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LEON ORRIS JACOBSON

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A Biographical Memoir by

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IN BIOLOGY AND MEDICINE there are occasionally singular personalities, people who affect the lives of students, colleagues, and patients to a memorable extent. One such singular person was Leon O. Jacobson, M.D., who combined clinical practice, teaching, academic administration, and innovative investigation to make an indelible impact on hematology and on all who knew him.

Leon Orris Jacobson was born on December 16, 1911, in Sims, North Dakota, a town that exists today only in memories because the Northern Pacific railroad changed its route leaving Sims an abandoned village which now doesn't even appear on maps. He died of complications of lung cancer in Chicago on September 20, 1992, after a rich scientific and personal life. His first wife Elizabeth died in 1983, and he is survived by his second wife Elise, his son Eric, his daughter Judith Bonacker, and their children. Dr. Jacobson was known to his friends and colleagues as Jake and it is fitting to refer to him that way in this memoir.

EARLY LIFE

Jake's family was made up of Norwegian immigrants, and he frequently and proudly showed his ability to speak Nor-

wegian and to sing Norwegian folk songs while accompanying himself on the piano. His early intention was to study agriculture and follow the family tradition of ranching in North Dakota, but, due to economic necessity during the depression, his education had to be interrupted during his second year at North Dakota State University. He then taught eight grades of elementary school in Sims for the next three years. During this period of teaching a number of grades in a one-room schoolhouse and observing the children getting a variety of illnesses he became interested in medicine and decided to forego ranching. He returned to college and eventually received a B.A. from North Dakota State University in 1935. To embark on a career in medicine he chose to apply to only one medical school, the University of Chicago.

POSTGRADUATE EDUCATION AND PROFESSIONAL CAREER

Jake completed medical school at the University of Chicago in the canonical four years and proceeded to spend the rest of his professional life at that university, never leaving even for a sabbatical. He was both an intern and resident at Chicago and became an instructor in the Department of Medicine in 1942. He was an assistant professor of medicine from 1945 to 1948 and associate professor from 1948 to 1951.

Although Jake professed not to enjoy administrative work, his intense loyalty to the institution did not permit him to decline such positions. He served as associate dean of the Division of Biological Sciences and the School of Medicine at the University of Chicago from 1945 to 1951.

World War II saw the establishment at the University of Chicago of war-related research and Jake was involved in two secret projects: the Toxicity Laboratory, where he served as consulting physician working with chemical warfare agents

and protection against them, and the Metallurgical Laboratory. The latter was the local code name for the nationwide Manhattan Project, work that resulted in the first chain-reacting atomic pile, which was designed and built by Enrico Fermi and his colleagues in a squash court under the stands of Stagg Field. In short order Jake became associate director and then director of the Biology and Medicine Branch of the Metallurgical Laboratory.

In 1951 Jake was appointed professor of medicine, head of the hematology service, and director of the Argonne Cancer Research Hospital. This latter was a direct postwar outgrowth of the Metallurgy Laboratory. It was established on the University of Chicago campus, was completely funded by the Atomic Energy Commission, and had a loose connection with Argonne National Laboratory some 30 miles away. The establishment of Argonne Cancer Research Hospital was due largely to Jake's efforts. He, in essence, designed the hospital as a research institute which included research beds and ample laboratory space. It was devoted to the use of the products of the atomic era in research on cancer-related problems and therapies. He staffed the hospital with members of the various departments in the Division of the Biological Sciences and included investigators in fields ranging from protein chemistry, steroid biochemistry, and experimental and clinical hematology to the use of high energy radiation (an intense ^{60}Co source, a Van de Graff generator, and a linear accelerator) for cancer therapy. The staff consisted of physicians, surgeons, chemists, biochemists, physicists, and radiologists. The synergy resulting from this mixture of disciplines and the complete freedom to follow interesting phenomena led to many important advances in these fields and made the Argonne Cancer Research Hospital known throughout the world.

Jake continued to rise through the academic ranks, be-

coming chairman of the Department of Medicine in 1961, the Joseph Regenstein professor in 1965, and dean of the Division of the Biological Sciences and Pritzker School of Medicine in 1966, a position he held until 1975. During this period he also returned to direct, for a short time, the Franklin McLean Institute, which was the Argonne Cancer Research Hospital under a new name. He became professor emeritus in 1976 but continued an active interest in research and in taking care of patients. He did not actually retire from the faculty until 1981 and even then remained very active in a number of extra-university activities until his death. He also devoted time to making wild-fruit jellies and to sculpting hardwoods from trees on his country place after chemically curing the wood.

His activities included a number of national boards, most especially those connected with the National Academy of Sciences and the Institute of Medicine. He was past chairman of the Section of Medical Sciences as well as chairman of the Committee on the Study of Postdoctoral Fellowship and Traineeship Programs in the Biomedical Sciences, chairman of the Committee on Science Policy for Medicine and Health. He also served on the Committee on Cancer Diagnosis and Therapy. In addition he was a member of the Committee for Radiation Studies (USPHS) and the Advisory Committee on Isotope Distribution (USAEC) and was the U.S. representative at the First and Second International Conferences on Peaceful Uses of Atomic Energy. Jake also was a member of thirty-seven other committees and boards.

HONORS

Jake was honored many times by many institutions; a partial list follows:

• Election to the National Academy of Sciences (1965), the American Academy of Arts and Sciences (1967), and the Institute of Medicine (1970) ;

• Election as a master of the American College of Physicians (1968);

• Recipient of the Janeway Medal of the American Radium Society (1953), de Villiers Award of the Leukemia Society (1956), American Nuclear Society Award (1963), Phillips Award of the American College of Physicians (1975), Theodore Roosevelt Rough Riders Award and Hall of Fame from the State of North Dakota (1976), Gold Medal of Merit and Knight of the First Order from King Olaf V of Norway, and the Borden Award of the AAMC;

• Honorary Sc.D. degrees from North Dakota State University (1966) and Acadia University, Nova Scotia (1972); and

• Election as a laureate of the Lincoln Academy of Illinois and recipient of its Order of Lincoln in Medicine and Health (1979).

RESEARCH ON THE START OF CHEMOTHERAPY

Jake's war-time association with the Toxicity Laboratory led him to the study of nitrogen mustards and their effects on hemopoiesis. In collaboration with Clarence Lushbaugh he studied dose effects of these toxic compounds in causing severe decrease in white cell number of experimental animals. In 1943, based on these experimental studies, he started to study the clinical efficacy of one nitrogen mustard [methyl-bis (β-chloroethyl) amine hydrochloride] as an anticancer agent. The first patient treated had lymphatic leukemia and had not responded to any of the then therapeutic regimens. Treatment with nitrogen mustard did cause a partial remission although the side effects were very severe. A quotation from Jake's article "From Atom to Eve"

gives a sense of what it was like to embark on such a bold adventure in an unprecedented therapy of a devastating disease:

It may be difficult for many to understand the deep concern one has when one is giving an extremely toxic but potentially therapeutically effective chemical to a patient for the first time. True, one has the advantage, in a deliberately planned human experiment such as this, that the dose is controlled or calculated from experience with animals and from knowledge of all the specific organ and systemic effects of a wide variety of dose schedules. Human beings generally, but not always, respond to a drug or to a toxic substance in a way similar to animals. Therefore the first trial is inevitably a time of great concern. Obviously, to proceed with this clinical trial, we had to obtain the permission of Dr. George Dick, chief of medicine, as well as of Franklin McLean, the director of the Toxicity Laboratory. Dick was experienced as a clinical investigator, and his cautious supportive role in the venture cannot be overemphasized. The participation of Dr. Charles Spurr and Dr. Taylor Smith as part of the clinical research team was essential. Lushbaugh, with his vast biological and pathological experience with the nitrogen mustard gases in general, and with the particular one we employed (methyl-bis), was a constant observer and advisor and, in fact, must be credited not only with the idea to proceed but with invaluable suggestions on dose schedules and possible toxic manifestations of the drug.

After I gave the injection, I remained with the patient for 24 hours. Within 15 minutes the patient became extremely nauseated and for several hours had severe vomiting; but about 8 hours after the injection, he was able to drink water, although he had no appetite. All vital signs were normal and remained so. Two and 4 days after the first injection, the same dose was repeated. Each time severe nausea and vomiting followed. But the high blood count came down, and the leukemia-infiltrated lymph nodes and spleen became smaller. The patient definitely had a remission.

At about this time investigators at Yale were also using these compounds for the same purpose and the studies at both the University of Chicago and Yale University initiated the present era of cancer chemotherapy. Soon after the patient was treated Jake used nitrogen mustard to treat a

second patient, with Hodgkin's disease, who showed a lasting remission. These results were so promising that an extensive series of clinical trials were undertaken. War-time restriction prevented publication of the results of these trials and by the time the censorship was lifted the Chicago group had treated close to fifty patients with long-term remissions in about two-thirds of them. Treatment of leukemias remained a lasting interest of Jake.

In addition to nitrogen mustards Jake explored the treatment of several neoplasias of the blood-forming system with radioisotopes with indications of success, especially with ^{32}P.

RESEARCH ON RECOVERY FROM RADIATION INJURY

Another outgrowth of Jake's war-time work derived from the Manhattan Project (Jake wrote an engaging account titled "From Atom to Even" in 1981 of how he became involved in that project and what ensued). He had done an extensive study of the effects of ionizing radiation on hemopoiesis and found that the blood-forming system was among the most sensitive to radiation. In an attempt to determine the relative importance of spleen versus bone marrow in overall hemopoiesis he subjected mice to an otherwise lethal dose of X rays to destroy the bone marrow while the spleen was exteriorized and shielded from the radiation. Surprisingly the mice survived the radiation. This was true even when the shielded spleen was removed a few minutes after the radiation or when spleen cells were injected into nonshielded, radiated mice. A large number of experiments led him to the tentative conclusion that a blood-borne, humoral factor was responsible for the recovery from severe radiation injury. The conclusion that the effect was due to a humoral factor was largely based on Jake's observations that heterologous spleen cells (e.g., rabbit) were as effective as isologous cells in promoting the survival of the

irradiated mice. Since he expected that an immune response to heterologous cells would have eliminated them from the irradiated host mouse, it seemed reasonable to infer that the effect was due to a noncellular substance that was not immediately inactivated by antibodies. At the time these experiments were done it was not widely known that ionizing radiation severely damaged the immune system, so that antibodies to foreign cells would not be made. Eventually the humoral hypothesis was shown to be wrong; the effect was found to be due to repopulation of the blood-forming system of the radiated animal with either cells coming from the shielded spleen or exogenous cells. Even if the first interpretation was wrong these experiments led directly to the concept of hemopoietic stem cell repopulation of radiated hosts and to the whole field of bone marrow transplantation as it is now practiced therapeutically.

RESEARCH ON ERYTHROPOIETIN AND ERYTHROPOIESIS

In the midst of these experiments while Jake was carrying out his clinical duties (he always considered this his most important work), his administrative duties as head of hematology and chair of medicine, and while being an inspiring teacher of medical students and administering a research institute, he made time to embark on a new field of studies in hemopoiesis. In collaboration with two medical students and the writer of this memoir he started to study the role of the substance termed erythropoietin in the regulation of red cell formation. Evidence for the possible existence of this substance and its nature was, at best, sparse. His intuition, guidance, and unstinting support led to major advances in the study of erythropoietin including the findings that it was made in the kidney and that its production was regulated by the need for oxygen relative to the availability of hemoglobin. Jake's leadership and initia-

tive in erythropoietin research led eventually to the purification of human erythropoietin, its later cloning and expression in "commercial" quantities, and its present use in the therapy of anemia of chronic renal disease.

My own interaction with Jake during many years of joint research, especially on erythropoietin, was characterized by an interesting duality in approach. Jake's vast knowledge of biology, derived from his deep study of medicine, permitted him to use an intuitive approach to research. He "knew" aspects of biology that he could not explain, especially to a literal biochemist who felt more comfortable with data. Surprisingly, we collaborated easily—without friction—and complemented each other's approach. In addition, his support both intellectually and with research funds was unstinting. This was especially important when the work went slowly, when we had to develop a large-scale source of erythropoietin and new assay methods, and when publications were not numerous.

Those of us who worked on the second floor of Argonne hospital will always associate Jake with noontime music. His two longtime technicians, Edna Marks and Evelyn Gaston, spent their lunch hours practicing flute and recorder, filling the hall and Jake's office with music.

Despite his great achievements Jake remained a humorous, compassionate, and generous person who took great pleasure in being the catalyst for other people's successes in science. His devotion to his patients was legendary and his influence on clinical and experimental hematology will be lasting, especially through the continuing contributions being made by the large number of eminent hematologists and other scientists who trained with him or who had the great good fortune to be part of his staff in the Argonne Cancer Research Hospital.

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