ABSTRACTS

JOSEPH F. ROSS, M.D., Editor

ABSTRACTS

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ERYTHROCYTE PHYSIOLOGY


This study is concerned with the use of glucose carbon by the erythrocytes for the formation of lactic acid, carbon dioxide, cell polymers, and the pool of metabolic intermediates. The latter was divided into a study of phosphorus, glucose, fructose, adenosine, triose, pentose, and pyridine nucleotide, and from these analyses an estimation was made of a number of known carbohydrate intermediates and coenzymes.

After a period of incubation with C\textsuperscript{14}-labeled glucose, human red blood cells were fractionated to determine the pathways of metabolism and the nature of the cell permanent pool of carbohydrate intermediates. Although lactic acid was formed equivalent in quantity to the glucose used, the time of incubation was such that only 50 per cent of the lactic acid carbon was derived from glucose, the remainder coming from the nonlabeled carbohydrate storage mixture of the cell which, in turn, was replaced by labeled carbons from glucose.

Essentially negative activity appeared in the trichloroacetic acid insolubles emphasizing the red cell's lack of capacity for protein or fat synthesis.

Slightly less than 1 per cent of the glucose carbon went to carbon dioxide, and it was calculated that this was probably due to contaminating reticulocytes and leukocytes rather than a demonstration of any real respiratory capacity of the mature red cell.

The entry of C\textsuperscript{14} into other metabolic components of the erythrocyte was investigated and discussed.—T.R.T.


In the previous paper the authors reported a survey of the trichloroacetic acid (TCA) extractable components of the human erythrocyte, in particular those which can be related to carbohydrate metabolism. The TCA-soluble components were divided into fractions depending on the solubilities of their barium salts. This report concerns itself with the chromatographic separation of the barium insoluble compounds and demonstrates by radioassay the extent of their participation as intermediates in glucose breakdown. The phosphoglycerates showed a high turnover rate with glucose carbon, adenosine none, and ribose-5-phosphate possibly a trace.—T.R.T.


196
ABSTRACTS

The incentive for this study was the fact that ionizing radiation was known to affect certain enzymes concerned in the glycolytic scheme and in the Kreb's cycle, and since radioactive phosphorus ($^{32}P$) might have varying degrees of uptake by erythrocytes after such exposure, a measure of normal $^{32}P$ uptake was sought.

The amount of $^{32}P$ taken up by erythrocytes in vitro was noted to be influenced by such factors as: (1) length of time, temperature, and medium of suspension prior to incubation with $^{32}P$; and (2) length of time, temperature, and mixing of the suspension during incubation. When these factors are held constant the intrinsic factors which affect the erythrocyte $^{32}P$ uptake are the quantity of $^{32}P$ added, the total volume of the suspension, and the volume of erythrocytes in the suspension. This has been expressed as an equation $K = \frac{D}{U} \left( \frac{V_i}{V_t} \right)$, where $U$ is the uptake in the red cell mass, $D$ is the incubated dose of $^{32}P$, $V_t$ is the total suspension volume, and $V_i$ is the volume of the packed red cells. $K$ represents the affinity of red cells for $^{32}P$ under standard conditions.

This formula was subjected to extensive experimental confirmation.

Suspensions of red cells were subjected to ionizing radiation from a 250 KV machine, using total doses of from 20,000 to 100,000 r. No significant change in $K$ was found.

A wide variety of clinical conditions was investigated and no variation in $K$ found.

The effects of erythrocyte storage were studied by the somewhat artificial means of adding heparinized blood samples to varying concentrations of glucose in saline. These mixtures were then stored for 29 hours at 5 C., at 25 C., and at 37 C.; and for 72 hours at 37 C. They were then brought to 37 C., $^{32}P$ added, and incubated for 2 hours at 37 C. The greatest effect of increasing glucose concentration was observed at 5 C., and the highest $K$ values irrespective of glucose concentration were observed at 5 C. The authors suggest that these findings may parallel those with a Warburg apparatus, and indicate that this might be a simpler tool for studying methods of blood preservation from the point of view of metabolic activity.—T.R.T.


Stroma-free hemolysates prepared from blood of patients with typical sickle-cell anemia often reveal, on electrophoretic analysis, the presence of S (sickle-cell) hemoglobin, and also a second component in amounts of from 5 to 20 per cent. This latter component has a mobility slightly slower than S hemoglobin but identical with that of normal adult (type A—previously called type N) hemoglobin. Fetal (type F) hemoglobin has the same mobility as the A pigment.

F hemoglobin can be distinguished from A hemoglobin by its increased resistance to alkali denaturation, and this method has shown that blood of patients with sickle-cell anemia contains from 2 to 24 per cent of F hemoglobin.

The present study was designed to determine whether or not the non-S hemoglobin fraction is solely composed of the alkali resistant compound or contains a mixture of A and F hemoglobin. It was shown by means of a comparative study using electrophoresis and alkali denaturation that the non-S fraction is composed almost entirely of the alkali resistant (F) hemoglobin. Whether or not small amounts of A hemoglobin also exist in this fraction could not be definitely decided due to the relative insensitivity of the methods. For practical purposes the quantity of S hemoglobin in typical sickle-cell anemia hemolysates may be expressed as the difference between the total hemoglobin and the percentage of the F pigment.

That atypical cases may exist is given additional support by studies of two atypical cases whose bloods contain relatively large amounts of A and F pigments, in addition to S hemoglobin.—T.R.T.

Since streptolysin O may play an important role in lethal intoxications resulting from inoculation with streptococcal filtrates, red cells of some common laboratory animals were studied to find out how far their resistance differed to its lytic action. Further, because of certain similarities between the modes of action of streptolysin O and saponin, notably their common neutralizability by cholesterol, comparable resistances were determined for both lytic agents. Although cells from seventeen species of animals can be lysed by both agents, mouse cells were found to be exceptionally resistant to streptolysin O.


This is a report of studies to determine (1) the nature of the combination of NaCr\textsuperscript{51}O\textsubscript{4} with the red cell; (2) the effect of the chromate on the cell, (3) the rate of elution of Cr\textsuperscript{51} from the cells, and (4) the normal apparent survival curves.

It was first noted that better labeling of cells was obtained in ACD than in heparin. Labeled cells were hemolyzed and stroma separated by repeated filtration through a Sietz filter; 22 per cent of the Cr\textsuperscript{51} was found on the washed stroma and 78 per cent in the hemoglobin solution. From the latter it was determined that the globin fraction contained 70 per cent of the Cr\textsuperscript{51} of the original solution.

The effect of chromate on mechanical fragility was investigated and it was found that 30 \(\mu\text{g}\) of chromium metal per ml. caused no increase in mechanical fragility.

Labeled washed red cells in 50 per cent suspension were dialyzed for 14 days against normal saline. The rate of elution of Cr\textsuperscript{51} was 1.009 per cent per day or a half time of seventy-five to eighty days.

The Cr\textsuperscript{51} labeling method was studied in fourteen normal subjects using three experimental conditions: (a) labeled group O blood in group A recipients; (b) labeled genotype-specific blood in compatible recipients; (c) the individual's own cells labeled and reinjected. In group a the apparent half survival time of blood labeled in ACD was twenty-nine, twenty-six, and twenty-five days. In group b the blood was drawn into heparin for labeling and the apparent half survival time was thirty-nine, thirty-five, thirty-four, thirty-eight, and thirty days. In group c the same anticoagulant was used and the results were thirty, thirty-three, thirty, thirty, and thirty-three days.

These times are shorter than the values obtained using the Ashby, or other isotope technics where one measures the actual rate of disappearance of individual cells of a mixed population of normal age distribution, but it appears that the Cr\textsuperscript{51} method, if corrected for elution of Cr\textsuperscript{51}, actually measures survival time.

It is believed by the authors that the method outlined is useful in normal or abnormal subjects.


1. Red Cells Labeled with Cr\textsuperscript{51} have been used to measure the apparent half survival time in patients with lymphatic leukemia, myeloid metaplasia, acquired hemolytic anemia, and primary aplastic anemia.

2. The Cr\textsuperscript{51} method provided a quantitative expression of the rate of blood destruction in frank hemolytic states which was in agreement with clinical judgment based on the usual laboratory procedures.
3. In one case of lymphatic leukemia, one of myeloid metaplasia, and one with chronic regional ileitis, the Cr\textsuperscript{41} method demonstrated the existence of a state of abnormal blood destruction which had not been suspected.—T.R.T.


Erythrocytes in vivo and in vitro may be rapidly labeled with p-iodophenylhydroxylamine containing radioactive iodine. This compound has a remarkable affinity for hemoglobin and rapidly penetrates red cells to combine with the cell pigment. The reaction seems to be irreversible as long as the hemo molecule remains intact.

In the rat, mouse, and dog, labeled red cells were rapidly absorbed from the peritoneal cavity. In the cat, about 10 per cent of the radioactivity administered as cells by the intraperitoneal route appeared in the urine within twenty-four hours and a similar quantity of activity was found in the spleen.—R.H.G.


In the cord blood of the human fetus the normal adult level of hemoglobin (14.8 Gm. per 100 ml.) is reached by the twenty-third to the twenty-fifth weeks. In most cases the hemoglobin remains at this level until the thirty-sixth week, and in some the forty-first week. A study of oxygen content and saturation in relation to hemoglobin readings shows that high oxygen levels are found only where the hemoglobin reading is at or about 14.8 Gm. The authors consider that the normal hemoglobin level of the cord blood should be 14.8 Gm. per 100 ml. and the red cell count about 4,000,000 per cu. mm. The rise in hemoglobin levels above 14.8 Gm. per 100 ml. in late pregnancy is taken to be a response of the fetus to a falling oxygen supply, and the higher the hemoglobin the more intrauterine anoxia there has been before the onset of labor. In pre-eclampsia and some other pathologic conditions of pregnancy a low oxygen content in the blood of the umbilical vessels is associated with an abnormal increase in hemoglobin and red cell figures.—R.H.G.

**PLATELETS and PLATELET DISEASE**


In the course of a review of modern work on the pathogenesis and discussion of various therapeutic measures in idiopathic thrombocytopenic purpura the authors tabulate the differences between the acute and chronic forms and prepare a comparative classification of idiopathic thrombocytopenic purpura and hemolytic anemia.

Intrinsic abnormalities may be hereditary or acquired. Hereditary abnormalities in hemolytic anemia include spherocytosis, leptocytosis and drepanocytosis; in idiopathic thrombocytopenic purpura they are thrombocytopenic purpura and thrombo-asthenia. Acquired intrinsic abnormalities include, in hemolytic anemia, the conditions paroxysmal nocturnal hemoglobinuria and pernicious anemia. Thrombocytopenic thrombocytopenic purpura may be an acquired disorder.

Extrinsic disturbances may occur in the hemolytic anemias and in idiopathic thrombocytopenic purpura. In the latter they may be autoimmune, hyperplenic, or perhaps bacterial or viral.

Combined types include autoimmune thrombocytopenia with hemolytic anemia and thrombotic thrombocytopenic purpura.—R.H.G.
ABSTRACTS


The authors reiterate the knowledge that splenectomy has not been uniformly successful in idiopathic thrombocytopenic purpura (ITP), and that ACTH and cortisone are capable of producing varying degrees of remission or symptomatic relief. They then state that the most consistent effect of these hormones has been reduction in capillary fragility with subsequent relief of hemorrhagic manifestations.

Seven patients with ITP, one of whom also had acquired hemolytic anemia, were studied. In addition to platelet counts, clot retraction and prothrombin utilization were also measured, but results correlated so closely with platelet counts that the authors did not include these data.

The main point that the authors wish to make appears to be that ACTH or cortisone improved vascular fragility in all cases, even if there was no platelet response. As far as the reviewer can tell from the data (in chart form) two of the three cases listed as complete vascular but no platelet response, in actuality may have had a significant platelet response. The one other case had what appears to be a variable or inadequate eosinophile response.

This report re-emphasizes the extreme variability of response of patients with ITP to any form of therapy. Two out of the seven of these cases relapsed after splenectomy, four obtained complete relief, and one had a partial response.—T. R. T.

NEOPLASTIC DISEASES


“With the advent of potent therapeutic agents capable of producing rapid and extensive nuclear destruction, there have been occasional reports of uremia following therapy in patients with lymphoma.” Although there have been fifteen such cases reported, thirteen were in patients with leukemia, and only one in a patient with lymphosarcoma. Two fatal cases of the authors’ led to a survey of this problem.

The records of all adult patients with lymphomas who had been admitted during the past ten years were studied to determine the incidence of renal calculi. This included not only lymphomas but also all acute and chronic leukemia and agnostic myeloid metaplasia.) The incidence in this group was compared with that of one hundred patients, chosen at random, with metastatic malignancies being treated by radiation therapy. The former group of two hundred and eighty-three patients contained fifteen cases of proven renal calculus. None of the latter group had calculi.

Five of these fifteen received no therapy other than blood transfusions and antibiotics. The others all received one or more forms of chemotherapy or x-ray therapy.

The authors recommend “maintenance of adequate urinary output, alkalinization of the urine and careful evaluation of renal function before and during therapy.”—T. R. T.


A clinicopathologic classification of the reticuloses is given, with sixteen illustrative case reports. Apart from Hodgkin’s disease, four main groups are recognized. Follicular lymphoreticulosis (Brill-Symmers syndrome) is a condition with a histologic picture in lymph glands and spleen of close-packed lymphoid follicles, usually with pale centers made up of large cells, including reticulum cells. It usually presents with enlarged lymph glands or with an enlarged spleen and evidence of hypersplenism. In lymphoid reticulosis there is uniform proliferation of lymphocytes obliterating normal structure. It presents either as enlarged lymph glands without a leukemia blood picture or enlarged lymph glands with leukemic blood and bone marrow. In giant cell reticulosis the predominating cells are giant multinucleate reticulum cells. The condition usually presents as an acute disease with a rapidly fatal course, either showing as a disease of enlarged lymph glands or as a refractory anemia, usually with splenic enlargement. Reticulum cell reticulosis is char-
ABSTRACTS

A STUDY OF ANTIBODY FORMATION IN PATIENTS WITH MALIGNANT LYMPHOMAS. W. Geller.

The purpose of this study was to confirm a number of previous reports that patients with malignant lymphomas are poor antibody formers.

Type-specific pneumococcus capsular polysaccharide I was used as the antigen. There were three groups of patients: group I, sixteen patients without malignant disease; group II, fourteen patients, nine with lymphosarcoma and five with Hodgkins disease, with no therapy for three months; group III, ten patients, six with Hodgkins disease and four with lymphosarcoma, treated with 0.4 mg. per Kg. of HN2 one to two days prior to receiving the group specific polysaccharide.

Sixty-two per cent of the controls developed significant antibody titers; 14 per cent of the untreated (group II) and 20 per cent of the treated (group III) patients developed significant antibody titers.—T.R.T.


The authors had previously observed that the level of nucleotide in the blood of patients with cancer, lymphoma, and various nonmalignant diseases was within the normal range except in some instances associated with anemia. It was also found that 20 mg. of sodium-5-adenylate given i.m. to normal persons brought about a temporary increase in the level of ATP in the blood without an increase in absolute level of blood nucleotide. This was interpreted to mean that the rise represented the conversion into ATP of nucleotide already present.

The present report concerns a study of fifty-two normal individuals, twenty-nine patients with Hodgkins disease, and nine patients with various other diseases. Injections of (usually) 20 mg. of sodium-5-adenylate were followed by examination of the blood for total purine, adenine as adenylic acid, ADP, and ATP. From 5 to 20 mg. were given to normals.

Ten mg. or more in aqueous solution and 20 mg. or more in gelatine produced, in most normals, a significant elevation above the normal level in blood ATP. Similar doses of aqueous solution produced little or no elevation in ATP in patients with Hodgkins disease, and a few even showed some diminution. Similar findings occurred in patients with carcinoma (3), cirrhosis of the liver (1), rheumatoid arthritis (1), congenital heart disease (1), and syphilitic heart disease (1).—T.R.T.

LYMPH NODE STRUCTURE IN PATIENTS WITH CANCER OF THE BREAST. M. M. Black, S. Kerpe, and F. D. Speer.
From Department of Pathology, N. Y. Medical College, Flower and Fifth Avenue Hospitals, New York, N. Y. Am. J. Path. 28: 505-521, 1953.

A chance observation on CFW mice bearing spontaneous mammary carcinomas showed that when the tumors regressed spontaneously, there was a replacement of the splenic follicular and sinusoidal architecture with sheets of large monocytoid cells. These findings prompted the present study on lymph nodes in human cancer cases to determine whether any association could be found between the microscopic appearance of the nodes and the biologic behavior of the tumor. Axillary lymph nodes from two hundred and twenty-six cases of breast carcinoma were examined, one hundred and twenty of which showed metastatic involvement. The microscopic appearance was evaluated in respect to the degrees of prominence of sinus histiocytosis and secondary follicles and the character of the pulp. Lymph nodes from patients with five year cures showed 3 and 4 plus sinus histiocytosis, whereas those from patients dead in three years did not show the same degree of nodal reactivity—with or without metastases. The reactive appearance of the lymph node is
associated with excellent clinical survivals. The microscopic appearance of the axillary lymph nodes appears to indicate the clinical course more closely than the histologic appearance of the tumor, age of the patient, the presence or absence of axillary metastases, or the stated duration of the tumor prior to surgery.—O.P.J.

STUDIES ON BONE MARROW. I. TUMORAL METASTASIS. R. Pimenta de Mello. From the Oswaldo Cruz Institute, Sao Paolo, Brasil. 0. Hospital 48: 173-177, 1953.

Following the Rohr classification, the author considers three kinds of tumors of B.M.: (1) from B.M. parenchyma (myeloid leukemia, erythroleukemia); (2) from the reticular stroma (myeloma or plasmacytoma); (3) true tumoral metastasis (cancer, sarcoma, hypernephroma). The last group may be divided in three kinds: (a) huge compact cellular mass; (b) micrometastasis; (c) diffuse distributions of tumoral cells. The author describes three cases of tumoral invasion of the B.M. representative of these different types of metastasis. The first case was of Krukenberg tumor, with micrometastasis of neoplastic tissue; the second case was a bronchogenic carcinoma with diffuse distribution of tumor cells in the B.M.; the third was a case of leukosarcoma with a complete substitution of parenchyma by tumor cells. The best technique for the demonstration of B.M. invasion, in the author's experience, is the paraffin inclusion sections.—C.F.M.

Announcement

The University of Minnesota will present a continuation course in Fundamental Advances in Internal Medicine for Internists at the Center for Continuation Study February 15 to 17, 1954. Basic concepts in the fields of infectious disease, gastroenterology, and hematology will be discussed. The faculty will include Dr. Walter Lincoln Palmer, Professor, Department of Medicine, University of Chicago School of Medicine, and Dr. David Shemin, Associate Professor, Department of Biochemistry, Columbia University College of Physicians and Surgeons, New York City. Dr. Shemin will also present the annual Journal-Lancet Lecture on February 16. The course will be presented under the direction of Dr. Cecil J. Watson, Professor and Head, Department of Medicine, and the remainder of the faculty will be made up of members of the University of Minnesota Medical School. Housing accommodations at the Center for Continuation Study will be available for Physicians registering for the course.
ABSTRACTS

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