NEWS & VIEWS

A REVIEW OF THE CONFERENCE ON HEMATOPOIETIC MECHANISMS

NEW YORK ACADEMY OF SCIENCES, MAY 1–2, 1958

The mechanisms by which normal leukocyte and erythrocyte levels in the peripheral blood are maintained have received increasing attention in the past few years. The New York Academy's conference on the subject, capably arranged by A. S. Gordon and Walter S. Root, proved a most timely undertaking. It delineated recent rapid progress, revealed large areas of agreement and brought the remaining points of controversy into sharper focus. The papers will appear in full in the Annals of the Academy, but a brief review was thought to be of interest to readers of Blood.

Regulation of normal leukocyte levels was discussed in the light of newer data on the life span of leukocytes. Bierman (City of Hope) and Craddock (UCLA) discussed labelling of white cell DNA with $^{32}$P. Athens, Cartwright and Wintrobe (Univ. of Utah) used diisopropyl fluorophosphonate (DFP) tagged with $^{32}$P as a granulocyte label. The simultaneously labelled platelets and erythrocytes were effectively separated by lysis and differential centrifugation. The use of tritium-labelled thymidine for tagging of cells in the stage of DNA synthesis and the subsequent tracing of the labelled cells by radioautography was described by Patt (Argonne) in dogs, and by Cronkite (Brookhaven) in hematologically normal, terminal cancer patients. The methods which label DNA provide an estimate of minimum maturation times from the last mitosis to the appearance of the mature cells in the peripheral blood. Labelled mature granulocytes appeared in the peripheral blood on the third day and reached a peak within 6 to 8 days. The peak for labelled band forms occurred a day earlier. Labelled medium and large lymphocytes were seen in the peripheral blood in less than 24 hours and reached a plateau on the second and third day in Cronkite's experience. Craddock reported the appearance of tagged lymphocytes in the thoracic lymph of dogs during the 24 hours after injection, but with his technic ($^{32}$P) he failed to observe measurable levels in the peripheral blood until the second or third day. Craddock suggested that, in accordance with Yoffee's theory, labelled lymphocytes may have been carried promptly to the bone marrow on the first day, to serve as stem cells for the granulocytes. In contrast to the general agreement, that the appearance of labelled cells in the periphery indicates the minimum maturation time after administration of the label, there was disagreement on the meaning of the subsequent decay curve of the radioactivity. Most authors felt that this was a function of the aged cells dying off, and therefore some measure of the cell life span, or at least their mean age. Cronkite pointed out that the decay curve in the peripheral blood was also dependent on the progressive dilution in the marrow of the label of white cell precursors by successive mitoses and that no reliable estimates of cell life span could be drawn from the data without further exploration of the many variables involved. Athens emphasized that the 3-phasic curve of granulocyte DFP$^{32}$P decay is open to a number of interpretations. One possible model was briefly analyzed and was compatible with a short circulation time of WBC with a half time of 5 to 6 hours, an equilibrium level for 12 days during which the rate of replacement from the marrow pool was equal to the rate of removal from the peripheral blood and a maturation or final logarithmic decay. If Cronkite's view is correct, the differences between the estimates of Ottesen and others of a granulocyte life span of 9 to 13 days, Bierman's estimate of multiple cell populations with distinct life spans of 4.5, 8.5, 13.5 and, in chronic myelocytic leukemia, of 23 days, would lose much of their apparent meaning.

Many of the essayists also discussed the distribution and fate of leukocytes. The frequently postulated extravascular pool, previously estimated at 50 to 100 times the circulating number of white cells, was computed by Patt at a substantially lower figure. Craddock's data on P32-labelled cells indicated that the largest reservoir of granulocytes is in the bone marrow rather than in the tissues. Several speakers emphasized that the existence of noncirculating leukocyte pool need not signify actual exit of white cells into the tissue with subsequent reentry, but rather margination and sequestration of white cells in vessels temporarily cut off from active circulation. This concept was supported by Stuart Finch (Yale) on the basis of cross-circulation experiments between leukemic and nonleukemic rats and between normal and irradiated rats with aplastic marrows, as well as by the Ambruses' (Roswell Park) observations on perfusion of individual organs some of which appeared to be able to sequestrate and release WBC. However, it is difficult to be certain whether the conditions, particularly those used by the Ambruses, duplicate the physiologic situation closely enough to be decisive.

Papers by Crafts (Cincinnati), Piliero (New York Medical College) and Van Dyke (California) were devoted to reevaluation of endocrine influences on erythropoiesis. The anemia that follows hypophysectomy in rats can now be completely prevented by substitution therapy with growth hormone, thyroid and corticoids, although the marrow may show some subtle differences. It now appears that the pituitary erythropoietic factor postulated by Van Dyke and his associates is, in fact, ACTH which can produce increases in total red cell mass in rats. In the discussion Stohlman (National Institutes of Health) drew attention to the fact that hypophysectomy in man is not followed by anemia, provided thyroid and corticoids are given. There is, then, general agreement that the important endocrine influence on marrow production is not a specific one, but resides in the various endocrine influences on metabolism in general, to which the bone marrow is particularly sensitive.

The remaining papers dealt with erythropoietine, now well established as a plasma factor elaborated in increasing amounts in response to hypoxia and capable of stimulating erythropoiesis. Since the normal animal is rather insensitive to its action, starved, hypophysectomized, irradiated and hypertransfused animals are being used for assay purposes. A new and very ingenious method utilizing the isolated perfused hind limb of the rat was described by Gordon (New York University). Erythropoietine is believed to be a mucoprotein, with an electrophoretic mobility between alpha 1 and alpha 2 globulin. Rambach and Alt (Northwestern), Gordon (NYU) and Borsook (Cal. Tech.) reported essential agreement in their partially successful attempts at purification and concentration. There is also agreement that a large portion of the plasma activity is lost on boiling, though the remaining activity appears heat stable for considerable periods. Borsook ascribed much of this loss simply to absorption on the coagulum, although there was some debate whether or not activity can be eluted from the coagulum. Most workers agreed that this partial heat stability did not necessitate assumption of two separate erythropoietines. The dissenting voice was that of Linman (Northwestern) and Bethell (Michigan), who believe that a heat labile and a heat stable factor exist. They believe that the heat stable factor stimulates cell division without increasing hemoglobin production, resulting experimentally in microcytic erythrocytosis without change in hematocrit and hemoglobin. They further suggested that the heat stable factor is butyl alcohol or closely related to it. C. J. Watson (Minnesota) indicated that butyl alcohol is likely to be a hemolytic agent which may explain Linman and Bethell's result of reticuloctyosis and possibly spherocytes, without changes in hematocrit and hemoglobin, in short a compensated hemolytic anemia of mild degree. It was also noted by Borsook that the daily doses of 12.5 and 25 mg. of butyl alcohol used by Linman and Bethell were far more than could possibly be present in any plasma. The production, action and metabolism of erythropoietine was discussed by Erslev (Harvard), Jacobson (Argonne) and Stohlman. Jacobson extended his previous observation on the inability of the nephrectomized rat to produce erythropoietin under a wide variety of conditions. He had not been able to reproduce the observations of Mirand (Roswell Park) who maintained that erythropoietine is still manufactured in nephrectomized animals in response to hypoxia, though not in response to bleeding.
Ersklev indicated that erythropoietine increases production of early erythroid forms, since colchicine delays but does not abolish the reticulocyte response. Stohlman presented data on the peak erythropoietine titer and disappearance rate in the plasma following bleeding and exposure to simulated altitude. The puzzling drop in the plasma level during continued exposure to altitude was interpreted as being due to utilization of erythropoietine by the marrow as it becomes hyperplastic. This thought of utilization of erythropoietine by an actively erythropoietic marrow was supported by the slower disappearance of erythropoietine in animals with aplastic marrows. It was also in keeping with the clinical observation that the highest erythropoietine titers have been observed in aplastic anemias. There was general agreement that erythropoietine is elaborated in response to hypoxia but considerable controversy centered around Stohlman's assertion that the sequence of erythropoietine in animals with aplastic marrows. It was also in keeping with the clinical observation that the highest erythropoietine titers have been observed in aplastic anemias. There was general agreement that erythropoietine is elaborated in response to hypoxia but considerable controversy centered around Stohlman's assertion that the sequence of erythropoietine in animals with aplastic marrows. It was also in keeping with the clinical observation that the highest erythropoietine titers have been observed in aplastic anemias.

Other presentations dealt primarily with methodology; the use of radio-iron and other technics in the study of erythropoiesis by Finch (University of Washington); Fe⁺ in radioautography by Alpen (Naval Radiologic Defense Lab.); technics employed in study of red cell survival and their interpretation by Eadie (Duke); tissue culture by Reisner (St. Lukes Hospital, N. Y.) and Osgood (Oregon).

On the first evening there was a comprehensive review of hemolytic mechanisms by Dameshek (Tufts) which was ably discussed by Crosby (Walter Reed).

Dameshek first discussed the mechanisms of normal hemolysis with particular reference to the "built-in" enzyme systems with which the red cell starts its career. He likened the erythrocyte to a missile containing various kinds and quantities of fuel, the cell dying when the nonreplicating enzymes and other chemicals became reduced to critical levels. To be sure, extrinsic factors including the "wear and tear" of the circulation, erythrostasis, potential lysins including tissue lysins, and the activities of the spleen are probably of importance. The old red cell is "fat" (spherocytic) and shows surface breaks by electron microscopy as well as metabolic defects (the "storage lesion"), and enzymatic deficiencies (cholinesterase, catalase, glyoxalase). The spleen may act both as a "slaughter house" and "cemetery" for the aged red cell, although obviously other sites for these functions are present.

Intrinsic defects of the red cell were first studied morphologically (spherocyte, leptocyte, sickle cell), then physiopathologically (trapping mechanism, etc.), but attention has recently been shifted to chemical modifications. These are more fundamental, as for example the valine defect (Ingram) determining the abnormal sickle cell hemoglobin and its various manifestations.

"Occult" chemical defects were then discussed with reference particularly to the brilliant work of Beutler and his associates on the genetically determined enzymatic deficiency leading to apparently completely normal red cells with the one exception of their inability to deal with such chemicals as primaquine and phenylhydrazine. This chapter was cited as among the most outstanding in modern day hematologic advance.

Immunologic hemolysis was then discussed in some detail, with reference being made to the different kinds of antibodies, their varying modes of action, their relationship in degree of hemolysis to the amount of antibody or the red cell surface, etc. Jandl's important work on the splenic sequestration (and hemolysis) of antibody-coated cells was cited, together with some changes in concepts of immune body hemolysis that have taken place in the past 10 years. The therapy of immunohemolysis was then discussed briefly, Dameshek holding to the concept that ACTH and the corticosteroids have their activity by a direct action on antibody-producing tissues (and thus on antibody production).
The second evening was devoted to a round table discussion centering around the fundamental question of the possible dual control of erythropoiesis. It became quite clear that even chemical identification of erythropoietine, which some believe is almost around the corner, will leave many questions on the detailed workings of this factor yet to be answered. These intriguing problems of fundamental physiology and homeostasis should be greatly aided, however, by isolation and concentration of the erythropoietine.

The necessary brevity of this report did not permit one even to mention all of the speakers, let alone to do full justice to each contribution. It is hoped, however, that this bird’s-eye view will convey the general trends of thought and the important areas of agreements and disagreements that emerged at the conference.

—George Brecher, M.D.

MARY PUTNAM JACOBI FELLOWSHIP

The Women’s Medical Association of the City of New York offers the Mary Putnam Jacobi Fellowship to a graduate woman physician, either American or foreign. This Fellowship will start October 1, 1959 and will amount to $2000, $1000 being available October 1, 1959. The recipient of the Fellowship will be expected to make a report to the committee at the end of the fourth month, following which the second $1000 will be awarded subject to the approval of the committee. The Fellowship is given for medical research, clinical investigation or postgraduate study in a special field of medicine. The recipient is expected to devote full time to the Fellowship, but exception may be made by the committee under special circumstances.

Applications for this Fellowship may be obtained from the secretary of the committee after August 1, 1958 and must be returned before February 1, 1959 with the following information: (1) curriculum vitae, (2) a statement from a physician of a recent physical examination, (3) transcripts of her college and medical school records, (4) personal letters of recommendation from two or more physicians under whom she has studied, (5) a statement by the applicant of the problems she proposes to investigate or the study she plans to undertake, (6) a statement from the person under whom she proposes to study of his or her interest in her subject, (7) recent photograph. All the above data must be at hand before the application will be considered.

Successful candidates will be notified not later than May 1, 1959.

Address correspondence to: Ada Chree Reid, M.D., Secretary, 118 Riverside Drive, New York 24, New York.

EUROPEAN SOCIETY OF HAEMATOLOGY, VII CONGRESS

The Seventh Congress of the European Society of Haematology will meet in London from September 7 to 12, 1959. Scientific sessions and scientific and technical exhibitions will take place at Bedford College, Regent’s Park, London, N.W.1.

The honorary officers of the Congress are: Drs. John F. Wilkinson, President; E. Neumark, Secretary; J. W. Stewart, Treasurer.

The Société Internationale de Transfusion Sanguine will arrange sessions in conjunction with the Congress.

Official languages will be English, French and German. Simultaneous translation will be provided.

The principal subjects of the Congress will be: anemia, leukemia, disorders of coagulation and their treatment, problems of bone marrow transplantation, hemoglobinopathies and newer hematological techniques.

A program of special events is being prepared. Further notices will appear in the medical press in due course. For further information write to Dr. E. Neumark, Department of Pathology, St. Mary’s Hospital, London, W.2.
SPECIAL SESSION OF THE FRENCH SOCIETY OF HEMATOLOGY

The next special session of the French Society of Hematology (February 19, 1959, 2:45 P.M., at Hopital Broussais, 96 rue Didot) will be devoted to the following subject:

COAGULATION INHIBITORS


Program:
1. J. P. Soulier (Paris): The role of inhibitors in normal coagulation.
4. J. Favre-Gilly (Lyon): The inhibitors of the initial phase of coagulation, in conditions other than hemophilia.
5. P. Frick (Zürich): The inhibitors of the terminal phase of coagulation.

Further information concerning this meeting may be requested from the Secretary General of the Society, M. Jean Bernard, 86 rue D'Assas, Paris, France.

BOOK REVIEW

IMMUNOPATHOLOGIE IN KLINIK UND FORSCHUNG, UND DAS PROBLEM DER AUTOANTIKÖRPER.

Miescher and Vorlaender have written a remarkable work, dealing with immunopathology and autoantibodies, and in it is a comprehensive survey of the entire field. This includes not only the antibodies related to the blood cells but such important subjects as the fundamentals of immunologic vascular purpuras, organ transplantation, antibodies causing glomerulitis and hepatitis, the L.E. factor, etc. This is a remarkably comprehensive and beautifully organized work and is highly recommended.

—W.D.