W. Elwood Briles

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Elwood Briles – Resolution of Avian Blood Groups

Dr. Worthie Elwood Briles, known to his scientific colleagues and friends as Elwood, has lived a career pioneering the identification of blood group systems and their role in immunogenetics, health, and reproductive fitness traits of poultry. This biographical sketch will emphasize his experiences and research that relate to poultry disease resistance. Elwood was the first of six children in his family and was born in Italy, Texas, on January 31, 1918. His father, Worthy (Jack) Harwood Briles, worked as a house painter, paperhanger, and sign or pictorial painter over the years. His mother was Leona Hays Connally Briles. In 1919 the family lived in Idabel, Oklahoma, where Jack worked with his father and an uncle. However, the family moved to Fort Worth soon after the birth of Elwood's brother, Connally, on December 10, 1919. They lived in eight different houses in the Fort Worth area between then and 1936. In January 1923, they moved into the fourth house on a plot containing 5 acres of land, and Elwood entered the first grade. From 1926 to 1930, the family lived in the fifth house on a farm with 70 acres of land. On this farm Elwood became interested in agriculture while caring for milking cows and hogs, and working with mules while growing crops. His mother also exposed him to chickens during these years. Elwood and Connally gained experience recording data as active 4H members.

During the depression in 1930 the family lost the farm. They then moved into the first of three rental homes in Forth Worth. Elwood attended Polytechnic Junior High School in 1932 and then Polytechnic High School. In high school he sometimes studied while grazing the family cow in open fields and nearby alleys. He and Connally joined the National Guard to make extra money. Elwood was Valedictorian of his graduation class in January 1936. He then enrolled at North Texas Agricultural College (NTAC) in Arlington (now a branch of the University of Texas) so he could live at home and study agriculture. Elwood funded college by working on the NTAC grounds crew, participating in the National Guard, and working as a chemistry lab instructor. One of his students, Clara Ruth Wilson, who also lived in the Polytech area of Fort Worth, later became his wife.

Sarah Bedechek Pipkin taught genetics classes at the NTAC and recognized Elwood's scientific prowess. At the University of Texas she had worked in the Drosophila genetics labs of J. T. Patterson and Wilson Stone, and she encouraged Elwood to collect specimens for them from the Fort Worth area. Some were the origin of unique strains. In 1939, Sarah Pipkin brought Elwood to the attention of Patterson and Stone and helped arrange for his transfer to the University of Texas with a job in their Drosophila lab. Ruth Wilson also transferred there after 1 year at NTAC. Elwood graduated from the University of Texas with a B.A. degree in Zoology in May 1941. Elwood and Ruth were married June 6, 1941, and Ruth received her B.A. in Zoology that August.

Wilson Stone queried Elwood if he would be interested in studying immunogenetics with a colleague, M. R. Irwin, at the University of Wisconsin in Madison. Elwood reviewed Irwin's publications and found his research on the inheritance of cellular antigens of doves and pigeons interesting. Elwood applied for and accepted an available assistantship with Irwin in September 1941. Elwood learned the rudiments of blood grouping techniques. He then attempted to identify chicken blood group(s) by differentially absorbing antisera Irwin's group had collected from hens immunized with blood from a sister. One antiserum had the potential of recognizing an antigen product from one gene. This antiserum failed to react with the red blood cells of newly hatched chicks from positive parents, but was found to be reactive with cells from the chicks two weeks later – a delayed reactivity now known to be characteristic of B system histocompatibility antigens.

In the summer of 1942 it was inevitable that World War II would interrupt Elwood's graduate work. Details of Elwood's experiences from September 1942-December 1946 are recorded on page 648 in "The Fighting Men of Texas," Historical Publishing Company of Dallas, Texas, 1948. Briefly, he worked as an inspector at the Badger Ordinance Plant north of Madison, then joined the Army Air Force and received pre-meterology training, and subsequently served in the Medical Corps as a serologist at Mitchell Field, Long Island, New York.

Elwood and Ruth's first child, Susan, was born December 26, 1943 in Amherst, Mass., and their son David was born May 26, 1945 in Hemstead, N.Y. That August World War II ended, and by November 17, Elwood was discharged from the army and they returned

to the University of Wisconsin. Upon resuming his research Elwood suggested to advisors M. R. Irwin (Genetics) and W. H. McGibbon (Poultry Science) that they study a few fair-sized families of chickens including dams and sires. Following several isoimmunizations and appropriate absorption of serum, analyses indicated several allelic specificities were detected. An evaluation of chicks from new matings revealed the presence of two blood group loci, ultimately designated as A and B. Each of these originally identified chicken blood group systems had several types (alleles) within the chicken lines analyzed, as published in 1950 and 1952. Meanwhile, Irwin suggested that Ruth investigate why bovine serum agglutinated erythrocytes of some chickens but not others, as previously reported by Carl Olsen. Following tests of chickens Elwood had produced and evaluated, it was discovered that the agglutination was attributable to antigens determined by alleles in the A blood group system. Elwood and Ruth both majored in immunogenetics. In 1948, they respectively received their Ph.D. and M.S. degrees.

In the fall of 1948, Elwood returned to Texas as Assistant Professor in the Department of Poultry Science at Texas A&M University, College Station. From 1951-1957 he was an Associate Professor. He taught poultry genetics and continued studies on the nature and inheritance of chicken blood group systems. Using lines at Texas A&M, he developed new antisera that identified antigenic products within the A and B locus systems based upon University of Wisconsin reference reagents. Furthermore, three new blood-group systems were identified, i.e., the C, D, and E loci. During this time Elwood was assisted by several graduate students including his brother Connally (Ph.D., 1955). Warren Johnson (Ph.D., 1956) studied the maturation of antigens within the A and B blood group systems and the ability of isoimmunizations of hens to induce hemolytic disease in chicks. Roy Fanguy (Ph.D., 1959) also trained in Elwood's lab. Fanguy wrote a very useful training bulletin on blood-typing, and he continued on the Poultry Science faculty following Elwood's departure. Elwood began research collaborations utilizing antisera he had developed at Texas A&M to evaluate chickens of defined lines at other universities and at commercial breeding companies. Three important collaborations began in 1950. I. M. Lerner at the University of California invited Elwood and Ruth to analyze chickens in specialty lines and in a production-bred flock studied by doctoral student Fred Shultz. Evaluation of the effect of blood types on fitness traits in commercial lines at Hy-Line Poultry Farms, Des Moines, Iowa, was initiated with Courtney P. Allen. Elwood also learned that Douglas Gilmour had established independent research on chicken blood groups at Cambridge University in England. Following exchange of antisera, the data revealed that Gilmour had independently verified existence of the A, B, C, D and E loci, as well as two new ones, i.e., the L and N systems. Elwood and Ruth's third child, Sara Jean, was born in Bryan, Texas, on March 14, 1953.

Elwood's research at Texas A&M impressed breeders at the DeKalb Agricultural Association, which bred and sold hybrid chicks (as well as hybrid corn, sorghum and pigs). Elwood accepted an opportunity to serve as Head of Immunogenetic Research at the DeKalb Ag in DeKalb, Illinois, from September 1957 to August 1970. Ruth worked as an associate, and along with others, provided excellent technical support. Using A, B, C, D, and E antisera purchased from Texas A&M, rapid progress was made in producing

reagents for these systems in DeKalb Ag chicken lines. Following the identification of alleles in the known systems, five new blood group systems, i.e., H, I, J, K, and P, as well as L (previously defined by Gilmour) were identified within 2 years.

Elwood desired to pursue full time academic research on chicken blood groups so in 1970 he was appointed a Professor of Biological Sciences at Northern Illinois University, DeKalb, Illinois. To help initiate Elwood's research at the new location, the DeKalb Agricultural Association agreeably furnished single-cross chicks and a supply of blood typing reagents. Elwood and Ruth bought a 30-acre farm in nearby Sycamore, and in 1971 they built the home they had dreamed of. Elwood also built a chicken house for their research chickens as they were too numerous and costly to maintain in university facilities. Over time, their farm increased to 101 acres containing many varieties of trees they planted. This farm is thoroughly appreciated by them and their three children and their families. In 1987 Elwood "retired", but retained an appointment as an Adjunct Professor of Biological Sciences and continued his research. Ruth worked as an NIU Research Associate from 1970-2001.

Extensive collaborations between Elwood's NIU blood-typing lab and other laboratories resulted in numerous, broad-ranging, significant achievements. His roles in delineating the extensive complexity of the B blood group system will be reviewed first. In 1961, Louis Schierman and Arne Nordskog showed that genes in the B blood group system were the major determinant of tissue histocompatibility in chickens. In 1976, Karel Hala published data showing that the B locus contained two systems of closely linked genes, now termed BG and BF region genes, and that the BF region determined histocompatibility. The B system was subsequently recognized as the major histocompatibility complex (MHC) in chickens, and the combined BG and BF regions were termed the B haplotype. In the 1970's**,** the Briles laboratory provided extensive confirmatory serological evidence for two B loci based on numerous independent crossovers between the BG and BF regions. Antigenic markers attributable to the BG genes were expressed only on erythrocytes, whereas those of the BF genes were expressed on all nucleated tissues including erythrocytes and lymphoid cells. Then in 1980, Donald Ewert at the Wistar Institute clarified how the BF region consisted of two separate gene systems that produced BF and BL antigens through experiments using antisera and chickens, some of which were provided by Elwood. The BL antigens were primarily on B-lymphocytes (produced by the bursa of Fabricius and associated with production of antibodies), whereas BF antigens were present on B and thymus (T) derived lymphocytes as well as on cells of other tissues. Recently others have sequenced the DNA of many BG, BF, and BL genes.

Additional complexity in the chicken MHC genes was identified in the 1990's. Marcia Miller at the Beckman Research Institute analyzed DNA from pedigreed chickens produced by Elwood, and an independent system of genes very similar to the BF and BL MHC genes was discovered. This gene system is on the same chromosome as the B MHC, but is inherited independently, and was termed the Rfp-Y complex. The genes in this system are now internationally termed the MHC-Y genes, and those in the B haplotype are termed the MHC-B genes.

In the 1980's, Stephen Bloom at Cornell University used cytological methods to identify trisomic chickens. These trisomic chickens had one extra small chromosome. Randy Cole suggested that this author should test some of Bloom's trisomic chickens with B locus specific antisera, and some were found to have antigens for three alleles. This linked the MHC-B haplotype to microchromosome 16 of the chicken. Bloom's group subsequently collaborated with Elwood for extensive additional studies on trisomic and tetrasomic inheritance, as well as on the expression of B genes involving several different B haplotypes.

Elwood has been a leader in defining the role of the B haplotype in resistance to disease. Marek's disease (MD) is a lymphoproliferative cancer disease of chickens caused by a cell-associated herpesvirus named Marek's disease virus (MDV). In 1967, an abstract by Hansen and colleagues at Hy-Line Poultry Farms first suggested that the B haplotype was associated with MD resistance. In the 1970's, Elwood conducted extensive studies in regards to Marek's disease in collaboration with Howard Stone at the USDA Regional Poultry Research Lab in East Lansing. The classical documentation of the B system's role in resistance to Marek's disease (MD) lymphomas was achieved in 1977 using crosses of Line N and P chickens, developed at Cornell University by R. K. Cole. Cole had selected Lines N and P, respectively, for MD resistance or susceptibility from a Cornell Randombred line. When chickens from crosses of Lines N and P produced by Stone and infected with MDV were blood-typed by Elwood, the B21 allele from Line N was found to be associated with resistance to MD. In contrast, B19 from Line P was associated with MD susceptibility. These results were substantiated using blood-typed chickens from the Regional Cornell Randombred stock provided by W. H. McGibbon at the University of Wisconsin. Importantly, B recombinant chickens developed by Elwood and analyzed with Stone indicated that MD resistance was attributable to the BF region of the B21 haplotype, whereas the BG region did not influence MD resistance. The influence of MHC-Y genes on MD resistance has also been analyzed in collaboration with Patricia Wakenell at the University of California. MHC-Y influenced MD resistance in some of their analyses, but this effect was weaker than the effect of MHC-B. MHC-Y did not influence MD resistance in studies by others using different chicken lines.

Exogenous avian leukosis viruses (ALV) are associated with lymphoid leukosis and other tumors in chickens. In the 1960's, Lyman Crittenden, at the USDA, Agricultural Research Center in Beltsville, MD, analyzed blood group antisera provided by Elwood to see if there was any association between various antisera and susceptibility to ALV. One antiserum termed "R" was shown to detect susceptibility to endogenous subgroup E ALV (i.e., ALVE). Using R antiserum, the expression of ALVE has been shown to lead to tolerance following infection with exogenous ALV, which culminated in increased development of tumors induced by the exogenous ALV, e.g. lymphoid leukosis and myeloblastosis. In 1974, with G. F. Springer at Northwestern University, the R_1 antigen was shown to be cross-related to the human blood-group MN antigens, apparently due to the expression of sialic acid. Additional R antiserum developed by the author at the USDA lab was shown to detect the receptor to endogenous ALV in conjunction with

expression of endogenous virus envelope. Special ALVE congenic strains of chickens have been developed with aid of R antiserum.

In 1910, Peyton Rous showed that a filterable agent extracted from chicken muscle sarcomas could be transmitted to other chickens. This was called Rous sarcoma virus (RSV). In the early 1960's Teruko Hanafusa and Harry Rubin showed that a strain of RSV, called Bryan strain, was replication defective and required a helper virus called Rous Associated Virus (RAV) for infectivity. RAV was soon shown to be a strain of ALV that induced avian leukosis and other neoplasms. These strains of ALV were called RSV(RAVn), where the n stands for the subgroup of ALV. The replication defective RSV was shown to contain the src oncogene required for induction of sarcomas. Chickens susceptible to RSV(RAVn) (called RSV below) develop a large sarcoma within 2 weeks of injection of the virus in the wingweb. Subsequently, the tumor would continue to grow and often metastasize and kill the chicken within 4-10 weeks, or regress, depending on the genetic line of chicken.

In 1977 chickens were produced by Walter Collins and colleagues at the University of New Hampshire from crosses between inbred lines obtained from the East Lansing USDA lab. Following infection with RSV (ALV containing the Rous sarcoma virus), Elwood's serological analysis of the B locus antigens of these chickens defined the B locus's dramatic effect on the regression or progression of the sarcoma tumors. Chickens with B2 generally completely regressed their tumors in contrast to tumor progression in chickens with B5. An independent paper by Schierman and others in the same 1977 issue of *Immunogenetics* confirmed this remarkable report. Additional collaborative studies at Collins lab using recombinant chickens provided by Elwood showed the BF region was responsible for tumor regression. Recent collaborations at the UNH with Robert L. Taylor, Jr., have continued to analyze the influence of the B haplotype as well as other blood group systems on RSV tumor regression. Genes in several other blood group systems, including the C and L loci, as well as MHC-Y, have been shown to influence RSV tumor regression. While genes at these loci significantly influence tumor regression, their effects are not as strong as those of MHC-B.

Elwood conducted numerous additional collaborative studies related to other disease organisms. For example, in 1973, with K. S. Brown at the National Institutes of Health, an antigen determined by a K system allele was shown to be the genetic basis for hemagglutination of some chickens' erythrocytes by the vaccinia virus. Moreover, Elwood has often provided or identified chickens of known blood types with a fixed B haplotype for use in cell transfer studies. In a recent collaboration with Ellen Collison's group at Texas A&M, Elwood provided MHC compatible chickens for analysis of the ability of a form of T cells from resistant chickens to transfer protection against infectious bronchitis virus.

The Elwood and Ruth Briles laboratory has been the principle site for production of blood-typing antisera for chickens since the 1950's. Elwood's willing assistance ultimately led to his laboratory becoming a world reference laboratory for those wishing to evaluate or substantiate blood types in chickens and other bird species. During

Elwood's tenure at Northern Illinois University, his lab often supplied antisera to numerous collaborators. Some of those collaborations are mentioned above, but there were many others. For example, an individual lab would request an antiserum evaluation to confirm that the antiserum was detecting the system specificity expected and did not contain antibodies to another system. Furthermore, Elwood's lab would often provide an antiserum once it was determined to be useful in blood-typing within a certain line of chickens. They also blood-typed chickens for many commercial companies. This was an extensive task requiring testing pedigreed chickens with a broad array of antisera before determining what antisera were useful for that flock. They wrote several articles on how to do blood-typing and interpret and use the results. Elwood also published information on how antisera are useful in forensically verifying the purity of genetic lines. Indeed, some of his antisera were supplied to the USDA lab at East Lansing to verify line purity until the author developed additional antisera for that purpose. Importantly, in the 1990's, Elwood began extending the use of chicken blood typing antisera to identify the MHC genes in wild fowl populations, e.g., sandhill cranes, ring-necked pheasants, and northern bobwhite and masked bobwhite quail. Results based on serology were further substantiated by DNA technologies developed in collaboration with Marcia Miller. NIU students receiving a Ph.D. while assisting in research were Edith Erkert, Farida Kopti and Susan Jarvi. The careful, extensive technical assistance of doctoral student Renee Kopulos and Research Associate Linda Yates in recent studies is gratefully acknowledged.

An important by-product of research during the production of specific blood-typing antisera over the years at NIU has been the gradual development of very valuable unique genetic resource lines of chickens. Elwood imported from the University of Wisconsin an Ancona line of chickens. Over the years many specific alleles for 13 blood-group system loci, as well as recombinant B haplotypes, have been introduced and maintained by breeding into the Ancona and two primarily White Leghorn lines. By immunizing chickens identical for genes at all systems except one locus, specific antisera are produced. It is important that these unique lines, containing many commonly seen forms of blood-type genes, are preserved both as living stocks and as frozen samples of semen and cells. Such stock preservation will assist future studies on the research that Elwood has pioneered over 65 years, i.e., to determine the relevance of blood-type genes in biology, particularly in regards to fitness traits and disease resistance.

In addition to landmark research achievements, Elwood provided strong leadership in national and international committees. Important service included his membership on an Expert Panel of Blood Group Scientists for the Food and Agricultural Organization, United Nations, from 1966-1981. Elwood was the Lead Participant of an International Workshop on Nomenclature for the Chicken Major Histocompatibility Complex, held at Innsbruck, Austria, in 1981. He was a major contributor of cells and antisera analyzed at the workshop, and was the first author of the important paper published from that conference. Most relevant has been his service as a Project Leader in the National NE-60 (recently, the NE-1016) CSREES Regional Project Technical Committee from 1970 to the present. The subject of the NE-60 has been "Genetic bases for resistance and immunity to avian diseases." The committee generally consisted of over 15 participants,

and Elwood was frequently an active cooperator in over one-fourth of the members' annual reports. Most of the collaborative studies since 1970 described above were with project members.

Extensive blood-typing of chickens at Northern Illinois University from 1970 onward would not have been possible without essential basic funding. Elwood was diligent and successful in obtaining competitive grant funds, initially from the National Institutes of Health and then from the National Science Foundation. Nominal funds were received for blood-typing services performed for many collaborators having grant support and as remuneration for blood typing analysis of commercial breeder lines. In addition, Elwood and Ruth provided both monetary and manual support, e.g., in providing chicken housing and husbandry. Finally, the provision by the Department of Biological Sciences, Northern Illinois University, of laboratory facilities, faculty and staff appointments, and academic infrastructure was essential for the knowledge gained during Elwood Briles's extensive research and teaching career.

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Additional biographical materials may be available from the AAAP Historical Archives located at Iowa State University. Contact information is as follows:

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