A landmark contribution to poultry science—Immunological function of the bursa of Fabricius¹,²

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ABSTRACT The article “The bursa of Fabricius and antibody production” by Bruce Glick, Timothy S. Chang, and R. George Jaap first demonstrated the role of the bursa in immune development. Birds, including chickens, possess a peculiar organ, the bursa of Fabricius. The organ was recognized for more than 300 yr before its function was described in 1956. Discovery of the bursa as an essential component of the immune response began by accident. Removal of the bursa, bursectomy, during the rapid growth period diminished the antibody response to Salmonella. A paper describing this exceptional finding was initially rejected by Science and ultimately published in Poultry Science. This revelation triggered sequential events leading to the understanding of the dichotomy of the immune response. Additional work in multiple laboratories over many years revealed fundamental immune mechanisms attributable to the bursa. Understanding those mechanisms advanced agricultural and biomedical science.

Key words: bursa, B cell, antibody, lymphoid tissue

INTRODUCTION

The bursa of Fabricius is a lymphoid organ of birds. The precise function of the organ was a mystery from its discovery in 1621 until the 1956 journal article designated as a Poultry Science landmark paper. That publication entitled “The bursa of Fabricius and antibody production” by Bruce Glick, Timothy S. Chang, and R. George Jaap appeared in Poultry Science (Glick et al., 1956). The central role of the bursa of Fabricius in the immune response of chickens was discovered by accident. Several factors including inspiring, enthusiastic teachers, an inquisitive student, serendipity, and the advantages of the land grant system converged to facilitate this discovery. The synergy of these factors facilitated a discovery fundamental to the understanding of the function of the immune system. The contribution of each factor and their synergies are explained below.

Prologue

The bursa of Fabricius was described by Hieronymus Fabricius ab Aquapendente in 1621 (Adelman, 1967). Preceded by other famous Italian anatomists, Vesalius and Fallopius, Fabricius was an anatomy professor at Padova who taught Sir William Harvey (Ribatti et al., 2006). Adelman (1967) translated the embryology writings of Fabricius. Included in the description of the bursa, Fabricius posited “…I think that this is the place into which the cock introduces semen so that it may be stored there” (Adelman, 1967). The contentious idea that the bursa was a semen receptacle or a semen storage vessel stimulated an experiment by Harvey. Sperm survived for 20 d after a single insemination, providing temporary support for the semen storage proposal. Jolly (1915) described the organ as “a dorsal diverticulum in the proctadael region of the cloaca.”

The function of the bursa remained a mystery. Following the path to the solution of the mystery takes us from the Whiteman Street School (Pittsburgh, PA) to Rutgers University (Piscataway, NJ) to the University of Massachusetts (Amherst) to The Ohio State University (Columbus). Once solved, the continuing story takes us to Mississippi State University (Mississippi

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State, MS) and finally to Clemson University (Clemson, SC).

Inquisitive, Enthusiastic Teachers

Bruce Glick grew up in Pittsburgh, Pennsylvania. His interest in birds originated at 10 yr old when he was a student in Miss Hildebrand’s fourth grade nature study class at the Whitehall Street School. Miss Hildebrand inspired the students by her methods of conducting various aspects of that class. She borrowed specimens from the Carnegie Museum to demonstrate particular principles to the students. She led the class on field trips to observe and identify local birds as well as museum visits (Weisse, 1992). This early exposure to the world of birds piqued Bruce’s interest. Bruce, in fact, stated “the influence of a given teacher is likely to be the predominant reason for selecting a vocation” (Glick, 1983). His interest was amplified after he observed an American bittern (Botaurus lentiginosus), a medium-size heron, atop his family garage after a storm (Weisse, 1992).

Bruce enrolled in the Rutgers University College of Science after his World War II army service. He described his concern that as a science major the opportunities for the scientific study of birds were limited to bird watching. From his initial interest in birds, he had observed and identified in excess of 200 species, so this avenue of study stimulated little interest. Access to the scientific study of birds necessitated a transfer to the College of Agriculture and the Poultry Science Department (Weisse, 1992).

The move to Poultry Science was fortuitous because the faculty of that unit had expertise in genetics, nutrition, pathology, and physiology. This departmental breadth of knowledge would provide much opportunity. His transfer process required considerable persistence and a promise to spend a summer working on a farm to persuade the Poultry Science Department head, Professor Thompson, to allow a student with a nonfarm background to transfer into the curriculum. Thus, he followed his dream of studying birds and began the academic journey into his chosen field. During his course of study at Rutgers, Bruce worked with another inspiring teacher, Paul Sturkie, who later authored the unequaled text Avian Physiology. The chicken continued to be the model during graduate study. After graduation from Rutgers, Glick moved to the University of Massachusetts to study genetics with J. Robert Smyth Jr. His final stop in graduate education was The Ohio State University for PhD study with R. George Jaap (Glick, 1983, 1994).

Inquisitive Student

Bruce relates his initial exposure to the bursa of Fabricius in this manner: “One fall night in 1952 at The Ohio State University, Dr. Jaap introduced me to the bursa of Fabricius when I asked him the name of a gland he had just removed from a goose.” “This is the bursa,” he replied.

Glick asked the function of the gland, to which Jaap responded, “Good question. You find the answer.” Neither the student nor the professor realized what a profound effect this brief exchange would have on immunology as well as poultry science (Glick, 1983, 1994; Weisse, 1992).

Several months after the initial encounter, other experiments on his project were not successful. Bruce recalled the exchange with his advisor about the bursa of Fabricius. Literature searches uncovered sparse information about the bursa. Most of the references required translation from either French or Italian. A French journal contained a detailed bursa study (Jolly, 1913) including data that bursal regression occurred at sexual maturity.

This information stimulated initial studies of bursa growth. Early experiments revealed 3 phases of bursa growth. The rapid growth phase occurred from hatch to 3 wk of age. The period from 4 to 8 wk of age represented the plateau phase. The regression phase, in which the bursa diminished in size, happened after 8 wk of age. Glick’s results (Glick, 1956) showed that bursal regression occurred before sexual maturity.

Further investigation uncovered the inverse relationship between bursal growth and testes or adrenal growth. Manipulation of hormone levels affected bursal growth. Injection of either corticosteroids or androgens caused bursal regression. Caponization enhanced growth of the bursa (Glick, 1957). The next step in the overall sequence of bursa studies involved the classical method of removing the gland to assess its individual effect and the effect on other systems. Glick’s bursectomy experiments removed the gland before the twelfth day posthatch. This time point was much earlier than that used by other investigators’ studies that had found no consequence of bursectomy (Riddle and Tange, 1928; Woodward, 1931; Taibel, 1941). Despite a wealth of data, when bursectomy was performed during the rapid growth period, no obvious effect of bursectomy was revealed. The function remained a mystery (Ribatti et al., 2006).

The next event in the bursa story is best described in the quote by Louis Pasteur “Dans les champs de l’observation le hasard ne favorise que les esprits préparés (In the field of observation, chance favors only the prepared mind).”

Serendipity

The island country of Sri Lanka lies in the Indian Ocean. The country was previously known as Ceylon, and before that by its Persian name, Serendip. A fairy tale from that country, the Three Princes of Serendip, described heroes who had a talent for making valuable discoveries by accident. Horace Walpole coined the term “serendipity” to describe this phenomenon in a 1754 letter to his friend Horace Mann (Remer, 1965).
Serendipity moved to the forefront of the bursa story in 1954. Fellow graduate student, Timothy Scott Chang, needed birds to produce antibody against Salmonella. Bruce had birds of the appropriate age. The birds and their antibody would be used in a demonstration for an undergraduate class. A week after immunization, the birds were bled to conduct the plate agglutination test. The results were that bird after bird produced no agglutinating antibody. In fact, 80% of the birds did not produce antibody. Glick examined the identifying wing band numbers and found that those chickens producing no antibody had been bursectomized. The control birds that produced antibody had undergone sham bursectomy.

The 2 students then undertook a series of experiments to investigate the finding. White Leghorn and Rhode Island Red chickens were either bursectomized or retained as controls. In both breeds, there was a significant effect of bursectomy on antibody production (Table 1). These experiments with larger numbers of birds confirmed the original serendipitous finding that removal of the bursa of Fabricius would inhibit antibody production.

The confirmed results were summarized in a manuscript prepared for Science. After review, the paper was rejected with the editor’s suggestion that “further elucidation of the mechanism...should be attempted before publication” (Glick, 1983). A revised manuscript was published in Poultry Science (Glick et al., 1956). In 1979, that influential paper was designated as a citation classic by Current Contents based upon the article being a highly cited publication (Glick, 1979). Current data indicates that the paper was cited 581 times between 1965 and 2008.

Three groups expanded the findings of the original paper. The suggested “further elucidation” after the manuscript rejection by Science had begun. However, Glick (1983) described the ultimate understanding of the bursal mechanisms as requiring “the resources of, at least, nine laboratories in the United States and Canada and major laboratories” around the world. Harold Wolfe’s University of Wisconsin laboratory (Madison), including Augie Mueller, conducted additional studies on the bursal role in antibody production (Mueller et al., 1960, 1962). A dichotomy of the immune response was proposed by Szenberg and Warner (1962). Max Cooper working with Robert A. Good at the University of Minnesota (Minneapolis) combined thymectomy, bursectomy, and sublethal radiation to demonstrate that the bursa controlled humoral immunity, whereas the thymus controlled cellular immunity (Cooper et al., 1966). This last paper was itself cited by the Journal of Immunology as a 2006 Pillar of Immunology (Webb and Kincade, 2006).

### Importance of the Land Grant System

The original bursa study and the subsequent career-long investigation of that organ were both enhanced by the land grant system. When Bruce Glick transferred to the Department of Poultry Science to follow his dream of studying birds, he could not have done this easily outside of the land grant system. His investigations at The Ohio State University clearly were intended to understand a fundamental process in a species crucial to agriculture. The fact that the results benefited agriculture as well as immunology demonstrates the interrelationship of the 2 fields. Investment in the land grant research has benefits far beyond those for agriculture. Funding from the Hatch projects ensured some continuity in the research. The flexibility afforded by the land grant institutions allowed multiple paths of investigation emanating from the bursa (Glick, 1979) and the ability to attract quality students.

The initial observation of the bursa role in antibody production led to other research in physiology, endocrinology, genetics, behavior, anatomy, as well as immunology. These research efforts opened the door to discoveries of an extra bursal site for IgM formation, chemical bursectomy using testosterone or cyclophosphamide, electron microscopy of bursal follicles, and the bursal role in immunoglobulin class switching. Corollary investigations revealed effects of embryonic exposure to exogenous hormones, a critical period of mating behavior, chicken lines derived from divergent selection for bursa size, temperature influences on immune responses, chicken lymph nodes, chicken lymphocyte life span, bone marrow cell types, and characteristics of lymphocyte inhibitory factor (Glick, 1977, 1991). In later years, Imre Olah and Bruce Glick described a secretory cell in the bursa of Fabricius (Olah and Glick, 1978). The secretory cell contributed to the bursal microenvironment involved in B-cell development.

### Serendipity II

The early research identified the bursa’s rapid growth period. Spurred by that result, Glick performed bursec-
tomy early in the rapid growth period, which proved integral to the demonstration of the bursa’s effect. Returning to the original bursal experiment, there is a second bit of serendipity. Antibody production to *Salmonella* develops later posthatch compared with responses to other antigens. Injection of the bursectomized and control chickens with an antigen other than *Salmonella* might not have shown a response difference.

Bruce identified 4 factors that contributed to the 1956 paper: his extreme interest in birds that led him to The Ohio State University; Jaap, who accepted Bruce as a student and first showed him the bursa; the 1952–1953 early bursa growth studies; and Timothy Chang (Bruce Glick, Clemson University, Clemson, SC, personal communication).

**Epilogue**

Bruce Glick moved to a faculty position in the Mississippi State University Poultry Science Department in 1955 followed by publication of his landmark paper in 1956. He concluded his productive research, teaching, and administrative career at Clemson University. The progression from student to department head spanned 48 yr. The bursa of Fabricius remained the central research theme. During his lengthy tenure at these 2 academic institutions, he published 225 scientific papers, review articles, and book chapters (see selected publications in Appendix). He educated 29 graduate students (Table 2) who received 33 degrees, either MS or PhD. No fewer than 13 of these students engaged in academic or government research careers. Other students entered fields including human or veterinary medicine. Table 3 lists 17 postdoctoral fellows who expanded their experience in the Glick laboratory. He continually recognized the contribution of the many graduate students, postdoctoral fellows, collaborators, as well as laboratory technicians and secretaries. Bruce often recognized supportive administrators such as James E. “Red” Hill, head of Poultry Science at Mississippi State, as contributors to his success.

His teaching included courses in immunobiology, avian physiology, and physiological genetics. Each course contained unique subject matter that was presented in an uncommon way. A course was divided into equal segments with each concluded by a student-led class discussion. Students would present classic papers and other relevant information on assigned topics from that course segment. The examinations were comprised of a subset of questions selected from

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<th>Year(s)</th>
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<td>MS</td>
<td>1959</td>
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<td>Robert L. Haynes</td>
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<td>D. S. V. Subha Rao</td>
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<td>F. Douglas Brewer</td>
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<td>Mahmooda S. Kulkarni</td>
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<td>Walter C. Crawford Jr.</td>
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<td>Kenneth Landreth</td>
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<td>Robert L. Taylor Jr.</td>
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<td>George W. Oluho</td>
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<td>Vergil Davis</td>
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<td>G. Todd Pharr</td>
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<td>Judy M. Salin</td>
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Table 2. Theses and dissertations directed by Bruce Glick

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<td>Koji Sato, PhD</td>
<td>Tokyo University</td>
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<td>August P. Mueller, PhD</td>
<td>University of Wisconsin</td>
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<td>Prakash Kulkarni, PhD</td>
<td>Mississippi State University</td>
<td>1970–1971</td>
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<td>Robert S. Stinson, PhD</td>
<td>University of Arkansas</td>
<td>1976–1979</td>
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<td>Imre Olah, MD, PhD</td>
<td>Semmelweis University Medical School</td>
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<td>Magdi M. Mashaly, PhD</td>
<td>University of Wisconsin</td>
<td>1976–1978</td>
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<td>Norman Mirtin, MS</td>
<td>City College of New York</td>
<td>1978–1979</td>
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<td>Larry A. Cogburn, PhD</td>
<td>University of Illinois</td>
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<td>George G. Jeng, PhD</td>
<td>Auburn University</td>
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<td>Thomas R. Scott, PhD</td>
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<td>Akke van der Zijpp, PhD</td>
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<td>Joe Bricker, PhD</td>
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<td>Margarita Gallego, PhD</td>
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<td>John Whitesides, PhD</td>
<td>Auburn University</td>
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<td>Oyula Soos, MD</td>
<td>Semmelweis University Medical School</td>
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Table 3. Postdoctoral and sabbatical fellows working in the laboratory of Bruce Glick
the total. This method was highly effective and remains in use by others who experienced it. Numerous students independently characterized Bruce Glick as their best teacher.

His work was supported by the National Cancer Institute (Bethesda, MD), National Institute of Allergy and Infectious Disease (Bethesda, MD), the National Science Foundation (Arlington, VA), USDA (Washington, DC), and the Food and Drug Administration (Rochester, MD). Additional support was provided by the Agricultural Experiment Stations of Mississippi and South Carolina. Bruce was recognized with the Merck Award for Research in Poultry Science in 1978. The Poultry Science Association elected him a fellow in 1986. Most recently, he served as a member of the Poultry Science Association Foundation Board.

ACKNOWLEDGMENTS

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REFERENCES


APPENDIX: SELECTED PUBLICATIONS OF BRUCE GLICK


