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John W. Rebuck MD, PhD

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Dr. John W. Rebuck is one of those rare individuals who can endear himself quickly and forever to his colleagues. Within this issue you will find a brief biographical sketch, several reprints that are classic examples of his scientific research, and selected original articles by those who have known him through the years as a student or otherwise have been allied with him through common scientific interests. The Editorial Board of the Henry Ford Hospital Medical Journal wishes to honor this unusual man, who has been the Editor of the Journal since 1972. All too often such an individual is commended for his contributions to science long after leaving the institution where he devoted his entire life.

The Editorial Board believes this issue is justified for those who have been influenced by him in the past, continue to be now, and will be in the future because of his many achievements as a man and as a scientist. To those of us who have enjoyed having him "right at our elbow" over the years, this issue serves to recognize a colleague who has contributed importantly to medicine not just within Henry Ford Hospital but nationally and internationally as well.

—Gilbert B. Bluhm, MD
Guest Editor

John W. Rebuck MD, PhD

John W. Rebuck's accomplishments as a physician and a scientist are so numerous that it is not possible to describe them fully. A native of Minnesota, he began his distinguished career at the University of Minnesota where he received his MD (1943) and his PhD (1947). While there, his interest in hematology was stimulated by his work with Hal Downey, considered by most to be the father of American hematology. During World War II, he was a Captain in the U.S. Medical Corps and served as a hematopathologist with the Armed Forces Institute of Pathology until 1947.

At this time, John began his long career at Henry Ford Hospital in Detroit. He had interned at the Hospital in 1943 and returned in 1947 to become Chief of the Division of Laboratory Hematology. The time, the place, and the man all proved propitious for the future of science. The elder Henry Ford had just bought a transmission electron microscope for the Department of Pathology. Only a few such microscopes were then available anywhere in the country and, thanks to Henry Ford, the Hospital had one of the first RCA instruments in use in a private institution. Although Wolpers and Ruska had used the transmission electron microscope in Germany just before the outbreak of World War II, Rebuck and his colleagues were the first to use it to study the ultrastructure of leukocytes and erythrocytes. By 1948, Rebuck had worked out a method for studying the sequence by which the red cells in sickle cell disease, so prevalent in the Detroit community, underwent their bizarre transformation from an apparently normal biconcave disc to the peculiar crescent shape that gives the disease its name.

One fall afternoon in 1949, Linus Pauling came to Detroit to lecture on his newly discovered biochemical molecular lesion in sickle cell hemoglobin, pinpointing a change in its electrophoretic mobility, a discovery that would later win him the Nobel Prize. After listening to Pauling lecture on his discovery, John invited him to the EM laboratory to show him the ultrastructural sequences of the intracorpuscular hemoglobin in the sickling process. With Pauling's help, he was able to give the appropriate physical/chemical names to the intracorpuscular crystallization of hemoglobin in the sickling red cells.

As a result, at the April 1950 meeting of the Federation of American Societies for Experimental Pathology, Rebuck was able to demonstrate the ultrastructural incipient crystallization of hemoglobin within the sickle cell. He was the first to report this discovery, which had been published as an abstract in the March 1950 Federation Proceedings as "Sickling processes in anemia and trait erythrocytes with the electron microscopy of their incipient crystallization" (1). In August 1950, Harris published his confirmatory report on tactoid crystallization of reduced sickle hemoglobin and cited Rebuck's prior work in his introduction. As Rebuck pointed out in his original report, incipient crystallization took place within the center of the sickle cell. Further stages of crystallization resulted in anisotropoid angulation of central aggregates followed by eccentric massing of the hemoglobin with intense peripheral spiculation characteristic of aberrant crystallization. He concluded that unipolar sickling and filamentation arising from one end of the red cell substantiated this concept of intracorpuscular crystallization. Although scanning electron microscopy was not yet available, the tridimensional nature of the crystallization inherent in the sickle cells was ingeniously demonstrated by applying shadow-casting.

Several years later, in 1955, Rebuck expanded and updated this report in a review entitled "Sequential electron micrography of sickling" published as part of a festschrift by the Journal of Laboratory Investigation to honor Dr. Frank Hartman (2).* Again, as was always his custom, John generously gave credit to his clinical colleagues and medical technologists for their contributions.

Two special honors were awarded to Rebuck for his discovery. In 1950, he received the Silver Medal of the American Society of Clinical Pathologists for Electron Microscopy in Clinical Pathology, and in 1954, he received the First Award of the American Academy of Obstetrics and Gynecology for Electron Microscopy of the Blood Groups.

During the 1950s, Rebuck expanded his ultrastructural studies using the transmission electron microscope to study other blood disorders, especially hereditary elliptocytosis. In this instance, Rebuck and his colleagues compared human elliptocytes with those from the llama (3). They used the electron microscope to show that human elliptocytes were characterized by hemoglobin aggregates at either end, making them susceptible to traumatic disruption, unlike the elliptocytes of the camel family, which were actually biconcave ellipses. Although camels were not available in Detroit for such studies, John was able to use the llamas at the Detroit Zoo to study their elliptical red blood cells. Furthermore, while demonstrating that human elliptocytes retained their oval outlines after hemolysis, which pointed to a membrane fault in this disorder, they were not able to hemolyse llama elliptocytes in distilled water when the cells were in a 2% suspension. From this failure came the important observation that red blood cells

* Reprinted on pp. 236-44 of this issue.

in members of the camel family were able to withstand great ranges of plasma hypotonicity and that water stored by camels was not, as legend would have it, in their humps, but more likely in their elliptical erythrocytes. Again, the three dimensional studies were done with the shadow-casting technique, but Hartsock, years later, using the scanning electron microscope, was able to confirm these findings for both the llama and man.

Perhaps Rebuck's greatest scientific contribution, the human skin window technique, was introduced in this same period. In 1955, his major report in a festschrift honoring his teacher Hal Downey was devoted to this technique, entitled "A method of studying leukocytic functions in vivo" (4).* A review of this method and its subsequent influence has been written by S. M. Saeed especially for this issue and appears on pp. 210-16. Ahead of its time, this technique has been a valuable contribution in showing functional leukocytic abnormalities in ulcerative colitis, diabetes mellitus, allergies, and in monitoring human organ transplantation rejection. It is a fitting tribute to its lasting importance that the generally accepted designation for this test, even in various medical indices, is the Rebuck skin window procedure.

One revealing example of how Rebuck used his skin window technique involves his early (1949) confirmation of Hargraves' discovery of the LE cell phenomenon. Intrigued by a report that several student nurses had acquired disseminated lupus erythematosus after they had received Dick tests, Rebuck and Lawrence Berman, who had been a classmate with John under Hal Downey and who had become a hematopathologist at Wayne State University, were able to induce LE cell formation in their own skin windows by adding serum from patients who had died of the disease. Rebuck then presented his findings at the 1949 fall meeting of the Central Society for Clinical Research. Hargraves himself was in the audience at the time and affirmed Rebuck's findings, an important affirmation because many false claims of LE cell induction were being made. In the original report, published the next year (5), Rebuck cautioned that once the experiment had been successfully completed, it need not be repeated by transferring LE plasma into normal individuals, not so much for fear of transferring LE in this way but because of the ever-present danger of transferring the hepatitis virus. It is for this reason that John always insisted on having serum transfer experiments done on himself. Rebuck, and later Stuart Finch of Yale (6), found that skin window testing for LE cells in patients with this disorder afforded an extremely sensitive monitor for the severity of the infection: if LE cells appeared spontaneously in the test site, the prognosis was especially grave. For his work in this field Rebuck was later honored by being named the first Gladys Dick Memorial Lecturer at Northwestern University (1968).

Another example of the usefulness of the skin window technique is the work Rebuck did with Robert Priest of the Hospital's Gastroenterology Department on patients with idiopathic ulcerative colitis (7,8). With an enteric antigen, diphtheria toxoid, as the inflammatory agent, Rebuck used the skin window technique to reveal a new type of human hypersensitivity disorder marked by massive outpourings of basophilic leukocytes. Working with the Division of Urology at the Hospital, Rebuck next demonstrated the same phenomenon in patients suffering from Hunner's ulcer and its less destructive form, idiopathic interstitial cystitis (9). He noted that the excessive basophilic granulocytic migrations were accompanied by a parallel tissue mast cell hyperplasia, a characteristic of the actual lesions of the colon as shown by Sommers for ulcerative colitis (10) and by the Ford Hospital group themselves for Hunner's ulcer and interstitial cystitis (9). Although the Danish group, headed by Wolf-Jurgensen, were at first reluctant to accept the concept of excessive basophil migrations in human hypersensitivity states, they later published a confirmatory monograph when they found the same basophilic predominance in the lesions that tested for histoincompatibility with the Medawar lymphocyte transfer test (11,12). The result of this work was a symposium on basophils and mast cells that John organized with Jacques Padawer and William Simpson for the New York Academy of Sciences in 1963 and that was later published as a book (13).

An offshoot of this work with the basophilic granulocytes was Rebuck's confirmation of the discovery by Robert Good (another Rebuck classmate under Hal Downey) that the skin window method was the most accurate diagnostic procedure available for identifying the Hunter-Hurler disorders (acid mucopolysaccharidoses) by eliciting easily identifiable Hurler cells in the macrophages at the test site (14). In turn, this work led to Scheie's use of the skin window to identify a forme fruste of Hurler's that bears Scheie's name (15,16). Still in pursuit of his understanding of the "pseudo-mast cells," as he called them, Rebuck next obtained purified samples of all the known acid mucopolysaccharides from Sarah Schiller, who had achieved their exacting purification. Together, they published their findings (17) on the induction of Hurler cells by dermatan sulfate, the abnormal AMP of the disease itself, in the skin windows of Rebuck himself and one of his own resident volunteers, Alex Ullman.

In addition to his pioneering work in discovering and developing the skin window technique, Rebuck was also instrumental in carrying out work done at Henry Ford Hospital in the later 1950s on the ultrastructure of blood

* Reprinted on pp. 184-209.

platelets (18-22*). This work is discussed in detail by Jeanne M. Riddle elsewhere in this issue (pp. 268-75). By making use of the greater capabilities of the electron microscope, Rebuck, Riddle, and I** were able to devise a method of categorizing and counting four stages of platelet surface activation. Rebuck and his co-workers were among the first to adapt this method for evaluating platelet responses in a variety of disease states. Again, as with his work on basophils, the work with platelets culminated in a symposium at Henry Ford Hospital on platelets organized by the late Shirley Johnson and subsequently published as a book (23).

It would also be remiss not to mention some of John's contributions which, although not related to experimentation in the laboratory, have helped modern medicine just as effectively. In the mid-1950s, he assembled most of the active hematologists of this country and many from abroad for two symposia on leukocytic function and leukemia, the first held in New York at the Academy of Sciences and the second held here at Henry Ford Hospital (24,25). Beyond the importance of the subjects discussed, these meetings proved to the participants that the time was propitious for establishing an American Society of Hematology. This society came into being in 1958 with John as its first secretary, a position he held in the first four formative years of the society and which, in no small way, has contributed to the preeminence this society holds today in American medicine.

In education, Rebuck has also been a leader. Beginning in 1954, he was one of two pathologists in this country to establish a continuing education program in hematology for the American Society of Pathologists, long before postgraduate medical education was considered mandatory. This program has continued up to the present, first with myself, then with John's student, the late Joseph Sieracki, and presently with S. M. Saeed. Few realize that for the last 30 years Rebuck has sent out, through the American Society of Pathology, slides of interesting hematology cases to some 1500 laboratories in this country with a critique attached that discusses the findings and literature pertinent to the problem slide submitted. Rebuck's educational interests are also reflected in his service on the editorial boards of several leading biomedical journals, as well as his editorship of the Journal of the Reticuloendothelial Society (1965-74) and of our own HFH Medical Journal from 1972 to the present.

One final facet of Rebuck's varied career deserves comment. Not many of his colleagues are aware of his longstanding interest in the American space program. When the first Russian cosmonaut orbited the earth in 1961, John sent him a letter of congratulations, and he still cherishes Gagarin's letter of reply. Unknown for a time to Rebuck himself, Werner von Braun planned to use the skin window method as early as 1965 to monitor the American astronauts' immunity during the interstellar flight. As a result, in 1969 Rebuck was asked by the director of the NASA space medical program to be the pathology consultant for the Apollo lunar landing program, an appointment that led to the enthusiastic use of Rebuck's work by the first medical astronaut in the Skylab program.

I am sure I have omitted much that would interest those who have followed John's medical career, such as his work in the Armed Forces during World War II and his consultations for them that continue to this day, or his work on the Lymphoma Panel and other committees of the National Institutes of Health. However, the pages that follow are the most fitting testimony to the long and outstanding career of this remarkable man.

—Raymond W. Monto, MD
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* Reprinted on pp. 255-67.

** Ed. note: Dr. Monto himself was an integral motivator in this work.

* A complete listing of Dr. Rebuck's publications appears on pp. 299-303.

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