Falk. From the Nuffield Unit for the Investigation of Pyrrole Pigment Metabolism, Department of Chemical Pathology, University College Hospital Medical School, London. (pp. 17-26.)

In studying patterns of porphyrin excretion in various disease states it is essential to include porphyrin precursors. Besides porphobilinogen, other uroporphyrin precursors have been found in urine, but their isolation and identification has not yet been possible. Coproporphyrin is excreted in part as colorless precursor, but no precursor of protoporphyrin has been recognized as an excretion product.

In the second part of the paper the author discusses some of the difficulties and complications which are encountered if one attempts to separate different porphyrins and porphyrin isomers by chromatographic methods. This section is particularly worth reading, because it presents a critical reevaluation of the proposed methods for separation of coproporphyrin isomers.

3. Pathology of Acute Porphyria: Experimental Porphyria. A. Goldberg. From the Nuffield Unit for the Investigation of Pyrrole Pigment Metabolism, Department of Chemical Pathology, University College Hospital Medical School, London. (pp. 27-33.)


The author gives an account of the experiments which have permitted him and his co-workers to separate the diazo-positive components of serum into three distinct fractions. According to these studies, the "indirect-reacting" pigment, which predominates in normal
serum and in serum of cases of hemolytic jaundice, appears to be very similar or identical with synthetic bilirubin. The pigment, which predominates in the serum in obstructive jaundice and in normal bile, and which gives a "direct" van den Bergh reaction, was found to be a mixture of two compounds, separable by chromatography. Both are considered to be metabolites of bilirubin, and the liver is believed to play an essential role in their formation. In "kernicterus," the pigment observed in the basal ganglia was found to be bilirubin, giving an "indirect" van den Bergh reaction.

These observations are of great interest, and may significantly contribute to a better understanding of the first steps of hemoglobin breakdown.

5. The Chemical Pathology of Bile Pigments. Part 2. Bilirubinoid Pigments of Urine and Faeces and Their Relation to Haem Pigment Metabolism. C. H. Gray. From the Department of Chemical Pathology, King's College Hospital Medical School, London, S. E. 5. (pp. 46–54.)

A short review is presented of the pathways of bile pigment breakdown in the gut. Major contributions in this field have recently been made by Watson and his co-workers, who have isolated dextra-rotatory urobilin from faeces of patients treated with aureomycin or terramycin. Mesobilirubinogen is the product of bacterial reduction in the gut, and is probably not formed in the liver, as has been advocated by Baumgärtel.

6. Methaemoglobin and Sulphaemoglobin. Q. H. Gibson. From the Department of Physiology, University of Sheffield. (pp. 55–70.)

7. The Chemical Pathology of Carotinoids. T. W. Goodwin. From the Department of Biochemistry, The University of Liverpool. (pp. 71–84.)

—R.S.

THE CONVERSION OF N15-LABELED MESOBIIRUBINOGEN TO STERCobilINOGEN BY FECAL BACTERIA. P. T. Lowry, N. R. Ziegler, R. Cardinal and C. J. Watson. From the Department of Medicine, Univ. of Minnesota Hospital, Minneapolis, Minn. J. Biol. Chem. 208: 543–548, 1954.

The authors have conclusively shown that N15-labeled mesobilirubinogen is reduced to stercobilinogen by fecal bacteria, both in vivo and in vitro. Thus any mesobilirubinogen formed in or entering the intestinal tract is subject to conversion to stercobilinogen. Hence mesobilirubinogen is an intermediate in the formation of stercobilin from bilirubin.

It has not been possible to determine the microorganisms in the fecal flora which are responsible for this conversion, but it was found that strict anaerobic conditions are not essential for the reduction.—R.S.


The authors give a condensed review of their extensive studies which have greatly contributed to the better understanding of the various reductive steps to which bilirubin is subjected in the intestinal tract. Under normal conditions, the prevalent faecal bile pigment is stercobilin and its chromogen, stercobilinogen. Aureo- and terramycin interrupt the chain of reductive steps in the intestine, thus leading to the formation and excretion of d-urobilinogen and d-urobilin. Stercobilinogen reappears in the faeces only weeks or months after cessation of antibiotic treatment. Prior to the reappearance of stercobilinogen, there is a transitional phase during which mesobilirubinogen is excreted in the faeces. The latter compound is an intermediate in the reduction of bilirubin to stercobilin. It is not known whether d-urobilinogen is a regular intermediate in the reduction of mesobilirubin to mesobilirubinogen, or whether it represents an alternative pathway.

Of clinical importance is the fact, that all three chromogens, i.e., d-urobilinogen, meso-
billirubinogen and stercobilinogen, give a positive Ehrlich reaction. Thus the "fecal urobilinogen" includes all three leucocompounds.—R.S.


Various porphyrins, porphobilinogen and porphobilin were tested in experimental animals and in isolated organs. No significant pharmacological action was observed. The authors doubt a causative relationship between porphobilinogen and the abdominal or vasomotor symptoms in acute porphyria.—R.S.


The authors report on the history, clinical findings, laboratory data and liver biopsy specimens of 12 young white patients exhibiting chronic jaundice of from 8 months' to 33 years' duration. The jaundice was usually mild (maximal level for total bilirubin 6 mg per 100 ml), fluctuated in intensity, and appeared to be aggravated by intercurrent diseases. Common symptoms included right upper quadrant pain, fatigue, dark urine and slight enlargement of the liver. The past and occupational histories were negative as to drug addiction, excessive use of alcohol, exposure to hepatotoxins, or transfusions. Six of the 12 patients had experienced previous episodes of jaundice. None of the patients had anemia, and reticulocyte counts, fecal urobilinogen and Coombs test, done in about a third of the patients, showed no abnormalities. In seven cases bile was present in the urine, and 6 cases had elevated urinary urobilinogen excretion. Both the direct and indirect bilirubin levels were elevated. In the majority of cases, liver function tests gave abnormal results.

The common denominator of all 12 cases was the presence in the liver of excessive amounts of coarsely granular, amorphous brown pigment. This as yet unidentified pigment was deposited in the hepatic cells of the centrolobular zones, with a tendency to spread to the periphery of the liver lobules. No other significant histological abnormalities were found. Fragments of liver taken at biopsy appeared "black."

The findings in these 12 patients are compared with those in constitutional hyperbilirubinemia, hyperbilirubinemia as a residue of viral hepatitis, hyperbilirubinemia associated with chronic gastrointestinal disturbances, obstructive bile stasis and hemolytic jaundice. Identification of the hepatic pigment may shed some light on the nature of this disorder and help to decide whether it is a separate entity or merely a variant of one of the other syndromes.—R.S.

ERYTHROCYTES AND ERYTHROCYTIC DISEASE


Though it is generally accepted that the jaundice which accompanies hemolytic anemia is much the result of impairment of hepatic secretory function or of breakdown of red cells, clinical, experimental and pathologic evidence of hepatic damage in adults is scarce. Therefore, experiments were undertaken to classify the morphology and pathogenesis of hepatic damage in experimental hemolytic anemia. Rabbits of both sexes were immunized with two courses of intravenous injections of washed red cells of the rat. The hemolytic serum thus obtained was administered subeuntaneously to albino rats in doses calculated from the known potency of the serum and the theoretical blood-volume of the animals. Sex made no difference and hemolytic serum was administered in several dosage levels. Control animals were injected with normal rabbit’s serum. Hemolytic serum could act on the liver: (1)
directly on the cells, (2) indirectly through anoxia, (3) indirectly through hemolytic products, or (4) indirectly through lack of nutrients diverted from the liver for hematopoiesis. Experiments with hypoxia were carried out to clarify point 2, phenylhydrazine was used in an attempt to answer point 3. Point 4 was investigated by a comparison of the right and left lobes of the liver. In the liver of the albino rat made anemic with hemolytic serum, necrotic lesions were common 24–48 hours after injection. Repair took place quickly without cirrhotic changes. Changes were not influenced by age or sex, but were proportional to the dose of serum and followed a pattern related to time. No necrosis occurred in the livers of rats exposed to low oxygen tension nor in those in which hemolyses was produced by phenylhydrazine. Apparently hepatic necrosis after injection of hemolytic serum is due to a direct effect of the antibody on the hepatic cells, the products of hemolysis possibly acting as a contributing factor.—O.P.J.


Following the previous studies, the neuropathologic features of experimental hemolytic anemia were investigated. Histopathologic changes were found in the cortex, basal ganglia, brain stem and cerebellum. The severity was more or less proportional to the dose of serum. The affected animals consistently showed extensive mid-zonal and centrilobular focal hepatic necrosis. The neurohistological changes produced by anoxia and phenylhydrazine were compared with those seen after administration of hemolytic serum. The latter were probably secondary to hepatic damage; bilirubin probably is not directly responsible.—O.P.J.


Two time constants are necessary to describe the entrance of sodium from plasma into human erythrocytes in vitro. On this basis it was concluded that the intracellular sodium was divided into two pools, one being "freely exchangeable," and the other "slowly exchangeable." Radioactive Na was injected into healthy young adult males in doses of about 350 microcuries. Over a 30-hour period following the injection samples of blood were drawn for determination of radioactivity and Na concentration of plasma and cells. The results indicate that all of the intracellular Na is not exchangeable in 24 hours, which confirms previous in vitro experiments. In hereditary spheroctosis the fraction of slowly exchanging Na may increase with the age of the red cell.—O.P.J.


During the course of experiments undertaken to investigate the efflux of potassium from human erythrocytes using K* as a tracer, it became apparent that the K efflux could not be described in terms of the two compartment system of plasma and cells. It has been found that when labeled cells are incubated with unlabeled plasma, a third compartment located in the cellular phase accounts for the apparently anomalous time curve of the appearance of K* in plasma.—O.P.J.


The hemolytic effect of aniline drugs on the red cells of primaquine-sensitive men (10 per cent of American negroes) was determined in vivo. It could be shown that primaquine-sensitive cells were also unusually susceptible to hemolysis by acetylilid, sulfanilamide,
thiazolsulfone, phenylhydrazine, sulfoxone and phenacetin. In very high doses or in combinations most of the active compounds were shown to be hemolytic to normal cells. The course of the severe hemolytic anemia resulting from administration of these compounds was self-limited and identical to that induced by primaquine. Immediately following administration of these compounds, a temporary primaquine insensitivity was observed. These observations suggest that only older cells are destroyed.—A.G.M.


When primaquine and other aniline drugs were administered to sensitive individuals, Heinz-body formation in vivo was considerable. In order to identify individuals who are sensitive to these drugs, an in-vitro test based on formation of Heinz bodies was developed. Red cells were incubated with acetylphenylhydrazine under standard conditions. Sensitive patients (18) developed more than five Heinz bodies in 45-92 per cent of erythrocytes, while normal individuals (86) only showed 0-28 per cent red cells with more than five Heinz bodies. Two false-positive but no false-negative results were obtained. The test was negative with red cells from patients with Hodgkin's disease, multiple myeloma, thalassemia, paroxysmal nocturnal hemoglobinuria, polycythemia vera and sickling-Hb C disease. Oxygenation of the incubation mixture was found to promote Heinz body formation. It is suggested that Heinz-body formation by this group of drugs may be due to oxidation of a red cell component. Drug-sensitive cells lack protective sulfhydryl compounds.—A.G.M.


A 5-week-old boy with seborrhoic dermatitis was admitted 2 days after external application of a resorcine lotion. The symptoms of intoxication were: severe cyanosis combined with paleness and subicterus, tachypnoea, tachycardia, fever, vomiting and convulsions. Increasing swelling of spleen and liver. Spectroscopy showed methemoglobin in the chocolate-colored blood. Hematologic studies revealed acute progressive hemolytic anemia characterized by intense Heinz-body formation (99%), destruction of red cells, pseudoleukemia blood picture and monocytosis. Treatment with partial exsanguino-transfusion (first introduced by Robertson in 1924) was followed by complete remission. First report on Heinz-body formation due to resorcine poisoning. Survey of the literature.—C.G.


A 3 year old boy was admitted 3 hours after having drunk a mouthful of marking ink. Clinically he was somnolent with obvious dyspnea, tachycardia, pale yellowish-brown color of the skin with increasing cyanosis. Blood was mahogany colored, spectroscopy showed methemoglobin. No remarks about blood morphology. Treatment with partial exchange-transfusion was followed by complete remission. Author gives a scheme of suitable therapy: gastric lavage, oxygen, thionine (10 ml. i.v. and 10 ml. i.m. in 0.2 per cent solution for adults) or methylene blue (1-2 mg./Kg. of body weight i.v. in 1-2 per cent solution) and exchange blood transfusion.—C.G.


Using glycine-2-C14 to measure the survival of the patient's own red blood cells in his own circulation the authors studied 3 cases of chronic lymphocytic leukemia and 5 of...
chronic granulocytic leukemia. In the first group, the red cells of one patient (who also had reticulocytosis and a slight increase in fecal urobilinogen) were found to have an 18-day life span with a random pattern of destruction indicating a hemolytic process. The cells of the other two patients showed a finite life span, normal or slightly less, suggesting defective red cells rather than an extrinsic cause for hemolysis.

The red cells of the 5 patients with chronic granulocytic leukemia all had a finite, shortened survival (70–100 days) suggesting that a defect is inherent in the cells. Red cell production was followed by means of Fe++ and found to be normal in 2 cases of chronic lymphocytic leukemia and greater than normal in 2 of 3 cases of chronic granulocytic leukemia.

- R. R. E.

**Immunohemolytic Anemia in Kapo’s Sarcoma with Visceral Involvement Only.**


A case of immunohemolytic anemia with positive Coombs test in a patient suffering from Kapo’s sarcoma is reported in detail. Splenectomy had no obvious effect on the hemolytic process, which, however, responded favorably to ACTH and cortisone. The patient died from his sarcoma.—M. S.

**Congenital Porphyria with Increased Hemolysis.** *Mario Pozzan.* From the Pediatric Clinic of the University of Padova, Italy. Acta paed. Latina, 6: 995–1012, 1953.

The author describes an authentic case of congenital (erythropoietic) porphyria in a 2 year old girl of Italian parents. The patient excreted red urine at birth, and hemolytic anemia, splenomegaly, erythroderma, and hypertrichosis were discovered at the age of 6 months. After the first year of life photodermatitis became severe and led to extensive scarring of hands and face. Of special interest is the observation that roentgenograms of the skull revealed a “hair-on-end” appearance, very similar to that seen in sickle cell anemia and thalassemia. As far as can be determined this is the first time that such a finding has been reported in congenital porphyria. It is however, not an unexpected observation, since marked normoblastic hyperplasia of the bone marrow and increased hemolysis appear to be regular features of this rare disease. In this patient, the hemolytic anemia was so severe as to require transfusions already at the age of 6 months.—R. S.


The authors have demonstrated that saline suspensions of normal red cells, cells sensitized with incomplete anti-D typing serum and cells from patients with acquired hemolytic anemia are agglutinated by protamine sulfate, while normal trypsinized cells are not. When protamine and trypsin are added simultaneously only cells sensitized with the anti-D agglutinated. This is interpreted as additional evidence of differences between auto- and iso-immune antibodies; the latter being gamma globulins, while the former are not.—J. H. A.

**Experiences with Treatment of Polycythemia by Radioactive Phosphorus.** *L. Donner and F. Helmansky.* From the 2nd and 1st Medical Clinic, Charles University, Prague. Čas. Lék. Čes. 92: 1089–1094, 1953.

A report dealing with the therapeutic effectiveness of treatment of 12 patients suffering from polycythemia vera is presented. Dosage: 3–12 millicuries in a single injection. In eight of twelve patients, complete remission with a fall of RBC below 6,000,000 and of hematocrit value below 55 per cent was obtained; the remission lasted one year. In two patients, a remission of the same type lasting less than one year was obtained; in two patients there was a marked improvement of clinical symptoms in spite of an increased number of RBC. In two patients complications appeared. In one, aplasia of bone marrow with temporary pancytopenia developed; in the second, the treatment was complicated by excessive uterine
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bleeding with prolonged bleeding time and mild thrombocytopenia. Both complications regressed very rapidly and without any consequences.—M.N.


Six patients with polycythemia vera were followed for 10 months to one year on Dara prim (2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine) an antimalarial that has antifolic activity. All six patients responded well with satisfactory falls in erythrocyte counts and associated clinical improvement. In all cases the initial dose was 25 mg. daily by mouth until the RBC level was between 4.5 and 5.0 million. The drug was then continued indefinitely unless the RBC continued to fall, in which case the dose was reduced to 12.5 mg. daily or discontinued temporarily if the RBC fall was rapid. There were no toxic manifestations and no leukopenia. No mention is made of platelet counts or hemorrhagic phenomena. All six patients developed multilobed polymorphonuclear leukocytes, peripheral macrocytosis, and marrow megaloblastosis after prolonged therapy with Dara prim.—R.R.E.

OBSERVATIONS ON THE INHERITANCE OF SICKLE-CELL HEMOGLOBIN AND HEMOGLOBIN C. H. M. Ranney, J. Clin. Investigation 33: 1634–1641, 1954. (From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital in the City of New York.)

It has been postulated that the genes determining sickling (S) and C hemoglobin are multiple alleles. The author observed ten families in which both hemoglobin C and S occurred. The hemoglobin types of children (S) from S-C x normal marriages (2) were either sickling trait or C-trait. Failure to find the type S-C among offspring suggests allelism of the genes for sickle and C hemoglobin. However, more data are needed. Observations on three offspring of individuals with S-C disease and marital partners heterozygous for an abnormal hemoglobin were also consistent with the multiple-allele theory. Since patients with S-C disease do not have any normal (A) hemoglobin, linkage and independence of the two genes were also rejected on theoretical grounds. Two additional cases of homozygous Hb C disease are described.—A.G.M.


Although it is established that the electrophoretic mobility of normal adult (A) hemoglobin, sickling (S) hemoglobin, and hemoglobin C differ under a certain standardized condition of electrophoresis (anodic mobility at pH 8.6: A>S>C), the chemical basis for the difference in electrophoretic mobility is not well understood.

The authors submitted specimens of pure hemoglobin A, hemoglobin S and hemoglobin C to paper electrophoresis with a variety of buffers at different pH ranges. Mobility differences of the three hemoglobins at an alkaline pH persisted up to pH 12. Since lysine and arginine groups lose their positive charge at pH 12, authors suggest that the difference in charge of the 3 hemoglobins could not be due to difference in content of lysine or arginine residues. In acid medium all 3 hemoglobins differed in net positive charges down to pH of 4.8. Below this pH, mobility of the 3 hemoglobins was equal. These findings were interpreted as evidence that the characteristic electrophoretic behavior of the three hemoglobins was due to differences in their content of carboxyl groups, since in a pH range where carboxyl groups alone are losing their charges there is disappearance of the differential electrophoretic migration of the three proteins.

The authors furthermore showed that equal mobility of hemoglobin A, S and C at pH of 4.1 and lower was not due to irreversible denaturation of hemoglobin.

The results are interpreted as being incompatible with changes in the histidine, tyrosine and phosphate content of the three hemoglobins. Differences in specific binding of buffer ions by the hemoglobins also were excluded.

The structural basis for the apparent difference in content of the carboxyl groups of the hemoglobins remains obscure.—A.G.M.
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