EDITORIAL

The Ten "Greats" in Hematology—1900–1950

KNOWLEDGE, more particularly scientific knowledge, increases exponentially. In recent years, with one discovery succeeding another in rapid succession, the rate of increase has been bewildering. This seems particularly true in the field of hematology in which, with the development of the physiologic approach—roughly since 1925, we have seen the introduction of liver feeding for pernicious anemia; the development of the concept of the deficiency syndromes and of "conditioned" deficiency; the discovery of vitamin K and of hypoprothrombinemia; the rediscovery that isoantibodies are related to hemolytic anemia; and the discovery of the Rh factor and its relation to erythroblastosis foetalis. We have witnessed the use of transfusions on a large scale, and the development of blood banks and of plasma fractionation. And we have seen the meteoric rise of the chemist in pharmacologic research and with it the discovery of folic acid, of vitamin B_{12}, and of folic acid antagonists. As the half century ends, the mystery of the sickle cell is being dispelled by studies of its hemoglobin chemistry. Study of coagulation factors is seething as we learn more and more of the complex interrelationships between the various enzymatic factors and their substrates. Even the strong citadel of leukemia is being stormed by such chemotherapeutic and hormonal agents as the folic acid antagonists, urethane, nitrogen mustard and ACTH.

The older hematology, which was largely descriptive and morphologic, is now in a state of renaissance, what with the development of phase microscopy, histochemical methods, and the great expansion in bone marrow studies. The finding of "L.E." cells in disseminated lupus and of granulomatous lesions in brucellosis may be mentioned.

With the advent of the half century mark it is customary to take stock of leading events of the past 50 years and of the great figures during that period. Various lists of the "greats" and near-greats have been compiled by leading magazines, educators and others. This harmless sport affords much comment, some of it useful. It struck the Editor that the readers of *Blood* might be amused (or perhaps irritated) by publication of such a list of hematologic "greats." It must be confessed straightaway that this compilation is purely a personal one and should in no wise be construed as infallible. Each reader must assuredly have his own ideas and for those who would like to take the time to complete it, an insert is provided.

The list, as presented, is made up of individuals who in our judgment have made the most significant contributions in the various fields of hematology during the period of 1900 to 1950. These contributions have done much to alter our thinking regarding the physiopathology of disease or have opened up new avenues in therapy. Since at some loci a single choice seemed either impossible or undesirable, it has been necessary to produce "twins"; these are not necessarily identical.

The list is as follows:

1. *Karl Landsteiner* (1868–1943), the father of the blood groups and one of the great figures in contemporary medicine. With Donath he discovered the autohemolysin of paroxysmal cold hemoglobinuria. At the beginning of the century he announced his discovery of the blood groups and thereby revolutionized concepts regarding blood transfusions. Later, with Levine, he discovered the M and N and P factors and with Wiener, the Rh factor. In his studies on iso- and autoimmunization and hypersensitivity he coupled dyes with simple proteins and was one of the founders of the science of immunochemistry. He was truly one of the greats, not only in hematology, but in the whole field of medicine and science.

2. *Arthur Pappenheim* (1870–1916), the morphologist and an active investigator in the now rather distant days when all of hematology seemed to center in the blood cells and their derivations. An active protagonist for his oft-changing ideas, he engaged in long-winded polemical squabbles with other morphologists in the old *Folia Haematologica*, which he founded. He was the teacher of Ferrata, Hirschfeld and of Downey, all of whom went on to make important contributions in the field of morphologic hematology. He was one of the first hematologists to attempt histochemical studies, which, having laid neglected for years, have now been revived, and with phase microscopy, supravital studies, etc., have served to create a renaissance in an almost moribund field.

3. *Anatole M. Chauffard* (1855–1932), the great French clinician and investigator, one of the first to study hemolytic anemia. He was the first to demonstrate the increased hypotonic fragility of the red cells and the marked reticulocytosis in the congenital type, which he discriminated sharply from the acquired types as described by Widal. With Troisier he was the first to explore the abnormal antibodies in acquired hemolytic anemia, and suggested in one of his articles the future development of a field of "immunohematology."

4. *Guido Banti* (1852–1925), the Italian pathologist, clinician, investigator, known chiefly for his studies on "splenic anemia," for which the eponymic but not very accurate designation of "Banti's disease" is often used. Recent investigations indicate that the splenic anemia of Banti was associated with various types of splenomegaly rather than with a single primary disorder of the spleen. His experimental studies in the mechanisms of hemolysis led him to suggest the bold possibility that splenectomy might be therapeutically useful in hemolytic anemia. The success of this operation led to its use by Kaznelson in idiopathic thrombocytopenic purpura.

5. *George H. Whipple* (b. 1878) and *George R. Minot* (1885–1950†). In the midst of a relatively static period in hematology, the experiments of George H. Whipple in dogs on the dietary factors concerned with hematopoiesis came as a fresh new breeze. Whipple also postulated that a defect of the red cell stroma might be operative in pernicious anemia. As a direct result of these experiments and by application of the principle of the "prepared mind," Minot's epoch-making introduction of liver feeding for the treatment of pernicious anemia and his exacting methods of clinical investigation led to a complete reorientation of the direction of hematology. The use of the reticulocyte as a "yardstick" became a model for future hematologic experimentation. Morphology took a back seat to physiology.

† Died February 25, 1950.

America became the hub of hematology and has retained this role ever since. 1926, the date of Minot and Murphy's publication, may be set as the dividing line between the older and the newer hematology.

6. *Edwin Cohn* (b. 1892) was in 1926 a young physical chemist. Methodically, and with the brilliant organizational ability which was later to show up so strongly in development of plasma fractionation methods, he proceeded to make a potent extract of whole liver. The principles used in developing this extract were later used for the manufacture of highly potent extracts for parenteral use. His more recent plasma fractionation studies, which involve splitting the plasma into many important constituents, including the antihemophilic globulin, have already proved epoch-making. His continued studies in this field bid fair to give us methods for preservation not only of plasma constituents, but of such cellular materials as the platelets.

7. *William B. Castle* (b. 1897). In 1929 this investigator faced a disease in which, although the practical aspect of treatment seemed well-nigh settled, causation was just as obscure as ever. By a series of logically contrived investigations he showed that pernicious anemia was conditioned fundamentally by the deficiency of an enzyme in the gastric juice—"intrinsic factor." Castle's investigations of sprue in Puerto Rico did much to dispel some rather foggy and bizarre notions as to the etiology of that disease. Although the recent introduction of vitamin B_{12} has necessitated some revision of his original concept, Castle's work is primarily responsible for the introduction of the concept of the conditioned deficiency syndromes and thus for the development of some of the dramatic "by-products" in this field, notably by Tom Spies and others. His constant emphasis on the physiology and physiopathology of disease is in keeping with the characteristically American approach to hematologic problems.

8. *Harry P. Smith* (b. 1895) and *Armand J. Quick* (b. 1894). Both these investigators have been in the very forefront of the seething and rapidly expanding field of the coagulation mechanism since its renaissance in the 30's Smith in 1934 described the first reliable method of measuring prothrombin, was the first to demonstrate conclusively hypoprothrombinemia of the new born and to show the relationship of hepatic disease to prothrombin formation. With his pupils, Seegers, Brinkhaus and Warner he began to purify prothrombin and foresaw that prothrombin conversion accelerators would be found. Quick placed prothrombin testing on a practical basis, correlated clinical hypoprothrombinemia with vitamin K deficiency, described prothrombin conversion accelerators and demonstrated the delay in prothrombin conversion in thrombocytopenic purpura. Quick's many investigations and his clear teaching methods have done much to place the field of the hemorrhagic diseases at the very forefront of hematologic advance.

9. *Philip Levine* (b. 1900) and *Alexander S. Wiener* (b. 1907). Discovery of the Rh factor and of its clinical significance must be considered as one of the epoch-making events in the field of medicine. This discovery has revolutionized the field of transfusion therapy, and has been the most important factor in furthering the development of the field of immunohematology. It has helped to save many lives, both among the newborn and in adults, has led to the discovery of newer blood group factors, and has uncovered such apparently remote possibilities as the rela-

tionship of blood group factors to idiocy. In the welter of articles it is impossible to untangle either where the work of Levine begins or of Wiener ends, or which is more important. With Landsteiner, Wiener discovered the Rh factor. Wiener described "blocking" antibody, "conglutinin," the genetic aspects of the Rh factor, and exsanguination transfusion technics. Levine, even before the Rh factor was described, found an antibody in certain pregnant women whose children died stillborn or with erythroblastosis foetalis. When the Rh factor was discovered, Levine demonstrated the exact parallelism between his human factor and the rhesus monkey factor and elaborated the accepted theory for the pathogenesis of erythroblastosis foetalis. Levine described the Hr factor, which is positive when the Rh factor is negative. Setting petty disagreements aside, the contributions of each investigator have been outstanding.

10. *Yellapragada SubbaRow* (1896–1948). This last name will probably come as a surprise since it is not known to many. In this list, SubbaRow stands mainly as a symbol of the growing importance in hematology, as elsewhere in medicine, of the pure chemist and of the great contributions of the "commercial" pharmaceutical houses to medical investigations. SubbaRow originated from India and at the time of his sudden death was chief of research at Lederle Laboratories. He organized first-rate research laboratories and research teams. Partly through his efforts and example the investigations of pharmaceutical houses were placed in a new and better light. Numerous fundamental discoveries and such first-rate therapeutic principles as pteroyl glutamic acid, aminopterin, vitamin B_{12}, and cortisone have eventuated. The chemist stands today at the very forefront of hematologic advance and achievement. Upon him we must rely for the unravelling of the mysteries of cellular metabolism and eventually for the control of such monstrous things as leukemia and leukosarcoma and for the eventual "medical" management of hemolytic anemia, thrombocytopenic purpura and the like.

The above list is admittedly incomplete and defective. It should be noted that such names as Ehrlich and Hayem belong to the last century and are therefore not included. One might venture to make up a list of the second ten. Some names have already been suggested; e.g., Hal Downey, Tom D. Spies. Others might include Ferrata of Italy; Florence R. Sabin, U. S. A.; Maxwell M. Wintrobe, U. S. A. (red cell indices, nutritional deficiency); Charles A. Doan, U. S. A. (splenic syndromes); Marcell Bessis of France (erythroblastosis, the newer morphology); Naegeli of Switzerland (morphology, clinical hematology); Eppinger of Austria (spleen-liver relationships, hemolytic anemia, hypersplenism, splenectomy); Heilmeyer, of Germany (porphyrins, hemolytic anemia); González-Guzmán of Mexico (nucleoli); Seegers, Tocantins and MacFarlane (coagulation problems); Whitby, Dacie and Mollison of England and R. R. Race, also of England (Rh-CDE factors).

It will be interesting to see what our readers think of this sort of listing; comments are invited. If sufficient response occurs to warrant counting (the previously mentioned insert for those interested may be found on page xii in the front of this issue), the results of a frequency distribution (balloting) will be published in a future issue.

WILLIAM DAMESHEK