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ERYTHROCYTES AND ERYTHROCYTIC DISEASE


This article summarizes the many attempts which have been made to assay the antianemic factor in pernicious anemia. The limitations of present knowledge of the intrinsic, extrinsic and liver factors are evident from this discussion. With the impetus provided by folic acid towards the isolation of these factors in their pure chemical state, the article is timely in expressing the need for a satisfactory method other than therapeutic trial in patients for assaying newly prepared compounds. One hundred and one references are cited.

C. A. F.


Tapeworm anemia of pernicious type is the classic problem of Finnish hematology. The author has published a series of very interesting investigations on the gastric secretion in this condition. It has been shown that liver extracts, either intramuscularly or perorally as well as desiccated stomach perorally, are able to induce a remission in this malady. The paper deals with the action of intrinsic plus extrinsic factor in tapeworm anemia. Bonsdorff has already shown that intrinsic factor is present in the gastric juice of these patients. There is no remission if the worm is expelled and the patient is living on a diet free from extrinsic factor. (Extrinsic factor however was obviously available in the diets of these anemic patients.)

A large series of very thorough experiments were performed and it was found that mixture of extrinsic factor (meat or yeast extracts) and intrinsic factor (human gastric juice) gave no response in tapeworm anemia. The same preparations were active in cryptogenetic pernicious anemia. The results were constantly negative regardless of whether the mixture was incubated for 6 hours before administration or not. The explanation of these data is discussed. It is pointed out that the liver principle itself is not formed in vitro. The hypothesis of Formijne that the interaction of the two factors (ex- and in-) takes place in the intestinal wall is discussed. The inhibiting effect of the tapeworm should then occur at this level.

J. W.


Agren has pointed out that the intrinsic factor may well be identical with the enzyme aminopolypeptidase that has been purified and investigated by him. Concentrated enzyme preparations were used as a source of intrinsic factor and incubated with beef muscles that had been predigested with pepsin. This preparation seemed to be active. Control experiments were performed on 2 patients with only aminopolypeptidase without beef. In one case the effect as regards reticulocytes and bone-marrow was negative. The serum iron possibly dropped somewhat. The effect of later peroral doses of folic acid was excellent. In the second case there was a definite drop of the serum iron and an irregular increase in

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reticulocytes with a normoblastic reaction in the bone marrow. There was no secondary effect of folic acid as regards reticulocytes, but there was a good increase in erythrocyte and hemoglobin. These results tend to show that the enzyme preparation may be active without the presence of extrinsic factor. The authors point out that further experiments are necessary.

J. W.

ON THE CURATIVE EFFECT OF PURE DUODENAL SECRETION FROM SWINE IN CASES OF PERNICIOUS ANEMIA.


The authors studied the effect of the juice from a duodenal pouch in swine. This is regarded as the only way of avoiding contamination with gastric secretions. One patient got 150 ml duodenal juice daily for two weeks. Some pepsin and some HCl were added. The food of the patient was not controlled. There was no immediate increase in reticulocytes but the second response to desiccated stomach also gave very poor results. In the second case 150 ml pure duodenal juice was given with a noncontrolled food intake for ten days. The reticulocyte response was quick and marked. The bone marrow changed from megalo- to normoblastic. Liver extracts gave no secondary reticulocyte reaction. The authors conclude that an antipernicious-anemia-factor is present in the duodenal secretion from swine. The authors point out that there may be differences between the conditions in man and in animals.

It seems to the reviewer that the effect of purified aminopolypeptidase solutions mentioned in the previous paper and the effectiveness of pure duodenal juice should be further investigated as it may give a clue to the real nature of Castle's principle.

J. W.

ANÉMIE HYPERCRÔME AVEC MIGALOCYTES, RFRACTAIRE À L’HÉPATOTHERAPIE. "ACHRESTIC ANÉMIA".


There has been considerable discussion about the real nature of achrestic anemia as described by Wilkinson and it seems as if most continental hematologists regard it as a type of aplastic anemia that has nothing to do with pernicious anemia. The recent successful treatment of such liver refractory cases with folic acid gives this problem more than academic interest. The author is of the opinion that these cases have a really megaloblastic bone marrow in spite of the presence of hydrochloric acid in the gastric juice. There were no symptoms from the nervous system. Potent liver extracts gave no reticulocytosis and no drop in the serum iron. Big transfusions were necessary. Nicotinic acid and yeast extracts were not of any help in the first case. The second one developed anemia during her pregnancy. After delivery the anemia progressed and was not influenced by large doses of different liver extracts. Later there was found an irregular rise in reticulocytes and there was a slow improvement of the blood values. After one year there was still a definite macrocytic anemia but the megaloblastic bone-marrow had become normal. In both cases it seems as if the gastric juice would have been free from intrinsic factor.

Possibly these cases might respond to treatment with folic acid.

J. W.

PERNICIOUS ANEMIA IN CHILDHOOD. II. RESPONSE TO FOLIC ACID. J. C. Peterson. From the Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tenn. Am. J. Dis. Child. 75: 578-580, 1947.

The author gives a brief follow-up report on a previously described (Am. J. Dis. Child. 72: 252-268, 1946) case of pernicious anemia in a 6 year old girl whose history of anemia dated back to the age of 8 months. There was maximal response to administration of liver extract, but continuous therapy was required to maintain a remission. From 1940 to 1946 she was observed during the course of five relapses, some specifically induced by withdrawal of treatment. During such a relapse in 1946 she was given 5 mg. of folic acid orally twice daily. The response to folic acid was similar to that previously observed following the administration of liver extract.

L. E. Y.


This article, which tabulates the signs and symptoms of 48 patients with sickle cell anemia, provides useful data as to the incidence of these various manifestations. Of interest is the height of fever (although
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it is not clear whether this is related to incident infection or to the sickle cell disease), the frequency of pain in the lower extremities and abdomen, the leg ulceration observed in 15 per cent of the cases, the presence of mental deficiency in 7 cases, and various cardiac manifestations. The authors also remark on the rapid change in size of the spleen and liver over a number of days.

C. A. F.

LIPID METABOLISM AND DEVELOPMENT OF ANEMIA IN SPLENECTOMIZED GUINEA PIGS FED CHOLESTEROL.

B. Kennedy and R. Okel. From the Department of Home Economics, University of California, Berkeley.


Guinea pigs fed diets containing 1 per cent cholesterol and 15 per cent fat develop, in chronologic order, fatty livers rich in cholesterol, splenomegaly, and severe anemia in which the red cells are both excessively fragile and excessively resistant to hypotonic solutions. The resulting syndrome is a hemolytic anemia and includes anemia, hyperbilirubinemia, bone marrow hyperplasia, pigment gallstones, and hemosiderosis. This disease is frequently cured by splenectomy. The authors wondered whether the anemia could, therefore, be due to the splenic hyperplasia, e.g., an enlarged spleen excessively destroying red cells.

They therefore first splenectomized guinea pigs and then, after a control period of waiting, fed them cholesterol and fat. The resulting animals lost weight and developed anemia with hemolysis just as the original guinea pigs. The liver and blood lipids, and the incidence of gallstones, were identical in splenectomized and intact guinea pigs. The conclusion was therefore reached that the spleen was not primarily responsible for the anemia.

A parallel may be drawn to the congenital spherocytosis of human beings, in which splenectomy, by removing the chief site of red cell destruction, 'cures' the hemolytic syndrome, although the fundamental aberration (spherocytosis) remains. It seems more than ever advantageous to divide hemolytic anemias into three types: (1) intrinsic defects of the red cells, making them especially vulnerable to the normal action of the spleen; (2) action of demonstrable or nondemonstrable plasma or tissue substances on originally normal red cells (e.g., circulating agglutinins). The guinea pig anemia probably fits best here. Such damaged red cells are also particularly liable to destruction, especially in the spleen; and (3) excessive destruction of normal red cells by a hyperactive spleen (spherosplenic hemolytic anemia). In all three types, splenectomy may be 'curative'; but it is only in the relatively rare third category that the spleen is fundamentally responsible for the disease.

S. E.

THE USE OF FOLIC ACID IN SPRUE.


This is a comprehensive report on the management of 50 cases of tropical sprue with folic acid. Twenty-two cases were acute and severe. These cases were thoroughly studied with sternal marrow differential counts, complete hematologic studies of the peripheral blood, blood chemistry, gastric analyses, stool urobilinogen, and the fat content and fat partition of the stools. Of particular interest are the changes in stool, glucose tolerance tests and hematologic picture after treatment. Admission stools on 12 patients averaged 19.18 per cent solid material in fresh feces, 16.46 per cent total fat in dried feces, 79.31 per cent free fatty acids and 83.24 per cent of total split fats. A few days after treatment the solid content of feces was 13.19 per cent, and there was 20.76 per cent total fat in dried feces, 67.33 per cent being free fatty acids and total split fat being 75.75 per cent. (Normal values for solids 25.23 per cent, total fat 75.75 per cent.) Oral glucose tolerance tests before treatment showed an increase in blood sugar of between 1 and 32.5 mg. per cent. After 1 to 2 months' treatment all but 1 showed improvement and 6 of 14 showed a rise of greater than 40 mg. per cent.

Ten cases were summarized with a discussion of reticulocyte and red cell responses to varying doses of folic acid. The patients were maintained on either a diet poor in proteins or a sprue diet rich in these materials. On the poor diet hematologic response was submaximal even with doses up to 100 mg. of folic acid. With an adequate diet a daily dose of 10 mg. of folic acid by mouth gave a good initial response. The authors state that the patients are maintained on as little as 1/2 to 5 mg. per day. Follow-up on these patients extended over only 1 to 4 months.

C. A. F.
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This is another report on the clinical efficacy, in the treatment of macrocytic anemias, of compounds similar chemically to folic acid. To date, these substances can be classified into three groups: (1) pteroyl-glutamic acid, which is the compound found in liver L. casei factor, in yeast L. casei factor, and vitamin B12; (2) pteroyl-diglutamyl glutamic acid, which is the fermentation L. casei factor; and (3) pteroyl-hexaglutamyl glutamic acid, which is the "vitamin B12 conjugate" material. The chemical difference among these substances lies in the number of glutamic acid residues per molecule.

The present report relates the response of patients with macrocytic anemias to pteroyl-diglutamyl glutamic acid, with the usual reticulocytosis and subsequent clinical and laboratory improvement. A similar response to pteroyl-glutamyl glutamic acid (2 glutamic acid residues) has previously been published (T. D. Spies, R. E. Stone, and R. L. Toca; South Med. J. 40: 175-6, 1947).

The authors suggest that the more complicated chemical compounds, such as the hexaglutamyl compound of vitamin B12 conjugate, may be broken down with difficulty by some patients with macrocytic anemias. The relative efficacies of these and other similar compounds may ultimately help to elucidate their manner of action in pernicious anemia, and perhaps to discover an ideal substance for clinical use.

S. E.


Under very trying war-time conditions the three groups of patients studied consisted of: (1) accidents other than those due to enemy action; (2) industrial accidents in which superficial burns were associated with fractures, and (3) accidents due to enemy action. The results of the various determinations showed that both erythrocyte and hemoglobin values fall during the first week and then rise to a higher level. Reticulocytes were low immediately following the injury, but rose to the upper limit of normal immediately preceding the rise in hemoglobin. The elevated sedimentation rate was very likely due to the increased plasma fibrinogen. Although the leukocytes decreased slightly during the period of observation, they remained within normal limits. Leukopenia was not encountered.

O. P. J.


In a preceding report this team of investigators had shown a correlation between the presence of anemia and evidence of malnutrition as indicated by muscular development and dermal and ocular signs of vitamin deficiency. There was found to be a direct correlation between the hemoglobin level and the cell volume and mean corpuscular hemoglobin concentration so that all severe or moderately severe anemias were microcytic and hypochromic. It was noted that the amount of hookworm infection could be correlated with the severity of the anemia in only the more malnourished third of the recruits.

During the first six months after induction there was a rise in the hemoglobin level in the group that was given the army diet alone, but the most severe anemias did not reach a normal level at the end of six months. It was found that three grains of ferrous sulfate daily cured all the anemias at the end of four months and was judged to be as effective as six grains daily. The rate of hemoglobin rise was less in both the treated and control group if milk was substituted for meat as the source of protein in the diet. It was found that hookworm infection did not interfere with the rate of hemoglobin regeneration but that septic infections of the areolar tissue, tonsillitis and malaria depressed hemoglobin regeneration. This is an excellently controlled mass study of the effect of iron therapy and gross alterations in the diet on hemoglobin regeneration in human subjects.

R. S. E.
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This important study is founded on 80 observations of erythemia (Erythroleukemia) most of them published in Italy and in particular by Di Guglielmo who was the first to describe the disease in 1917.

The author defines the disease as follows: Generalized primitive proliferation of the erythroblastic series, which may be acute or chronic, occur in all ages without sex preference. The acute form, the less rare, was the first to be known. The symptoms are the following: Anemia, fever, splenomegaly and hepatomegaly. In the blood young erythroblasts are seen, which is often atypical, and there is in the erythropoietic center an embryonic proliferation of erythroblasts. The evolution lasts only a few weeks. The chronic form is also marked by anemia and hepato-splenomegaly, but the erythroblasts found in the peripheral blood are more mature forms. The duration of this form is about two years.

In both forms, the anemia is a constant feature, and always severe. The mechanism is complex: lack of formation of normal erythroblasts and increased destruction of abnormal red cells in peripheral blood. The author supplies rich pathologic material from biopsies and postmortem examinations (illustrated by 18 microphotographic and color plates). There is a striking crythroblastic proliferation and an important reticulo-endothelial proliferation in the bone marrow, lymph nodes, liver, and also in the kidneys, heart, pancreas, and adrenals. A complete bibliography terminates this weighty study.

J. P. S.


The author of this short note has done a large amount of work on hereditary mechanisms of various anemias in the rat and the mouse. Most of the work is not obviously related to clinical mechanisms, but relationships between certain of these disorders and certain anemias in man have been suggested.

Seven disorders are discussed by Grüneberg. Among these several are of special interest. "Siderocytic anemia" of the mouse is associated with a recessive gene for certain other characteristics; the characteristic finding is the presence of nonhemoglobin iron in the erythrocytes. Grüneberg conceives of these cells as aged cells, counterparts of the reticulocytes; and notes that they are present in various human hemolytic anemias in proportion to the severity of the hemolysis.

A lethal spherocytic anemia occurs as a recessive characteristic in the rat which Grüneberg attributes to a faulty marrow which produces red cells of inferior quality, whose survival time in the circulation is reduced. This anemia is not analogous to familial spherocytosis of human beings. A second form of familial hemolytic anemia, however, occurs as the recessive acholuric jaundice of the rat. Homozygotes have microcytosis, increased hypotonic fragility, jaundice, and splenomegaly. Heterozygotes may show no abnormality, or may show increased hypotonic fragility and reticulo-endothelial reaction without jaundice. The possible relationship of this disorder, whose heredity has been worked out, to familial spherocytosis of humans is intriguing. The disease in the rat, however, is not cured by splenectomy; so that a definite parallel cannot be drawn.

As in other fields in medicine, study of disorders occurring in animals breeding under controlled laboratory conditions may be expected to shed light on similar disorders in the clinic. The use of known hereditary mechanisms in rodents to elucidate the mechanisms of similar human disorders is another line of attack in these still puzzling problems.

S. E.


Hemolytic anemias have been the center of much controversy ever since they were first studied. The present article contains evidence which indicates that congenital and acquired cases of hemolytic icterus are both physiologically and serologically different from each other. They are two etiologically different conditions within the syndrome of acholuric jaundice. Some of the evidence in support of this belief is that when normal blood is transfused to recipients with the congenital type of anemia, the survival of these cells is from 100–110 days. But when recipients with the acquired type of anemia are transfused with normal blood, the survival of the cells is markedly reduced. In addition to this, when washed red cells from cases of congenital acholuric jaundice are tested for agglutination with anti-human-serum serum they are not agglutinated, but cells from cases of acquired acholuric jaundice readily agglutinate. Loutit
and Mollison believe that the congenital type of hemolytic icterus is due to a hereditary defect of the erythroid elements and that in the acquired type an abnormal hemolysin co-hemolysin system is in action.

O. P. J.


The purpose of the experiments reported in this paper was to determine whether or not selective permeability depends on energy derived from metabolic activities within the cell. For this purpose beef and chicken blood was used. Substances, such as potassium cyanide, sodium fluoride, arsenious oxide and iodoacetate, which interfere with metabolic activities, were allowed to act on blood corpuscles at 37° ± 0.1°C for varying periods of time. Although metabolic systems were sensitive to these substances and inhibited by them, there was not a change in the permeability. Apparently the permeability of the erythrocyte to non-electrolytes does not depend on energy derived from either aerobic or anaerobic metabolism.

O. P. J.


In the previous paper, metabolic activities of erythrocytes were inhibited by the addition of various substances. In the present paper, similar activities have been influenced by removing certain components of the enzyme-substrate by washing chicken erythrocytes three or four times with Ringer-Locke solution. In so doing, anaerobic glycolysis was reduced to an immeasurable level. Unhemolyzed cells were present after they had been exposed to anaerobic conditions for as long as 384 hours. In these experiments, it was necessary to avoid contamination with hemolytic bacteria. The results of these experiments show that permeability of the chicken erythrocyte to glycerol does not depend on energy derived from cell metabolism.

O. P. J.

Immunohematology


The "Coombs test" which determines the red cell agglutinating effect of serum from rabbits immunized against human serum globulins, was applied with positive results in two cases with acquired hemolytic anemia, indicating the presence of an adsorbed immune body type of hemolytic agent attached to their erythrocytes. Normal blood transfused into these patients shared in the hemolytic process, presumably as a result of exposure of the donor cells to, and their adsorption of, a hemolytic agent present in the circulation of the recipients. It was not possible to demonstrate any hemolytic properties, or adsorbable antibodies in the sera of these patients, which may be explained on the basis of a continuous excess of antigen provided by the circulating red cell mass. Support for this thesis was obtained from experiments in which the immune substance, probably the active anti-red cell antibody, was eluted in warm saline from the affected red cells of the patients, and then combined, in vitro, with normal cells.

C. P. E.


The injection of anti-red cell serum into the rat provokes an acute syndrome with hemoglobinuria an acute hemolytic anemia, or a subacute curable anemia. These experiments with rats bring confirmation
to the Dameshek and Schwartz experiments with guinea pigs, and also show that increased osmotic fragility and microspherocytosis is easily induced. The personal contribution of the authors is as follows:

1. In a fresh preparation of red cells one notes a pseudo-agglutination of the spherocytes instead of normal rouleaux-formation. There are some spindle-shaped red cells and numerous erythroblasts. In the acute cases hemoglobin crystals may be seen in the cells.

2. There is a marked leukocytosis with a histiocyctic reaction and many leukocytes show erythrocytosis. Jaundice was present in subacute or acute form and when it was especially severe erythrocytosis was striking.

3. The histologic findings in liver, spleen, and kidneys are identical with those found in hemolytic disease of the human new-born, but nuclear jaundice was not encountered.

4. The causal antibody was found on the red cells of the injected animal (conglutination method).

5. The peroral administration of the anti-serum to the new-born rats induces trouble only if it has been given before the twentieth day.

The authors discuss the relationship between this experimental anemia and the human erythroblastosis of the new-born. This weighty study is illustrated with numerous microphotographs and colored plates. (18 pictures)

J. P. S.


The complex carbohydrates, apple pectin, citrus pectin, flaxseed mucilage, blood group A substance, gum acacia and gum myrrh, as well as an aqueous extract of chicken erythrocytes, were shown to inhibit the agglutination of chicken red cells by the PR8 strain of influenza A virus. Many, but not all, of the inhibitory substances were polysaccharides rich in galacturonic acid. Alginic acid, a polysaccharide largely composed of mannuronic acid units, was inactive, as were the simple carbohydrates such as galactose, galacturonic acid and aldobionic acid.

Detailed study of the action of apple pectin showed that this substance affected both virus and red cell and that it also inhibited the multiplication of virus in embryonated eggs.

These observations serve well to illustrate the usefulness of the erythrocyte as a tool for the study of virus-cell relationships. The results obtained also illustrate how antagonism between structurally similar compounds may be used as a guide in investigating the biology of viruses.

L. E. Y.

THE NATURE OF NON-SPECIFIC INHIBITION OF VIRUS HEMAGGLUTINATION. W. F. Friedewald, E. S. Miller, and L. R. Whatley. From the Department of Bacteriology and Immunology, Emory University School of Medicine, Atlanta, Georgia. J. Exp. Med. 86: 65-75, 1947.

Saline extracts of lung, liver, kidney and spleen from human beings, rabbits and guinea pigs were found to inhibit hemagglutination by mumps virus and by the PR8 and Lee strains of influenza virus. The inhibition titers of organ extracts were usually higher than the titers obtained with sera from the corresponding animals.

Saline extracts of human and chicken erythrocytes also contained an inhibitory substance in high titer, and these cells were markedly agglutinated by influenza and mumps viruses. Rabbit cells were not appreciably agglutinated by these viruses and extracts of rabbit cells were not inhibitory. Sheep red cells varied in their capacity to agglutinate and also in their yield of inhibitory substance. When the virus receptor substance was removed from chicken cells by adsorption and elution with influenza virus, extracts of the cells were no longer inhibitory.

Evidence is presented that the inhibitory substance is not an antibody and that it is distinct from the blood group factors A, B, and Rh. The findings with the virus inhibitory substance are, nevertheless, compared by the authors to those with A and B factors. Both are found in many types of mammalian cells in addition to erythrocytes and also in various body fluids. The A and B factors, moreover, may combine with isoantibodies to inhibit hemagglutination.

Failure of the inhibitory substance to neutralize influenza virus in vivo suggests that it is not an important factor in preventing infection. On the contrary, it is postulated that it may actually have a deleterious effect in human infections by preventing union of virus with antibody.
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A recent paper by Bovarnick and de Burgh (Science 105: 530-531, 1947) should also be cited here. These authors prepared lipid extracts of erythrocytes which inhibited agglutination of these cells by influenza and mumps viruses.

L. E. Y.


Sera from 1000 unselected European group O donors were titrated at 37°C with 1 per cent suspensions of fresh A and B cells. End points were read grossly after incubation for one hour and titers were expressed in terms of the dilution of serum itself and not of the final mixture of serum and cell suspension.

Taking a titer of 1/100 as "dangerous," 211 of the donors tested were classified as unsafe for transfusing patients belonging to groups other than O. Of these, 95 had high anti-A titers only, 62 had high anti-B titers only, and 64 of the 211 donors had both high anti-A and anti-B titers. The incidence of high titers is considerably lower in the experience of other investigators, probably due mainly to differences in technic.

The author urges that use of the term, "universal donor," be discontinued because it gives a false sense of security. He further recommends that all group O donors be classified according to isoagglutinin titer—a task which is considered reasonable since variations in titer from time to time are small in healthy persons. This procedure is preferred to that of adding A and B group specific substances to O blood prior to transfusion to A, B, or AB recipients.

Although no attempt is made in this paper to discuss the controversial issues involved in the use of universal donors, a timely warning is given.

L. E. Y.


Ninety volunteers were inoculated with P. vivax sporozoites in order to study the treatment of the disease. A battery of seven diagnostic tests was done for syphilis, including, in addition to the usual tests, a special test with cardiolipin antigen devised by Rein and Bossack. The following results were obtained:

1. 63.3 per cent of the subjects developed false positives with one or more tests at some time during the course of the malaria.
2. In no instance was there a positive test before the fever or the parasitemia.
3. The false positive test appeared on the average a little over eight days after the parasitemia (range 0-30 days).
4. The false positive test was usually transitory and of low titer. Its duration after a given attack of malaria was from 2 to 98 days, although in one patient who had successive relapses the false positive serologic reaction was present for 517 days.
5. The Kahn standard tests gave the most false positives. The Hinton flocculation test gave the least false positives. The new Rein-Bossack cardiolipin test, a microflocculation procedure, was also seldom falsely positive.

S. E.


The authors advance the hypothesis that Rh antibodies produced as a result of isoimmunization during pregnancy are of two types: erythrocyte-destroying antibodies and sensitizing antibodies. The former act upon the infant's Rh-positive erythrocytes in such a way that their destruction by phagocytosis is greatly accelerated. The sensitizing antibodies, according to the concept presented, exert their effect within tissue cells by reacting with Rh antigen freed by the destruction of Rh-positive erythrocytes.

The intracellular reaction injures the cell and causes the release of histamine and possibly other toxic substances into the circulation. These substances may then have a damaging effect on susceptible tissues elsewhere in the body.
It is emphasized that maternal antibodies are carried first to the fetal liver, and that hepatic cells suffer most from the "sensitization reaction." Jaundice due to rapid destruction of erythrocytes is intensified by hepatocellular injury, and liver damage is also held at least partly responsible for hemorrhagic diatheses and hypoproteinemia. Edema is attributed to hypoproteinemia and increased capillary permeability, the latter being caused by direct sensitization of the endothelium or by the action of histamine produced in organs such as the liver and lung. It is further suggested that histamine may be responsible for the development of pulmonary edema in the newborn and also for intrauterine asphyxia as a result of placental edema. Possible causes of brain injury are anoxia, intoxication (histamine) and direct sensitization of nuclear neurons. Kernicterus is attributed to the increased avidity of affected cells for bilirubin.

Three of the 5 erythroblastotic infants described were transfused with Rh-positive blood. It is suggested that the favorable results obtained were due in part to the "desensitizing" action of the Rh-positive cells.

The speculations set forth in this paper are supported to only a limited extent by the authors' personal observations. They should, nevertheless, serve to stimulate further investigation of hemolytic mechanisms, of the much-debated "toxic" effects of rapid red cell destruction, and the merits of exchange transfusions. Until more is known concerning the pathogenesis of erythroblastosis fetalis, most clinicians will probably prefer to continue their current practice of transfusing affected infants with Rh-negative blood.

L. E. Y.


The author makes a minute study (topographic and histologic) of two cases of nuclear jaundice due to Rh immunization. His conclusions are the following:

There is a very important extension of the histologic lesions which largely exceeds the macroscopic topography of the biliary impregnation. There is an edematous infiltration of nervous elements and also of the perivascular areas. The neuroganglionar degeneration is characterized by acute tumefaction, liquefaction, and "Schwererkrankung" of Nissl. The cerebral cortex, the paraventricular nuclei of the cerebral trunk, the "olives bulbaires" and the "noyau dentelé" are the more affected areas. All these lesions are degenerescences without much satellitar reaction (16 pictures and microphotographs.).

J. P. S.


The literature dealing with cold agglutinins is briefly reviewed. Eighteen published case reports of the association of autohemagglutination with peripheral vascular phenomena simulating Raynaud's disease are cited. The author presents clinical and laboratory studies of a case with symptoms of Raynaud's disease caused by the presence of an autohemagglutin activated by exposure to cold. The titer of this agglutinin was 1:014. There was no predisposing disease to account for the development of this agglutinin.

J. F. R.


The author presents a concise review of the subject and properly stresses the importance of (1) clerical errors, (2) masking effect of anesthesia, (3) examinations for presence of hemoglobinemia and hemoglobinuria, and (4) recheck of crossmatch with fresh specimens from donor and recipient.

Of particular interest with regard to therapy is the reference to Diamond's suggested administration of A and B group specific substances to group O patients who have been transfused with group A or group B blood. The object of this procedure is to neutralize the alpha and beta agglutinins in the recipient's serum and thus delay the destruction of remaining transfused incompatible cells.

A case is reported in which a group O Rh positive male was given 500 cc. of group A Rh positive blood. The patient made a satisfactory recovery following administration of alkali, group O blood and 40 cc. of a solution of A and B factors.

L. E. Y.
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LEUCOCYTES AND LEUCOCYTIC DISEASE

ALEUKEMIC MYELOSIS. CHRONIC NONLEUKEMIC MYELOSIS, AGNOCIC MYELOID METAPLASIA, OSTEOCLERO-

515, LEUKO-ERYTHROBLASTIC ANEMIA AND SYNONYMOUS DESIGNATIONS. E. L. Heller, M. G. Lewisohn

and W. E. Palm. From Department of Pathology, University of Pittsburgh and the Presbyterian


It is well known that patients with myelogenous leukemia may differ markedly from one another

with respect to their quantitative as well as their qualitative blood pictures. There has been a question

as to whether or not some cases are permanently aleukemic. The present article reviews the literature and

offers 3 new cases in support of the thesis that there is a disease, aleukemic myelosis, which is funda-

mentally leukemic in nature. The peripheral blood may contain immature myeloid cells but not in the

same degree as a frank leukemia. On the other hand, it may not present a leukemoid reaction. Tissue

responses in these patients have been interpreted to indicate a local origin of leukemic cells from the

reticulo-endothelial system rather than a metastatic one.

O. P. J.

THE FURTHER EFFECT OF LEUKOCYTOSIS-PROMOTING FACTOR OF EXUDATES WHEN INJECTED IN CONNECTION

WITH INFLAMMATION. V. Menkin. From Chase Foundation for Cancer Research, Temple University


This is a continuation of the many studies on inflammation which the author has been conducting in

recent years. When dogs were caused to develop acute pleurisy by intrapleural injections of turpentine,

the leukocyte count returned to normal in about one day. The leukocyte count responded in a similar

manner when single intravascular injections of leukocytosis-promoting factor were administered to

healthy dogs. But when leukocytosis-promoting factor was administered to dogs with an acute pleurisy,

the leukocyte count reached a higher level and remained there for about nine days. The clinical implica-

tions are that natural leukocytosis might be re-enforced even during antibiotic therapy.

O. P. J.

GLYCOGEN CONTENT OF ISOLATED WHITE BLOOD CELLS IN GLYCOGEN STORAGE DISEASE. R. Wagner. From

The Boston Floating Hospital and the Department of Pediatrics, Tufts College Medical School,


The glycogen concentration in whole blood, plasma, red cells, and in isolated leukocytes was deter-

mined repeatedly in a case of the hepatic form of glycogen storage disease (von Gierke’s disease). In no

case could glycogen be demonstrated in the erythrocytes. Glycogen determinations in whole blood were

considered unsatisfactory technically and of limited diagnostic value. In contrast to the plasma of normal

persons, which was always found free of glycogen, the plasma in the case described contained 8.7 to 15.6

mg. per 100 cc. Determinations of glycogen in isolated leukocytes were considered of greatest diagnostic

value. In normal blood the granulated white cell, which is the only carrier of glycogen, was calculated

to contain this substance in an average concentration of 4.13 micrograms per million cells. In the case of

glycogen storage disease studied, the range of glycogen concentration per million adult polymorphonu-

clear cells was 1.7 to 7.4 times greater than in normal leukocytes. Evidence is cited that granulocytes are

incorporated in the system of tissues serving carbohydrate metabolism.

L. E. Y.

THE EFFECT OF AGE ON THE LEUKOCYTE COUNT. A COMPARISON OF WHITE BLOOD CELL COUNTS IN AGED

AND YOUNG INDIVIDUALS, WITH SPECIAL REFERENCE TO THE RESPONSE TO INFECTION. W. R. Gilbert,

L. W. Hextall, and G. T. Harrell. From the Bowman Gray School of Medicine, Winston-Salem. Geria-

trics 2: 96-100, 1947.

Since aging results in a deterioration of various systems of the body, a wearing-out process might be

expected in the bone-marrow with resultant changes in the values of the circulating blood elements.

It might also be expected that changes in the white blood cells might interfere with the anti-infective

powers of the patients. This article reports hematologic studies on hospitalized patients of various ages,

with analysis of the counts for various age groups.

It was found that the mean white blood count was the same at various ages from 20 to 49 as after the
age of 50 years. It was found also that the response of the white cell count to infection was the same in all decades. These negative results suggest that there is little "wearing-out" of the hematopoietic system in the course of the usual adult life.

S. E.


Although Downey and his associates have divided the leukocytoid lymphocytes found in infectious mononucleosis into three main types, it has long been recognized that there is considerable pleomorphism within a given category. The qualitative blood picture not only varies among individuals but also within a given patient, depending upon the severity and stage of the disease. In like manner, the clinical features of this disease have been characterized as protean. The present article deals with the autopsy findings in a 23 year old American Army Air Forces pilot, who was killed in an accident following a previous acute illness. The diagnosis was established by the clinical picture, hematologic findings and strongly positive heterophil antibody tests. At autopsy focal cellular infiltrations were found in the liver, kidneys, heart, lungs, adrenals, testes and brain. From this it became apparent that infectious mononucleosis is a generalized disease with changes in almost every organ in the body.

O. P. J.


An additional case of rupture of the enlarged spleen of infectious mononucleosis is reported. The patient was a 25 year old man whose immediate complaints were headache, malaise, weakness, sore throat, and upper abdominal pain. Before admission to the hospital, the patient had sudden agonizing left upper quadrant pain followed by fainting; and several days later developed tenderness and rigidity in the left upper quadrant, pain in the left shoulder, and signs of consolidation or fluid at the left chest. The liver and spleen were not palpable. A blood count was normal. Exploration revealed 1500 cc. of free blood in the abdomen; and two lacerations of the spleen with corresponding subcapsular hematomata. The spleen showed only hyperplasia (weight 695 grams). Blood studies showed abnormal cells on only one occasion, but the heterophile antibody test was positive in a dilution of 1:48 six days after operation. The patient did well.

The authors note that 12 cases of such rupture have been reported from 1944 to 1946.

S. E.

BLOOD COAGULATION AND HEMORRHAGIC DISEASES


Quick's hypothesis that prothrombin is a complex consisting of two substances, prothrombin A and prothrombin B, has been accepted by many workers, although it has been violently negated by others, who believe that "prothrombin A" is merely plasma fibrinogen (E. C. Loomis and W. H. Seegers. Am. J. Physiol. 148: 563-567, 1947). The present authors, working on Quick's hypothesis, found that hypercoagulability in the dog was followed by a reduction in both the A and B components, and that an excess of either could partially compensate for a deficiency in the other.

They therefore studied mixtures of plasmas artificially so modified as to contain large amounts of either prothrombin A or B, respectively. In such mixtures, where from 0 to 100 per cent of the "A" plasma was added to 100 per cent to 0 per cent of the "B" plasma respectively, they found that an increase in the prothrombin time appeared only when the concentration of prothrombin A was over 5 per cent and that of prothrombin B under 50 per cent; or when prothrombin B was over 70 per cent and A less than 10 per cent. In other combinations, the two plasmas were mutually complementary. The conclusion was reached that a given clinical prothrombin time might be the result of varying degrees of deficiency of each complex, but that the exact nature of the abnormality might remain unknown.

These results are open, as the authors realize, to the criticism that the available plasmas must all be...
mixtures of the A and B components, since it is virtually impossible to prepare completely purified substances; and that plasma from several species—dog, rabbit, human—were mixed. They are open to the greater criticism that the Quick hypothesis of two such separate substances is probably incorrect, and that results based on such hypothesis must be explained on other bases. The unitary nature of prothrombin seems in the stage of becoming well established.
of this study, Frédéricq stresses the necessity of opposing the tissue extracts (lipoproteins) to the cephalin (lipoid). They differ on three main points: (1) Tissue extracts act in the same way on glass and paraffined glass, whereas lipoids are nonactive in the presence of paraffin; (2) Intravenous injection of lipoids is harmless, while tissue extracts provoke intravascular clotting; (3) Coagulation of hemophiliac plasma is strongly accelerated by tissue extracts, but hardly affected by lipoids. According to Frédéricq, this discrepancy is explained by the necessity for the lipoids to react with a plasma factor. This factor quickly disappears in stored blood, and is named by Frédéricq "Tryptase"; it is a thermolabile euglobulin, probably identical to the plasma factors described by Widenbauer, Reichel, Leggenhager, Lozner and Taylor, Feissly, etc., and is lacking in hemophilia. It is through this tryptase that the calcium-platelet system, which is not in itself proteolytic, is able to activate the prothrombin. According to Frédéricq, the Quick's time does not only refer to the prothrombin level, but also to the tryptase concentration. To him, the A and B components described by Quick for the prothrombin, are the tryptase (A) and the prothrombin itself (B). The Russell venom, in opposition, is concerned only with prothrombin, being itself proteolytic. This thorough study includes 303 bibliographic references.

A CASE OF PURPURA FULMINANS WITH FIBRINOGENOPENIA IN ASSOCIATION WITH SCARLATINA. H. Dyggse.

The author discusses the history of purpura fulminans first described by Henoch in 1887 and points out that one third to one half of the cases occur after scarlet fever. A number of cases, however, showed no preceding disease. In scarlet fever the purpura generally appears in the second to fourth week of the primary disease, which may be strikingly mild. Hematologic data are usually normal, except for secondary anemia after the bleedings. Blood cultures almost always are negative. The author found a prolonged coagulation time and this has also been noted by another observer.

The case was a boy of 3 years. Scarlet fever was not severe. On the twenty-first day after the beginning of the disease large blood spots appeared after a hot bath. Both legs were swollen and later there was swelling and bluish discoloration of the lumbar region. A coagulation time of 14 minutes, with a small, loose clot later increasing to 30 minutes was the most remarkable hematologic finding. The patient ran a high fever and the hematoma increased. He was treated with two large blood transfusions and vitamin K as the "prothrombin time" was increased. Determinations of fibrinogen were then performed and the very low value of 0.06 grams per cent was noted. Probably the fibrinogen content was still lower before the transfusions. After two further transfusions the condition improved in spite of several abscesses which formed in the hematomata. The antistreptolysin titer increased from 160 to 900. There was continued improvement and an examination nine months later was normal.

This is obviously an instance of the very rare condition, fibrinogenopenia. It should be noted that the patient was first regarded as suffering from hypoprothrombinemia as the Quick test was positive. The poor quality of the clot however led to the correct diagnosis.

Fibrinogenopenia has been noted in 2 cases of purpura fulminans. In one case following chicken pox the patient recovered after large transfusions. The blood remained fluid for two days and the plasma fibrinogen was 0.015. The other case died 14 hours after the bleeding was noted, and there was no previous malady.

Penicillin against the streptococcal infection and large blood transfusions combined with convalescent serum from scarlet fever patients is obviously the treatment of choice.

Another instance of purpura fulminans was lately published by S. Heinild, Acta Paediatrica, 34: 147, 1947.

In this instance there was no previous malady noted in a 3 weeks old child which died in 46 hours from the onset of the disease. Hemolytic streptococci were cultured post mortem from the hematomata, the liver and the ascitic fluid. Penicillin and blood transfusions were not given, nor was plasma fibrinogen determined.


The case is that of a boy 5 years old, who, on the fifty-seventh day after scarlet fever developed typical erythema exudativum multiforme with slight temperature. On the sixty-third day ecchymoses spread over both legs, and small petechiae were noted on the trunk. Hematuria developed. Penicillin and blood
transfusions were given. There were maximally prolonged bleeding, coagulation and prothrombin times, but fibrinogen was not determined. Blood culture was negative. Exitus after three days of purpura. The very long coagulation time seems to indicate that a lack in fibrinogen may have been the cause of the bleeding and makes the importance of large blood transfusions obvious.

A survey of the cases with purpura from the Hospital for Infectious Diseases in Stockholm during the last 15 years showed no other instances of purpura fulminans.

**PURPURA NECROTICA. A POSSIBLE CLINICAL APPLICATION OF THE SHWARTZMAN PHENOMENON. J. H. Sheldon.**


The differential diagnosis of purpuric lesions is often very difficult, especially in children; and if the purpura cannot be readily explained as a symptom of one of the more commonly recognized diseases (leukemia, idiopathic thrombocytopenia, hemophilia) there is a tendency to list it as one of the heterogeneous group known as 'vascular purpura.' From this wastebasket, from time to time, specific subtypes of vascular purpura are collected and reported as entities. Among such more or less definite disorders are pseudohemophilia, Schönlein-Henoch purpura, and purpura simplex. In the present report, Sheldon separates an additional small group of purpuric disease to which he gives the name 'purpura necrotica.'

Three cases are described in girls aged 11 months, 3 years, and 5 years respectively. In each the history was essentially the same: there was a sudden onset of pains in the limbs, sometimes with swelling of the eyelids, hands, feet, knees, and ankles; then easy bruising and severe purpuric eruptions best described as 'hemorrhagic bullae.' The notable feature of these purpurae was their geometric contours: they formed triangles, squares, and linear structures. After two weeks of acute illness, recovery began. During this stage, the lesions became stony hard; then the black overlying skin peeled off to leave healthy granulation tissue; and finally healing occurred by the slow granulation process over a period of from six weeks to two years. The large lesions left tremendous sears which resembled, because of their depth and extent, healed gunshot wounds. The children had no other residua. Little detailed laboratory study was possible. The platelets were normal in the three cases in which they were enumerated. Slight 'secondary' anemia and leukocytosis were present. The bleeding and coagulation times were normal in one case. Cultures of the lesions gave no growth.

Two other similar cases were gathered from the literature by Sheldon, in one of whom splenectomy was followed by death because of sepsis. Sheldon speculates upon the nature of the disorder, and especially upon the curious configuration of the lesions. He notes that several of the angulated lesions occurred in areas of pressure; for example, one large buttock lesion corresponded to the pressure exerted by a pillow upon which the patient had sat for some time; and other smaller lesions were consistent with pressure from wrinkled bedclothes. He points out that, if somehow the area had become sensitized, subsequent prolonged pressure over a period of time might result in severe local tissue damage with accompanying hemorrhage (purpura). In the experimental Shwartzman phenomenon, an intradermal injection is used to sensitize a local area which becomes engorged and necrotic after a subsequent systemic (intravenous) injection. In the present disease, according to Sheldon, it is possible that the angioneurotic edema and periarticular swelling seen early in the course may sensitize the tissue cells which, upon pressure by bedclothes, chairs, etc., break down in geometric patterns with the resulting curious picture of purpura. This concept, of course, does not explain the fundamental nature of the disorder, which Sheldon believes is probably an allergic purpura, the subsequent peculiarities being the result of the Shwartzman-like phenomena.

**CONGENITAL THROMBOCYTOPENIC PURPURA. J. Tulmadge and B. Berman.** From the Pediatric Service, St. Louis City Hospital, St. Louis, Missouri. J. Pediat. 30: 691-695, 1947.

Thrombocytopenic purpura, developing in the neonatal period, is reported in three successive offspring of a mother with idiopathic thrombocytopenic purpura treated with complete relief by splenectomy three years prior to the first pregnancy. No observations are recorded pertaining to the course of her hemorrhagic diathesis following splenectomy, apart from prenatal examinations when she constantly exhibited
marked thrombopenia, prolongation of the bleeding time and, during the latter months of the first and third pregnancies, the recurrence of spontaneous bleeding. The three infants exhibited at birth a profound thrombocytopenia and associated manifestations of the disease, spontaneous recovery proceeding in each instance from the third to sixth week post partum and becoming complete within two months.

C. P. E.


Microscopic observations were made under relatively physiologic conditions of the mesenteric capillary bed in normal and scorbutic guinea pigs. The size of the capillaries, the nature of the capillary wall, the status of capillary blood flow, the occurrence of petechiae, and the effects of trauma and of adrenalin were studied.

Scurvy was found to be associated with certain definite abnormalities of the capillaries, especially a dilated peripheral vascular system and a slowing of blood flow. The small arterioles and the precapillary sphincters were found to be unresponsive to adrenalin. Atony and sluggish flow of the venules were marked. No petechiae were present in either the normal or the scorbutic animals, but slight traumata frequently produced petechiae in the guinea pigs with scurvy, but rarely in normals.

Scurvy, therefore, resulted in a decreased responsiveness of the contractile elements of the peripheral blood system; and in dilatation and engorgement of the small venules. The means by which the vascular hypotonia is produced is discussed by the authors, who speculate on the possible implication of the adrenal glands (it is known that the ascorbic acid content of the adrenal glands is low in scurvy, and that a reduction in ascorbic acid results in a depression of the activity of the adrenal cortex). The vascular atony, by allowing sluggishness of blood flow and therefore engorgement, may allow the vascular hemorrhages which are characteristic of scurvy.

S. E.
ABSTRACTS