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MALCOLM ROBERT IRWIN
1897—1987

A Biographical Memoir by
RAY D. OWEN

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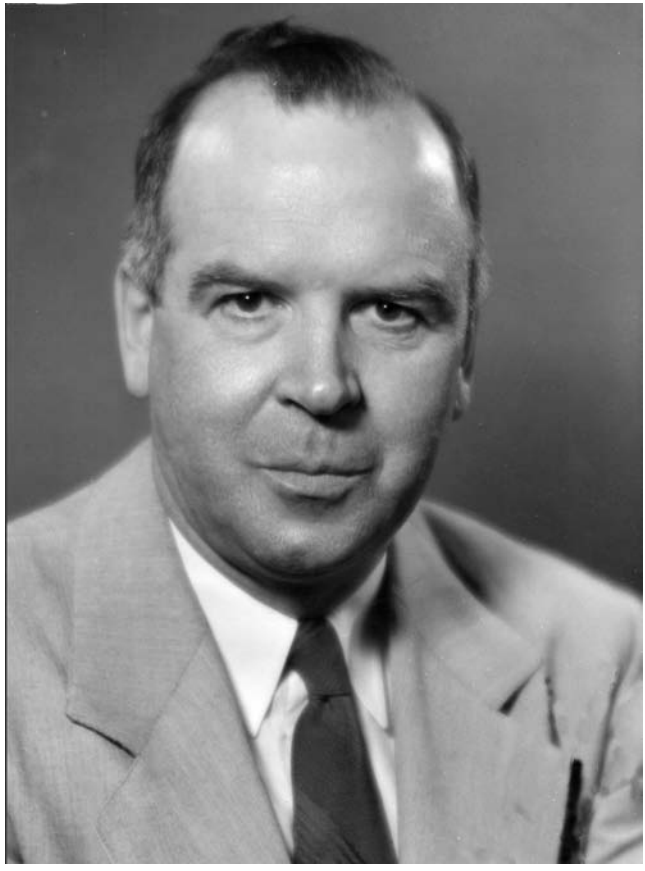
Biographical Memoir



MALCOLM ROBERT IRWIN

March 2, 1897–October 12, 1987

BY RAY D. OWEN

M. R. ("BOB") IRWIN DEVOTED his scientific research life to two related areas. First, contrary to what he believed to be the prevailing opinion when he began, he maintained that genetic susceptibility or resistance of the host affects the processes of infection by a pathogen. Inventing the term "immunogenetics," he became recognized as a pioneer in that vital field, a leader over many decades. Second, he reasoned that antibodies provide tools for defining antigens segregating as inherited variations within and among species. His assumed one gene-one antigen concept developed insight into evolutionary relationships difficult to assess in other ways. Working at first with pigeons and doves, he and his group extended their studies to domestic birds and animals, into areas of important agricultural concern. As a leader he achieved important goals for the University of Wisconsin and for science in the nation and the world.

Born in Artesian, South Dakota, three-year-old Bob Irwin moved in 1900 with his family to an Iowa farm near the town of Ireton. He attended a country school but transferred at sixth grade to the larger school in Ireton, where there were six in his graduating class. "My father," he wrote, "died when I was 15 years old, and since each of the three children wished to attend college, I spent three years at work

to acquire enough money for a part of the cost of a college education."[1] He valued growing up on a family farm in a rural area, learning about work, industry, and efficiency on the farm and making lifelong friends in the community.

In 1916 he entered Iowa State College but remembered that on graduation in 1920 no interest in natural science had been awakened by his undergraduate experience. He liked reading, history, and mathematics, but his main interest was baseball. Later in life handball and tennis provided regular, welcome relief from the stresses of work.

On graduating from Iowa State and faced with uncertainty of what career path to follow, he chose to spend three years at the American Farm School at Salonika in Greece. That experience stimulated thoughts of using scientific procedures to improve farm animals and plants. Returning to Iowa State in 1924, he began graduate studies to that end, inspired especially by Professor E. W. Lindstrom of the Department of Genetics. It was then that his first area of lifetime interest took form. In the main part of his Ph.D. thesis research he reported that rats, surviving generally lethal induced infections with *Salmonella enteritidis*, produced progeny more resistant to the pathogen than the average of the original population. Surviving parents, therefore, passed on to their offspring a degree of inherited resistance. His first research paper briefly reporting this result was published in the *Iowa State College Journal of Science* in 1928. A long extension followed in *Genetics* in 1929.

He believed that the next step should be to determine the physiological basis for natural resistance by applying the methods of immunology and genetics. He was awarded a National Research Council Fellowship to study with W. E. Castle at the Bussey Institution of Harvard University, and for a second year, 1929, with L. T. Webster at the Rockefeller Institute for Medical Research in New York City. Although it

resulted in no publication, the Rockefeller experience was definitive, especially his interactions with Karl Landsteiner, O. T. Avery, and Michael Heidelberger, whom he always admired. He had further thoughts of studying genes and their effects by immunological techniques, which he carried to the University of Wisconsin when he took a position there in the summer of 1930.

His appointment at Wisconsin was jointly with bacteriology and genetics, in the College of Agriculture and the U.S. Department of Agriculture Experiment Station. The Department of Genetics had been founded 20 years earlier by L. J. Cole, the first genetics department at an American university. E. W. Lindstrom, who was later to influence young Bob Irwin at Iowa State, had joined Cole at Wisconsin in 1919 but left for Iowa State in 1922, the year R. A. Brink came to Wisconsin. Irwin was therefore only the fourth member of the genetics faculty over its first two decades, and one of only three in residence in 1930.

The Genetics Department had originally been established in the College of Agriculture in the expectation that the emerging science of heredity would make important contributions to the productivity of farm animals and plants. However, Cole, its chair, was not at home in an agricultural environment; he was known as a basic scientist devoted to comparisons of species and using pigeons and doves rather than farm animals for his observations. When R. A. Brink joined the faculty in 1922, his appointment was partly to make the connection of genetics with agriculture, in his case cultivated plants, more realistic and valuable.[2] Irwin's appointment, too, was regarded as strengthening the practical basis of genetics, and his interest in the hereditary aspects of disease resistance seemed a good fit, especially when he turned his attention to brucellosis, contagious abortion in

dairy cattle. The first of his lifetime areas of research was therefore well suited to the position at Wisconsin.

The second area found even better opportunity. Cole maintained extensive breeding collections of backcross and species hybrids of pigeons and doves. Irwin saw these populations as ideal for his goal of using antibody reagents to identify inherited antigens on blood cells as an approach to understanding the genetic basis of species relationships in evolution. The first set of a long series of papers was published in 1936, and achieved wide recognition.

Meanwhile, the study of genes and their physiological effects on disease resistance was proving difficult. Contagious abortion, caused by *Brucella abortus* in cattle, was a major concern in Wisconsin's dairy industry. In 1936 Irwin, with veterinarians B. A. Beach and F. N. Bell and in 1937 with E. W. Shrigley, published laborious studies on the bactericidal action of blood and the activity of serum complement without evident relation to variations in disease susceptibility. I became a graduate student under Cole in 1937, and was given the opportunity to earn for my education by working in Irwin's laboratory during the summer. I recall long hours with a hand-cranked Burroughs calculator and a sorter for punched cards, enumerating the various blood cells in differential counts and testing for correlations with *Brucella* infection. It was not work that stimulated intellectual enthusiasm, and the consequent publication, by Irwin and Bell in the *Journal of Infectious Diseases* in 1938, escaped notice of my routine part in the analysis. There was no significant correlation in the proportions of the various types of leukocytes with resistance or susceptibility, or with any aspect of reaction to the infection. Irwin's regretful conclusion in 1951 that "there is at present no known substance in the blood which may be used as an index of the response to an infection of a normal or immunized animal"[1] had to await other approaches, based

on molecular genetics of the immune system. In those later approaches he was to play no part.

Working in the second main field of his interests, using antibodies to define inherited cellular antigens in species comparisons, proved to be much more rewarding. The initial approach was straightforward: Blood from a species of dove injected into a rabbit produced an antiserum that reacted with cells from the donor species. It also reacted with cells of related doves. But when the antibodies that reacted with, for example, the related ring dove were removed, there remained antibodies specific for the original donor. These donor-specific antigens were individually recognizable when, in Cole's collection of backcross hybrids, genetic segregation and assortment had separated one from another. Irwin could conclude that any particular antigen, say d-1 of the pearlneck dove, was a unit if all of the backcross hybrids having it reacted to the same antibodies. Under the one gene-one antigen hypothesis this reflected a gene in the pearlneck dove distinguishing it from other doves. Another antigen, to be labeled d-2, could be similarly recognized, independent both serologically and genetically of d-1. His 1939 paper in *Genetics* listed nine such units distinguishing pearlneck from ring doves, and two others not yet fully defined. Other papers over that interval, most with Cole as a coauthor, reported similar studies with other species. Irwin received the Daniel Girard Elliot Medal of the National Academy of Sciences in recognition of that work.

The idea that the cellular antigens were closely related to their corresponding genes was based mainly on the absence of gene interaction in their appearance; one gene-one antigen was the rule. The gene-antigen effect was expressed without modification by developmental or environmental factors—a strikingly direct relationship. In his 1939 paper Irwin quoted J. B. S. Haldane's 1937 suggestion that "the gene is a

catalyst making a particular antigen, or the antigen is simply the gene or part of it let loose from its connection with the chromosome."[3] But as early as 1932 Irwin had encountered a clear exception to the one-to-one relationship. When an antiserum to the cells of a species hybrid was absorbed to remove all of the antibodies to which either parent reacted, there remained antibodies specific only for the hybrid. This hybrid substance reflected the interaction of genes from the parent species and was not the direct result of a gene in either of them. In 1976 Irwin recalled Haldane's reaction on being told of the hybrid substance: "There goes a beautiful theory exploded by a single fact." Again, real understanding of genes and their actions had to await later developments by others in molecular genetics and immunology.

The extension of Irwin's program into studies of inherited individual similarities and differences in farm animals and birds became the prime lasting source of his laboratory's preeminence. In a herd of dairy cattle kept for the studies of contagious abortion, blood from one cow could be injected into another. This gave rise to antibodies specific for inherited antigenic differences segregating within the species. With L. C. Ferguson, a veterinarian working postdoctorally in his laboratory, and graduate student C. Stormont, Irwin published in the 1942 *Journal of Immunology* the definitive follow-up of the initial publication on the immunogenetics of cattle blood cell antigens. Two dairy cattle breed associations, the Holstein-Friesian Association and the American Guernsey Cattle Club, saw very practical uses for this work. For example, a purebred cow bred to a purebred bull could produce a purebred, registered calf, but if the sire of the calf was in question, the calf could not be registered and was less valuable. Blood tests in Irwin's lab could offer reliable evidence in cases of questionable paternity. About this time artificial insemination from selected bulls began to play a

large role in the improvement of dairy cattle. Blood tests could now identify the progeny of these bulls when questions arose. The tests became a vehicle for individual identification.

The support of the breed associations, in those days before the National Institutes of Health and other sources of grants, greatly implemented the work. When I took up postdoctoral work in the laboratory in 1941, it was the cattle program I joined, with Stormont as my mentor. We provided paid services to the breed associations, and in the process collected a great deal of information from the blood samples they shipped to us, often including whole herds and large families of cattle, ideal for our basic genetic and immunological studies.

Others in the laboratory initiated extensions of the methods to chickens, ducks, swine, and sheep; we even studied bison. The Wisconsin laboratory became an internationally recognized resource for research and training in the immunogenetics of domestic animals. The many younger people who passed through his laboratory and the Department of Genetics—undergraduate and graduate students, postdoctorals, and participants from all over the world, and fellow faculty members—remember "his concern for the healthy growth of science and his innate generosity—a loyal friend and colleague."[4] My own recollections include the memory that he was not, in a formal sense, a particularly good lecturer. "When I took my first Genetics course at Wisconsin in 1937, Irwin was the teacher. His first lecture was largely a detailed listing, written on the blackboard, of genera and species of birds and the results of crosses among them. My lecture notes have a marginal comment: 'If you ever teach Genetics, don't start this way.'"[5] But "he was exceedingly loyal to the University and to the genetics program. His was a participating loyalty, not lip service … He was

modest … with an unfailing pleasant manner and sense of humor."[6] Elected to the National Academy of Sciences in 1950, he succeeded R. A. Brink as chair of the Genetics Department in 1951. Irwin's period in that position, to 1965, was marked by a great expansion of the department, including a new building completed in 1963. He was involved in bringing several distinguished scientists to the genetics faculty, including Sewall Wright and Joshua Lederberg, among others. Outside the university he served as treasurer, vice president, and president of the Genetics Society of America, and in active roles in other societies and on editorial boards of several journals. Not a seeker for honors, he nevertheless was honored by the Royal Swedish Academy of Agriculture, American Society of Animal Science (the Morrison Award), and Deutsch Gesellschft f. Zuchtungskunde (the H. von-Nathusius Medal). At the time of his death he was survived by his wife, Margaret ("Peggy"); his daughter, Harriet Anne; his son, Joseph Robert; and four grandchildren.

When Bob Irwin was elected to the National Academy of Sciences, there was no Genetics Section. He, R. A. Brink, and others worked to have the emerging discipline of genetics recognized with its own section, and in the early 1960s their efforts bore fruit. Irwin served as de facto chair of the new Section 26 until an elected chair could be installed. All through his life until very near the end, he continued to serve others in many unselfish ways, and he deserves to be long remembered for that, as well as for his research and other professional achievements. He disappears into the past, but his influence spreads widely, becoming increasingly dilute with time.

NOTES

1. A manuscript copy of Irwin's autobiographical sketch was submitted to the National Academy of Sciences in 1951. The quotation is from that document.
2. O. E. Nelson and R. D. Owen. Royal Alexander Brink, 1897-1984. In *Biographical Memoirs*, vol. 66, p. 8. Washington, D.C.: National Academy Press, 1995.
3. J. B. S. Haldane. The biochemistry of the individual. In *Perspectives in Biochemistry*, eds. J. Needham and D. Green, pp. 1-10. Cambridge: Cambridge University Press, 1937.
4. W. H. Stone. In memoriam, M. R. Irwin 1897-1987. *Immunogenetics* 30(1989):1-4.
5. R. D. Owen. M. R. Irwin and the beginnings of immunogenetics. *Genetics* 123(1989):1-4.
6. J. Adler, J. F. Crow, O. Nelson, and R. M. Shackelford. Memorial Resolution of the Faculty of the University of Wisconsin-Madison. On the Death of Emeritus Professor Malcolm R. Irwin. 1987.

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