Review of the French Hematological Literature (1959)

By Jean Bernard

The contributions of French workers to hematological progress in 1959 covered a broad field. They included studies on mechanisms of cell physiology by electron microscopy and investigation of the carcinogenic activity of cellular extracts of leukemic tissue. The first successful bone marrow transfusions in radiation victims were reported and attempts to apply this experience to the treatment of leukemia described. Somatic mutations of blood group substances in acute leukemia were also investigated and additional descriptions of lesser known forms of this disease were made. Further work included an attempt to arrive at an improved classification of chronic pancytopenias, an effort to clarify the difficult problem of coagulation inhibitors and additional documentation of the usefulness of bentonite, a new adsorbent of coagulation factors.

Most of this work was presented at the regular sessions and symposia of the Societe Francaise d'Hematologie (the world's oldest Society of hematology). It was published, for the most part, in the journals Le Sang, Revue d'Hematologie, Revue Francaise d'Etudes Cliniques et Biologiques.

The Erythroblastic Islet and Rhopheocytosis of Ferritin

The name rhopheocytosis was given to a phenomenon related to, but different from, pinocytosis. It is the process by which tiny invaginations several hundredths of an angstrom in diameter incorporate molecules adhering to a cellular surface. M. Bessis continued the study of this phenomenon as it relates to incorporation of ferritin by erythroblasts. His work further clarified the process and was illustrated by excellent electron photomicrographs. These demonstrated erythroblastic islets with a central nourishing cell surrounded by several rows of erythroblasts, the more mature forms, lying in the periphery. Elongated, fine dendrites extended from the central cell to enmesh the erythroblasts. These dendrites are usually destroyed in the process of making ordinary smears. Rhopheocytosis of ferritin molecules was rapid and occurred from moment to moment at various sites on the cell surface. The phenomenon certainly represents a method of incorporation of iron by erythroblasts, but the proportion of iron which enters the erythroblast by rhopheocytosis rather than by the better known route of transferrin is not known.

Carcinogenic Activity of Acellular Extracts and Nucleic Acids from AK Leukemia Tissue

Several facts were established or clarified by R. Latarjet and his co-workers. The method of successive passage in new-born mice made it possible to prepare the leukemogenic agent in a very virulent form. Extracts obtained by the original method of Gross produced leukemia in 90 per cent of animals.
in about 6 months; the new preparations were 100 per cent successful in less than 4 months. Furthermore, the new extracts were effective not only in newborn mice but also in animals as old as 3 weeks.

Further studies, based on observations made in 1958, confirmed the fact that desoxyribonucleic acid (DNA) from AK leukemia tissue is carcinogenic when injected into certain newborn mice. Of 260 animals, 14 (5.4 per cent) developed multiple cancers. However, 49 animals treated with the same DNA first digested by desoxyribonuclease remained unaffected. As studies in the U. S. A. confirmed, the active agent of these preparations was very probably DNA of polyoma virus carried by the AK strain. This work is being continued using two families of AK mice, one carrying the polyoma virus and the other virus-free.

**Bone Marrow Transfusions**

French groups (Mathé, Jammet et al.) developed technics of bone marrow transfusion applicable to man. They were able to use this experience in the treatment of 5 physicists who were accidentally exposed to a high dose of neutron and gamma wave radiation. In 4 of these patients, transfusion of adult bone marrow resulted in rapid clinical improvement and corrected the medullary and peripheral cytopenia. There was evidence suggesting that for about a month the transfused bone marrow was responsible for myeloid activity. The most important evidence was furnished by identification of blood group phenotypes of two erythrocyte populations, the patients' red cells and those from the transfused marrow. These patients have subsequently remained well. Two important new facts were thus established:

1. The transfusion of homologous myeloid cells after lethal doses of radiation is possible in man, as in other animals.
2. The transfusion of myeloid cells represents the treatment of choice and can be life-saving for victims of accidental irradiation.

Attempts to treat human leukemia by high dose radiation and marrow transfusion were based both on this clinical experience and on experimental data. The experimental work demonstrated that:

1. The treatment of mouse 1210 leukemia by lethal radiation and bone marrow transfusion was not effective unless the number of leukemic cells was small.
2. Homologous cells, probably because of an immunity to the leukemia, were more effective than isologous cells in these transfusions.
3. Transfusion of homologous cells was generally followed by "secondary" illness, which has been thought to result from immunization of donor cells against the host.

In order to have as few leukemia cells as possible, the first clinical trials were made on children with acute lymphoblastic leukemia in remission. Total irradiation with 850 r of CO was followed by homologous marrow transfusion. These trials confirmed the feasibility of such transfusions. The activity of the transfused cells was proven not only by red blood cell studies but by demonstrating female sex-linked lobes on polymorphonuclear cells in a
male infant transfused with his mother’s marrow. This work also produced the first description of human “secondary” illness comparable to that of the mouse, with gastrointestinal and cutaneous disturbances, lymphoid aplasia, and a course which may be reversible or fatal. Finally, results of these trials demonstrated that this procedure can prolong the final remission in patients with acute leukemia for several months, although fatal relapse was not prevented.

High dose irradiation followed by bone marrow transfusion cannot be considered as a routine treatment for acute leukemia; however, the patient pursuit of such studies should yield many new pathophysiological findings.

**Acute Leukemia and Somatic Mutations of Blood Group Substances**

Alteration of blood group substances synthesized by the erythroblast were observed in some patients with acute leukemia. Salmon, André and Dreyfus described two patients exhibiting double populations of red blood cells. One had a mixture of 75 per cent type A1 cells and 25 per cent type O, another a mixture of 80 per cent type A1 and 25 per cent “weakly-reacting” type A. In other cases all the circulating red blood cells were “weak-reacting” type A. These anomalies were believed to be acquired since no unusual blood types had been noted in several patients tested prior to their illness. Anomalies were also more frequent in patients with leukemia (4 in several hundred) than other individuals (18 in 300,000).

Filitti-Wurmser and Wurmser, studying the natural antibody anti-B, supplied additional information concerning “weak-reacting” red blood cells in patients with acute leukemia. They found several categories of anti-B antibodies which varied according to the genotype of the subject. Their observations suggested that the alteration was not confined to the erythrocyte but also affected the antibody-forming cell. The initial mutation (which one may logically assume to occur although this is not absolutely proven) may therefore originate not in the erythrocyte but rather in the primitive reticuloendothelial cell which can produce, by division, both cells of the erythroid series and cells capable of synthesizing natural antibody.

**Acute Promyelocytic Leukemia**

Hematologists of the Anglo-Saxon countries generally neglect the promyelocyte and seldom describe any cell form between the myeloblast and the myelocyte. The importance of the promyelocyte was re-emphasized, however, by a recent study describing 20 patients with acute promyelocytic leukemia. This group demonstrated several salient features of this form of leukemia, including a greater intensity of hemorrhagic manifestations, frequently secondary to increased fibrinolytic activity, and a fulminating course usually resistant to all modes of therapy. This interesting disease is probably the most serious of all the acute leukemias.

**Chronic Idiopathic Pancytopenia Without Splenomegaly**

At a symposium held in Paris, 81 cases of chronic pancytopenia without splenomegaly were discussed. The most significant observations concerned
(1) the bone marrow characteristics and (2) the natural history of the disease. The cytology of the bone marrow was variable—sometimes hypoplastic, often normal or hyperplastic. The hyperplastic marrows had the following features:

1. A clear-cut erythroblastosis with decreased M:E ratio.
2. Often an increased ratio of myelocytes to polymorphonuclear leukocytes.
3. Megakaryocytes markedly decreased or absent.

The course could be fatal, due to hemorrhage, anemia, etc. (43 per cent). Very often (50 per cent) a chronic state was reached which was precarious but, by judiciously spaced transfusions, it was compatible with a satisfactory existence. Gradual spontaneous improvement may occur after several years (18 cases). Two of the three cell deficiencies may disappear or there may be complete and permanent remission. The marrow status was important prognostically since stabilization or improvement was much more frequent when marrows were normal or hyperplastic.

These possibilities must be borne in mind when considering splenectomy, since this procedure carries a high operative risk and favorable results are often delayed, incomplete, and seldom exceed 50 per cent.

The Direct Coombs Consumption Test on Platelets and Leukocytes

The existence of immunological leukopenia and thrombopenia have been claimed for several years but any direct evidence has not yet been given. J. Dausset tried to devise a test capable of detecting the presence of gamma globulin on the patients own leukocytes or platelets. He proposed the direct Coombs consumption test on leukocytes or platelets which derives from the indirect test proposed in France by Moulinier and in Austria by Steffen. This test was more penetrating than the direct Coombs test. It was able to detect not only the surface gamma globulin, but also the gamma globulin fixed in the interior of the cell.

One hundred fifty-eight subjects were studied; 400 tests were performed.

In S.L.E. both tests on leukocytes and on platelets were simultaneously positive in most of the cases (84.7 per cent).

In thrombocytopenic patients, only the test on platelets was found positive in 71.4 per cent of the cases, while the test on leukocytes remained always negative.

In leukothrombocytopenia, both tests were found simultaneously positive in 32.6 per cent of the cases.

In the noncytopenic group (control group) all the tests were negative except the platelet tests found positive in 5 cases.

Coagulation Inhibitors

A symposium of the Société Française d'Hématologie directed by J. L. Beaumont and J. Caen was devoted to coagulation inhibitors. The etiology of coagulation inhibitors associated with hemophilia was studied and a general review made of the role of anticoagulants influencing formation of active endogenous thromboplastin and tissue thromboplastin.
The technics used to demonstrate anticoagulants associated with various pathologic states (hemophilia, myeloma, disseminated lupus erythematosus, chronic rheumatic disease, pregnancy and abortion) were evaluated. It was pointed out that the varied, often imperfect technics employed by different workers should be codified and an effort was made to sift out the most useful ones. The inhibitors of the conversion of fibrinogen to fibrin were considered, particularly with reference to those associated with dysglobulinemias and myelomas. The discussion between immunologists and coagulationists concerning anticoagulants and their relation to antibodies revealed that whatever the arguments employed—etiologic, physicochemical, immunologic—or whether one referred to iso-antibodies or auto-antibodies, the true immunologic nature of the anticoagulants has still not been clearly demonstrated.

BENTONITE, A NEW ADSORBENT OF COAGULATION FACTORS

Bentonite is an argillaceous mineral whose deposits were first recognized at Fort Benton in Wyoming, whence its name. It has remarkable capacities for adsorption. J. P. Soulier17,18 first studied the action of bentonite on coagulation factors and found it capable of adsorbing fibrinogen from normal plasma in very weak concentrations (5 mg./ml.). At higher concentrations (20 mg./ml.) it could separate prothrombin from proconvertin and factor IX (“Christmas factor”). A very small amount of bentonite (1 mg./ml.) permitted optimal activation of the contact factor.

Other feasible applications of this new adsorbent include (1) separation of anti-hemophilic globulin and fibrinogen in human plasma and (2) preparation of a purified prothrombin containing only immeasurable traces of factor IX and proconvertin.

It is evident that important progress has been made in the purification of clotting factors, a longstanding preoccupation of workers in the field of blood coagulation.

REFERENCES

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