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RADIATION AND RADIOACTIVE ISOTOPES

MEDICAL APPLICATIONS OF ARTIFICIAL RADIOACTIVE ISOTOPES. K. A. Evelyn. From the Department of Medicine, McGill University, Montreal, Quebec, and the Hypertension Research Committee, Massachusetts General Hospital, Boston, Mass. Canad. M. A. J. 16: 547-554, 1947.

The author presents a remarkably lucid review of some of the fundamental principles pertaining to the medical use of artificial radioactive isotopes. Definitions of the terms "isotope," "radioactivity," "hard ray," "soft ray" and "rate of disintegration" will be particularly helpful to the uninitiated. The uses of the Lauritsen electroscope, Geiger counter and the radio-autograph technic are briefly explained. The present status of tracer research is summarized with especial reference to some of the technical difficulties involved. Characteristics of some of the more important artificial radio-elements are given in easily understood tabular form. Data are included on radio-hydrogen, -carbon, -oxygen and -nitrogen because of their potential value, despite the fact that various difficulties are delaying their widespread use.

Discussion of the use of artificial radio-elements for internal radiation therapy is largely confined to radio-phosphorus and radio-iodine. The health hazards involved in the use of artificial radioactive isotopes are properly emphasized.


This report is a brief, lucid presentation of certain of the fundamental principles in the applications of isotopes in medical investigation and therapy. Isotopes are forms of a given element which have different atomic weights; certain isotopes not only have different weights, but also emit rays of various types, and are, therefore, known as "radioactive" isotopes. The amounts of such substances can be determined by means of the Geiger-Müller counter and similar devices. Artificially radioactive elements can be produced either by use of the cyclotron (which bombards given elements with positively charged nuclear particles) or by means of the uranium pile (which bombards elements with slow, uncharged neutrons). In general, such isotopes have two uses for medicine: (1) for therapeutic irradiation; and (2) for tracer studies of the metabolism of the particular element.

Lawrence tabulates a number of radioactive substances in use in research, and discusses three principal technics used in such studies. (1) In the autoradiographic technic, a tracer dose of a substance is given; tissues are sectioned at various intervals and placed against photographic film; these photographs are then examined to determine which organs have taken up the substance. (2) In the in vitro technic, a radioactive substance is given, and samples of blood, urine, etc., are taken at various intervals and measured for radioactivity. (3) In the in vivo technic, a Geiger counter is placed successively over various parts of the body after administration of a radioactive substance, and the uptake by various organs thus determined. Cobalt, for example, is taken up largely by the liver, and iodine by the thyroid gland.

This article is an excellent brief introduction to the methods and principles of radioactive research in medicine.

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The plutonium project was that section of the Manhattan District which had the specific task of preparing and purifying plutonium for use in atomic bombs, according to the general formula, $U^{235} + \text{neutron} \rightarrow \text{chain reaction}$, which gives a neutron which bombards $U^{235}$ (in the pile) to give plutonium. Studies of the physical, biologic, and clinical effects of irradiation were made throughout the work. It was the task of Jacobson and Marks to study the hematologic data in individuals exposed to irradiation within the "permissible" or "tolerance" range, i.e., up to 0.1 roentgens per day. Some of their results are summarized in this report.

Rabbits, mice, and guinea pigs were exposed to irradiations under conditions meant to duplicate the laboratory exposure which scientists and their assistants received in radiation laboratories. The animals were given whole body chronic exposure to external radiations, in various groups (0.1, 1.1, 2.2, 4.4, and 8.8 roentgens for eight to twenty-four hours daily, six days a week, for over three years). Tolerance doses (0.1 r/day) had no effect on the blood. Doses of 2.2 r/day or more resulted in changes in all 3 species, including lymphocytopenia (the earliest change), anemia, and, in the highest doses, death. No lymphocytosis, eosinophilia, or monocytosis occurred in any species at any dosage levels. It was of interest that, in female mice, ovarian tumors developed in doses of even 0.1 to 1.1 r/day, i.e., in the absence of hematologic changes.

The hematopoietic system of man was found to have the same sensitivity to irradiation as that of the guinea pig and the dog. When exposed to chronic tolerance doses, man sometimes developed leukopenia due to lymphocytopenia, and macrocytic anemia. These changes always disappeared, but in varying intervals of time. All radioisotopes studied produced lymphocytopenia as the first indicator of effect, even in the absence of histologic evidence of changes in the lymphatic tissue of the body (animals). However, as demonstrated in the case of mouse ovarian tumors, pathologic changes might occur in the absence of blood and hematopoietic tissue changes at autopsy.

In studies on laboratory personnel, rarely could peripheral blood changes, notably leukopenia, be attributed to radiation. Both exposed and nonexposed groups often developed similar blood changes from extraneous causes (e.g., rubella). In other words, no blood changes could be found which occurred in the tolerance range of radiation exposure, and it was finally concluded that the appearance of hematologic changes should be considered very serious and indicative, probably, of overexposure beyond tolerance doses.


This report summarizes sixteen years of experience with x-ray therapy in polycythemia vera. Spray irradiation is given with a target distance of 1.5 to 2.5 cm., over a field from neck to knees, a kilovoltage of 100, 0.5 mm. copper and 1.0 mm. aluminum filtration. Daily dosage varies from 10 to 30 r measured in air and the total dose is approximately 300 to 500 r in any one series of treatments divided between anterior and posterior fields. Treatment is stopped if white blood count falls below 6,000.

Twenty-eight cases of polycythemia vera treated in this manner arc reported with a five and one-half year average follow-up. Radiation sickness is minimized in this report. Results obtained compare very favorably with the best results achieved by radioactive phosphorus with remissions of as long as eight years following one course of treatment. One patient developed aplastic anemia. No patients developed leukemia or a leukemoid picture. This latter is of particular interest in view of recent case reports of acute leukemia following radioactive phosphorus treatment.


When suspensions of finely minced rat or rabbit thymi are incubated at 37°C., they undergo certain aging and degenerative processes which are manifested as vacuolar-like structures by dark-field illumination. In similar suspensions irradiated with 1000 r, the development of these structures is accelerated. Irradiation also decreases the number of viable cells as indicated by their resistance to a 1:2000 solution of eosin in Tyrode. Two types of vacuoles were observed in dark-field preparations. The primary ones were either single or multiple, small or large, usually round and clearly outlined. Secondary vacuoles were
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large, dark, and round or oval. Feulgen preparations revealed that the primary vacuoles were intranuclear and that the secondary vacuoles actually represented pyknotic nuclei. When the latter were extruded they behaved as spherical fluid globules immiscible with water. A hypothesis of the action of x-rays on lymphocytes is discussed.

O.P.J.

HEMORRHAGIC DISEASES AND BLOOD COAGULATION


Dogs exposed to 450 units of roentgen radiation over the whole body developed infection and hemorrhage associated with neutropenia, thrombocytopenia and prolonged clotting and bleeding times. The prothrombin time remained normal until about twenty-four hours before death, and the concentrations of calcium, phosphorus and magnesium in the blood were not altered. Actual measurements of fibrinogen were not made, but the formation of clots was interpreted as evidence of the presence of fibrinogen. Delay or absence of clot retraction was related to platelet deficiency. The blood of irradiated animals appeared to gel before an actual clot was formed, and the gelled blood could be reverted to a fluid state if shaken before a solid clot formed.

Toluidine blue and protamine sulfate, substances known to inhibit the action of heparin, restored clotting time to normal and were the only agents effective in arresting hemorrhage in the dogs. Transfusions, vitamin K and vitamin C did not alter the hemorrhagic state. It is concluded that the bleeding tendency of the irradiated dogs was due, at least in large part, to the presence of an anticoagulant whose properties were indistinguishable from those of heparin. The material isolated with difficulty from the blood of the dogs appeared in no way dissimilar from a standard sodium heparin salt, but was classed as "heparin-like" because the exact identity of heparin itself is unknown.

The contention that bleeding was not due to thrombocytopenia alone was supported by the observations (1) that the reduction of platelets did not always coincide with the onset of bleeding, and (2) that toluidine blue and protamine sulfate stopped the tendency to bleed but did not elevate the platelet count.

In connection with this report, the highly beneficial effect of rutin in irradiated dogs described by Rekers and Field (Science 107: 16-17, 1948) is of considerable interest. It appears that loss of vascular integrity may be another factor to be considered in exploring the mechanisms responsible for hemorrhage in irradiated animals.

L.E.Y.


During the course of investigations on the effects of atomic radiations on living tissues, it was found that such ionizing radiations often resulted in multiple petechiae and death of a hemorrhagic diathesis. The reduction in platelets was not the entire answer to the development of the hemorrhagic tendency, for these patients showed, in addition to a reduction in platelets and an increase in bleeding time, a marked prolongation of the coagulation time. Further studies disclosed that the blood often contained an anticoagulant, the nature of which seemed to be heparin, for anti-heparin materials (toluidine blue, protamine) restored the coagulation time to normal both in vivo and in vitro. The return of the coagulation time to normal occurred independently of the platelet level, which usually remained low. Calcium, phosphorus, magnesium, prothrombin time, and fibrin formation were all normal in these cases. Finally, when dogs were exposed to ionizing radiation over the body, their plasma was found to contain an anticoagulant having the activity of heparin.

The mode of production of excessive plasma heparin by body irradiation remains to be determined. In the light of such studies, the reported effect of x-radiation in reducing the coagulation time of the blood of patients with hemophilia (Ostro and Macht, South. M. J. 39: 860-867, 1946) must be held in abeyance until confirmatory evidence is presented. Certainly it would be strange if the hemophilic

The author suggests that a plasma factor is involved in the release of thromboplastin from platelets, and that the factor is deficient in patients with hemophilia. Normal citrated plasmas which coagulated slowly on recalcification were prepared by prolonged centrifugation at 5°C in glassware treated with silicone. Such plasmas were much less effective than ordinary plasmas in correcting the delayed clotting of platelet-free hemophilic plasma, but retained their corrective effect on the coagulation of whole hemophilic blood. After the addition of washed suspensions of platelets, normal or hemophilic, the plasma regularly corrected the coagulation defect of hemophilic plasmas. The platelet suspensions themselves did not do so. It must be concluded, therefore, that the presence in one medium of both platelets and plasma was required for the production of whatever substance was involved in the reduction of hemophilic coagulation time. Brinkhaus prefers to consider that some plasma factor acts upon platelets to release contained thromboplastin. Quick (Fed. Proc. 6: 284, 1947) believes that the platelets release something which activates a thromboplastin-precursor in the plasma. The normalcy of hemophilic platelets is indicated by both their investigations; and the occurrence of some defect in the plasma of hemophilia is now generally accepted. Whether the defect consists of absence of thromboplastin, absence of activator, absence of some unspecified globulin, or excess of heparin still remains to be unequivocally demonstrated.


Only a few isolated cases of intracranial hemorrhage in hemophiliacs have been reported. The following 3 cases of this quite exceptional complication of hemophilia are thus of some interest.

The 3 cases are almost identical. After a minimum amount of trauma (a slight fall on to the head in two cases, and compression of the neck and jugular veins in the third), the downhill course was progressive after an initial symptomless period. In 2 of the cases, there were signs of progressive intracranial hypertension, with increasing headache, somnolence and papillary congestion, together with motor signs and aphasia. The diagnosis was clear. The great problem was treatment.

In all 3 cases, surgical intervention was necessary. Great subdural hematomata composed of liquid blood with numerous clots were found. All 3 patients died despite a transfusion one hour before operation. Intervention was inevitable in all 3 cases because of the onset of coma. The patients died, 2, 2, and 24 hours, respectively, after the operation. In none of the cases were thrombin, fibrin, gelatine or oxyccelulose used.

It is to be regretted that the authors do not give more details of the quantity and number of transfusions, nor of the clotting time, information which would be of great value in ascertaining the exact cause of the operative failures.

QUANTITATIVE STUDIES ON THE COAGULATION DEFECT IN HEMOPHILIA. A. J. Quick. From the Department of Biochemistry, Marquette University School of Medicine, Milwaukee. Fed. Proc. 6: 284, 1947.

The three commonly held theories of the pathogenesis of hemophilia include absence of some factor from hemophilic plasma, presence of some anticoagulant in hemophilic plasma, and poor breakdown of hemophilic platelets to initiate coagulation. Recent studies by Quick tend to reconcile, according to him, the differences between the first and the third of these theories.

Quick found that the serum obtained immediately after hemophilic blood has been allowed to coagulate contains unchanged fibrinogen and virtually as much prothrombin as the original blood. Incubation at 37°C produces coagulation of all the fibrinogen in one hour, but the prothrombin is unchanged (i.e.,
only a small amount of thrombin is formed). Thromboplastin converts the prothrombin of hemophilic blood to thrombin stoichiometrically, not enzymatically. Platelets, however, contain little thromboplastin; when an extract of platelets is added to prothrombin in plasma, little conversion to thrombin occurs. Normal plasma deprived of platelets by centrifugation shows a poor conversion of prothrombin to thrombin; but when such platelet-free plasma is added to hemophilic blood, the prothrombin of this blood is rapidly changed to thrombin and rapid clotting follows. When normal platelet-free plasma is added to hemophilic plasma also low in platelets, little thrombin is formed.

These data signify that thromboplastin may occur in plasma in an inactive form, and Quick believes that the platelets furnish an agent which enzymatically converts this inactive thromboplastin to an active form. Hemophilic platelets behave normally, but hemophilic plasma, according to this work, lacks the inactive thromboplastin, and hence coagulates poorly. Quick feels that the inactive thromboplastin is probably identical with Howell’s plasma thromboplastin and with the anti-hemophilic globulin of the Harvard investigators. The nature of the latter substance has not yet been chemically determined, but its identity with thromboplastin is an interesting, if undemonstrated, suggestion.


Fresh human urine was found to contain thromboplastic substances which act by accelerating the conversion of prothrombin to thrombin. Urine from hemophilic patients was found to have as high or even higher activity in this regard as urine from normal men. The source of this material, and its nature, are not clear; but the authors suggest that it may come from the kidney itself, or may be the product of disintegrated tissue or blood cells cleared from the blood by the kidneys.

THE PROTECTIVE ACTION OF RUTIN AGAINST CAPILLARY INJURY. A. M. Ambrose and F. DeEds.


These workers studied capillary permeability in rabbits by means of intravenous trypan blue injections: the dye accumulates in areas of injury. Capillary injury was produced in the rabbit’s abdominal wall by various agents including chloroform, histamine, and negative pressure. Untreated rabbits were compared with animals who had previously received rutin.

In 12 rabbits to whom rutin had previously been administered, the appearance of trypan blue dye in chloroform-produced wheals was delayed as much as eight times above control, nonrutinized animals. (Dosages and times are not given in this brief report.) Rutin also prevented the appearance of dye after the application of negative pressure to the abdominal skin. These are further data to be added to the rather meager experimental evidence supporting the clinical impression that rutin has a beneficial effect on capillary resistance.

BLOOD LEVELS OF CERTAIN CONSTITUENTS IN NORMAL ADULTS BEFORE AND AFTER INGESTION OF RUTIN. E. Papageorge and F. Adam.

From Emory University, Georgia. Fed. Proc. 6: 283, 1947.

Despite the vague clinical impression that rutin is useful in certain patients with excessive capillary permeability, little objective experimental evidence has been presented to confirm this feeling. The authors placed 15 normal adults on a low ascorbic acid diet for four weeks, and then tested them during successive two week intervals with rutin in the absence of ascorbic acid, ascorbic acid without rutin, and both drugs together. The dose of rutin was 100 mg. daily, as was also that of ascorbic acid.

Rutin was found to have no influence on the serum levels of cholesterol, calcium, sodium, or vitamin K. Ascorbic acid levels, although done, were not reported, but they were said to suggest that rutin tends to maintain a high serum level of this substance. The relationship of these findings in the normal individual, to that in the abnormal patient with forms of vascular purpura (in whom rutin may be of value), remains to be found. There is still no agreement on the mode of action of rutin, and little beyond an impression as to whether it is even efficacious.
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The authors studied fibrin formation in solutions of human fibrinogen and thrombin, in the absence of prothrombin and of fibrinolytic materials. They found that the initial rate of coagulation was linearly proportional to the concentrations of thrombin (within certain limits) and fibrinogen. By altering the pH, ionic strength, and chemical composition of the medium, they were able to produce various types of clot structures, including a clot which was coarse and readily contractile, and a clot which was translucent and friable.

SE.


A technic is described for preparing clots from bovine fibrinogen and thrombin which are suitable for study with the electron microscope. The observations of this report are concerned chiefly with the effects of alterations of pH. It was found that clots are composed of meshworks of single and compound fibers, and that unit fibers have greater diameter and greater tendency for lateral association into compound fibers as the pH is decreased from 8.5 to 6.3. Cross striation of unit fibers was a striking feature of all clots studied. The periodicity of these striae was found to be constant (approximately 10 A) and there was a precise coincidence of striations of unit fibers when these were associated side by side to form compound fibers.

The authors present a cautious discussion of the possible relationship between their observations and the supposed molecular structure of fibrinogen. Excellent photographs are included in the paper.

L.E.Y.


This paper attempts to elucidate the increased coagulability of blood following certain hemolytic episodes. The authors, having found a sharp drop in coagulation time in hemophilic swine immediately after the injection of hemolyzed erythrocytes, determined that the same effect could be obtained by giving acetylphenylhydrazine, thiodiphenylamine, and other hemolytic agents. Analysis revealed that, simultaneous with the reduction in coagulation time, there was a sharp decrease in the fibrinogen, the cell volume, and the amount of prothrombin (sic). For certain agents—notably saponin and sodium oleate—the fall in coagulation time was followed by a negative phase during which the coagulation time was increased above normal despite an increase in fibrinogen. This refractory phase was due to a further decrease in the amount of prothrombin which occurred with these agents.

It is not clear to what the reduction in coagulation time could be attributed. It should be pointed out that, clinically, transfusion reactions, which result in severe intravenous hemolysis, result in a hemorrhagic tendency, rather than the opposite; but presumably this is the result of damage to the endothelial lining of the vascular system.

S.E.

THROMBOPLASTIC FACTORS IN THE ESTIMATION OF PROTHROMBIN CONCENTRATION. C. L. Conley, W. I. Morse, II. From the Department of Medicine, Johns Hopkins University and Hospital, Baltimore, Maryland. Am. J. M. Sc. 215: 158-169, 1948.

The purpose of this study was to determine, by Quick's method, whether prothrombin determinations in which different thromboplastin solutions were used gave comparable results. Rabbit foam emulsion prepared by the authors, two acceptable commercial thromboplastin preparations, and viper venom were employed. Very divergent results were obtained on human hypoprothrombic plasmas when saline dilution curves were used for reference. In dogs, the authors found that barium sulfate-treated plasma behaved more like that of dicumarolized (prothrombin-free) plasma than did plasma treated with aluminum
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Hydroxide. Even with human plasma prepared with barium, discrepancies between various thromboplastins persisted. The authors point out the apparent complexity of the factors involved. This again emphasizes the difficulty in quantitating the prothrombin test and in comparing results of various laboratories using different thromboplastin preparations.

C.A.F.


This case report of a patient whose self medication with "8 or 10" tablets of dicumarol was followed by hematuria, bloody diarrhea, oral bleeding, and multiple ecchymoses, outlines a method of treatment for such cases of excessive dicumarolization. The patient received 150 mg. of vitamin K as "synkayvite" on the first day (17.0 intravenously in two doses, 30 mg. intramuscularly), and 60 mg. of "synkayvite" daily by vein on the second, fourth, and fifth day. Response was prompt and sustained.

S.E.


Bone marrow studies of three cases of idiopathic thrombocytopenic purpura showed an increase in total number and a striking decrease in platelet forming in megakaryocytes. These studies give further confirmation to the previous report of Limanzi and the careful morphologic studies of Dameshek and Miller, and emphasize the importance of sternal puncture in the diagnosis of this form of purpura.

C.A.F.

Two Cases of Thrombocytopenic Purpura Treated with Folic Acid. T. H. Gridley and T. R. Waugh. From the Department of Medicine of the Homeopathic Hospital of Montreal, (Quebec), and the Department of Pathology, McGill University. Canad. M. A. J. 111: 487-488, 1947.

The first patient described was a 52 year old female who had had attacks of purpura for ten years. She was found to have a platelet count of 3000 per cu. mm., a prolonged bleeding time and positive Rumpel-Leede test. Splenectomy was followed by a remission lasting only a few months. Thrombocytopenic purpura again developed and persisted with varying severity for eighteen months. The platelet count rose and bleeding ceased at this time following administration of 10 mg. of folic acid per day. This form of therapy was continued for an additional fourteen months without exacerbation of symptoms. The results in this case of idiopathic thrombocytopenic purpura are considered sufficiently encouraging to justify further clinical trials.

In the second case presented, thrombocytopenic purpura followed administration of bismuth. Since use of this drug was apparently discontinued before folic acid was given, the favorable response described cannot be attributed to folic acid therapy.

L.E.Y.


Intravenous injections of suspension of mouse brain tissue into mice were observed to produce generalized ataxia, clonic convulsions and coma. This reaction was associated with cessation of capillary flow and formation of cell aggregates along with shortening of the coagulation time. The coagulation time then became prolonged and the mice were resistant to toxic doses of the suspension. The factor in tissue suspensions which produced the reaction could be sedimented at 1,000 r.p.m., a procedure which increased its heat stability. The active factor was considered to be thromboplastin and its coagulating effect could be inhibited by heparin and congo red. Incubation with normal rabbit serum was found to be...
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inhibit the activity of the suspensions. The factor in normal serum producing the inhibition was found within the globulin fraction and was thermolabile at 60°C. A second factor, probably calcium alone, was shown to be necessary for the inhibitory activity of serum. These observations are of unusual interest in that they remove the study of blood coagulation from the highly artificial environment of the glass container to in vivo observations. Demonstration of the reversability of coagulation reaction in vivo, at least in its early phases, introduces a new concept.

R.S.E.


The interest of this detailed study lies in the fact that all the 114 cases have been studied with the aid of the same technics over one year. The first part of the article is a critical study of these technics. The hemorrhagic syndromes are then classified according to the results of tests for hemostasis and the stage of hemostasis involved.

The classification was therefore as follows:
1. Involvement of the third, or 'plasma' stage of hemostasis. These are the true disorders of coagulation (e.g.: hemophilia, hypofibrinemia, hypothyrombinemia, anti-coagulants).
2. Disorders of the second, or thrombocyte stage of hemostasis (e.g.: thrombocytopenic purpuras and the very rare thrombasthenias).
3. The purpuras without thrombocytopenia but with abnormal results for one test (e.g.: bleeding-time or capillary resistance).
4. Hemorrhagic syndromes in which all the tests for hemostasis are normal. (e.g.: allergic purpuras, dermatologic purpuras, and hemorrhagic syndromes without purpura).
5. Unclassifiable syndromes of the Banti type in which many hemostatic factors are involved.

The article ends with some therapeutic applications, in particular the necessity of studying the megaloblasts in the marrow before every splenectomy, and the importance of neuro-endocrine factors in the involvement of the first or 'parietal' stage of hemostasis.

J.P.S.

FUNDAMENTAL WORKING CONCEPTS IN THE STUDY AND MANAGEMENT OF PATIENTS WITH ABNORMAL BLEEDING. L. M. Tocantins. From the Department of Medicine, Jefferson Medical College and Hospital, Philadelphia, Pa. Amer. Practitioner 2: 479-485, 1948.

This paper elaborates on the thesis that abnormal bleeding results from an upset in the balance between hemostatic functions and forces exerting stresses on the vessels. The various extrinsic (physical and chemical trauma) and intrinsic (muscular contractions, blood pressure, etc.) forces which are often disregarded by the practitioner, are enumerated and their importance with respect to diagnosis and treatment is emphasized. The use of splints and elastic bandages in the management of bleeding in hemophiliacs is illustrated, and the necessity for minimizing surgical trauma in these patients is stressed.

J.P.S.


This is a discussion of the etiologic factors of the hemorrhage in Banti's syndrome, based upon a study of 22 patients in whom the diagnosis was made. All 22 patients had various forms of hemorrhage, of which hematemesis and melena were most common (17 patients). It is pointed out that the spleen may shrink with acute hemorrhage, so that it is not palpable on admission of the patient to the hospital, but becomes palpable only several days (as long as ten days) later. The periodicity of episodes of hemorrhage is considered to be due to a cycle of (1) gradual increase in portal hypertension, which gives rise to (2) rupture of vessels (esophageal, gastric, hemorrhoidal), which results in (3) hemorrhage, giving (4) decompression, which ultimately gives rise to (5) another increase in portal tension, etc. The actual
causes of bleeding are (1) varices of the esophageal and rectal veins, with weakening of the vein walls; (2) thinning of the mucosa overlying these veins; (3) thrombocytopenia; (4) hypoprothrombinemia due to hepatic damage. Treatment in such cases includes the use of transfusions, vitamin K, bed rest, and pressure at the site of bleeding, if necessary. Splenectomy was performed in 9 of the 11 patients, with improvement and long survivals in most.

S.E.


Investigations of the effect of penicillin on the coagulation time are somewhat confused at the present time. Moldovsky and his co-workers (Science 102: 38, 1945) first pointed out that the parenteral or oral administration of penicillin to normal subjects was followed by a marked fall in the coagulation time of the blood. The degree of reduction was inversely correlated with the level of penicillin in the blood, but the effect persisted after penicillin was no longer demonstrable in the blood. Hines and Kessler, on the other hand (J.A.M.A. 128: 744, 1945) found that penicillin sometimes aggravated the effect of heparin (i.e., tended to increase the coagulation time) in certain patients.

Macht, in this report, found a reduction in the coagulation time of patients receiving parenteral penicillin (or streptomycin), but was unable to find such an effect in patients with hemophilia. Some 100 studies were therefore carried out on rabbits and cats, which showed a shortening of the coagulation time after the injection of penicillin. Penicillin acted within thirty minutes to cause a reduction of the coagulation time, and continued to act for several hours. Penicillin X was found the most potent in this regard; penicillin F, weakest; and penicillins K and G, intermediate. (See also Macht, Science 105: 313-314, 1947.)

Clinical significance of these findings must await evaluation of these and contradictory results, especially those of Fleming and Fish (Brit. M. J. 2: 241, 1947). These authors found that a concentration of penicillin as little as 140 units per cc. increased the coagulation time of blood, and 13,000 units per cc. might result in incoagulability. They were led to their investigations by the finding that apicectomy, a dental procedure which requires good local coagulation of blood for its efficacy, was being hampered by lack of coagulation in patients who had had penicillin powder instilled into the wound. They suggest, therefore, that penicillin not be used locally if coagulation is important; but comment that the parenteral use of penicillin, which results in small unitage of the drug in the blood, has no effect on the coagulation time.

S.E.


The author reports the combination of Henoch-Schönlein purpura and intestinal intussusception in a 5 year old child. Four days before admission to the hospital, the patient suddenly developed migrating polyarthritis, involving successively the knee, the elbow and the wrist; and then complained of severe abdominal pain and purpuric spots on the buttocks and arms. On physical examination, in addition, a mass was felt in the right iliac fossa. Blood studies showed no thrombocytopenia; and bleeding time, coagulation time, and tourniquet tests were negative. At exploratory operation, an ileo-ileal intussusception was found and repaired. The boy subsequently recovered completely, except for a single attack of abdominal pain plus bloody stool six months after operation.

There are nineteen previous reports in the literature of intestinal intussusception in association with Henoch-Schönlein purpura. Sixteen of the total of 20 cases occurred in males; but both Henoch-Schönlein purpura itself, and intestinal intussusception without purpura, are more common in males than in females. Joint pains were present in 11 of 17 reported cases, and purpura was present in all 20.

The coincidence of the two conditions—intussusception and purpura—is too great to be accounted for by chance. The author considers explanations for this coincidence, and notes that it is probable that extravasation of blood occurs into the various coats of the small intestine, the resulting mass of submucosal blood favoring intussusception. Recovery from this complication occurred in 12 of the 20 cases in the literature, either spontaneously or following operative interference. The causes for the purpura,
which is supposed to be allergenic, remain obscure; in this case, there was no evidence in family or patient for allergy.

S.E.

LEUKOCYTES AND LEUKOCYTIC DISEASE

EXPERIMENTAL ATTEMPTS TO TRANSMIT INFECTIOUS MONONUCLEOSIS TO MAN. A. S. Evans. From the Section of Preventive Medicine, Yale University School of Medicine, New Haven, Conn. Yale J. Biol. & Med. 20: 1926, 1947.

Twenty-one experiments with human volunteers were carried out in an attempt to transmit infectious mononucleosis by means of serum, whole blood and throat washings. Transitory symptoms consisting of pharyngitis, lymphadenopathy and lymphocytosis with atypical cells appeared in a few subjects, but in no instance did an unequivocal example of the disease develop. Failure to transmit the disease may be due to extreme lability of the agent or low degree of susceptibility of the 17 subjects. These results indicate that the refusal of some blood banks to accept individuals who have a past history of mononucleosis is overcautious.

R.S.E.


Nearly all of the important aspects of infectious mononucleosis are discussed briefly in this up-to-date review with well-chosen bibliography. Of particular interest are the references to jaundice, thrombocytopenia, recently reported autopsy and biopsy findings and experimental transmission of the disease.

L.E.Y.


The first case is that of a pseudo-phlegmonous throat infection. The finding of Klebs-Loeffler bacilli in the throat, led to the injection of 100,000 units of serum. The general condition was good, the temperature was 39.7°C. The blood count showed 5,620.00 red cells, and 21,000 white cells of which only 50 per cent were polymorphs. On the eighth day of the disease, the movements of respiration began to be obstructed both behind and below the sternum. Respiratory which had been noisy for several days now became more difficult. The dyspnea increased the following day and the patient died suddenly on the ninth day of the disease. Pericardial puncture provided 2.0 cc. of liquid which gave a positive Paul Bunnell reaction. No autopsy was performed.

The second case characterized by the severity of the pharyngeal signs, also caused one to think of diphtheria (the culture was negative). A diagnosis of infectious mononucleosis was made from the blood-count (16,000 leucocytes, of which 42 per cent were polymorphs) and the positive Paul Bunnell reaction. Laryngoscopic examination showed massive hypertrophy of the lingual tonsil which resembled that of the pharyngeal tonsil, and appeared to be responsible for the severe dyspnea.

On the seventh day, the dyspnea increased with obstruction both above and below the sternum. Tracheotomy was performed. The signs disappeared and the tube was removed on the twelfth day. Cure resulted.

The authors attribute the progressive dyspnea to the severity of the pharyngeal signs. It is possible that a neurologic factor plays a part and the torpor of the two patients was intense.

We think that it is interesting to note these observations which, added to the reported cases of rupture of the spleen, show that prognosis should be reserved despite the usual benignity of infectious mononucleosis.

J.P.S.
ABSTRACTS


The author gives a brief review of the literature on acute infectious lymphocytosis and reports the case of a 4 year old girl who appeared to be suffering from this disease. She had vomited, was drowsy, had enlarged tonsils and an injected pharynx, but spleen and lymph nodes were not palpable. The highest white blood cell count was 39,350 at which time there were 69 per cent small lymphocytes. Four days later when the lymphocyte count was the same, there were 8 per cent eosinophils, a finding also noted by others. Tibial marrow showed 12 per cent lymphocytes. Sheep cell agglutination test was negative. The spinal fluid was not examined.

There is an apparent need for studies on the etiologic agent of this disorder.

L.E.Y.


The authors present a study of a very rare affection, observed by Gansslen in 1941 in 4 families. They describe here 3 members of the same family with a permanent leukopenia of between 1,500 and 3,500, with a neutropenia of between 35 and 50 polymorphs, without modification of the Ament count. The red cell and platelet counts (in the case in which these last were estimated) were normal. Nothing abnormal was found clinically, the general state of health was good and the condition was discovered by chance. These subjects did not seem to be particularly prone to infection.

In the case most completely studied by the authors, the myelogram showed 49 per cent of granular cells and 41 per cent of erythroblasts. This defect is transmitted as a dominant non-sex-linked character.

The authors discuss the differential diagnosis between this condition, the splenic neutropenia of Wismann and Doan, the chronic sporadic neutropenias and Fanconi's disease.

One should add that there may be a connection also between this condition and the syndrome recently described by Estren and Dameshek (Am. J. Dis. Child. 73: 671, 1947).

J.P.S.


Six patients with acute leukemia (blasts in the peripheral blood) showed a change in the blood picture to that of chronic leukemia, plus an associated remission in the clinical picture, after the oral ingestion of crude tyrosinase. Details are not given, and no follow-up is reported, beyond the statement that the patients lived from five months to one year after the initial diagnosis of "acute" leukemia.

S.E.


The production of traumatic shock in normal rats was found to be accompanied by a marked relative and absolute lymphocytopenia in the circulating blood. The greater the trauma, it was found, the greater the reduction in lymphocytes. In all cases which survived, however, the lymphocytes had returned to normal with forty-eight hours. When shock was so severe that death ensued, the most severe depression of lymphocytes occurred.

When, however, identical trauma was applied to trauma-resistant rats, it was found that the initial lymphocyte level was higher than in trauma-sensitive rats, the fall in lymphocytes less, and the recovery quicker. The authors believed, therefore, that the degree of resistance could be related to the lymphocyte level after trauma.

These are further studies in line with the general thesis that the lymphocytes and lymphocyte-producing areas of the body are important in the immune mechanisms of the body.

S.E.
ABSTRACTS


The author presents further evidence of a possible relationship between the adrenal cortex and lymphatic leukemia, in line with the studies of White and Dougherty of a reciprocal balance between adrenal cortex and lymphocyte-producing centers of the body. The present work attempts to discover the nature of the anatomic alterations in the adrenals of mice with lymphatic leukemia.

In Furth's AK strain of mice, lymphatic leukemia is associated with an increase in the size of the adrenal glands, but this occurs only in males (38 per cent increase) and not in females (5 per cent increase). Levin analyzed the adrenals, and found that in all mice, male and female, with lymphatic leukemia, the concentration of the cholesterol in the adrenal was lower after leukemia (3.64 per cent) than before leukemia develops (4.78 per cent). He found too that injection of pituitary adrenocorticotropic hormone did not affect the course of the disease or the alterations in the adrenals, even though it was given from the time of transmission of leukemic cells. Attempts to study the excretion of 17-ketosteroids in clinical patients with lymphatic leukemia, in order to test their adrenal cortical activity, yielded equivocal results.

These results suggested that there might well be a relationship between the adrenal and lymphatic leukemia, although they did not prove such a relationship.

S.E.


Records of 262 patients with Hodgkin's disease were reviewed for evidence of their ability to form antibodies. Only 1 of 38 patients showed a positive tuberculin in contrast to an expected frequency of 50 per cent. There was likewise a low incidence of positive serologic tests for syphilis and apparent inability to make antibodies against Brucella and typhoid vaccine.

The authors feel that this immunologic deficiency is attributable to the damage to the reticuloendothelial system by the disease, and that this explains the susceptibility of these patients to bacterial infection.

C. A. F.


The author presents a brief review of the newer concepts of hormonal factors concerned in immunity, a field in which he and his associates have made important contributions. Particular reference is made to the effects of adrenal cortical steroids in stimulating the development of phagocytic cells in lymphoid structures and in accelerating the release of gamma globulin from lymphocytes. It is further pointed out that these steroids may produce an elevation of antibody titre either in a hyperimmunized animal or in a previously immunized animal with no circulating antibody. Such observations suggest to the author that pituitary-adrenal cortical control of lymphocyte structure and function may play an important role in anamnestic responses and may explain why various unrelated stimuli produce these responses. It is acknowledged, however, that antibody production does not cease in adrenalectomized animals and that other recent experiments make it clear that much remains to be learned concerning the relation of adrenals and other endocrine glands to immunity.

L. E. Y.


This is one of a series of articles (in the same publication) comprising a symposium on the use of several derivatives of folic acid in neoplastic diseases. Other articles discuss the chemistry and synthesis of "anti-folic" compounds, and their employment in carcinoma, sarcoma, lymphoma, and Rous.
chicken sarcoma. The present report discusses experience with such compounds in chronic and acute leukemia, and multiple myeloma.

Several different compounds were used. 'Teropterin' or pteroyl-diglutamyl-glutamic acid was used without effect on blood, bone marrow, liver, spleen, or lymph nodes, in 2 cases of multiple myeloma, 2 cases of chronic myelogenous leukemia, and 7 cases of chronic lymphatic leukemia. In an additional patient with acute ('lymphoblastic') leukemia, however, there was a fall in the number of white cells and blasts in the peripheral blood, a reduction in the percentage of blasts in the marrow with a corresponding increase in mature lymphocytes, and some transient clinical improvement. There was rapid relapse, however, and death.

'Diopterin' (pteroyldiglutamic acid) had a similar effect in one other patient with acute lymphoblastic leukemia.

Five further cases of acute leukemia were treated with two other derivatives of folic acid, which have anti-folic-acid activity in bioassays: pteroyl-aspartic acid and methyl-folic acid. Similar results were noted in all these cases; namely, a reduction in the total white count in the peripheral blood, a reduction in the percentage of blasts, and a tendency for similar changes within the bone marrow. All these effects were transient, although their importance is suggested by the author’s comment that the possibility that their occurrence was spontaneous, rather than related to the medication, was, according to his experience, negligible.

Regardless of hematologic effect, all treated patients, both in this and the other series (carcinoma, sarcoma, myeloma), felt clinically much improved. It was suggested by Gellhorn, in a discussion of this paper, that this effect was not specific and might be related to the known feeling of well-being following the use of glutamic acid in mental disorders. This discusser emphasized, too, that the results reported were fragmentary and not necessarily attributable to the various drugs utilized. They are at least, however, suggestive, and further reports will prove of interest.

S. E.

**TRANSFUSION JAUNDICE**


The authors investigated the incidence of homologous serum jaundice in patients who were given plasma for therapeutic purposes, and the incidence of plasma transfusions in patients whose death was wholly or partly attributed to ‘hepatitis.’ No attempt was made to make a complete survey of each case, but the study was done in such a way as to give more or less minimum incidence value. The site of study was New York State, exclusive of New York City, and the time, apparently, was 1946-7.

Of 649 patients who received dried pooled plasma, hepatitis subsequently occurred in 2.9 (4.5 per cent). A statistically significant variation occurred with age: 8.7 per cent of 351 patients over 50 developed hepatitis; 2.2 per cent of 193 aged 10 to 50; and none of 78 aged under 10. No jaundice occurred in 1,597 household contacts of the recipients of the plasma, including 66 contacts of jaundiced patients. Calculated on the basis of an estimated 15,000 persons receiving plasma per year in the area involved, a yearly figure of some 675 cases of hepatitis might be anticipated. It was impossible to determine which lots of plasma might have been responsible, although a minimum figure of 4.7 per cent of all the lots used was calculated to have been icterogenic.

Of 51 deaths due to acute hepatitis, 15 patients (30 per cent) had received transfusions in the six months preceding death. Of these, 12 had received only plasma, 1 had received both plasma and blood, and only 2 had received only blood. American Red Cross dried pooled plasma was used in these cases, as well as in the entire study.

Granted incompleteness of the investigation, the results presented seem to give minimum values for icterogenicity of pooled-plasma lots. The authors suggest two methods of dealing with the situation: (1) ultraviolet irradiation of plasma as part of its processing; and (2) substitution of albumin, which can be heated to destroy the virus before distribution, for whole plasma.

S. E.