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History of Infectious Bursal Disease in the U.S.A.— The First Two Decades

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SUMMARY. Infectious bursal disease (IBD) emerged in 1957 as a clinical entity responsible for acute morbidity and mortality in broilers on the Delmarva peninsula. The condition spread rapidly and was recognized throughout the U.S. broiler and commercial egg production areas by 1965. Early attempts to isolate the etiologic agent were impeded by a lack of specific-pathogen-free (SPF) eggs and by deficiencies in viral and serologic techniques.

By 1967, the highly infectious nature of the agent was recognized. Reliable methods were developed to isolate the virus in embryonated eggs and to adapt it to tissue culture. The agent was characterized as a virus belonging to a new taxonomic group in 1976. The immunosuppressive property of IBD virus was first recognized in 1970 and was confirmed in structured trials in 1976. An early method of control involved planned infection of chickens. This technique lowered IBD mortality but often resulted in immunosuppression and further dissemination of field virus.

A live attenuated vaccine was then developed, based on mild field isolates passaged in SPF eggs. This vaccine was federally licensed as the first of its kind for interstate use in 1968. It remains widely used today in breeders as a primer and in the control of very virulent IBD in many countries.

The first two decades following emergence of IBD were characterized by close cooperation among scientists in academia, the biologics industry, and the USDA. By 1976, mortality caused by IBD was effectively controlled by vaccination. However, the more subtle effects of immunosuppression and the tremendous economic impact of the disease were just starting to be appreciated. Recognition of Delaware variants in the mid-1980s and emergence of very virulent forms of the condition in Europe and Asia beginning in 1989 attest to the continuing importance of IBD.

Key words: infectious bursal disease, history, control, planned infection, vaccine, Vero cell

Abbreviations: AS = amnioallantoic sac; CAM = chorioallantoic membrane; DPL = Delaware Poultry Laboratories; IBA = infectious bursal agent; IBD = infectious bursal disease; IBDV = infectious bursal disease virus; IBV = infectious bronchitis virus; NDV = Newcastle disease virus

The scientific aspects of infectious bursal disease (IBD), including the molecular biology, pathogenesis, and epidemiology, have been extensively reviewed (26,30,31,36). On the occasion of the 40th anniversary of the recognition of IBD, it is appropriate to revisit some of the events and individuals responsible for developing the foundation on which subsequent control and prevention programs were based. This paper attempts to cover historical aspects of the first 20 years of IBD research. Despite significant technical progress during the past two decades, economic forces and the interaction of individual scientists in industry, government, and academia will continue to determine the direction and pace of such progress. This review will highlight the noteworthy events in diagnosis and control of the disease and will recognize key contributors to the early (1957–1977) work leading to an understanding of IBD, a significant immunosuppressive infection of chickens (45).

EARLY HISTORY

In 1957, Albert S. Cosgrove, while working as an associate of Hiram N. Lasher at Delaware Poultry Laboratories (DPL), Millsboro, Delaware, recognized a syndrome later termed "avian nephrosis" on a broiler farm near the community of Gumboro, Delaware (8,51,52,53). The syndrome became known as "Gumboro

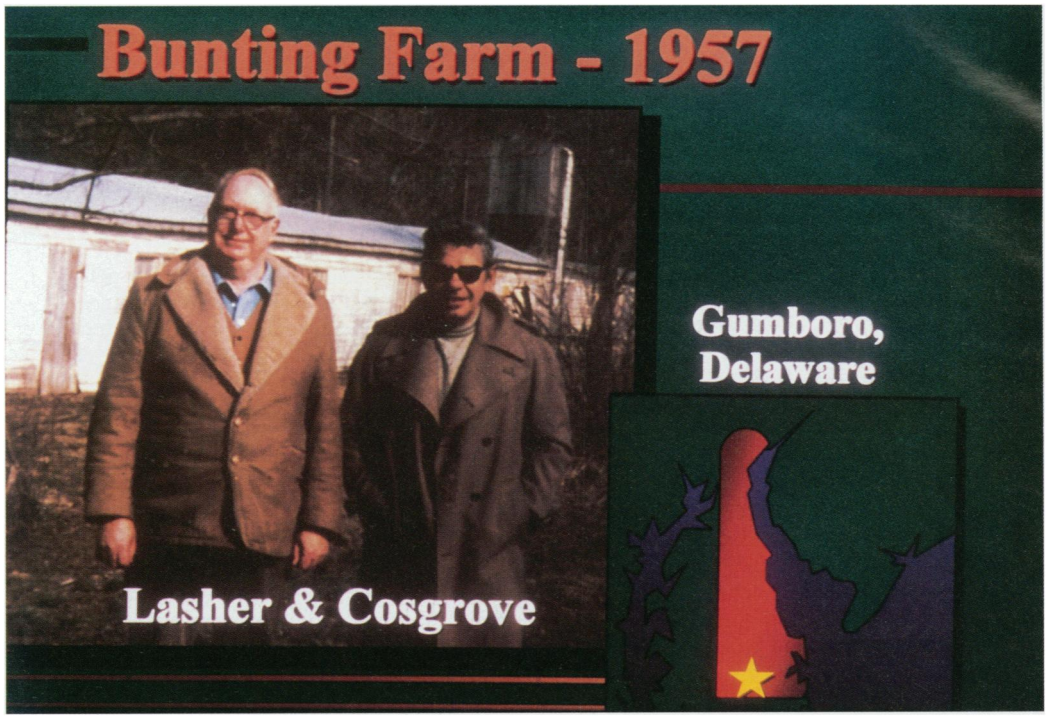

Fig. 1. The first farm known to be affected by IBD in Gumboro, Delaware. Dr. Hiram Lasher (L) and Dr. A. S. Cosgrove (R).

disease" and was the central point of discussion among professional groups such as the Del-Mar-Va Poultry Pathologists (9). This association, comprising poultry diagnosticians, vaccine development scientists, and technical service veterinarians on Delmarva, was formed in 1957. Ernest W. Waller, head of the Animal Science Department, University of Delaware, served as the first leader. In March 1959, Morris S. Cover assumed Waller's position and led the group for more than a decade. Monthly meetings of the association were held to discuss poultry disease problems in the area. The meeting minutes, circulated to attendees as the "Poultry Pathology Letter," recorded some of the first observations on Gumboro disease.

The syndrome, characterized by 10% flock morbidity and mortality varying from 1% to 10%, began to appear frequently throughout the Delmarva region. It was noted to recur successively in five or more flocks on the same farm (9,10). The early consensus was that avian nephrosis, or Gumboro disease as it came to be called, was caused by a variant infectious bronchitis virus (Gray strain) because of gross changes in the kidney. As it would turn out, this misconception arose because the two infections were concurrent in many cases and the causative agent was difficult to isolate using available diagnostic tools.

Within 3 yr of recognition of Gumboro disease on the East Coast, the condition was detected in other regions of the U.S.A. Following an outbreak of Gumboro disease in Mississippi in early 1960 (17), the syndrome was reported in Alabama, Georgia, and North Carolina (11,12). By 1964, all 13 southeastern poultry-producing states had reported cases (47). Investigations to determine the cause and the best means to control the disease were initiated in the South by several workers. USDA-ARS veterinarian Raymond Parkhurst reported that the condition occurred year-round and appeared, as it had on Delmarva, in sequential placements on the same farm. None of the conventional treatments, such as antibiotics, vitamin supplements, or molasses, altered the course of the disease. Different management practices also

had a negligible or extremely variable effect on severity or recurrence (39,40,41).

In 1961, Parkhurst's studies were complemented by the team of Allen Edgar and Yung Cho at Auburn University. They observed rapid spread of the disease from farm to farm, which they correlated with the removal and transportation for reuse of leftover feed from affected farms (14,15,17). In a paper that designated the syndrome "infectious bursal disease" for the first time, instead of "Gumboro disease," Edgar suggested using planned infection as a control measure on premises where IBD was already established. The infection could be accomplished by placing chicks on contaminated litter, spiking clean litter with contaminated material, or commingling infected chickens with the new brood (13).

One of the most concerted efforts to identify the agent responsible for Gumboro disease was initiated at L&M Laboratories, Berlin, Maryland. In the early 1960s, Donald Lynch and Elbridge Murray formed L&M by successfully recruiting a research team from American Scientific Laboratories, Madison, Wisconsin, consisting of Rollie Winterfield, Steve Hitchner, and George Appleton. In addition, they recruited Cosgrove from DPL as a diagnostic veterinarian.

The L&M group determined that the etiologic agent was indeed very different from that of bronchitis. Hitchner helped unravel the confused picture by distinguishing clinical manifestations of infectious bursal agent (IBA) and infectious bronchitis virus (IBV) (23). He astutely observed that one reason IBA had not been readily identified was that nonsusceptible embryos were often used in isolation attempts.

INVESTIGATIONS *IN VIVO*

In vivo characterization studies were conducted in several laboratories. Charles Helmboldt and E. Garner evaluated the pathogenesis of the disease with the use of tissue homogenate supplied by Winterfield of L&M Laboratories (22). In 1967, Norman Cheville of the National Animal Disease Laboratory examined the adverse effects of the agent (Edgar strain) on bursal lymphoid cells (4). Cho and Edgar complemented their field observations with characterization of IBA in experimentally infected chickens. They documented gross changes in the bursa and population shifts in circulating blood cells over the course of the infection (6). William J. Benton's group in Delaware studied the factors involved in transmission of the disease under controlled conditions (2). For these studies, Benton used virus that he had isolated from tissue samples recovered from case accession no. 2512 at the Georgetown Substation. This was the same isolate that would later be modified for vaccine production and become known as "Winterfield 2512" (49).

The team of Irwin M. Moulthrop and Carol Snedeker-Wills worked with their own field isolates at the Maryland Department of Agriculture Diagnostic Laboratory, Salisbury, Maryland. In 1967, they were able to adapt a mild isolate to the chicken embryo system (46). This ultimately became the first licensed vaccine, Bursa Vac®. Moulthrop and Snedeker-Wills also demonstrated that a homogenate of lesser mealworm larvae from a house containing an infected flock could produce lesions typical of Gumboro disease (37).

At about the same time, Malcolm C. Peckham, a poultry diagnostician at Cornell University, adapted a field isolate to embryos. He used the eighth passage to successfully immunize about 5000 chickens by the drinking water route (42). However, this vaccine was not commercialized, perhaps due to the failure of an interested industry partner to come forward and to the prospect of infringing upon a previously issued patent for the Moulthrop vaccine.

These early studies were soon augmented by work from the original L&M group. Although the Winterfield, Hitchner, and Appleton team disbanded after L&M was purchased by Abbott in 1964, Winterfield and Hitchner continued to make significant contributions. Winterfield's laboratory at Purdue University conducted controlled studies on an isolate that originated from the 20th passage of the 2512 strain obtained from Benton at the University of Delaware. Winterfield found both eyedrop and water application to be efficacious (49). His studies on the tissue tropism and persistence of the virus resulted in one of the first descriptions of the pathogenesis of infectious bursal disease virus (IBDV) (50).

Hitchner's distinguished career at Cornell began with an exploration of the phenomenon he had noted while at L&M that accounted for

some of the early difficulty in isolating IBDV (24). He found that embryonated eggs sometimes appeared refractory to viral infection for one or two unrelated reasons. First, there was the obvious finding that embryos derived from immune dams were resistant to infection. Because the immune status of breeders supplying test eggs was not evaluated by early researchers looking for Gumboro disease's etiologic agent, the effect of passive neutralizing antibodies was not considered. It should be noted that specific-pathogen-free eggs were not readily available during the mid-1960s.

Hitchner also noted that attempts to isolate or maintain serial passage of some field isolates failed even when using eggs from known susceptible flocks. The key to understanding this observation was found in the choice of inoculation routes. One of Hitchner's low-passage isolates replicated well when inoculated onto the chorioallantoic membrane (CAM) and into the yolk sac but failed to replicate when inoculated into the amnioallantoic sac (AS). A higher passaged isolate, designated 2512, did replicate when deposited into the AS but to a lower level than when inoculated onto the CAM. Hitchner concluded that the route of inoculation was critical to efficient replication of the virus and that the AS was nonpermissive for infection by an IBDV that was not well adapted to the embryo system. Thus, Hitchner further elucidated the difficulty in isolating IBDV in very early outbreaks by suggesting that some passages of virus obtained from field outbreaks had been attempted using the AS. This theory validated the independent findings of Moulthrop and Lasher, who had already determined that yolk sac inoculation was the most efficient route for vaccine production. In early isolation attempts where a mixed infection of IBV and IBDV occurred, IBV would probably have been the only virus recovered from amnioallantoic fluids. In most cases where flocks were infected with IBDV alone, inoculating into the AS would not have resulted in virus isolation.

Hitchner's interest in the influence of maternal antibodies of IBDV led him to look at the effect in chickens as well as embryos (25). He compared the resistance to virulent challenge of progeny from immune and nonimmune flocks. Maternal antibodies protected chickens from bursal pathology up to 3 wk of age. Furthermore, clinical disease, that is, obvious signs of morbidity, was prevented until 3 wk of age in challenged chickens. The fact that progeny from nonimmune hens were refractory to clinical IBD when infected during the first 21 days was also noted. This observation agreed well with most field observations. The subclinical manifestation of IBD occurring prior to 3 wk of age was not recognized until several years later when the role of the agent in immunosuppression was elucidated.

BIOCHEMICAL CHARACTERIZATION

Studies to characterize the biochemical properties of IBA were carried out on several fronts beginning in 1967. Almost simultaneous contributions came from two key teams—Benton's group at the University of Delaware (3) and Edgar's group based at Auburn University (7). Both teams concluded that the etiologic agent must indeed be a virus, relatively resistant to extreme conditions of pH and temperature and a wide range of chemical treatments. These findings readily explained the important role of contaminated litter and equipment in the transmission of the disease.

Because of the unusual nature of the virus, it was not until 1976 that Nick, Cursiefen, and Becht (38) in Germany were able to describe its structural and growth characteristics in sufficient detail to be able to conclude that the agent could not be classified into any previously recognized group. The two strands of RNA, the size and number of proteins comprising the nonenveloped capsid, and the replication cycle all were indications that the virus should be placed in a new taxonomic category.

CONTROL

The failure to control the disease by conventional methods spurred vigorous efforts to develop a vaccine that could be administered safely and effectively. Edgar, Moulthrop, and Winterfield worked independently to make such a vaccine available to the poultry industry. They were all successful in establishing different viable vaccine candidates, which, in turn, each became a progenitor of lines of many commercial vaccines used in the world's poultry industry to the present time.

The first IBDV vaccine was prepared by Edgar at Auburn University (16). The "vaccine"

was aptly termed unattenuated because it consisted of a bursal homogenate obtained from chickens infected with a field isolate. This was not only the first vaccine for field use but the first and only live "bursal-derived" product. It was used successfully in more than 3 million chickens. The vaccine satisfied an important need at the time by suppressing IBD mortality. It was a more precise method of delivering a planned infection and represented an improvement over conventional practices such as spreading virus-laden litter.

Significant progress toward controlling IBD by vaccination came only after careful selection of a relatively mild field isolate and propagation of that isolate in chicken embryos. Moulthrop and Snedeker-Wills, working for the state of Maryland at Salisbury, were the first to accomplish this. Initially, Moulthrop and Snedeker-Wills felt their isolate would have limited application as a vaccine (46). However, working closely with Lasher, who provided technical and financial support, Moulthrop was able to patent the vaccine and then assign the rights to DPL.

The 10th Annual Poultry Health and Management Short Course at Clemson University in February 1966 proved to be a watershed in the history of IBD. During the program, Edgar presented a paper entitled, "Infectious Bursal Disease (Gumboro Disease), Prevention and Control" (13). At the time, Edgar's vaccine was being widely used in the field while the Moulthrop strain was in the early stages of development. In the afternoon following the presentations, Allen Edgar, Morris Cover, Frank Craig, Irwin Moulthrop, Dale Oshel, J. Kimsey, Charles Hall, Hiram Lasher, and Gerald Peacock met in private session. One of the results of that session was the adoption of Edgar's nomenclature for the syndrome. Agreement was reached to drop the term "avian nephrosis-nephritis" in preference for "infectious bursal disease." Another outcome of the session was a recommendation against interstate movement of live bursal-derived vaccine. It was agreed that each state should be responsible for its own control program. This decision had two outcomes. First, Edgar made arrangements with John Love to produce an intrastate vaccine for Mississippi using spent chickens transported from the Sterwin coccidiosis vaccine facility at Opelika, Alabama, to Jackson, Mississippi. Second, within the next 30 days, USDA invoked the Virus-Serum-Toxin Act, which resulted in the banning of interstate movement of Edgar's vaccine, considered to be a "planned infection."

Immediately following the afternoon meeting at Clemson, Lasher and Moulthrop met informally over dinner with Gerald Peacock of the USDA. This opportunity allowed Peacock to gain a deeper understanding of the urgency attached to the problem of developing a suitable vaccine against IBD. General guidelines were discussed for licensing an interstate chicken embryo-origin vaccine. After returning from Clemson, Lasher was able to move rapidly to obtain the first federal license for an IBDV vaccine. Continued guidance and expeditious review by Bernard LaSalle, a Veterinary Biologics reviewer, further accelerated the licensing process. The interchange of information and the cooperation of Peacock and LaSalle with Lasher to license the first IBD vaccine provide an example of what can be done when government and industry decide to act together to meet an emergency. Similar collaboration between federal authorities and the vaccine industry still occurs today whenever pressing needs arise.

In 1968, DPL was granted a federal product license (29) with an indication for use in 4-to-12-day-old chickens on problem premises (16), subject to approval by state regulatory officials. It is noteworthy that, because of severe outbreaks, the vaccine was "airlifted" from Arkansas to California by poultry companies before approval by the Department of Agriculture in Sacramento. DPL (later Sterwin) supplied the entire U.S. IBD vaccine market for more than a decade. In addition, a considerable quantity of vaccine was exported. This unusually prolonged market advantage stemmed from the fact that other biologics manufacturers apparently either failed to realize the future widespread demand for such a product or, realizing the demand, did not move expeditiously to fulfill it. Even if neighboring L&M labs had recognized this opportunity, the team that could have licensed the vaccine had already disbanded.

Alongside their development of the chicken embryo vaccine, Lasher and Emil Gelenczei proceeded to adapt three field isolates to chicken and duck embryo fibroblasts with the use of blind passages (20). Fibroblasts were then, and still are, the only practical primary cell culture type for production of poultry vaccines. The

pair had noted that Landgraf, Vielitz, and Kirsch, working in Germany, had reported cytopathic effects in fibroblasts caused by IBA (28). Lasher and Gelenczei were ultimately successful in their adaptation and in proving that these isolates passed through fibroblast cell culture were immunogenic, protecting against virulent challenge. Although a notice of invention was filed, no attempt was made to license the isolates for a vaccine. The IBD tissue culture project was abandoned because the available tissue culture facilities at DPL were assigned to manufacture one of the first commercial Marek's disease vaccines. Had it not been for this capacity problem, DPL would have achieved another industry first—an IBD vaccine of tissue culture origin.

Almost simultaneous with the development occurring on the Moulthrop vaccine strain, Winterfield and his colleagues in Indiana were evaluating the promising University of Delaware isolate designated 2512 (49). After making several passages in chicken embryos, Winterfield demonstrated in 1969 that 2512 could protect against challenge with a virulent IBDV field strain isolated by Moulthrop (the IM challenge strain, not to be confused with the vaccine strain). However, as mentioned previously, commercialization of Winterfield's 2512 strain was delayed more than 10 years by the departure of key members of the L&M scientific staff.

Although the original Edgar vaccine was not acceptable for USDA licensure, a derivative of the Edgar strain was used to develop several federally approved products. In the early 1970s, Phil Lukert, Joan Leonard, and Richard Davis at the University of Georgia adapted the Edgar strain to various tissue culture systems. They first co-cultivated the virus in bursal and kidney cells and then inoculated a kidney cell passage onto Vero cells. After several blind passages, gross plaques were observed, providing evidence of the first successful propagation in a continuous cell line (32,33,34,35). Shortly after returning from Munich in 1973, Lukert adapted the virus to chicken embryo fibroblasts and then transferred the technology to P&C Biologics, Colbert, Georgia, for production of an intrastate vaccine. Although the vaccine was produced for only a short time during the mid-1970s, the adaptation was successful enough that it became known as the "Lukert strain." Derivatives of the Lukert strain have become widely used today in vaccines around the world. Subsequently, Lukert went on to make many important contributions toward our knowledge of IBD.

It might be noted that Lasher and Gelenczei's fibroblast cell culture adaptation preceded Lukert's work in that system by at least 4 years. Lukert was not aware of the fibroblast adaptation until he visited Europe in 1973 (32), illustrating the fact that results of proprietary research conducted in industry might remain unreported for years because of commercial considerations.

To fulfill a need for a milder IBD vaccine that could be used safely in day-old susceptible chickens, Lasher negotiated an agreement in 1976 with Intervet B.V. to import and develop licensing data for the Baxendale strain. This highly modified vaccine, Bursa Vac® M, did not induce bursal pathology in susceptible chickens and had no immunosuppressive effect. However, upon licensure, the mild vaccine served only as an interim measure for an industry just learning to control the new disease. Need for such a vaccine was generally limited to a 2-year period during which producers implemented breeder IBD vaccination programs resulting in transfer of maternal antibodies to progeny.

RECOGNITION OF IMMUNOSUPPRESSIVE ROLE

While the early efforts to effectively control this devastating disease were underway, new understandings of its pathophysiology were coming to light. The broader implications of the lymphoid system damage reported by Helmboldt and Garner (22) were being explored in various laboratories. In 1970, Byung-R Cho of Washington State University demonstrated that White Leghorn chickens exposed to IBDV at 1 day of age were consistently more susceptible to nerve enlargement, and, in one trial, to visceral tumors as well, following challenge with Marek's disease virus. He suggested that IBD infection was equivalent to "biological bursectomy" (5). Reports from Britain during 1972 on the interaction of IBD and Newcastle disease virus (NDV) pointed to the same phenomenon—significant immunosuppression (1,18,19) following exposure to IBDV.

Walter S. Staples, Poultry Health Director for Cobb Research Laboratory, observed the field occurrence of IBD for several years. He noted that different unrelated syndromes such as gangrenous dermatitis, airsacculitis, peritonitis, and septicemia could not be correlated to breed, age, common etiologic agent, or any defined environmental or management factor. Staples and his colleagues were led to believe that these various syndromes resulted more from enhanced susceptibility to a wide range of infectious agents than to the presence of the agents themselves. In so-called "catastrophe" flocks, the broilers were found to have high titers to IBDV whereas the source breeder flocks had low or nonexistent titers. In addition, breeder flocks experiencing very early exposure to IBD did not respond appropriately to other vaccines. Their progeny incurred higher mortality resulting from other disease agents. According to Staples, Gumboro disease could be differentiated from other diseases, such as viral arthritis, which invariably produced overt signs. Gumboro disease itself was often a clinically silent infection (48).

In 1975, Staples concluded from his field experiences that chickens used for breeding purposes should be vaccinated against IBD. He did not recommend the currently available vaccine for use in the broiler population. However, he suggested that this vaccine could be administered to 12-wk-old breeder flocks in the drinking water.

Scientists at the University of Delaware, including John K. Rosenberger, Spangler Klopp, Robert J. Eckroade, and William C. Krauss, conducted several controlled trials to study the potential role of IBD in increased susceptibility to various diseases. They successfully correlated the immune status of a breeder flock with progeny susceptibility to IBD and with the incidence of the so-called "hemorrhagic-aplastic-anemia syndrome." In a sampling of 39 flocks, the Delaware group confirmed Staples' observations that problem progeny were derived, in most cases, from IBDV-susceptible breeders (43,44).

In what may have been the first study of its kind, the Delaware group immunized immature breeders with no measurable titer to IBD and assessed progeny susceptibility to IBDV challenge at 1 day of age. The majority of progeny from immunized breeders had detectable levels of precipitating antibodies to IBDV at 1 wk of age, in contrast to a small proportion of progeny from nonimmunized breeders. As the progeny were monitored through the grow-out period, a significantly higher prevalence of IBD, gangrenous dermatitis, and aplastic anemia was noted in chickens derived from the nonimmunized dams (27).

In variations of both B. Cho's (5) and Faragher's (19) studies, Joseph J. Giambrone and coworkers at the University of Georgia studied the effect of early natural exposure to IBDV on the immune response induced by either NDV or Marek's disease vaccination (21). When day-old chickens were placed in houses contaminated with IBDV and vaccinated at 1 and 28 days of age with NDV vaccine, their immune response to the vaccine was significantly depressed compared with vaccinates placed in a clean house. The same phenomenon was observed when chickens were vaccinated against Marek's disease.

Both Rosenberger and Giambrone conducted their studies with knowledge of Peter J. Wyeth's 1975 report of the effect of IBDV on the immune response to two bacterial antigens (54). Wyeth infected chickens either at 1 day of age or 3 wk of age followed by challenge 3 wk later with either *Escherichia coli* or *Salmonella typhimurium*. He found that resistance to *E. coli* challenge was depressed in chicks exposed to IBDV either at 1 day or at 3 wk of age. The resistance to challenge with salmonella was also adversely affected in the chicks exposed to IBDV at 1 day of age. On the other hand, there appeared to be no effect on the immune response in chickens exposed to IBDV at 3 wk of age. Wyeth's study was one of the first to indicate that the age of exposure to IBDV influenced the immunosuppressive effect against specific antigens.

EPILOGUE

This review has covered only the first 20 years since recognition of infectious bursal disease. Because of its continuing importance and the extensive research efforts expended, many more events have yet to be chronicled from 1976 until the present. The recent emergence of variants in the U.S. and very virulent strains in other countries in the 1980s ensures that IBD history will continue to be made well into the next millennium.

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