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# FRANK JAMES DIXON
1920—2008

*A Biographical Memoir by*

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*Biographical Memoir*

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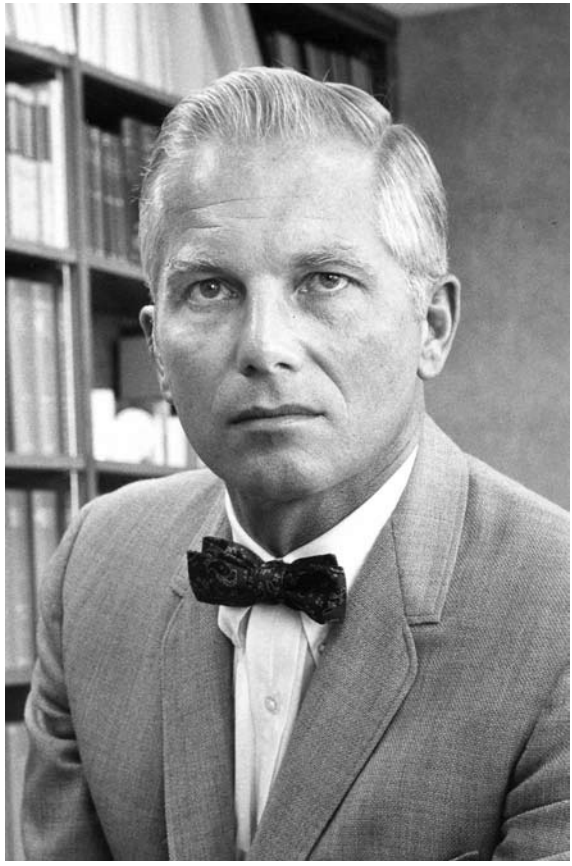

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# FRANK JAMES DIXON

*March 9, 1920—February 8, 2008*

BY MICHAEL B. A. OLDSTONE

FRANK J. DIXON, AN EXCEPTIONAL SCIENTIST who merged the fields of experimental pathology and immunology to develop immunopathology as a coherent discipline, died February 8, 2008, in his La Jolla, California, home from complications of valvular heart disease. He was 87.

His scientific achievements began with understanding the nature of antibody formation and antigen-antibody relationships and interaction. In the late 1940s he developed techniques to tag proteins and other molecules with radioactive iodine, a procedure still in use today. This method allows one to map and follow the progress of such molecules through the body to their ultimate location, where they can be quantitated. As a result, such antigen-antibody immune complexes and the inflammatory mediators they induce can be identified and linked with the diseases they cause.

Using experimental animal models, Dixon was able to show specific antigen-antibody complexes concentrated at sites of tissue damage, especially in the kidneys, blood vessels, heart, and joints, and the activation at those sites of inflammatory mediators such as complement. He extended those findings in laboratory animals to humans with kidney and heart disease and lupus erythematosus. With his students and colleagues he expanded that inquiry by tracking

antibody-mediated injury to membranes. Later he linked those results with chronic persistent viral infection caused by Aleutian disease of mink, lymphocytic choriomeningitis, and retroviruses. Studies of the last two pathogens indicated for the first time that a host with a persistent infection induced congenitally or in utero is not immunologically tolerant to the infecting agent. Instead, the infected host mounts an antiviral immune response at the B cell level that results in the formation of virus-antibody immune complexes, leading to immune-complex disease in the renal glomeruli and blood vessels later in life.

The fruits of his labor were recognized early when, in 1951, the American Association for the Advancement of Science named him the nation's leading medical researcher under the age of 35. In 1971 he was elected to the National Academy of Sciences and in 1975 he received the Albert Lasker Medical Research Award for his pioneering work defining the immunological basis of tissue diseases, especially renal and vascular injury.

Frank Dixon was a highly motivated and complex man whose most distinguishing traits focused on his drive for excellence in himself, his coworkers, and their joint work. His leadership skills were extraordinary, always governed by his strong vision of important and doable scientific tasks to explore. Those of us working intimately with him, and eventually independent of his orbit, recognize that Frank had the intelligence, charisma, and leadership to have been a great U.S. senator or chief executive officer of a major corporation. I have selected just a few episodes that exemplify his management style, persuasive force, and commitment to excellence overall, as well as to biomedical research in particular.

He was the youngest chair of pathology or of any department at the University of Pittsburgh School of Medicine, hav-

ing achieved that role at age 30. There he recruited a cadre of experimental pathologists to focus on inflammation of the immune response. He assembled a critical core of faculty to engage in experimental work and ensured that they had sufficient time for research while also fulfilling the requirements for teaching pathology to medical students and providing pathology service for the hospital. To achieve his goal of doing unimpeded research Dixon recruited pathologists to perform solely anatomical and clinical pathology with little or no requirement to do research and utilizing one faculty salary to pay for visiting experts in the noninflammatory and nonimmunologic disciplines of pathology required to complete medical school requirements. When the administration at Pittsburgh became confining and threatened to limit the ability of Dixon and his experimental team to do research, Dixon looked for a new location.

His vision, determination, and leadership enabled him to convince four of his faculty at Pittsburgh to give up salaried positions, move to La Jolla, California, and devote themselves to full-time research, assuring their financial support by garnering National Institutes of Health grants. These four, along with Frank Dixon, were the founders of the Scripps Research Institute. One was Joe Feldman, a longtime colleague who worked with Dixon in Shields Warren's laboratory at Harvard. Feldman went on to a distinguished career in immunology, doing research primarily on the fine structure of immune reactants and later taking over and modernizing *The Journal of Immunology*. Another was Bill Weigle, whom Frank inspired to move from work as a technician to become a graduate student and then faculty member. Bill, who had no plans to enter graduate school, came from a working-class steel-mill environment and was a club boxer. The initial molding of Bill Weigle's career reflected the humanism-worker background that passed from Dixon's father and Frank himself.

In time Bill Weigle became a dominant player in the area of autoimmune disease and tolerance. The third member was Joe Vasquez, among the first to use the Albert Coons fluorescent antibody technique, who later left to become the chair of pathology at Duke. The last member of the five founders who came to La Jolla was Charlie Cochrane. After finishing his medical training at Rochester, Charlie joined the Pittsburgh team, initially to work with Bill Weigle, then went on to manage his own laboratory and achieve importance in the field of identifying inflammatory mediators.

Undoubtedly Dixon's most remarkable accomplishment was the move in 1961 when he deliberately and in the face of considerable risk created his new research institution. His plan was to concentrate entire independent laboratories on researching experimental models of human disease. This goal led Dixon and his carefully chosen faculty to accept an invitation from the small, financially limited Scripps medical clinic, which offered no institutional barriers to full-time research provided it paid its own way. This enterprise preceded the building of the Salk Institute and the University of California, San Diego, in La Jolla. From a beginning with five staff members and seven postdoctoral fellows, the institute evolved into one of the world's premier research institutions, which launched and enhanced the careers of many prominent immunologists, virologists, and experimentalists. The five original faculty members expanded to 180 in 2009; the seven initial postdoctoral fellows rose to over 650; and a newly formed graduate school now accommodates 220 students—in all, more than 2,000 professors, postdocs, and other personnel.

My personal observations of Frank Dixon's leadership, love of basic biomedical research, commitment to institution building, and mentoring ability began in late 1966 when I entered his laboratory in La Jolla as a postdoctoral fellow.

This was five years after Dixon's move from Pittsburgh to establish a new research institute and one year after the first research building was completed. I joined his laboratory with Paul-Henri Lambert, Jean-Charles Cerottini, and William Willoughby. Lambert, who came from Liege, Belgium, was to work on autoimmune disease in the lupus mouse model (NZB/NZBxW)$F_1$). Following his training with Dixon, he returned to Belgium but eventually moved to Geneva, where he worked at the World Health Organization, becoming a distinguished scientist there and at the University of Geneva. Paul later became head of the WHO Immunology Program. Jean-Charles Cerottini came from Lausanne, Switzerland, and the laboratory of the well-known immunochemist Henri Isliker. Jean-Charles worked on purification of membranes and immune reactions. Cerottini returned to Lausanne, where on the basis of his academic work he replaced Islicker and became director of the Ludwig Institute in Lausanne. Bill Willoughby returned to Johns Hopkins, where he joined the faculty of the pathology department and eventually left to become head of the Department of Pathology at the University of South Carolina. Already in Dixon's laboratory when I arrived were Howard Grey, Emil Unanue, Richard Lerner, and Tom Edgington. All were eventually elected to the National Academy of Sciences (Unanue, Grey, Lerner, myself) or the Institute of Medicine (Unanue, Lerner, Edgington, myself). Unanue went on to receive the Lasker Award as his mentor had earlier. In 1986 Lerner succeeded Dixon as the second director of the research institute.

After my first month in Dixon's laboratory, I received a phone call from Eugene Braunwald, chair of the Department of Medicine at the University of California, San Diego, located near Scripps in the seaside hills of La Jolla. The call was an invitation to attend in the hospital's medical ward for one month a year. Encouraged and flattered by Dr.

Braunwald's invitation, I met with Dr. Dixon to inform him of my good luck. Looking at me intently and narrowing his eyes, Frank Dixon first congratulated me on the invitation and then suggested I might do it 12 months a year. The message was interpreted easily and instantaneously. I declined Braunwald's invitation, understanding clearly that Dixon's rule of full-time commitment to basic biomedical research was a privilege and not a luxury.

Frank James Dixon was born in St. Paul, Minnesota, on March 9, 1920. His maternal grandfather was Albert Kuhfeld, who emigrated from Austria as an orphan and became a railroad engineer in Minnesota. He had three children: a daughter, Rosa, Frank's mother; and two sons, one of whom had a son who became a major general in the U.S. Army. Frank's father was a machinist and an activist in the Farmer-Labor Party. As a consequence Frank Dixon was reared in a progressive, liberal environment with an appreciation of the workingman, traits that colored his political views throughout his life. The first award of the many he eventually received was granted by the Mankato (Minn.) Free Press, a prize given him as an outstanding news delivery boy in appreciation of hard work and excellent performance in all weather conditions, including the winter months. It was an award that Frank cherished, along with his Lasker Award.

After high school, Frank entered the University of Minnesota undergraduate school in 1936 with a major in mathematics. Under pressure from some instructors warning that mathematics was a difficult arena in which to earn a living, Dixon switched to a premedical curriculum. It was at the first dance for newcomers at the university that he met Marion Edwards, who became his wife of 62 years. With the coming of World War II the undergraduate and medical school course was shortened, resulting in Dixon receiving his medical degree in 1942. From there he was shipped first to the

Great Lakes Naval Station and then to Pensacola, Florida, as a lieutenant in the medical corps of the U.S. Marines. He went to the Japanese theater of war in the Pacific, received a Purple Heart for wounds suffered at Okinawa, and was subsequently sent to Japan as a member of the U.S. occupation army. He returned to the States in 1946 and worked with Shields Warren at Harvard Medical School, Department of Pathology, for two years as a research assistant. During this time, he was introduced to and trained in the use of radioisotopes. Robert Moore recruited Frank to the Department of Pathology at Washington University, St. Louis, where he remained as an instructor from 1948 to 1951.

In 1951 at the age of 30 he and his family moved to Pennsylvania for his ascent to chair of the Department of Pathology at the University of Pittsburgh, a position he held for 10 years before his final move to California to found the Department of Experimental Pathology and assume directorship of the new research institute at Scripps Clinic.

Those who knew and worked with Dixon were well aware of his enthusiasm for fitness and athletic pursuits. His competitiveness was obvious when playing tennis or squash or jogging with him at noontime through Torrey Pines State Park adjacent to the Scripps Clinic complex, by 1974 relocated out of the downtown La Jolla area. In terms of running he persisted usually until those with him quit. It was a contest of wills rather than a friendly sport. Even into his 70th year he ran several miles up steep inclines and paths until his back, knees, and ankles rebelled.

Over the years Dixon received numerous nationally and internationally recognized awards for his professional efforts: The Honorary Fellow Award from the Royal College of Pathologists, an honorary degree from Washington University, the Jean Hamburger Award from the International Society of Nephrology, Paul Klemperer Award from the New York

Academy of Medicine, Distinguished Service Award from the Lupus Foundation of America, Flame of Hope Award from the Terri Gotthelf Research Institute, Gold-Headed Cane Award of the American Association of Pathologists, Theobald Smith Award in Medical Sciences from American Association for the Advancement of Science, Parke-Davis Award from the American Society for Experimental Pathology, and the Lasker Award from the Albert and Mary Lasker Foundation. He also served as president of the American Association of Immunologists and of the American Association of Pathologists. He was for many years associated as editor with *Advances in Immunology*.

In addition to being an outstanding scientist Frank Dixon was a terrific mentor, having trained over 78 postdoctoral fellows (the first being David Talmage), a number of them going on to election to the Academy and many to senior research and academic positions in the United States and Europe. Frank Dixon was a great builder. The foundation for today's Scripps Research Institute was built during the 25 years of Dixon's directorship from 1961 to 1986.

Frank Dixon is survived by his wife, Marion; their three children, Janet, Frank, and Michael; four grandchildren; over 78 postdoctoral fellows whom he personally mentored; and the institution to which he gave birth.

## SELECTED BIBLIOGRAPHY

1951

With D. W. Talmage, S. C. Bukantz, and G. J. Dammin. Antigen elimination as an index of immune response. *Fed. Proc.* 67:243-255.

1952

With D. W. Talmage, P. H. Maurer, and M. Deichmiller. The half-life of homologous gamma globulin (antibody) in several species. *J. Exp. Med.* 96:313-318.

1957

With W. O. Weigle and J. C. Roberts. Comparison of antibody responses associated with the transfer of rabbit lymph-node, peritoneal exudate, and thymus cells. *J. Immunol.* 78:56-62.

1959

With C. G. Cochrane and W. O. Weigle. The role of polymorphonuclear leukocytes in the initiation and cessation of the arthus vasculitis. *J. Exp. Med.* 110:481-494.

1961

With J. D. Feldman and J. J. Vazquez. Experimental glomerulonephritis—pathogenesis of a laboratory model resembling spectrum of human glomerulonephritis. *J. Exp. Med.* 113:899-920.

1964

With E. R. Unanue. Experimental glomerulonephritis. IV. Participation of complement in nephrotoxic nephritis. *J. Exp. Med.* 119:965-982.

1965

With E. R. Unanue. Experimental glomerulonephritis. V. Studies on the interaction of nephrotoxic antibodies with tissues of the rat. *J. Exp. Med.* 121:697-714.

With E. R. Unanue. Experimental glomerulonephritis. VI. The autologous phase of nephrotoxic serum nephritis. *J. Exp. Med.* 121:715-725.

With C. G. Cochrane and E. R. Unanue. A role of polymorphonuclear leukocytes and complement in nephrotoxic nephritis. *J. Exp. Med.* 122:99-116.

1966

With P. J. McConahey. A method of trace iodination of proteins for immunologic studies. *Int. Arch. Allergy Appl. Immunol.* 29:185-189.

1967

With R. A. Lerner and R. J. Glassock. Role of anti-glomerular basement membrane antibody in pathogenesis of human glomerulonephritis. *J. Exp. Med.* 126:989-1004.

With T. S. Edgington and R. J. Glassock. Autologous immune-complex pathogenesis of experimental allergic glomerulonephritis. *Science* 155:1432-1434.

With M. B. A. Oldstone. Lymphocytic choriomeningitis: Production of antibody by "tolerant" infected mice. *Science* 158:1193-1195.

1968

With P. H. Lambert. Pathogenesis of glomerulonephritis of NZB/W mice. *J. Exp. Med.* 127:507-522.

With T. S. Edgington and R. J. Glassock. Autologous immune complex nephritis induced with renal tubular antigen. I. Identification and isolation of pathogenetic antigen. *J. Exp. Med.* 127:555-572.

Pathogenesis of glomerulonephritis. *Am. J. Med.* 44:493-498.

1969

With M. B. A. Oldstone. Pathogenesis of chronic disease associated with persistent lymphocytic choriomeningitis viral infection. I. Relationship of antibody production to disease in neonatally infected mice. *J. Exp. Med.* 129:483-505.

1970

With G. Tonietti and M. B. A. Oldstone. Effect of induced chronic viral infections on immunologic diseases of New Zealand mice. *J. Exp. Med.* 132:89-109

With M. B. A. Oldstone. Pathogenesis of chronic disease associated with persistent lymphocytic choriomeningitis viral infection. II. Relationship of anti-lymphocytic choriomeningitis immune response to tissue injury in chronic lymphocytic choriomeningitis disease. *J. Exp. Med.* 131:1-19.

1972

With M. B. A. Oldstone and T. Aoki. Antibody-response of mice to murine leukemia virus in spontaneous infection—absence of classical immunological tolerance. *Proc. Natl. Acad. Sci. U. S. A.* 69:134-138.

1973

With C. B. Wilson. Anti-glomerular basement membrane antibody-induced glomerulonephritis. *Kidney Int.* 3:74-89.

With M. B. A. Oldstone, G. F. Mitchell, and H. O. McDevitt. Histocompatibility-linked genetic-control of disease susceptibility—murine lymphocytic choriomeningitis virus infection. *J. Exp. Med.* 137:1201-1212.

1974

With A. N. Theofilopoulos and V. A. Bokisch. Binding of soluble immune complexes to human lymphoblastoid cells. I. Characterization of receptors for IgG Fc and complement and description of the binding mechanism. *J. Exp. Med.* 140:877-894.

1976

With A. N. Theofilopoulos and C. B. Wilson. Raji cell radioimmune assay for detecting immune complexes in human sera. *J. Clin. Invest.* 57:169-182.

1978

With B. S. Andrews, R. A. Eisenberg, A. N. Theofilopoulos, S. Izui, C. B. Wilson, P. J. McConahey, E. D. Murphy, and J. B. Roths. Spontaneous murine lupus-like syndromes—clinical and immunopathological manifestations in several strains. *J. Exp. Med.* 148:1198-1215.