Avian Disease and Oncology Laboratory: a 75 year history (1939-2014)

The Avian Disease and Oncology Laboratory, formerly known as
the Regional Poultry Research Laboratory, is part of the
Agricultural Research Service, United States Department of Agriculture
and is located in East Lansing, Michigan, USA

Richard L. Witter

About the book

This is a brief history of the USDA-ARS-Avian Disease and Oncology Laboratory, East Lansing, MI during its first 75 years. The author describes the circumstances of the Laboratory's origin as well as activities and accomplishments during the tenure of each of its five Directors. It also places these activities in the context of current concerns of the poultry industry on avian tumors and tumor virus infections. The book includes photographs of some current and former employees, visiting scientists, and collaborators. Also included are lists of professional staff, graduate students, postdoctoral research associates and visiting scientists.

As the Laboratory has been generally recognized as a leader in its field for much of its history, this book also explores the underlying reasons for its success during a particularly exciting period in the field of tumor virology.

The book also documents the close association of the Laboratory with the United States poultry industry, a partnership that has provided dividends to both parties over the years.

About the author

Richard L. Witter, D.V.M., Ph.D., joined the USDA-ARS Avian Disease and Oncology Laboratory in 1964, serving for 38 years as Veterinary Medical Officer and for 23 years as the Director. Following retirement in 2002, he continued an association with the Laboratory as a collaborator. This year (2014) marks his 50th year of association with Laboratory programs.

Witter is probably best known for his work on Marek's disease, including the isolation of turkey herpesvirus, vaccine development, and epidemiology – as well as viral strain characterization and evolution of virulence. He also contributed to knowledge on the pathology, virology, and epidemiology of lymphoid leukosis and reticuloendotheliosis. He has received numerous awards and was elected to the National Academy of Sciences in 1998.

Avian Disease and Oncology Laboratory: a 75 Year History

1939-2014

Richard L. Witter

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East Lansing, MI 49923

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in recognition of the role played by the Laboratory both in this symposium and in the field of avian tumor virus research

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Cover Photo:

Front view of the Avian Disease and Oncology Laboratory in the 1980s

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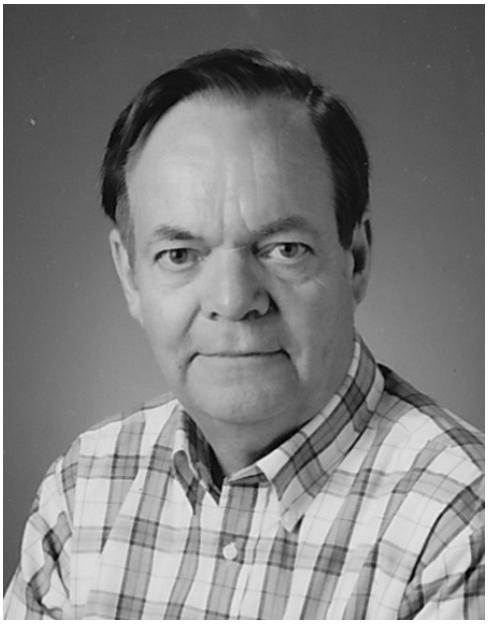
Dedication

Ben R. Burmester
1910-2009



Lyman B. Crittenden
1926-2012

This history is dedicated to two exceptional scientists who, through their vision, leadership and scientific excellence, contributed to the success of the Laboratory in an exemplary fashion.

Ben Burmester served 34 years with the Laboratory, first as Poultry Physiologist, later as Veterinary Medical Officer and the last 12 years as the Director. Ben was instrumental in the discovery of the virus that causes lymphoid leukosis in the 1940s and contributed much information about its transmission and epidemiology using the laborious assay techniques of the day, thus setting the stage for later successful eradication programs. He guided the Laboratory during the exciting years in the 1960s when the Laboratory discovered the causative virus of Marek's disease (along with others) and the related turkey herpesvirus, which was the basis for an effective vaccine against the disease. He recruited many of the scientists who carried the torch for the Laboratory during the rest of the 20th century.

Lyman Crittenden also devoted 34 years to the study of the genetics of avian tumor viruses, joining the Laboratory in 1960 as a Research Geneticist, relocating his program in 1966 to ARS facilities in Beltsville, MD, and then returning to East Lansing in 1975 for the rest of his career. Critt retired in 1989 but continued his research at the Laboratory as a collaborator through 1994. He elevated the breeding program of the Laboratory, improving and developing many new chicken lines. He discovered mechanisms for cellular resistance to avian leukosis virus and advanced the understanding of endogenous viruses in chickens. He used retroviral vectors to insert foreign genes into the chicken germline, producing the first transgenic chicken (the first case of "pathogen-derived resistance). He conceived and launched a long range project on genome mapping with many collaborators, which ultimately resulted in elucidation of the complete genomic sequence of the chicken.

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Foreword

It is an honor for me to write the foreword of this book that documents 75 years of history and achievements of the USDA-ARS Avian Disease and Oncology Laboratory (ADOL), formerly known as Regional Poultry Research Laboratory. I'm privileged to have worked 38 years at ADOL, and to have served in the position of Research Leader and Laboratory Director since 1998.

On behalf of the current and former ADOL staff, I thank my predecessor, Dr. Richard L. Witter for preparing this book for distribution at the ADOL 75th anniversary celebration. Dr. Witter joined ADOL as a research scientist in 1964, and served as Director from 1975 to 1998. Obviously, Dr. Witter with his unique institutional knowledge was an excellent choice for preparing this publication; and indeed, he has done an excellent job.

I'm also pleased that this book was made available for distribution during our celebration of the 75th anniversary of ADOL that coincided with the 10th International Symposium on Marek's disease and Avian Herpesviruses held in July 2014 in East Lansing, Michigan. This coincidence allowed scientists from various countries around the world who attended the symposium to also participate in this milestone celebration of ADOL, a laboratory with world-wide recognition in genetics, genomics, pathology and immunology of tumorous diseases of the chicken.

Finally, for 75 years, ADOL has prided itself by conducting research and providing services that are extremely relevant and critical to the poultry industry including poultry breeders and growers, vaccine manufacturers, and diagnosticians.

As we celebrate this important event, I hope this book provides a useful and interesting narrative about the history and achievements of ADOL.

ALY M. FADLY, DVM, Ph.D., dACPV
Research Leader and Laboratory Director

Acknowledgments

This book has been a group effort. Aly Fadly encouraged me to start the project and has supported it enthusiastically, providing access to the needed resources maintained by the Laboratory. Our steering and review committee, composed of Hans Cheng, John Dunn and Aly Fadly, has provided important guidance and critical review. John Dunn was largely responsible for the photographic layouts and final formatting – a Herculean effort.

Larry Bacon, Don Salter, Jerry Dodgson, Jagdev Sharma, Max Cooper, Lucy Lee, Sarah Crittenden and others have provided critical pieces of information. Kris Foight, Becky Horn and LuAnn Therrian helped with information and administrative matters. Several professional colleagues submitted pieces that are included in the concluding chapter. My profound thanks to all of the above.

The project would not have been possible without the robust collection of historical records and photographs maintained by the Laboratory. The "vault" of the Laboratory, still a locked and secure place, contains a trove of useful materials. The Laboratory has also a collection of photo albums assembled during different eras by Berley Winton, Maybelle Lott and myself – valuable sources of names, dates and images. Thanks to all who created and preserved these materials.

A thank you is due to Bruce W. Calnek, who more than 50 years ago recommended this author for a position in East Lansing. His excellent departmental history and his interesting photo section for the AAAP anniversary book were useful models for the development of this document.

This book is published by the organizing committee of the 10th International Symposium on Marek's Disease and Avian Herpesviruses. We thank the committee for its encouragement and financial support.

Abbreviations

AAAP = American Association of Avian Pathologists
ADOL = Avian Disease and Oncology Laboratory
ALV = avian leukosis virus
ALV-J = avian leukosis virus, subgroup J
ARS = Agricultural Research Service
CRADA = cooperative research and development agreement
FAPP = filtered air, positive pressure
FANP = filtered air, negative pressure
HB = Horsfall-Bauer type isolators
HEV = hemorrhagic enteritis virus
HVT = Herpesvirus of turkeys (turkey herpesvirus)
Laboratory = when capitalized, refers to RPRL or ADOL
LL = lymphoid leukosis
MD = Marek's disease
MDV = Marek's disease virus
MHC = major histocompatibility complex
ML = myeloid leukosis
REV = reticuloendotheliosis virus
RPRL = Regional Poultry Research Laboratory
SPF = specific pathogen free
US = United States of America
USDA = United States Department of Agriculture

Introduction

One may rightfully ask why the history of the Avian Disease and Oncology Laboratory (herein designated as "Laboratory") deserves to be recorded. There are several reasons. To start, the Laboratory is associated with events that have changed the poultry industry of the world and advanced science. It is associated with the lives of persons important to agriculture and science. It embodies distinctive organizational and sociological characteristics that may be considered, at least to a degree, uncommon among agricultural research institutes of the period. And it has achieved, arguably, a high degree of success.

This history is crafted from a variety of documents but is interpreted from the personal viewpoint of the author who has, at the time of this writing, a 50 year history with the Laboratory. It is thus a composite of facts and memories. Source materials are mostly from the Laboratory archives (annual reports, folders, notebooks, photographs, etc.) and are not specifically identified with citations.

This history records the story of a successful government research institution of the 20th and 21st centuries dedicated to the betterment of the poultry industry. It also contains details that may be of interest to the many persons who have a personal association with the Laboratory or whom have been influenced by its activities or its staff.

The focus is on the institution rather than individuals, but the Laboratory is surely defined by the many individuals who made it successful. References have been kept to a minimum. Accomplishments are representative of the respective eras but represent only a fraction of the total contributions of the Laboratory. Some of the accomplishments have practical application to the poultry industry and others have served to advance scientific knowledge. There is no intent to rank or prioritize these accomplishments as this task is better left to the reader.

Nomenclature for avian tumors and related diseases has changed over time. In this history, the term lymphoid leukosis (LL) is used in lieu of earlier designations such as visceral lymphomatosis. Likewise Marek's disease (MD) is used in lieu of fowl paralysis, neural lymphomatosis, ocular lymphomatosis and other similar designations. However, there are some instances where the earlier terminology, which did not recognize etiological distinctions, appears more appropriate.

Creation of the Laboratory

The Beginnings

The early history of the USDA-ARS Avian Disease and Oncology Laboratory (ADOL) has been documented by the writings of the first two directors, J. Holmes Martin and Berley Winton (4,12), as well as in documents in the Laboratory archives. The Winton history, published as a monograph in 1966, covers the first 25 years in detail and is an important complement to the present document.

It all traces back to a need, an opportunity and an idea. The need was articulated by the US poultry industry, which between 1925 and 1935 had experienced devastating mortality in growing and mature chickens from range paralysis and avian leukosis. The opportunity was created by the passage of the Bankhead-Jones Act of 1935, which provided federal funds to create regional laboratories to conduct research into "the basic laws and principles relating to agriculture."

The idea may have originated from a meeting of the directors of the 12 northeastern Agricultural Experiment Stations on September 12-13, 1935. As an outcome of this meeting, the directors petitioned the Secretary of Agriculture to designate one of the new regional laboratories, to be funded by Bankhead-Jones funds, for research to improve the viability of poultry. However, no action was taken.

Second meeting. Thus, a second meeting was organized by Prof. E.L. Dakan of Ohio State University and held in Cleveland, OH on April 5, 1937. This meeting included over 200 representatives of the poultry industry and Agricultural Experiment Stations in the Northeastern and North Central regions. As an outcome of this meeting, a 6 person subcommittee was appointed, chaired by Dr. L. E. Card (University of Illinois), and charged to prepare a detailed proposal for a regional laboratory.

The ensuing proposal was approved by North Central Experiment Station Directors in Urbana, IL on October 12, 1937, and was concurred by the Experiment Station Directors from both North Central and Northeastern regions in Washington DC on November 14, 1937. A draft of the proposed Memorandum of Understanding was approved in Cleveland OH on December 10 and 11, 1937 and submitted to the Secretary of Agriculture, Henry A. Wallace, who approved the establishment of the Regional Poultry Research Laboratory (RPRL) on December 23, 1937.

According to records at Michigan State University, the Federal budget for construction of the laboratory/office building was $85,000, with an additional $100,000 to be appropriated later for operation and additional buildings.

Property. On January 27, 1938, the Michigan State Board of Agriculture voted to recommend to USDA that the laboratory be located at Michigan State College on property located at the corner of Mt. Hope and Harrison roads. The Board further indicated that it would acquire the necessary lands and deed it to the USDA. The memo was signed by John A. Hannah, secretary to the State Board of Agriculture. Hannah, who started his career in poultry science, would later become President of Michigan State University.

After consideration of potential sites in New York, Ohio, Indiana and Michigan by a USDA committee (which included Berley Winton), the 50 acre site at Michigan State College in East Lansing, MI was selected in February 1938. This parcel of land was deeded to the US Department of Agriculture by the Michigan State Board of Agriculture on March 22, 1938.

A memorandum of understanding between the Department of Agriculture and the various Experiment Stations was signed in March 1938.

USDA oversight. The record is silent on who in the USDA took charge of the project in 1938, making the necessary arrangements for construction and initial staffing. Administratively, the Laboratory was created as part of the Bureau of Animal Industry, Animal Husbandry Research Division, Hugh C. McPhee, Director. From the surviving files, it seems clear that Berley Winton, Senior Poultry Husbandman, who reported to McPhee, was the lead person in preparation of equipment lists and coordinating the logistics with bidders, suppliers,

contractors and Michigan State University. Others may have been responsible for other aspects. This team deserves accolades for their quick and effective response to a complex mandate with a short timeline.

Construction. Construction began in July 1938 and the facility was dedicated 13 months later, on August 8, 1939. Much time and cost was saved by utilizing designs and plans prepared earlier for a USDA research complex in Beltsville, MD (now known as the Beltsville Agricultural Research Center). Clearly, the construction was on a fast track by current standards.

Lab building. The main office/laboratory building was a classic design of the period. The first and second floors were divided into quadrants; each quadrant consisted of a larger room adjacent to the main hall and an office in the rear. Most of these larger rooms served as laboratories although two on the first floor served as office and administrative space. A conference room was located on the 3rd floor. The basement contained utilities, a necropsy room, a walk-in cooler, dishwashing facilities and an autoclave.

Over the years, the space has been renovated repeatedly, so that the original concept is now difficult to discern. There was, however, a vault in the basement equipped with a steel door and bank vault-type lock system, apparently for the protection of research data against fire hazard. This room has from the beginning been the repository for administrative records, and was the location of much of the historical material used in preparation of this report.

Staff. The original senior research staff consisted of were established and well-respected scientists. Dr. J. Holmes Martin, formerly in charge of Poultry Husbandry and Genetics at the University of Kentucky was appointed as director in January 1939. Dr. Nelson Waters, formerly at Iowa State College, was also appointed as geneticist in January 1939. Dr. Carl Brandly, formerly at University of Illinois, was appointed as veterinarian in March 1939. These 3 individuals launched the operations and set the tone for much of what followed. Their stature and experience surely contributed to the launching of the research program.

Experiment Stations. The laboratory was conceived as a cooperative venture with 25 cooperating Agricultural Experiment Stations in the Northeastern and North Central regions. This arrangement reflected the role of the Experiment Stations in the creation of the Laboratory and also was practical given that none of the recruited staff were experienced in the field.

The first meeting of this consortium occurred in East Lansing in February, 1939, and resulted in the appointment of an advisory council of 3 pathologists, 3 geneticists, and 3 specialists in management and nutrition to work with the staff in developing and conducting a research program. Prominent among council members were Dr. Erwin Jungherr, pathologist at the University of Connecticut, who was a world authority on avian tumors, and Dr. Frederick B. Hutt, geneticist at Cornell University, who was a world authority on genetic resistance to avian tumors. Dr. L. E. Card from University of Illinois, who chaired the earlier committee to develop the original proposal for establishment of the Laboratory, represented the nutrition and management area.

Laboratory Name

The original facility as dedicated in 1939 was named the *Regional Poultry Research Laboratory* (RPRL). A photo exists of what appears to be the Laboratory front with a sign "*US Regional Laboratory – Poultry Research*" (photo album). If this was indeed the first sign erected on the Laboratory structure, it did not remain long and was soon replaced with a curved placard sign with the proper identification.

A shortened (but unofficial) name, *"Regional Poultry Laboratory (RPL),"* soon came into popular use. This term may have been inadvertently encouraged through the convention of designating tumor or viral strains isolated at the Laboratory with the prefix "RPL" (e.g., RPL-12). The result was at least some confusion as to the true name of the Laboratory.

In 1991, the laboratory's name was changed to *Avian Disease and Oncology Laboratory* (ADOL) in an effort to more clearly designate the mission and to recognize that the laboratory was no longer regional. In this report, the

terms "the Laboratory," RPRL and ADOL are used interchangeably. The chronology of the signage used to designate the Laboratory is provided in the photo album.

Michigan State University

Although the Laboratory was launched with formal connections to 25 Agricultural Experiment Stations, proximity dictated a special relationship with the Experiment Station at Michigan State University. Over the years, there has been especially close collaboration between scientists at the Laboratory and University faculty, including Carl Card, Philip Schaible, Henrik Stafseth, Charles Cunningham, Howard Zindel, Theo Coleman, Bob Ringer, Lloyd Champion, Timothy Chang, Leland Velicer, Hsing-Jien Kung, Paul Coussens, Willie Reed, Jerry Dodgson, Richard (Mick) Fulton, Scott Fitzgerald and many others.

The Laboratory staff frequently served on the committees of graduate students at the University, and some Laboratory staff took courses and received degrees from the University. Laboratory staff members were listed in the University directory. Some of the Laboratory staff were appointed as adjunct faculty members. This mutually beneficial relationship quickly became one of the cornerstones of the Laboratory's programs and has endured.

Mutual benefits. In 1985 the Laboratory prepared a list of the various services provided by the University. These included library access, diagnostic pathology service, statistical consultation, project review by the institutional recombinant DNA committee, computer training, animal housing, assistance with marketing of eggs, Chinese scholar program, cooperation on seminars and meeting rooms, and waivers of indirect costs on projects. Presumably the University, in turn, received benefits from the Laboratory in graduate student training, staff collaborations and other areas.

Recently, the Laboratory purchased specialized sequencing equipment that is located at the University and is available for its use. For many years the Laboratory has made some of its property available to the University for its annual Ag Expo event. From time to time the University would publicize the work of the Laboratory as its own, much to the dismay of some in USDA-ARS, but indicating that the University took pride in the Laboratory and its activities.

Philosophy

Multiple disciplines. The Laboratory was conceived as a multidisciplinary unit at the very earliest stages. However, this must surely have been a unique concept at the time. R.C. Cochrane (2) credits George Ellery Hale as the first to articulate, in 1909, the idea of applying different scientific disciplines to discovery and identifies Isaiah Bowman, chairman of the National Research Council, as an early proponent (1935) of the interdependence of scientific disciplines. Perhaps this seminal orientation of the Laboratory simply reflected that neither the cause nor control measures for the neoplastic diseases of chickens were known and that it would be prudent to cover all the bases.

Genetics. On the other hand, Fred Hutt (member of the advisory council) would have fully appreciated the application of genetics to fowl paralysis through his own studies at Cornell and L.E. Card (chair of the original committee) contributed to research on genetic resistance to Pullorum disease at Illinois. Thus the strong role of genetics in the original concept is not likely an accident.

Pathology. Pathology was also an obvious original pillar, as "leukosis" in chickens was clearly recognized as a disease. Other disciplines were soon added to the mix. Berley Winton, recruited as Laboratory Director in 1940, brought expertise in sanitation and management. Ben Burmester was hired as a physiologist in 1940, although he later earned a veterinary degree and focused his later work on the study of disease and its causative agents.

Other disciplines. Alfred Lucas was recruited in 1944 and established a strong program in avian anatomy. This trend continued in later years with the addition of immunologists, virologists, microbiologists and molecular biologists. There was, for a short time, a position dedicated to electron microscopy.

Regardless of the original basis, the in-house multidisciplinary approach in which genetics and pathology were on an equal footing was years ahead of its

time and is still unique among laboratories specializing on diseases of animals. It appears to have been a fortuitous arrangement that proved to be well suited to the diseases under study. This system has served the Laboratory and the poultry industry well, which, in turn, has resulted in its perpetuation.

Several other conditions have emerged as fundamental pillars of the Laboratory's programs:

Basic and applied science. Ben Burmester's first research paper at the Laboratory was published in 1944 in Cancer Research, a journal dedicated to basic biomedical research and human health. In the ensuing years, a strong connection was established between the Laboratory and the basic science research community. Burmester may have led the way but this philosophy was embraced by others throughout the history of the laboratory. This connection was not only revealed by the journals where Laboratory research was published, but also by the choice of collaborators, which included many of the giants in cancer research, virology, immunology and other basic disciplines.

That said, the Laboratory has from the start recognized a primary responsibility to and partnership with the poultry industry of the United States. Much Laboratory research was published in applied journals such as Poultry Science or Avian Diseases. Collaborators with specialties in poultry genetics or disease were found in prominent state universities. Strong relationships were also forged with the research departments of large poultry breeding or vaccine production companies.

The orientation of the Laboratory research program to basic and applied research has generated occasional criticism from those who would tip the balance differently at a particular time. This dual orientation was not likely fore planned, and probably evolved from the personal orientation of certain key scientists, becoming enshrined as a guiding principle only after experience demonstrated its success.

Cancer research. Of course, Laboratory research became closely linked with "cancer research," an emerging field in the 1940s, which was focused on the human disease and tended to be rich with basic science. Researchers on cancer in humans were, at least for a period, highly interested in cancers of other animals and especially those with a virus etiology – a field known as comparative oncology.

Cooperative research. As previously stated, the Laboratory was conceived as a collaborative effort between ARS scientists and workers in various Agricultural Experiment Stations. Although this initial concept began to fade as Laboratory scientists established credible research programs, the advantages of productive collaborations remained obvious and stimulated relationships with many scientists in other laboratories over the years. Although this style of research is now the norm, the Laboratory exploited its advantages from a very early time.

One of the features of the Laboratory has been the availability of defined lines of chickens and the facilities to conduct experiments with infectious agents in live chickens under isolation conditions. These assets have allowed the Laboratory to partner with many other laboratories that had complementary strengths.

A casual perusal of Laboratory publications will reveal the large proportion of research with contributors from outside laboratories as well as the impressive diversity of such outside collaborators. This has been a major strength of the Laboratory over the years.

Linkage with the poultry industry. As mentioned earlier, the Laboratory has from the beginning recognized that its primary mission is to provide assistance to the poultry industry. This mission has not changed.

The Laboratory has looked to the poultry industry for guidance on specific needs and issues that can be addressed through research. It has looked to the poultry industry for access to the biological materials and the chickens that are essential to the work. It has sought advice from the poultry industry in policy and program matters.

In return it has provided the industry with a series of scientific accomplishments including vaccines, diagnostic

tests and breeding principles that have improved the health of chickens and the profitability of the poultry industry. It is a strong partnership, which has endured to the present time.

Linkage with ARS. Administratively, the Laboratory was established under the Bureau of Animal Industry of the U.S. Department of Agriculture, which was later renamed the Agricultural Research Service (ARS). Interestingly, although the Laboratory was administratively under the Animal Husbandry Research Division (AHRD), there was apparently an early decision that the programs would have input also from the Animal Pathology Research Division (APRD). Although H.W. Schoening, Head of APRD, was involved in some of the early planning, it seems clear that AHRD was the lead agency and input from APRD ultimately disappeared. Questions on why this laboratory was not under APRD, which was involved with veterinary matters, continued to arise until the major reorganizations of ARS in the 1960s.

Although other ARS laboratories were developed to conduct work on animal diseases or genetics, none duplicated work performed at ADOL. The single exception was the establishment, in 2004, of a single-person research unit on Marek's disease at the Southeast Poultry Research Laboratory in Athens, GA.

Within ARS, administrative oversight has, for many years, been provided by the Midwest Area Office in Peoria, IL whereas oversight of the research program was provided by the National Program Staff in Beltsville, MD. From the experience of this author, specific research programs have traditionally been conceptualized by the Laboratory with approval at higher levels as required by ARS.

A close interaction with the National Program Staff has been important to insure the Laboratory's programs properly support the National Research Programs of the Agency. Whereas the Laboratory Director's role was originally focused on administrative management, in more modern times the Director is also responsible for research program management and the conduct of a personal research program.

The Farm Facility

Details of the Laboratory facilities will not be enumerated here. However, it is fundamental that the Laboratory was established on a 50 acre parcel of land with the intent of establishing a working research farm where chickens could be bred, raised and used in experiments. The generous amount of land was designed to provide a degree of spatial isolation between buildings (and also between the farm and surrounding agricultural operations). This farm facility has contributed immeasurably to the research of the Laboratory over the years. Even today, as other laboratories find the need to increasingly limit animal research, the Laboratory conducts animal research on a significant scale, under appropriate animal welfare guidelines, using chickens of defined genotypes in isolation environments to prevent the spread of infection. This is a unique resource that supports and defines the entire research program.

Mission

For the first quarter century, the official mission of the Laboratory was "improvement of the viability of poultry." However, it is clear that the original intent was to focus on fowl paralysis. Quickly this focus became enlarged to include other forms of leukosis, especially visceral lymphomatosis (lymphoid leukosis), which dominated the Laboratory's research in its first quarter century. In the 1960s, the mission focused again on fowl paralysis, now called Marek's disease. By the 1980s, the mission included *all* neoplastic diseases of chickens and other poultry, and also a few selected other diseases. The name, Avian Disease and Oncology Laboratory, reflects this larger mission, which has endured to the present time.

Expectations

The poultry industry and all others launched this project expecting great things. The publication by Don Turnbull in the April 1939 edition of Poultry Supply Dealer is entitled "The Fight Is On – Science girds for battle on fowl paralysis at new Federal research laboratory." Turnbull goes on to say *"Science virtually will be working behind closed doors from which it will not emerge until a satisfactory solution to the problems of fowl paralysis has been obtained. When this will be, no one can say. Important results are not expected before three years…..It might be 8, 10 or 20 years."*

Dedication of Laboratory. *Persons in attendance not identified. Waters is in first row (far right). Winton is in second row (3rd from left). Martin is in 2nd row (center)*

Visual evidence that John Hannah of Michigan State University took a personal interest in the launching of the Laboratory

The Martin Years (1939-1940)

The poultry industry situation

The Laboratory was created at the behest of a poultry industry in the US that was increasingly burdened by excessive mortality during the growing and laying periods. The need for improved livability of poultry was critical. Few could have anticipated that these problems would continue to worsen for the next 30 years.

Staffing

J. Holmes Martin was appointed the first director on January 3, 1939. He resigned 18 months later on July 9, 1940. Martin had been in charge, since 1917, of Poultry Husbandry and Genetics at the University of Kentucky where he received both M.S. and Ph.D. degrees. After his tenure at the Laboratory, he assumed the position of chair of the Poultry Department at Purdue University. Clearly, Martin was a prominent and respected figure in the field of poultry science at the time. The reasons for his short tenure with the Laboratory are not clear.

Nelson Waters (senior geneticist) and Carl Brandly (senior veterinarian) joined the staff in January and March of 1939, respectively. Thus, the USDA-ARS officials in Beltsville charged with launching the new Laboratory were successful in attracting senior workers, already well established in their careers, for the principal leadership positions. Also recruited during Martin's tenure were J.H. Bywaters (geneticist), N.M. Nelson (veterinarian), and George E. Cottral (veterinarian). The role played by Martin in these latter recruitments is not known; it is likely that the earliest staffing decisions were made by Hugh McPhee and associates in the Animal Husbandry Research Division, who were directing the establishment activities of the Laboratory. Surviving correspondence indicates, however, that Martin did play a role in the recruitment of Ben Burmester, who arrived at the Laboratory just after Martin's departure in 1940.

It is worth noting that an entire support staff of technicians, animal caretakers, clerical and maintenance workers had to be recruited. This was no small matter but appeared to be done effectively.

In addition, none of the initial staff (except possibly for Brandly) came to the Laboratory with specific expertise with chicken tumors. None had worked together previously. It would be a learning experience.

Facilities

The 50-acre tract of land on the corner of Mount Hope and Harrison Roads in East Lansing has been critical to the functionality and identity of the laboratory. Originally, this property was in a remote section of the University land holdings. A 1938 memo from Dr. John Hannah, of Michigan State University, asked employees of the laboratory to refrain from hunting on the land. Indeed, wildlife of many types, including an abundant population of pheasants, occupied this property over the years. In time, this property was encircled by University farm units and Mount Hope Road became a major artery.

Identity. The location and nature of the property served to create a sense of identity for the Laboratory. It was not only administratively separated from the University and from other ARS units imbedded in University departments, it was physically separated as well. This also served to distinguish the Laboratory from most other government or university research units of the time, which tended to be integrated into the institutional infrastructure.

Construction. During 1938, construction of the physical plant was not only started but also largely completed. By January 1939, the administration-laboratory building, the east and west brooder houses and the east and west isolation houses were nearing completion. The farm was divided into west and east sides, with the west side dedicated to rearing of disease-free stock and the east side to the conduct of inoculation trials. By the summer of 1939 the well and storage tank and the east and west laying houses were finished. The water was turned on June 14, 1939. By August, 1939, most of the fixed equipment for the main laboratory building was in place.

Construction continued at a brisk pace and by 1940, a total of nine structures were completed. These consisted of the main laboratory, shop, East Brooder, East Isolation, East Layer, West Brooder, West Isolation, West Layer, and West Mating. All of these buildings survive to the present

time. Oversight of the process of construction and initial utilization would have been an important part of Martin's duties during his short tenure.

Research program and administration

It is likely that the initial research program was largely determined by the plan prepared by the committee chaired by L.E. Card in 1937. This was augmented by the several meetings of the collaborators from the 25 affiliated State Experiment Stations during 1939 and 1940. The organization of these meetings and the processing of the resulting recommendations would have been another early task for Martin and his group.

Fast start. Research work commenced almost immediately. The first chickens were hatched on April 3, 1939, just 3 months after Martin's arrival on site. Nelson Waters would surely have been directly involved and he had been on board only 2 months. Inoculations for fowl paralysis were started on May 9, 1939. The speed with which research commenced indicated considerable planning had occurred prior to the onsite arrival of the first professional staff. It also suggested a sense of urgency – that there was no time to waste.

Communications. Martin served as principal spokesperson for the new Laboratory, promoting its mission in several publications. He authored the Laboratory's first publication (4) in which he reported the importance of poultry to the agricultural economy of the United States and the devastating effect of mortality in adult chickens, estimated at 15% of all adult stock in 1937. He goes on to recognize the role of the veterinarian in poultry disease control and announces the formation of a new laboratory in East Lansing dedicated to the reduction of mortality in commercial chicken flocks.

Another early Martin publication (5) describes the potential of selective breeding to create lines resistant and susceptible to fowl paralysis. It is clear from this and other publications that the original mission of the Laboratory was focused on fowl paralysis, with genetics as a principal avenue of approach. The etiologic distinction between fowl paralysis (later named Marek's disease) and lymphoid leukosis would not be revealed until later but it was clear even then that there were two manifestations of leukosis and that fowl paralysis was important enough to the poultry industry to be the initial target.

Genetics. The most important research achievement during the Martin era was the development and launching of a breeding program for the Laboratory. Details were presented by Waters and James Bywaters at the Annual Meeting of the Poultry Science Association in June 1940 (10). The objectives were (1) to identify the resistance and susceptibility of poultry strains to fowl paralysis and (2) to determine the effectiveness of breeding for resistance and susceptibility to fowl paralysis. The approach was to form families that were resistant or susceptible to fowl paralysis and which possessed characteristics of general economic value.

The availability of susceptible stocks was recognized as important as a resource for pathologic studies. In the spring of 1939, 1000 pedigreed hatching eggs from each of 10 different White Leghorn strains (flocks) were introduced to the laboratory, hatched and full sibs held in isolation or in exposed groups (held on different sides of the farm). These sources represented the best commercial strains in the United States along with two laboratory strains.

The breeding approach was based on the principal of inbreeding, considered at the time to be the most powerful tool for establishing uniform strains that differ from each other.

Pathology. Research on the pathology of fowl paralysis was also launched. The objectives were (1) to determine the disease-inducing potency of various inocula and (2) a general study of the pathology of the disease and development of methods for cytological studies. Inocula from several sources were used and appeared to induce disease but results were difficult to interpret as a significant incidence of fowl paralysis and leukosis occurred also in uninoculated control chickens.

Biosecurity. A strict sanitary and quarantine procedure was instituted at the Laboratory to prevent unwanted introduction or escape of infections. Also, a policy was introduced to necropsy all chickens that died in breeding or inoculation studies. These policies have endured, with some modifications, to the present time and illustrated that

the infectious nature of fowl paralysis and leukosis was recognized from the very first.

Key conferences

A conference of collaborators was called in February 1939, just after the arrival of Martin and Waters at the Laboratory. By fall of 1939, a series of semi-monthly scientific conferences had become established that included staff from Michigan State University as well as the Laboratory professional staff. It is not known how long the collaborator conferences remained at this frequency, but conferences continued at least annually into the 1950s (see later).

The conference of December 18-19, 1939 included reports by collaborators F.B. Hutt, Erwin Jungherr, and L.E. Card as well as laboratory staff and a number of others.

The dedication of the Laboratory on August 8, 1939, although not a proper conference, brought together at least 50 persons representing Government, Michigan State University, and the poultry industry to celebrate the official beginning of the program. A photo taken on the front steps of the Laboratory shows the group in attendance (12).

Selected Research Advances

Breeding program. The short duration of the Martin era left little opportunity for true research accomplishments. But at this early point in the Laboratory's research program, the design and implementation of the breeding program should be considered an important advance. The hatching was successful and a flock of approximately 2000 pedigreed chickens was in place by the fall of 1939, representing the progeny of 10 hens of each of the 10 strains. Results during the first year showed differences in tumor frequency between the 10 strains and also among the 100 individual family groups, thus providing a basis to commence selection in the next generation. The fact that the newly hatched chickens held on the west (clean) side of the farm began to die of leukosis without intentional exposure, although not considered helpful at the time, proved fortuitous in the long run as this created an effective internal system with which to compare the susceptibility of different strains.

The foresight of those who crafted this breeding plan was indeed remarkable. The value of specialized lines of chickens to Laboratory research continues to increase with time.

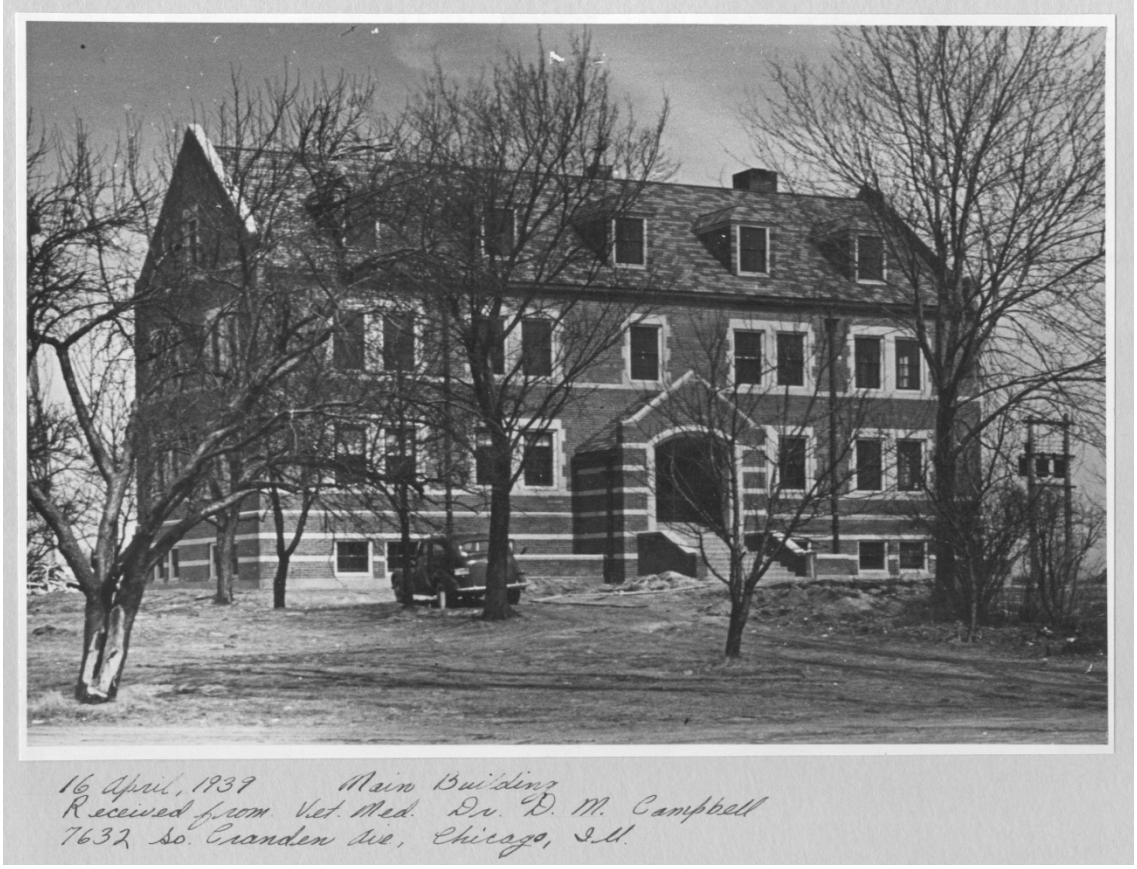
Synopsis

This period is very short and poorly documented. However, one can presume that the trio of Martin, Waters, and Brandly were selected for a purpose – to jump start a program of critical importance to the US poultry industry. Each of these persons was highly qualified and in the middle of their careers. The Laboratory surely benefited from their collective wisdom, experience and dedication. Martin, in particular, became a visible spokesperson for the Laboratory and presided over a number of the early recruitments. It is noteworthy that of this trio, only Waters finished his career at the Laboratory.

One can presume that, at the end of this period, the staff, USDA, and the poultry industry could agree that the project was successfully launched.

J. Holmes Martin joined Purdue as chair of the Poultry Science Department in 1940 where he enjoyed a long and productive career in service to the poultry industry. He was elected a life member of the Poultry Science Association in 1966. Hopefully, he had the chance to reflect with satisfaction on his brief efforts in East Lansing.

Brandly went on to a distinguished career in veterinary medicine, serving for many years as Dean of the College of Veterinary Medicine at the University of Illinois.



This photo was taken about 3 months after J. Holmes Martin first arrived on site and about the time the first eggs received from outside sources were hatched. The environment appears bleak in this photo but was full of promise. It is not known whether the existing staff realized this at the time.

The Winton Years (1940-1963)

Mr. Berley Winton joined the Laboratory as Director in July, 1940. Winton was formerly Principal Poultry Husbandman in charge of Poultry Investigations and the National Poultry Improvement Plan at the USDA's Agricultural Research Center at Beltsville, MD. He also was intimately involved with the planning and construction of the Laboratory (see prior section).

The poultry industry situation

Winton estimated that in 1940 at least half of the adult mortality in US chicken flocks was due to fowl paralysis and leukosis, representing a loss of $50 million annually. By 1947, mortality from all causes had increased in US chicken flocks to 17.9% of all adult chickens representing an annual loss of $122 million. This dire situation only became worse in ensuing years, with fowl paralysis and leukosis as the principal causes. By 1963, the annual loss due to leukosis was estimated at $65 million.

Staffing

Ben Burmester (physiology) joined the Laboratory staff in September 1940. He was followed by Norman Nelson (pathology) in 1943 and by Cavett Pricket (pathology) and Alfred Lucas (anatomy) in 1944. Staff was also required for many support roles. By 1942, the total staff at the Laboratory numbered 30.

Staffing suffered somewhat during the Second World War years. The 1944 annual report lists 3 professional staff on active military duty and 1 other on special assignment.

By 1950, the professional staff consisted of Winton, Waters, Burmester, Cottral, Dennington, Oakberg, Gentry, and Lucas (photo album). At this point, the professional staff entered a decade of flux where a number of new faces emerged but did not stay long.

The next group of professionals (mid 1950s) included M. Adrian Gross (pathology), Willard G. Walter (pathology), and A.K. Fontes (microbiology). Frank Piriano (microbiology) joined this group a bit later, but by the early 1960s, this entire group had left. Norman Frederickson (pathology) was employed briefly in the early 1960s. Also, the retirement of Nelson Waters in 1960 ended his stewardship of the critical genetics and breeding programs of the Laboratory.

It was at this point that a new wave of professionals was recruited – a class that would define the laboratory activities for the next several decades. In the first 2-3 years of the 1960s, Lyman Crittenden (genetics), William Okazaki (microbiology), John Solomon (microbiology), and Graham Purchase (pathology) were added to the staff – representing a nearly complete overhaul prior to Winton's retirement at the end of 1963. Only Burmester remained from the original group.

Perhaps the first graduate students to complete thesis work at the Laboratory were Ahmad H. El Dardiry (1950) who studied the susceptibility of inbred lines to tumor transplants and Robert Gentry (1952) who studied the epidemiology of LL. In most cases, Laboratory staff persons served as the thesis advisor while the University provided the major professor. It is notable that Ben Burmester received the DVM degree from Michigan State College in 1951, completing the requirements while a full time employee of the Laboratory.

Facilities

By 1941, the physical plant included a 4-story laboratory and administration building, and 11 secondary buildings. Although each building was assigned a numerical designation, which persists to this day, there were also common names assigned, e.g., "*East Layer*," "*West Isolation*," which tended to take precedence in common usage. The common names still exist but are no longer relevant to the purpose of the building and are less often used. A current site plan is located in the Appendix.

There was also a 75,000 gallon water storage tank and an incinerator. Included was a 5-room residence building for the plant superintendent, which was present prior to the acquisition of the property by the Federal Government. This on-site residence (with detached garage) was occupied by a laboratory employee into the 1960s. The incinerator was initially used for disposal of litter and droppings from chicken houses, as well as dead chickens. The 60 ft flag pole was installed on April 8, 1941.

Biosecurity. A set of quarantine and sanitation procedures were established at the outset. This included restrictions on visitors, feed in new bags, heat-treated litter, dedicated farm vehicles, screening of buildings, clothing and shoe change upon entry and between buildings. Employees were restricted from contact with poultry outside the Laboratory. Vaccines were not used. Although unremarkable today, these procedures were viewed as extreme security and ahead of the times in 1940. Extreme types of protective clothing were also used in the most secure areas (photo album). Winton authored a publication on these procedures in 1942 (11). A comprehensive set of procedures for employees was published in 1956.

Facility needs. A need for additional physical facilities was soon recognized and may have been first articulated in 1944, citing the small monetary investment in the laboratory compared to the annual losses from leukosis in commercial flocks.

One additional building was constructed in 1949 for housing of adult stock (Quonset). In 1951, a new poultry housing facility was constructed with funds from the International Baby Chick Association (later the American Poultry and Hatchery Federation). This building (number 17) was long known to laboratory personnel simply as "*IBCA*."

In 1957, eight Army barracks were donated by Michigan State University and used as temporary housing for chickens (photo album). As one tended chickens in what were now pens in the various sections of these simple and fragile structures, thoughts turned to the student families who previously occupied the rooms in these simple quarters.

Facility improvement. However, facilities remained inadequate. Requests were made for additional funds for facility improvement as early as 1956. In the late 1950s, plans were prepared for 2 new isolation buildings and an extension of the main laboratory building. In 1962, Congress appropriated $450,000 (of $1.4 million requested) for an addition to the current laboratory-office building. More will be said on this subject in the next chapter.

Pen types. Experimental facilities during this era were confined to pens (mainly in East Isolation, East Layer and East Brooder buildings). Some plywood cubicles were constructed (6'x3' with 4' walls) in the Shop Loft, which served as isolation pens for some of the LL trials (photo album).

Chemicals. An unfortunate development was the burial close by several farm buildings of underground fuel oil tanks (which ultimately leaked), and the creation of dumping sites for laboratory chemicals. Although these situations reflected standard practice at the time, the sites required costly remediation in later years.

Research program and administration

By 1941, the research focus was broadened to include studies of the etiologic agents of the avian leukosis complex (including fowl paralysis) and to develop practical control measures based on etiology, genetics, management and nutrition. The research was now divided into 3 sectors – genetics and physiology, management, and pathology. By 1942, nutrition was included among the disciplines with the proviso that the Laboratory research was to be integrated across all constituent disciplines. Anatomy was added soon after.

Early studies. The spontaneous occurrence of avian leukosis in uninoculated chickens complicated the interpretation of transmission studies. It appeared, however, that at least some of the transmission experiments were successful because the incidence of disease was 4 times higher in inoculated chickens than in uninoculated controls. The studies also revealed that many chickens were normal on gross necropsy but positive on histological examination, a new observation at the time, which focused new attention on microscopic pathology. These data illustrate the primitive starting point for the Laboratory's research.

Research focus. Early in this period, the research focus shifted from fowl paralysis (now known as MD) to visceral lymphomatosis (now known as LL) This may have been more a matter of convenience than a conscious shift of priorities as LL was occurring with regularity in Laboratory chickens and seemed to be transmitted by certain inocula. In fact, both LL and MD were surely

present in chickens maintained at the Laboratory, but the former condition proved more amenable to study through transmission experiments than the latter.

Anatomy. The studies on anatomy and cytology were originally prompted by the need to better understand how to differentiate neoplastic lesions from normal tissue, by both gross and histological examination. The presence of lymphocytes in tissue sections was confusing, as even normal appearing chickens housed in strict isolation had lymphoid aggregates in tissues. Also, knowledge of the basic anatomical and cytological features of the chicken was primitive at best.

Originally conceived as an adjunct to the disease-based research of the Laboratory, the anatomy group eventually took on an identity of its own, operating with increasing independence.

In 1963, the anatomy unit moved to new facilities provided by the Poultry Science Department of Michigan State University and henceforth was not considered an integral part of the Laboratory. This program was closed by ARS in 1970 upon the retirement of Lucas and after publication of two further books on the integument of avian species.

Physiology. A program focusing on physiology was initiated in 1940 and several papers were published on the effects of hormones and drugs on tumor incidence. But physiology took a back seat once transmission studies achieved success. Indeed, the physiologist (Burmester) subsequently redirected his program to pathology and virology, fields that ultimately proved more fruitful.

Tumor virology. Once transmission of LL had been achieved with cell-free preparations in the mid 1940s, presumably due to a virus-like agent, the effort was quickly refocused on modes of transmission and epidemiology. The Laboratory was now entering the field of tumor virology, joining with other groups that were simultaneously discovering viral causes of tumors in mice, cattle, and other species. This spawned collaborations with a new group of basic scientists focused on cancer in animals and man. Burmester was communicating with Jacob Furth and Duran-Reynals as early as 1945, and many more would follow. The "tumor virus mafia" of the 1950s would have included Ludwig Gross, Leon Dmochowski, Joe and Dorothy Beard, Werner Schäfer, as well as Frank Rauscher, Ray Bryan, and Robert Huebner – and Burmester ran with this group. From this point, the Laboratory was recognized as an important player in the virus cancer field, representing chickens and other avian species.

Genetics. The genetics program continued to focus on the two core objectives – to develop lines resistant or susceptible to tumors, and to maintain susceptible chickens free of disease for use in experiments. The first of these objectives was aided by the spontaneous occurrence of LL (and other related tumors) in the breeding population.

In retrospect, it seems clear that the original hatching eggs imported to the Laboratory in 1939 contained ALV (which was later shown to be transmitted from infected dams to progeny via the embryo). Indeed, Waters recognized this phenomenon in the early 1940s. Firm proof of egg transmission of ALV would come a decade later. This provided a built-in challenge environment that permitted evaluation of tumor susceptibility without the need for experimental challenge. However, experimental challenges were also employed to advantage. Almost every successive generation of breeding stock incurred a variable incidence of LL until exogenous ALVs were finally eradicated from the Laboratory breeding population in the 1960s.

The high rates of natural tumor losses from lymphomatosis provided the data on which selections for resistance and susceptibility could be made. In 1951, this loss was about 20% over 300 days. However, beginning with chicks hatched in 1951, the incidence of spontaneous lymphomatosis mysteriously declined to single digits (1.4% in 1955) and remained low throughout the 1950s, effectively precluding the use of data from natural exposure as criteria for selection.

Disease-free chickens. The second objective, to develop susceptible chickens free of disease (or infection), was more difficult. An isolated population of chickens from line 15 (later called line 15I) was derived in the early

1940s. This line had good susceptibility to tumors but continued to have a variable but usually low incidence of spontaneous lymphoid tumors. Much effort was spent by both geneticists and pathologists during this era to derive a population free of tumors, but success would only be realized later when better tools for detection of virus became available. In the meantime, the value of 15I chickens was recognized and this line was utilized in virtually all experiments on LL conducted during the period. This was surely one reason so much progress was made.

Collaborators. The series of annual collaborators conferences was continued. An annual report of the Laboratory was published from 1940 (1st) through 1954 (13th) that included contributions from the various cooperating Agricultural Experiment Stations along with Laboratory research. These reports were, in essence, a "Proceedings" of the annual conference. Sometime after 1954, it appears a decision was made to discontinue the original collaborative arrangements with the several Agricultural Experiment Stations and to cease holding the annual collaborator's conferences. Presumably, the need for such a structure had decreased over the years. This was an important change and, unfortunately, documentation of this decision is no longer available.

Library. A library was established at the Laboratory in 1943, complete with a staff librarian. It was continued for many years after the Winton era.

Disease Nomenclature. The first collaborator's conference in 1940 was notable in that a need for standardized nomenclature for avian neoplastic diseases was recognized. To address this need, it was agreed that E.L. Jungherr, L.P. Doyle, and E.P. Johnson would develop a proposal on nomenclature. The outcome was a classification under a single heading, "*Avian Leukosis Complex*," which included neural, visceral, and ocular forms as well as osteopetrosis. This classification was published in the American Journal of Veterinary Research in 1941 and became the standard for the next quarter century (3). This may be one of the first significant scientific achievements to have emanated from discussions in the Laboratory's third-floor conference room.

Although not intended by the authors, this nomenclature seemed in common usage to imply etiologic unity and thus may have obscured (and delayed) the recognition of separate etiologies for LL and MD. However, there are other reasons as well.

Bronchitis. An outbreak of infectious bronchitis in May, 1950 disrupted the Laboratory research programs. The disease spread quickly to all units housing breeder chickens, resulting in widespread clinical disease and an overall mortality of 16%. In a quick response, the poultry industry supplied a new housing facility on the west side of the farm that housed the most essential breeders needed for reproducing the genetic lines. All other chickens were killed. Infection experiments were terminated early. Contaminated facilities were disinfected and quarantine procedures tightened. Fortunately, surviving breeders resumed egg production. Subsequent outbreaks of infectious bronchitis occurred in 1955, 1959 and 1963, but with less devastating effects.

USDA. By 1954 the structure of the USDA changed. The original Bureau of Animal Industry was now replaced by the Agricultural Research Service. The Laboratory was made part of Animal and Poultry Husbandry Research.

LL *vs* MD. A key issue debated during the 1950s and early 1960s was whether the tumors of the so-called avian leukosis complex were a single disease or multiple diseases. In studies at the Laboratory, chickens inoculated with ALV developed a variety of different neoplasms, including, occasionally, neural or ocular lesions, suggesting (incorrectly) that all these tumors were a single disease. Moreover, there was strong evidence that these diseases could be transmitted from dam to progeny through the egg.

In contrast, chicken lines selected for resistance or susceptibility to leukosis by Fred Hutt and Randall Cole at Cornell University developed mostly the neural form of the disease. Moreover, there was no evidence that the causative agent was transmitted through the egg. This was a serious challenge to the single disease theory.

A prescient, if not seminal, paper by Waters in 1954 (9) proposed that the two scenarios above could be explained

by two diseases, each with different etiologies. His data showed that susceptibility to visceral and neural forms among 6 selected lines did not vary in parallel. For example, the line most resistant to the visceral form was the line most susceptible to the neural form (line 7). In addition, the 1951 annual report indicated that attempts to transmit neural lymphomatosis or ocular lymphomatosis by inoculation of cell-free filtrates were uniformly unsuccessful, implying different etiologies for the neural and visceral forms.

A letter from Randy Cole (Cornell) to Winton in 1955 indicated that line 15 was just as resistant to tumor challenge as lines K and C. Since line 15 was highly susceptible to challenge in East Lansing, this should have been a clear indication that there was more than one disease, thus supporting Water's conclusion. Several English workers also provided evidence supporting the two disease hypothesis during the 1950s.

But this view was not universally accepted among Laboratory staff. In particular, Burmester continued to favor a single disease hypothesis. This enigma dogged the Laboratory for the next decade.

Relevance of RPRL Research. By the late 1950s, it had become clear that the pathology associated with LL, as induced by inoculation with RPL-12, differed from that of many tumors occurring in the field. These field tumors were called "acute leukosis" because of the young age at onset and presence of both visceral and neural lesions. Indeed, the Laboratory began to be criticized for working on the wrong disease.

In response, a major effort was launched by the Laboratory to collect samples from representative field tumors and characterize the viruses obtained. The methodology involved preparation of cell-free filtrates for inoculation into chickens, as had been done at the laboratory for many years. A total of 22 new isolates were obtained, all of which induced typical LL; none induced neural or ocular lesions. Thus, once again the experimental disease failed to mimic the field disease.

A Laboratory report (1962) on these data surprisingly concludes that the findings of the Laboratory "can with assurance be generally applied to the disease as it occurs in the field." Whereas this was correct in the limited sense that ALV from the field was similar to that studied in the laboratory, it failed to recognize that a second disease (MD) was also present.

However, this would soon change. On June 21, 1962, a group of Cornell S-line chickens inoculated with the JM strain of MD was transported by T.N. Fredrickson from Martin Sevoian's laboratory in Amherst, MA to the Laboratory and placed in Barracks #1 (the most spatially isolated of the Laboratory's farm buildings). The Laboratory had accepted the existence of a second disease and work on MD had finally commenced.

Reticuloendotheliosis. Another exploration for new strains led to a collaboration beginning in 1958 with Marvin Twiehaus, then at Kansas State University, who had a particularly virulent tumor strain, designated as strain T, isolated from turkeys that would kill both chickens and turkeys in a few days. This work was partly sponsored by funds from the Laboratory and Twiehaus made periodic reports that still survive. Apparently, the Laboratory did not consider this work relevant (or valid?) and an opportunity to characterize this new strain, ultimately designated as a member of the reticulo-endotheliosis virus group, was lost. Instead, Martin Sevoian at the University of Massachusetts, who also received material from Twiehaus, characterized the strain and published the first paper in 1964. It is my understanding that Twiehaus was so put off by the lack of enthusiasm for his work in East Lansing, that he elected not to publish himself – an oversight not rectified until 1974 (6). The records show that the Laboratory received shipments of material from his passages starting in March 1958.

Progress. Looking back from the vantage point of current time and place, it is important to recognize what was lacking at the outset of the Laboratory's research program. There were no disease-free chickens and no understanding of the viral etiology of avian leukosis and fowl paralysis. There were few if any characterized tumor strains. The isolation facilities were inadequate to prevent spread of disease. And there was little or no institutional expertise on avian tumors – none of the staff had worked on these

diseases before. However, there was a physical facility, a quality staff, a clear mission, and a solid collaboration with State Agricultural Experiment Stations and the poultry industry. The results speak for themselves.

Key conferences

It can be argued that each of the annual collaborator conferences hosted by the Laboratory from 1940 through 1954 was a key conference. Most of these conferences involved collaborators from several outside Agricultural Experiment Stations, some of which were conducting complementary studies on avian leukosis. Their reports were combined with Laboratory reports in preparation of the annual report for that year. Presumably, the discussions materially influenced the Laboratory's research programs. For example, the complete proceedings book of the 1941 conference included specific recommendations to the Laboratory from the Genetics Committee (F.B. Hutt, chair), the Pathology Committee (E.L. Jungherr, chair), and the Poultry Husbandry Committee (L.E. Card, chair).

1962 Conference. The Laboratory hosted on April 25-26, 1962 an Avian Leukosis Conference that represented a watershed moment in the continuum of research on these diseases. In addition to numerous presentations by Laboratory staff on current research, mostly dealing with LL and genetic resistance to tumors, the conference showcased new and exciting developments in three emerging fields. Walter Hughes described his work with Harry Rubin on the use of the RIF (resistance inducing factor) test for deriving flocks of chickens completely free of ALV. Several workers described the recent uptick in leukosis mortality and condemnations in growing chickens that seemed to reflect a disease that was different in many respects from LL. Martin Sevoian described the induction of what we now know as MD with cell-associated tumor material, using genetically susceptible S-line chickens and Horsfall-Bauer isolators to prevent cross infection with this highly contagious disease.

This new information effectively launched the era of ALV eradication and research on MD in the United States. Incidentally, this conference also launched Bruce Calnek on his illustrious career in avian tumor virus research at Cornell University, which also impacted a number of his students (including this author). The conference was attended by 111 persons representing 25 State Agricultural Experiment Stations.

Selected Research Advances

Genetic Lines. The development of inbred lines of chickens, resistant or susceptible to LL and MD, is arguably one of the most significant accomplishments of the Winton era. The original 10 strains were mated in different combinations to develop 15 lines (numbered 1 through 15). By 1945, 14 different lines were being maintained at the laboratory. Of these, 7 were deemed susceptible (Nos. 2, 4, 7, 9, 11, 14 and 15) and 7 were resistant (Nos. 1, 3, 5, 6, 10, 12 and 13). Line 15I, a subset of line 15, is discussed below.

By 1950, the menu of lines had been reduced to 3 susceptible lines (7, 9, 15) and 3 resistant lines (6, 10, 14), each with inbreeding coefficients in excess of 0.95. By the mid 1960, only lines 6, 7, 15 (and 15I) remained. These lines, selected on the basis of strong resistance or susceptibility to LL, also turned out to differ in susceptibility to MD, and remain critical to Laboratory programs to the present day.

Disease-free chickens. Although the goal of a susceptible chicken totally free of tumors and tumor virus infection was not achieved in this era, it was not for lack of effort. The origin of line 15I is detailed in the 1975 monograph by Howard Stone (8). Two high-producing families of line 15 from the 1941 hatch remained healthy for an extended period. Their progeny, hatched in 1942 and reared in isolation pens under strict quarantine and sanitation procedures, remained free of lymphoid tumors for 300 days. Full sibs reared with other lines of chickens developed a 27% incidence of tumors during the same period, establishing the high susceptibility of this line. With hindsight, this may have been the first leukosis-free flock. However, its status was not totally clear as subsequent generations developed variable (but low) frequencies of leukotic lesions.

Tumor strains. Transmission experiments were pursued from the very beginning, searching for strains that would induce a high level of tumors to facilitate studies. Rapid serial transfers led predictably to tumor transplantation,

which induced high rates of response very quickly. In 1943, work commenced with a transplantable tumor from Carl Olson, Jr., then of the Massachusetts Agricultural Experiment Station. This strain was designated by the Laboratory as RPL-12. A number of other strains were isolated from the field and each was assigned an RPL number. The collection of strains grew, numbering more than 30 by 1965.

Etiology of LL. The induction of LL by cell-free inocula prepared from the RPL-12 transplantable tumor was a major breakthrough, leading to establishment of the viral etiology for this disease and providing a more reliable method for its experimental induction. Filtered plasma from chickens receiving cell-free tumor inocula was also infectious indicating replication of an agent in the host. The 1946 annual report cautiously suggested this agent had some properties associated with viruses, but the word "virus" entered quickly into informal communications at the Laboratory. The viral strain originating from the RPL-12 tumor was also designated RPL-12, and became a prototype ALV.

Embryo transmission. The possibility that LL could be transmitted from dams to progeny through the egg was first suggested in the 1943 annual report, along with the idea that the disease might ultimately be controlled in the field by breeding from flocks free of infection. By 1949, it was clear that the causative agent of LL was transmitted from clinically normal carrier hens through the egg to progeny and that the virus could be demonstrated in embryos. Much of the data came from breeding experiments where hens could be classified as shedders on the basis of the tumor incidence in their progeny.

Contact transmission. Evidence for contact transmission of LL was observed from the very first, as uninoculated chickens in direct contact with inoculated chickens always had increased incidence of disease compared to isolated controls. Transmission from infected to uninfected chickens in the hatchery was reported in the 1948 annual report.

Pluripotency. In the 1950s, the propensity of ALV isolates to induce multiple types of tumors was important. It was not known whether the stocks contained multiple viruses or whether one virus could induce multiple tumor types. Studies at the Laboratory revealed that every stock tested, including strains that produced mainly erythroblastosis or myeloblastosis, could also induce LL, thus by 1960 providing strong evidence for the pluripotency of the virus.

In vitro propagation and assay. Attempts by the Laboratory to grow ALV in cell cultures date from at least 1951, when tumor cells maintained for 139 days in culture were still capable of inducing disease when inoculated into chickens. Work continued but real success was realized only after work by Rubin and others (1960) determined a method for detecting ALV by its ability to interfere with Rous sarcoma virus in cell culture. This RIF test was quickly adopted at the Laboratory and formed the basis for the assay of ALV and its antibody, tools that would prove indispensable for subsequent studies on avian leukosis.

Genetic basis of tumor resistance. Using chickens exposed by intracerebral inoculation of Rous sarcoma virus, extreme variation was noted between lines and, in some cases, within lines. Reciprocal crosses between susceptible and resistant lines showed that susceptibility was dominant to resistance and was dependent for expression on a single pair of autosomal genes. This seminal study (1961) effectively launched a new era in the study of genetic resistance to tumors in chickens.

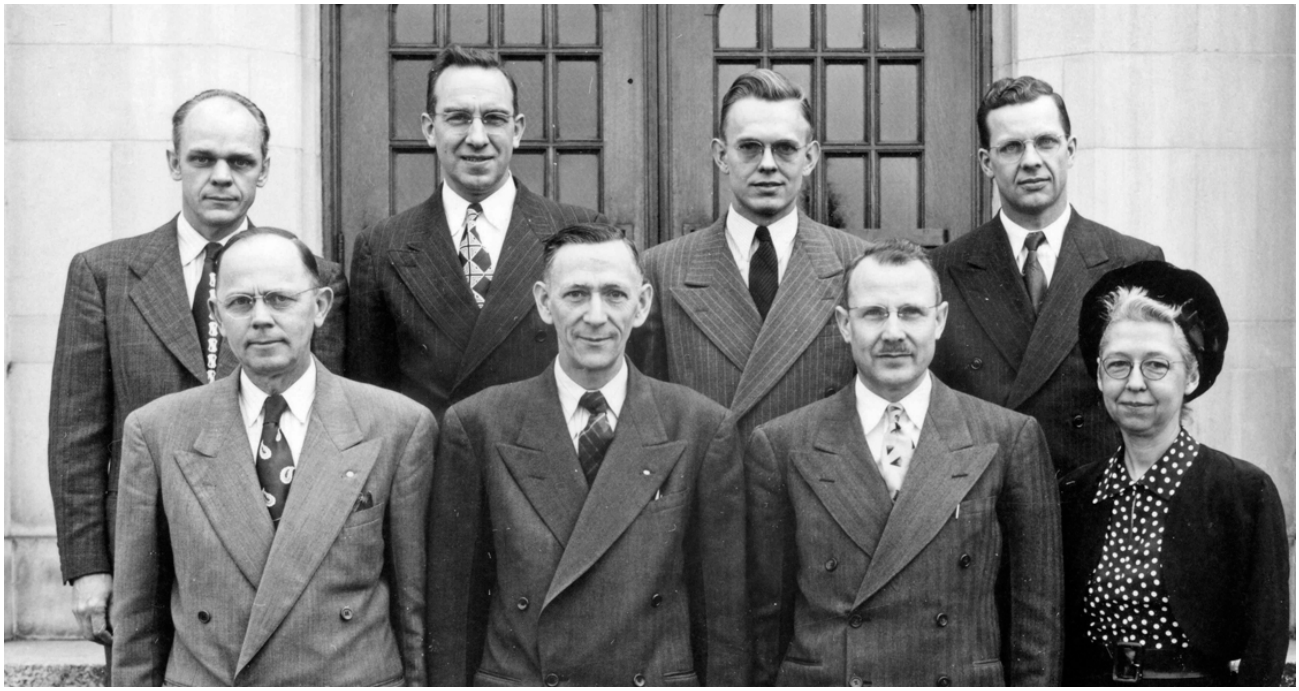
Anatomy. Studies on anatomy and histology were prompted by the realization during the initial years that there was insufficient information about normal morphology of tissues for critical assessment of pathologic changes. In a collaborative effort with the Laboratory, F.W.A. Chamberlain of Michigan State University authored an "Atlas of Avian Anatomy" in 1943.

By 1950, the program had evaluated the role of ectopic lymphoid foci in histological sections of various tissues. Throughout this period the program was also focused on hematology, culminating with the publication of the *Atlas of Avian Hematology*. This was a monumental and important work, initiated in 1944, completed in 1955 and published in 1961.

Synopsis

This era was characterized by huge changes. It started with a group of scientists who had to develop everything from scratch and also learn to work with each other. It ended with a rather comprehensive understanding of LL and its causative virus as well as a glimpse into the next era, which would focus on MD. Indeed, most of what is known about the epidemiology of ALV was learned in the 1950s using cumbersome bioassays in chickens. It was guided by wise choices regarding scientific approach and staffing. It benefited from the fortuitous presence of ALV in the embryos of the original eggs imported for the breeding program, which, in turn, provided the means by which the original lines could be selected. The science of the era was defined by Waters and Burmester who held differing views but possessed substantial expertise. Not every decision or interpretation was correct but the foundation was solidly laid. The Laboratory had gained stature, become established as a world resource, and was well positioned for the ample challenges that lay ahead.

Berley Winton started his association with the Laboratory in 1938 in Beltsville, MD where he did critical logistical work as the Laboratory was being designed, constructed and occupied. For more than a quarter century, he dedicated himself to the task. He no doubt deferred to his staff on scientific matters but was an able poultry husbandman and administrator who kept the ship afloat and moving in the right direction. He was clearly dedicated to the Laboratory's success, which, in turn, became his life work. After retirement in 1963, he continued to reside in East Lansing where he died in 1972. He served as an employee of USDA for 44 years.



Laboratory professional staff (1950): First row (L-R): Berley Winton, Nelson Waters, Alfred Lucas, Effie Dennington. Second row (L-R): George Cottral, Ben Burmester, Robert Gentry, Eugene Oakberg

The Burmester Years (1964-1974)

The poultry industry situation

By 1964, losses to the poultry industry to leukosis had reached unprecedented levels and, importantly, were now being felt by the broiler industry due to the advent in 1959 of mandatory federal inspection of poultry at slaughter. Adult mortality was still a problem but there was now also significant death loss in growing pullets. Broilers were condemned at processing with tumors or skin lesions. Thus, all phases of the chicken industry were feeling increased pain from a disease that would soon be identified as Marek's disease (MD).

Also, it was increasingly evident that the disease causing losses in young chickens was both new and fundamentally different from that which was associated with lymphoid leukosis (LL) in older stocks. Problems would continue to increase until the toll from MD became so great as to threaten the viability of the industry. By 1970 broiler condemnations had increased to 1.57% (US average) with individual flocks as high as 10% and mortality in layers as high as 50%. The poultry industry was in crisis due to tumors and neoplastic disease had become the most important disease condition of poultry.

However, the industry condition changed in 1972 consequent to the licensing and widespread use of the HVT vaccine for MD. The vaccine was so effective that, for a period, there was an oversupply of chickens and egg prices dropped. Condemnations of broiler chickens in US processing plants for "leukosis" (MD) dropped by 82% between 1970 and 1974. On balance, the industry viewed the advent of vaccination as miraculous.

Staffing

Ben Burmester was appointed Director in January 1964. The increased industry concerns translated into additional funding for the Laboratory and a chance to further increase the professional staff. Richard Witter (pathology) and Ron Hinz (electron microscopy) joined the staff in 1964.

Keyvan Nazerian (pathology and electron microscopy) joined in 1965 and Lucy F. Lee (biochemistry) joined in 1968. Also recruited during this period were Philip Long (pathology) and Frank Siccardi (pathology).

As the reputation of the Laboratory increased, the Laboratory started receiving visiting scientists from other laboratories. L.N. (Jim) Payne (England) joined the Laboratory in 1965 for a year as part of an exchange whereby Graham Purchase went to the Houghton Poultry Research Station. Bart Rispens (The Netherlands) visited in 1968 for several months.

Importantly, it became possible during this period for Laboratory scientists to have extended training leaves in other laboratories, something akin to a sabbatical leave. This provided a unique opportunity for training and academic refreshment. Purchase was the first to go (see above). He was followed by Crittenden (Peter Vogt, Denver, 1966), Witter (Werner Schäfer, Tűbingen, 1971-72) and Nazerian (George Klein, Stockholm, 1972-73).

Howard Stone (genetics) was recruited in 1966 to replace Crittenden, who had transferred his program to ARS facilities in Beltsville, MD (Animal Physiology and Genetics Institute). Jagdev M. Sharma (pathology) was recruited in 1971. Ben Burmester retired in December, 1974 but continued as a collaborator for several additional years.

During this period Harvey Burgoyne, Richard Reamer, and Ann Stephens (Holly) joined the Laboratory as support scientists.

In 1965, an "Employees Welfare and Recreation Association" was formed for the benefit of the then 43 full and part-time employees. This organization served the Laboratory for many years, but was finally disbanded. The first president was Harvey Burgoyne. The Association sponsored holiday parties, picnics, and outings for canoeing and skiing – all contributing to a positive workplace environment. Participation by the professional and support staff at the outset was strong.

In the late 1960s, the Laboratory made available a plot of

land, located on the east side of the farm (just east of East Isolation) for employee garden plots. Bill Payne, along with Burmester, was the chief architect of the project. Although this project was disbanded in the 1980s, many stories survived about the difficulties of dry land farming and the ravages of local wildlife on crop production. After all, this was "agriculture" in practice.

Facilities

After years of efforts to secure additional funding, Congress approved in 1962 the sum of $450,000 for expansion of the Laboratory physical plant.

New laboratory. In April 1963, Michigan State University (John A. Hannah, president) proposed to Secretary Orville Freeman of the US Department of Agriculture that the Laboratory be relocated to a new site on campus property, as the present site would be needed for University expansion. This implied not just an expansion, but the construction of an entirely new laboratory and physical plant. This was an exciting new development

A protracted set of negotiations with Michigan State University followed over the next several years including the development of a detailed plan for the new facility; however these negotiations broke down in 1968 over a relatively small issue of utility costs and the matter was ultimately abandoned.

Several other alternate sites for relocating the Laboratory had been proposed in the meantime. These included moves to USDA facilities at Athens, GA, Ames, IA, or State College, MS. A site committee was formed and visits made to the several locations – the report (January 1969) listed four options, including a move to Georgia.

Move to Georgia. By May 1969, George W. Irving, Administrator of ARS, announced a decision to move the Laboratory to Georgia. During a brief stint as Acting Director in Burmester's absence, this author remembers receiving a call from headquarters with instructions to inform employees immediately of this decision. By June 1969, the cost estimate of moving (with new construction) was in excess of $2.7 million (Carl Hess memo).

Remain in East Lansing. By fall of 1969, the decision to relocate in Georgia had been rescinded in favor of the option "to utilize and add to the present office-laboratory building at East Lansing," the first option listed in the January study. Thus, the Laboratory proceeded with an expansion on site, albeit after years of unfortunate delays.

As time and planning fees had eroded the original principal, it was only possible to construct a 6700 sq. ft. addition to the existing laboratory-office building. The addition, located north of and connected to the main building, was completed in late 1972. This was indeed a major improvement, increasing the laboratory-office space by 63%.

This story is related in detail since it bears on the subsequent series of discussions involving a move to Georgia, some 40 years later.

Isolators. It quickly became clear that isolation cages would be essential for animal experiments on MD. Burmester's first assignment to Witter on his arrival in 1964 was to visit the USDA laboratory at Ames, Iowa and evaluate their plexiglass isolator systems for possible adaptation at the Laboratory.

Burmester ultimately designed a modification of the standard Horsfall-Bauer (HB) type isolator that was fabricated from stainless steel. A group of 62 HB isolators were installed in the East Isolation house in 1965 at a cost of $406 per unit (including installation and air handling). Another 120 HB isolators were installed in the following year in East Layer house. The design was functional and durable; the isolators remain in current use, with only minimal modification over the years (photo album).

Also in 1965, 20 stainless steel lifetime isolators were designed, fabricated and installed in the Shop Loft, replacing the plywood cubicles. These isolators were designed for longer term studies and supplied filtered air under negative pressure (FANP). These isolators were later relocated in Building 19 (photo album).

Shortly thereafter, Burmester designed a larger isolator with a stainless steel base (water filled) and a plastic

canopy with glove ports. Filtered air was supplied under positive pressure (FAPP). This system was designed for the long term maintenance of breeding chickens in laying cages and was installed in West Layer house for housing SPF breeders (photo album). A similar cage was designed for brooding in colony cages.

It became clear that, in addition to his scientific expertise, Burmester was something of an engineer. He took personal responsibility for the custom design of these and other isolator systems that were used on both West and East sides of the farm. Both positive pressure systems with flexible canopies and negative pressure systems with rigid canopies were designed and installed. By 1974, there were sufficient isolators not only to contain MD experiments, but also to house at least small flocks of SPF breeder chickens. This investment quickly proved its worth.

In 1971, a new pen-type house, Building 19, was constructed on the East Side. This was designed for longer term studies where birds would be housed in floor pens or cages. Two of these pens were used for alternate populations of breeder ducks that had been introduced to the Laboratory in the late 1960s to supply embryos for cell culture. Pen 8 was later used to house stainless steel FANP isolators, moved from Shop Loft, to provide a high security environment for infected chickens.

After years of poultry house waste disposal via the county drain system, a connection to the sanitary sewer system was completed in 1970.

Barracks buildings and shop loft cubicles are examples of suboptimal poultry housing that needed to be phased out. This process was speeded when a 1965 fire destroyed Barracks #4 along with a number of chickens inoculated with the JM strain of MD. Witter's research program, only a few months old at that time, was off to a "hot" start.

Building 20 was constructed in 1972 as a change room access to the west side and an incubation facility for the disease-free breeding flock. A decontamination garage was also included which provided for the sanitation of vehicles before entry to the isolated area, an important and welcome improvement.

About 1973, two existing buildings on the West Side (West Mating and West Isolation) were redesigned as FAPP houses with positive pressure filtered air where chickens could be reared on the floor. Caretakers showered in and out. The purpose was to rear flocks of chickens on the floor free of MD antibodies, much as was being done by commercial SPF chicken companies. The experiment worked the first time through, but later failed and the project was abandoned.

The necropsy facility, originally located in the basement of the laboratory building where chickens were introduced through a chute from the outside, was relocated to space in a wing of the Shop building complex. This eliminated the noise, physical contamination, and the occasional chicken feather that tended to migrate up the staircase to the front business office, causing much concern for the secretarial staff. This space also proved suboptimal, and was ultimately replaced by a new building in the next era.

An electron microscope was installed about 1966, and was utilized by Keyvan Nazerian to considerable advantage for a period. The previous electron microscopist, Ron Hinz, had to use equipment located at Michigan State University. But both the technology and the microscope eventually had its day, and the microscope was removed about 1993 to make room for postdoc offices and other activities.

Research program and administration

Burmester institutionalized in 1964 a system of quarterly research reports where the professional staff would prepare and present written summaries of the current work in an environment conducive for discussions (actually started in 1963 or earlier). In time, the frequency of the reports decreased to semi-annual, and eventually annual reports – a system that has endured nearly to the present time and appears to be unique within ARS. The purpose was to provide for serious discussions on the work, as it was being designed and as the results were obtained, by the entire staff. It has worked well.

In 1965, the first project (RPL #30) expressly dedicated to the study of MD was initiated with Witter as lead scientist. This was quickly followed by other MD projects so by the end of the decade, at least 90% of the Laboratory effort

was directed to studies on MD. This represented a dramatic shift of research emphasis.

MD was a fertile field. None of the staff had much if any experience. Little was known and all questions remained open for exploration. The most fundamental question related to the cause of the disease. Once this had been determined, there was the need to develop tests for assay of virus and antibody and to apply these tests to epidemiological studies. A paper from the Houghton Laboratory in 1969 established the feasibility of vaccination and stimulated comparable studies at the Laboratory. There was even a program on biochemical and morphological characteristics of the virus. The inbred lines of the Laboratory were reassessed for susceptibility to MD and the highly susceptible line 7 was used for most experiments. The basis of genetic resistance was also investigated. By this time, the staff represented multiple areas of expertise and all relevant questions were pursued.

One of the issues during this time was "turf." With so many people newly entering a field at the same time, there were conflicts on who should be doing what. Burmester did his best to smooth out these issues, but it was not always easy.

LL was not completely forgotten. A collaborative project with Bob Good, Ray Peterson and the University of Minnesota group elegantly established the role of the bursa of Fabricius in the pathogenesis of the disease. This information was utilized as the basis of new criteria for differential diagnosis – a topic of increased significance since now there were two distinct diseases and the lesions of each included frank lymphomas in various organs and tissues which could be easily confused.

This was also a time of abundant funding. Not only was there pressure from the poultry industry for more and more funding, but also the cancer virology community began to see avian tumors as an interesting and useful model system – and they had grant money to give away. ARS also had money also with which contract research was established at a number of universities including Cornell, Connecticut, Massachusetts, Georgia, Arkansas, California and others in the period from 1965 to 1971. Laboratory personnel served as liaisons (see earlier).

Burmester established a Research Advisory Committee in 1968, mainly to review new project proposals. One recommendation of this committee was to continue the internal numbering system for projects, essentially establishing a dual system since projects had just recently received new numerical designations under the newly instituted CRIS system. At the time of this writing, the newest of the internal projects is assigned number 113. Project number 1 was established in 1939.

An SPF committee was established in 1972. The charge was to develop protocols for the maintenance of infection free chicken lines on the West side of the farm. Integral to this initiative was the installation of FAPP isolators and the conversion of one or more conventional house to FAPP, modifications needed to prevent introduction of MDV infections.

At about the same time, the staff was organized into 5 discipline areas, probably not greatly different than had been done in earlier (or later) eras.

Key conferences

Georgia workshop. The Laboratory co-sponsored a Technical Workshop Conference on Diseases of the Avian Leukosis Complex, which was held October 12-13, 1965, at the University of Georgia, Athens, GA. Progress on experimental transmission of MD was shared. Also, this conference marked the entry of several laboratories into the field of avian tumors. Several committees addressed the important issues of nomenclature, classification of ALVs, areas in need of further research, and methods for the practical control of both these diseases – thereby relating the deliberations to the needs of the poultry industry.

Also, the relocation of Crittenden to Beltsville in 1966 created, in essence, a satellite laboratory that continued to cooperate with the East Lansing Laboratory. While East Lansing had turned its attention largely to MD, Crittenden's group was still working on avian leukosis.

AAAP workshops. Two workshop conferences sponsored by the Leukosis Committee of the American Association of Avian Pathologists (AAAP) were held in 1967 and 1970, respectively. Although not directly sponsored by

the Laboratory, Laboratory scientists played key roles. The 1967 workshop featured reports by the Houghton Poultry Research Laboratory and also by the RPRL on identification of a herpesvirus as the causative agent of MD. The 1970 conference was chaired by Dick Witter and featured reports on the HVT vaccine for MD by Laboratory scientists.

Genetics study. A Genetics Research workshop and study was conducted at the Laboratory in January, 1971. The report recognized that the genetics program, historically and presently, is a basic and integral part of the research effort at the Laboratory and should continue as an important segment of the total effort. Recommendations were made for facilities improvement, including more FAPP housing for breeders, for further line development and for studies on the underlying mechanisms of genetic resistance to tumors.

AAAP symposium. An international symposium sponsored by AAAP was held in Detroit in 1971. Again organized by Dick Witter, this meeting featured work on MD vaccines by Laboratory scientists and others, and appeared to document the solution to this persistent problem. How little did we know!

Selected Research Advances

Development of chicken lines. Lyman Crittenden initiated in 1962 a brother-sister mating program for all inbred lines, a development which produced a number of sublines within each line. He also introduced the techniques of artificial insemination to the breeding program. He developed line 100 from lines 6 and 7, resulting in a line that was homozygous susceptible to viruses of ALV subgroups A and B, and was susceptible to induction of MD.

Genetic resistance to ALV. A series of studies conducted throughout the 1960s established that two single-autosomal-recessive genes (tva^r, tvb^r) control specific cellular resistance to subgroup A and B avian leukosis viruses both *in vivo* and *in vitro*. The two genes are independent; the resistance operates at the level of viral penetration of the cellular membrane. Neither gene system influenced susceptibility to MD. Thus, resistance induced to subgroup A ALV by the tva locus will prevent both tumors and virus infection but is, of course, specific for this viral subgroup.

Specific-pathogen-free (SPF) program. Given the new assays for ALV and MDV, and a better understanding of the epidemiology of these viruses, it now became possible for the Laboratory to develop flocks of breeder chickens free of these infections, and to prove it – this satisfying at last an objective established in 1939 by the Laboratory. A small population of SPF birds free of both viruses was housed in FAPP isolators (or FAPP buildings) on the West Side throughout their productive lives. Other chickens, free of exogenous ALVs, were housed in more conventional quarters albeit under tight biosecurity conditions, and were vaccinated with HVT in case of accidental MDV exposure.

Reticuloendotheliosis virus (REV). By the late 1960s, there were several reports of viruses that could induce tumors in chickens and other avian species but which were distinct from ALVs. This included the strain T virus from the turkey tumor passaged by Twiehaus and further studied by Sevoian (see previous) and several others. The Laboratory reported in 1974 on the antigenic relationship between several of these viral strains. In addition, some of the strains induced lymphoproliferative lesions in the peripheral nerves that resembled those of MD, thus complicating differential diagnosis. Although these viruses did not appear to be major problems for the poultry industry at the time, a new field of science had been launched. Problems with vaccine contamination would be recognized later.

MD virus. Identification of the causative agent of MD had long been the holy grail of research in this field. A virus had been suspected for years but not confirmed. The disease could be easily transmitted by contact and inoculation of intact cells. The Laboratory effort to identify the causative agent probably started in 1964 with the recruitment of Witter, who had the entire MD program to himself for a year. By 1966, Nazerian had joined the Laboratory and observed herpesvirus particles in some MD tumors. John Solomon, working with Witter, had observed morphological changes (CPE) in cultures of duck embryo fibroblasts inoculated with cells from chickens with MD. Chickens inoculated with these

cultures developed MD at a high rate. In addition, herpesvirus particles were observed in the cultures. As these results were being readied for presentation at the 1967 AVMA meeting in Dallas, a visit by Peter Biggs revealed that his group at the Houghton Poultry Research Station had identical findings. Mutually confirming data from both groups was strong evidence that the riddle had been solved. Importantly, this evidence was quickly accepted by the scientific community as a basis on which the field could move forward.

Turkey herpesvirus. During 1968, the year following the isolation of MDV, techniques for detection of the virus and its antibody had come into use. Armed with these tools, it seemed appropriate for the Laboratory to study the epidemiology of MDV infection in field flocks. A project was launched in broiler chickens, but there was also an interest in turkey flocks, especially those flocks where lymphoid tumors had been observed. Was MDV also a problem in turkeys? Blood from a turkey flock in Indiana was received in September 1968 and inoculated into cell cultures. In a few days, virus plaques were observed that resembled those of MDV but were clearly different in morphology and growth.

These cultures induced no disease in either chickens or turkeys. However, the virus shared some antigens with MDV and proved to be a herpesvirus. Importantly, chickens inoculated at hatch with this virus were protected against challenge with virulent strains of MDV. These observations were presented in the summer of 1969 and attracted much attention, as there was at the time no vaccine against MD available in the US.

The virus was first described as "turkey herpesvirus" but published as "herpesvirus of turkeys (HVT)" in order to avoid a perceived conflict in acronyms with another virus (turkey hepatitis virus, now known as turkey viral hepatitis).

The vaccine was approved for Federal licensing on March 1, 1971. The benefits were dramatic. For a while, there was an excess of laying hens which caused egg prices to plummet. The HVT vaccine quickly achieved nearly universal use in US breeder, layer and broiler flocks and is still used worldwide.

The two previous stories (above) are surely among the signature achievements in the 75 year history of the Laboratory. More detail is available in excellent biographies for Burmester, Witter, Purchase, Nazerian and Lasher (http://www.aaap.info/biographies).

Although much of the credit for the HVT vaccine accrued to Okazaki, Purchase, Burmester and Witter, many others in the Laboratory played important roles. This was recognized by the awarding by ARS of the Distinguished Service Award to the entire Laboratory in 1972 (photo album).

Vaccine studies. As soon as the first promising results with the HVT vaccine were reported, the Laboratory mounted a crash program to validate the vaccine for licensing. Indeed, the urgent need for a vaccine prompted USDA licensing authorities to deviate from common practice and accept safety and efficacy data from the Laboratory to support license applications from commercial vaccine companies.

Field studies were conducted (with impressive results). Studies on vaccine administration and the effect of vaccine on the pathogenesis and transmission of MD were conducted. A multilayer technique for large scale production of vaccine in roller bottles was developed. In a very short time, much was learned about the HVT vaccine that materially speeded Federal licensing by 3 commercial companies in 1971 and assisted the poultry industry as it quickly adopted this technology over the ensuing months.

Turkeys. Almost forgotten in the vaccine excitement was the finding that most commercial turkeys harbored a previously unknown virus. Studies by the Laboratory defined the prevalence and transmission of HVT in turkey flocks where it spread readily and showed a lack of oncogenicity for its primary host species. In contrast, MDV did induce tumors when inoculated into turkeys but this virus spread poorly in this species. The question of exactly how HVT affects turkeys was not answered, and remains an enigma.

Bursa role in LL. According to Max Cooper, in the early 1960s, Bob Good was the leader of an important immunology group located at the University of Minnesota

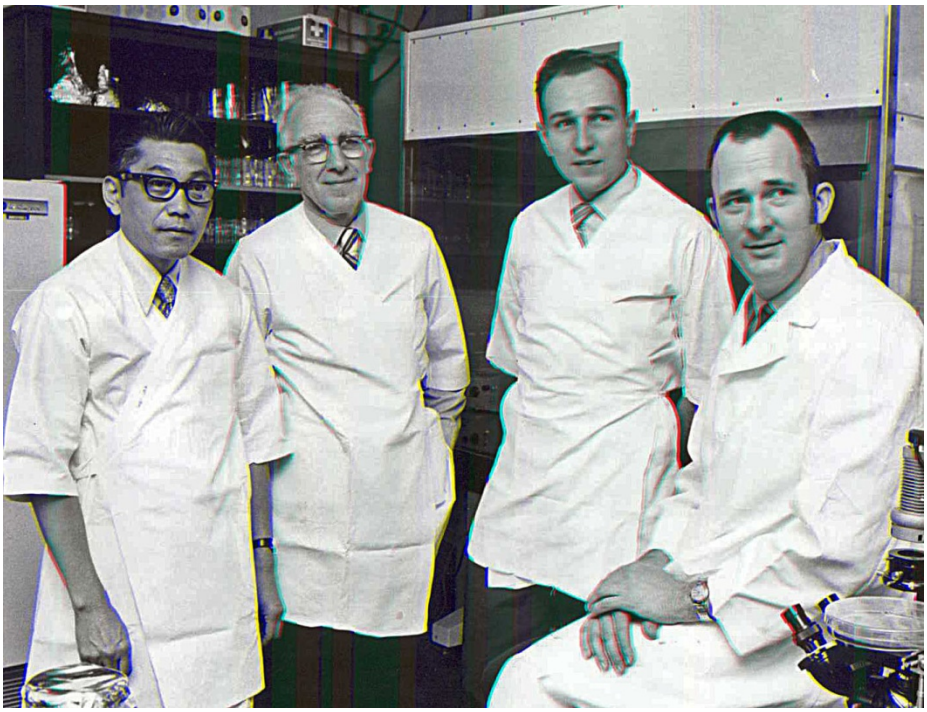
Medical School. He turned to the chicken model to answer fundamental questions on lymphocyte roles in immune response and cancer. Thus he and his colleague, Ray Peterson, sought Burmester's help with a study that ultimately showed removal of the bursa would prevent induction of LL tumors. Max Cooper joined the Good group in 1963 and conducted several follow-on studies with the Laboratory on LL. Cooper's work led to other studies with chickens that established clearly the bursal and thymic lymphocyte lineages, a landmark achievement in both avian and mammalian immunology. This work also provided fundamental knowledge on the pathogenesis of LL and established lesions in the bursa as pathognomonic for the disease.

Differential diagnosis. Since it now appeared that bursal tumors were pathognomonic for lymphoid leukosis and nerve lesions were pathognomonic for MD, new and improved criteria for differential diagnosis became possible. A monograph published in 1970 provided the gold standard for tumor diagnosis for the next 35 years (7).

Synopsis

The Burmester years are distinguished by the major re-staffing that commenced in the latter years of the Winton era and continued through the 1960s. It is likely that Burmester, as the principal laboratory scientist after the retirement of Waters, was instrumental in the recruitment of all these persons. In addition, Burmester presided over the agonizing and protracted process, which ended with the completion of a new addition to the laboratory-office building in 1972. Science-wise, this was the period during which MD was accepted by the Laboratory as a separate disease. Research emphasis swung sharply away from LL to focus on MD during this period. But the defining scientific advances were, first, the discovery of the herpesvirus etiology of MD, which although diminished somewhat by the parallel findings reported from England, was still very big. This was followed by the identification of HVT and development of the HVT vaccine, which was even bigger. These two accomplishments focused much attention on the Laboratory and cemented its credibility with the poultry industry and the scientific community. This was a very special time, indeed.

After retirement, Burmester continued to live in East Lansing. He served as a collaborator to the Laboratory for several years, later moving to Idaho and then to California where he died in 2009 at the age of 99 years (see biography at http://www.aaap.info/biographies).



Bill Okazaki, Ben Burmester, Graham Purchase, and Dick Witter (circa 1970). These were the persons most directly involved with the HVT vaccine for Marek's disease. Others helped as well.

The Witter Years (1975-1998)

The poultry industry situation

With the advent of the HVT vaccine for MD, the poultry industry enjoyed a few good years before it became apparent in the late 1970s that vaccination was losing its efficacy. Bivalent vaccination in 1984 relieved the situation but by 1990, losses were again mounting. The answer this time was licensing in the US of the CVI988 vaccine strain for MD. The Laboratory worked closely with the poultry industry and played key roles in both events.

On the LL side, the layer industry continued to have significant losses due to LL in mature stock, mostly due to infection with avian leukosis virus, subgroup A. With the advent of new simple techniques to detect shedder hens, some layer breeder companies initiated eradication programs in the late 1970s, some of which reported significant success by the mid 1980s. Again, the Laboratory was intimately involved in all phases of these programs.

By 1992, problems commenced with myeloid leukosis (ML) – a new disease discovered in England but which spread quickly to breeders of meat strain chickens around the world. This disease was caused by a new subgroup of avian leukosis virus (ALV-J). The disease caused high losses in all the major broiler breeder companies. However, eradication programs were established by some companies and, again, efforts were ultimately successful. By the early 2000s, ML had ceased to be a major problem in the US. Smaller companies, including some in other countries, lacked the resources required for eradication and some ultimately were forced out of business.

Thus, in this era the US poultry industry was challenged by four distinct outbreaks of oncogenic disease (or infection) that fell within the purview of the Laboratory. It was a busy and exciting time. And the poultry industry was looking to the Laboratory for help with all of these issues, a challenge which the Laboratory welcomed.

Staffing

The beginning of this era (1974-75) saw the departures of Burmester and Purchase, the appointment of Witter as director, and the reassignment of Crittenden to East Lansing. Crittenden had left the Laboratory in 1966 and spent the ensuing decade in Beltsville conducting an independent research program on genetics and avian tumor viruses for ARS. Joining Crittenden in East Lansing was two of his Beltsville colleagues, Gene Smith (biochemistry) and John Motta (animal scientist). These changes occurred in just a few months and substantially changed the profile of the Laboratory.

Following the retirements of Stone and Solomon, Aly Fadly (pathology) joined the staff in 1976 and Larry Bacon (immunogenetics) was hired in 1978. Bob Silva (virology) joined the laboratory in 1983, following Okazaki's retirement. The final changes of this era were the additions of Henry Hunt (immunology) in 1991 and Hans Cheng (molecular genetics) in 1992 following the departures of Sharma and Crittenden. Importantly, Bacon assumed responsibility for the Laboratory breeding program after Crittenden's resignation. Nazerian retired and was replaced in 1997 by Sanjay Reddy (molecular virology).

Crittenden, who had contributed so much prior to his retirement in 1989, continued on a part-time basis, with modest support through a cooperative agreement with Michigan State University until 1995. The Laboratory even renovated new office and laboratory space for him during this period.

Postdocs. Starting in the early 1980s, funds from outside grants and cooperative agreements became available to fund postdocs, graduate students and visiting scientists. Lucy Lee recruited a series of scholars from China that materially assisted her programs for the next 20 years. Almost every professional staff member became involved in this program. The list is too long to relate here. Patrick Shen was the first postdoc. He was followed by Don Salter who contributed to Crittenden's program in retroviral vectors, transgenic chickens and other subjects for most of the 1980s. Masahiro Niikura and Janet Fulton also enjoyed long tenures as postdocs. There were many visiting scientists, but Noboru Yanagida and Ryohei Ogawa spent several years in the 1990s working with

Nazerian and Lee on fowl pox virus vectors, the result of a cooperative agreement with Nippon Zeon, Inc. (Japan). It was a busy time and lab space became increasingly limited.

Training. The program under which Laboratory scientists could do a sabbatical training leave at another laboratory was continued. Jagdev Sharma was at the National Cancer Institute working with Ron Herberman in 1977-78. Lucy Lee visited the Houghton Poultry Research Station in 1978-79 where she worked with Patrick Powell. Aly Fadly also did a training year at the Houghton Poultry Research Station in 1985-86 with Jim Payne.

Crittenden worked for several months at NIH facilities in Frederick, MD in the laboratory of Neil Copeland and Nancy Jenkins (1984-85). Larry Bacon visited the University of Guelph in 1996-97 where he worked with Rob Etches on germ cell manipulation in embryos, a technique of potential value in the creation of transgenic chickens.

Other staff. The program depended on a competent support staff, many of whom are included in the photo album.

Other issues. Productive communications among employees were encouraged through research meetings, staff meetings (usually weekly), and all employee meetings (usually monthly).

A severe snowstorm in 1978 essentially closed the Laboratory for several days but some of the staff, along with Uli Neumann, a visitor from Germany, braved the conditions and provided essential care for the experimental chickens, earning the gratitude of all.

The garden club, organized in the previous era, continued through 1980 before it disbanded, at least partly due to concerns about Laboratory security.

A no-smoking policy was implemented at the Laboratory in 1993. This initiative was driven by the support staff, as ARS did not have a general policy at this time. However, it received widespread support. Again, the Laboratory was at the forefront of change in ARS.

Facilities

The process of expanding and upgrading the Laboratory farm and chicken housing facilities continued. Three significant new facilities were constructed – all on the East side of the farm.

A change room/necropsy facility (Building 21) was constructed on the East side in 1981. The necropsy facility, complete with an attached incinerator, was a big improvement. A change room and lunch room was located in a separate wing for the use of east side personnel.

Building 22 was constructed on the East side (1982) to house high containment isolators for work with hemorrhagic enteritis and infectious bursal disease viruses and to expand pen housing for longer term chicken experiments.

About 1991, a heat treatment facility (Building 24) was constructed on the East side to receive and sterilize waste from the high security isolators located in buildings 19 and 22. With this facility in operation, the Laboratory had the equivalent of biosafety level-3 containment available for the first time.

Isolators (East side). A group of 19 large stainless steel FANP isolators, originally located in the shop loft (Building 6) were relocated to Building 19 pen 8 in the mid 1970s.

This facility was so useful that more isolators of this larger FANP type soon became necessary. However, stainless steel was becoming more costly. To meet this need, the Laboratory maintenance staff designed and produced a hard canopy isolator and base made from fiberglass using custom designed molds. Ultimately, 32 units were installed in Building 22 pen 13. The cost savings were substantial and the units worked so well that the design was borrowed by other laboratories. Tim Caswell and Brian Doyle of the maintenance staff received awards for the unique design.

In the meantime, back in the 1970s, the several pens in building 4 were equipped with 38 isolators with stainless steel bases and plastic bubble tops. These FAPP-type

isolators, although not ideal for infection work, were larger and permitted longer term studies to be conducted. They were used mainly for studies with avian leukosis viruses. Further design improvements would be made later.

Thus, by the early 1980s, there were 182 Horsfall-Bauer isolators, 57 large FANP isolators and 38 large FAPP isolators available on the East side for use in animal experiments.

Pens (East side). And in addition, there were several pens in buildings 19 and 22 where chickens were reared in floor pens, colony cages or individual bird cages. Two of these pens were used to maintain the Laboratory duck flock. Other pens were used to maintain a small flock of line 7 chickens (mated to line 15 males). These birds were vaccinated with all 3 serotypes of MD vaccine to insure maternal antibodies in their progeny. This flock had been maintained by Witter since 1980 as part of his research program but was taken over by the Laboratory in 1985.

Thus, in the 1980s, the Laboratory farm seemed well set for large scale animal experimentation. And the facilities were heavily used. Usually, it was necessary to book isolator space months in advance. The farm was a busy place.

Breeding farm. A new fence system was installed in 1988, securing access to the farm area and buildings. This fence would be improved further in subsequent periods.

The SPF program was fully established by 1975 and chickens were being reared successfully from hatch to egg production in FAPP environments. Another building on the west side had been converted to FAPP (modeled after FAPP houses as developed for the SPF chicken industry). At least one flock was reared free of infection in this environment, but later flocks broke with MD and ultimately the Laboratory focused on the rearing of chickens in FAPP isolators.

All breeding chickens (housed on the west side) were now considered SPF, based on annual serological testing. Most were vaccinated with HVT to protect against possible MDV infections. However, some breeders were maintained for their entire lives in FAPP-type isolator environments to produce line 15x7 chickens for experimental studies that lacked MD maternal antibodies. As antibody-positive 15x7 chickens were being produced on the east side, it was now possible to compare the response of antibody negative and positive chickens from exactly the same strain cross.

By the 1990s, buildings 3, 9 and 16 had been taken out of service, thus streamlining the breeding program. Otherwise, the west side facilities did not experience much change during this era.

Deficiencies and problems. In 1988, the Laboratory was called to task for transporting fill dirt to a part of the farm that had been designated an official wetland. The situation was corrected by creating a wetlands project that reclaimed this area and earned the Laboratory recognition under the USDA Take Pride in America Program. Unfortunately, not all facility issues were solved this easily.

Both long and short range problems were identified in the physical plant (laboratory and farm) during the 1988 workshop at Sauk Valley (see later). Just weeks after this workshop, in November 1988, a comprehensive ARS Facilities Survey identified many of the same problems.

New facility project. This resulted in a preliminary decision by ARS in February 1990 to proceed with a comprehensive facility renovation project. The first drawings were in hand by May 1990. The plan involved construction of a new 6000 sq. foot laboratory wing, renovation of existing laboratories and office space, construction of a biocontainment facility for experimentally-infected chickens, construction of FAPP facilities for the pathogen-free breeding flock, and related improvements including improvement of security of grounds, removal of obsolete structures and hook up to the municipal water supply.

In addition, a pre-accreditation survey by AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care) determined that accreditation of the Laboratory would not be possible without improvement in the physical facilities for housing animals.

The facilities project was formally approved by Dean Plowman, Administrator of ARS, in May 1991.

At the time of the 2nd meeting of the Users Liaison Group in 1994, this project, now estimated to cost $13.1 million, was included on the ARS list of facilities improvement projects. The project was supported by several US poultry organizations. More importantly, Congressional appropriations of $250,000 (FY92) and $212,000 (FY93) permitted initiation of a contract for predesign and environmental assessment, to be completed by June, 1994. We were advised by our "politically savvy" colleagues that funding, once initiated by Congress, would continue to completion. However, it was not to be.

For the next several years, the prospects for a new facility project dimmed. But, unexpectedly, a major appropriation of $1.8 million was received in FY98, and effort restarted. A planning committee was formed and design work commenced. However, at about this time, Witter stepped down as Director and his era came to an end. The rest of this saga is continued in the next section.

Registry of Historic Places. The Laboratory was formally identified on the Michigan Registry of Historic Places in 1995. Witter initially opposed this, as it would limit the options for architectural changes, but in hindsight this determination was based on some of the same reasons that prompted the preparation of this historical account – that the Laboratory indeed has a special place in history.

Water supply. In 1996, the Laboratory changed its water supply to the city water system, abandoning the well that had supplied water since 1939. This also prompted the construction of a sanitary pumping station and a water meter house. The water tower, which has been a prominent landmark for the Laboratory since 1939, is still present, but contains no water.

This was also a period that saw remediation of leaking underground storage tanks and chemical dumping sites.

Summary. By the end of this era, the physical footprint of the Laboratory included 29 structures of different types. Most were showing their age and maintenance was a continuing issue. However, functionality was maintained with the help of a robust in-house maintenance staff, and the research program thrived.

Research program and administration

During this period the research was influenced by emerging technologies as well as by the evolving needs of the industry. It was also a time when the creativity of the professional staff generated a number of new initiatives. A formalized structure for research program development was established in the Laboratory, which insured focus and coordination. Research was first written as a "phase proposal" (actually a subunit of a project) that was then discussed by the group and reviewed by a research advisory committee before approval by the Director. Semiannual (later annual) reports insured that progress was shared amongst the staff on a continuing basis. In many ways, the professional staff functioned as a committee of the whole, which was not always an easy task. Witter promoted and guided this process, emphasizing communications and teamwork.

Research at the laboratory was traditionally designed by one principal investigator who then might invite other professional staff to collaborate as would be needed, thus, forming the required research team. In the 1980s, however, this paradigm changed. As principal investigators increasingly assembled cadres of postdocs and graduate students, the requisite team was more frequently internal, and less frequently was it necessary to involve other professional staff in order to assemble a critical mass of effort. Yet, diversity was a strength of the Laboratory, a fact well understood by all scientists. Publication authorship of the time revealed that collaborative arrangements on projects continued to be common.

MD programs continued to have strong emphasis, especially once HVT vaccine became less effective in the late 1970s, but emphasis on LL increased, especially after the return of the Crittenden program from the Beltsville location to the Laboratory in 1975. There was also an expansion of the program to embrace other virus diseases, such as reticuloendotheliosis.

During the 1980s, there were many changes in the research program.

By 1980, the Laboratory was fully engaged in programs to assist poultry breeders in the control of LL through eradication programs. Programs on endogenous leukosis virus have been mounted and congenic lines for genes determining endogenous virus expression were under development. The identification of more virulent pathotypes of MDV prompted new efforts towards next generation vaccines for MD.

Newly developed technologies for monoclonal antibodies were being adapted by the Laboratory to identify selected MDV and major histocompatibility antigens. A new program on immunogenetics was also developed, designed to detect alloantigen-determining loci that influence host resistance to tumors or tumor viruses. This program also involved the development of new congenic lines for B blood group alleles.

Chicken lines. With leadership from Crittenden and Bacon, the Laboratory breeding program generated a large number of specialized chicken lines (1) some of which were congenic, semicongenic, or recombinant congenic. Much of this effort was directed at ways to elucidate the genetics of endogenous virus genes, or the basis of the resistance (line 6) and susceptibility (line 7) expressed in lines 6 and 7 to both avian leukosis virus and MDV.

In addition, Bacon and Hunt produced specialized antisera and developed blood typing schemes to ascertain the purity of all genetic lines, which were evaluated annually as a complement to other serology to ascertain their freedom from unwanted infections.

Technology for semen freezing was instituted in 1980 and served to provide a backup in case of an unexpected problem with reproduction of the inbred lines.

This investment in the breeding and maintenance of highly specialized (and SPF) chicken lines paid large dividends to the Laboratory research program, and established the Laboratory as a world resource for workers in the avian tumor virus field.

Embryo vaccination. In 1980, Sharma started work on ways to improve the efficacy of MD vaccination by *in ovo* inoculation, thinking that this would give the vaccine a head start and chicks would be protected earlier. The first experiment totally failed but fortunately the work continued. Automation of the process seemed important from the outset and the Laboratory maintenance department designed a crude device that could deliver vaccine through a set of syringes to 3 eggs at a time. Results in 1982 showed that chicks vaccinated *in ovo* with HVT were protected at least as well as by conventional vaccination at hatch, and possibly better. Further refinements and study quickly followed.

However, the technology might have languished without the vision of the broiler industry, which saw this as a way to save labor and reduce costs. The biggest hurdle was how to administer vaccine to embryos effectively and safely on a large scale. This was an engineering issue. At this point, a fledgling commercial company (Embrex, Inc.) licensed the technology and, with the Laboratory as consultant, proceeded to develop specialized machines for administering the vaccine (a process that took more than 5 years).

Ultimately, *in ovo* vaccination technology has come into widespread use by the broiler industry in the US and 35 other countries. This was one of the early successes of the ARS patent licensing program and provided much visibility for the Laboratory's research.

Other diseases. In 1979, a new program on infectious bursal disease and hemorrhagic enteritis of turkeys had been created in an attempt to expand the overall scope and thus better secure the future of the Laboratory's research program. An integral part of this initiative was the installation of high security isolators in building 19 and the later construction of building 22. This program had a relatively short life at the Laboratory, but there were a number of successes.

During the period of research on hemorrhagic enteritis, the Laboratory was heavily engaged with turkeys. Over 500 turkeys a month were supplied by the National Animal Disease Center from their SPF turkey flock during parts of 1982. This is probably the only time in its history that an avian species other than the chicken has seen such extensive utilization in experimental infection studies at the Laboratory.

Avian leukosis virus eradication. Although the Laboratory had been working with the layer breeder industry since the late 1970s on eradication of exogenous avian leukosis virus, progress in the industry was measured at best. By the mid 1980s, a new line of research was initiated pursuant to discussions with a commercial breeder company on the role of serotype 2 MD vaccines as a contributing factor to excessive lymphoid leukosis mortality in the field, especially in slow feathering strains of chickens. This initiative yielded important new information and provided additional incentives for the layer breeder industry to complete the eradication program.

Monoclonal antibodies. In May 1980, a plan was under discussion to bring the newly developed monoclonal antibody technology to the Laboratory. It was further proposed that a mouse colony be established as it would be cheaper and more convenient than purchasing mice from other sources. The colony and the technology both thrived and became important parts of the Laboratory's research.

Vectors. The Laboratory also instituted a comprehensive new program on viral vectors for vaccine delivery, taking advantage of newly emerging technologies. Some of these vectors were also designed to deliver foreign genes to germ cells, a technology important for the production of transgenic chickens. This was initially conceived as a 3 pronged attack utilizing herpesviruses, pox viruses, and retroviruses. This also marked the Laboratory's entry into recombinant DNA research, another emerging technology that would have broad application to the research program. A special (P-2) lab was designated in 1982 for the growing of bacteria for these studies.

MD vaccines. Efforts to improve the effectiveness of MD vaccination through development of new products and other strategies continued throughout this era. In parallel studies, MDV was isolated from the field and characterized so that vaccines could be tested against the most virulent of current field strains. The ability of serotype 2 MD viral strains to augment the efficacy of the original HVT vaccine created a novel opportunity to expand knowledge on vaccine protection. By the end of the 1990s, work had also focused on attenuated serotype 1 vaccines (including strain CVI988) and on natural recombinant viral strains. Work with strains modified by recombinant DNA technology was just starting.

Some vaccines were received from other sources for evaluation. CVI988 clone C was received in the mid 1980s from Hiram Lasher, and CVI988 (original strain) was received in the early 1990s from Daniel Gaudry.

Genetics. Also in the mid 1980s, the genetics program was reinvented as the host gene group, which also included new efforts on germline integration of specific genes and eventually embraced the new field of genomics. Programs on transgenic chickens initially created much excitement in the mid 1980s as the Laboratory created the first chicken carrying an inserted foreign gene in its germline. Visions of a continuing program towards transgenic technologies applicable to the poultry industry prompted collaborations in the 1990s with the University of Guelph. However, programmatic decisions by ARS resulted in a cessation of activity on transgenic chickens at the Laboratory.

By 1992, a specific program in genome mapping had been established. The initial goal was to generate a molecular genetic map of the chicken genome, and use this to identify quantitative trait loci accounting for resistance to MD, which could further be used as markers for genetic selection in commercial flocks.

ALV subgroup J. The emergence of ALV-J infection in broiler breeders in the 1990s prompted a major shift in laboratory priorities. For a period, virtually all the professional staff redirected at least some effort to this new challenge for the poultry industry in the US and around the world. Direction of this expanded research initiative was determined, in part, by input received during a workshop convened by the Laboratory for the major US broiler breeder companies on May 10, 1994.

Soft money. The Laboratory submitted its first proposals to the ARS Research Associateship Program in 1981. Competitive grants in agriculture became available in 1985. These and other grant opportunities opened the door to new sources of funding for postdocs and graduate students. Laboratory scientists had considerable success

with these programs, illustrating the competitive nature of the research being conducted.

The Federal Technology Transfer Act of 1986 paved the way for Federal labs to enter into partnerships with private companies. In December 1987, the Laboratory held a meeting attended by representatives from 38 companies to showcase its current portfolio of projects. As a result of this and other initiatives, Cooperative Research and Development Agreements (CRADAs) were signed with Solvay, Inc., Nippon Zeon, Inc., and a number of other companies. CRADAs were also executed with companies interested in monoclonal antibody technology. Funds from these agreements supported postdocs, graduate students and visiting scientists in ensuing years.

Committees. By 1985, a computer committee had been established (as personal computers had been first introduced to the laboratory in 1984). It was 1988 before every professional staff office had a computer. Time and attendance sheets were first transmitted electronically in 1988. Email first became available in 1993 followed by internet service in 1996. The computer age had arrived.

In addition, there was an animal welfare committee and a safety committee – an indication of the change in priorities in the laboratory and in science policy regulation. Projects involving recombinant DNA needed review by a special committee. The Laboratory formed its own institutional animal care and use committee but utilized committees at Michigan State University for some of the other required oversight functions.

Name Change. Discussion on a new name for the Laboratory first occurred during the Sauk Valley Conference in 1988 (see later). Discussions continued at the Laboratory starting in 1989. Proposals for a new name were solicited from and vetted by the Laboratory staff. The new name, Avian Disease and Oncology Laboratory, better communicated the mission of the Laboratory and was officially adopted on May 17, 1991.

Reference Lists. During the 1970s and 1980s the Laboratory compiled and distributed a list of references relating to the avian tumor viruses to more than 100 scientists. This was a time when hard copy reprints of articles were purchased and distributed on request. During at least part of this same period "preprints" (manuscripts accepted for publication by a journal) were exchanged with select research laboratories where especially close ties existed. All these practices were ultimately abandoned, but seemed to serve a useful purpose at the time.

Users Liaison Group. Acting on a suggestion from Darwin Murrell, Area Director, the Laboratory took steps to create an ad hoc council of industry representatives to advise the Laboratory on programs and advocate for its future. Attending the first meeting on February 3-4, 1992, was a an 8-person industry committee chaired by Bill Chase, of Hy-Vac Laboratory Eggs, Co., plus several other industry and institutional guests and Laboratory personnel. The summary of this meeting is given in the box below:

First ULG Meeting (1992)
Summary recommendations:

- *There is a need for the research being done at ADOL.*
- *The staff is unique in abilities and interests.*
- *The research focus has been "on target."*
- *We need to continue to invest in proper facilities and staff.*
- *The ADOL is a unique asset and deserves our help and support.*

The Users Liaison Group was convened again in 1993 and 1995, and sporadically thereafter on an as needed basis. The primary purpose was to assure program relevance and, thereby, the future of the Laboratory.

Key conferences

This era was characterized by an unprecedented number of important conferences and workshops, reflecting the need for communication with the poultry industry and others on a variety of issues.

Leukosis Virus Control Workshop. A workshop was held at the Laboratory on January 24, 1978. Organized by Graham Purchase, National Program Staff of ARS in Beltsville, MD, the workshop was directed to the needs of

primary breeders in the development of eradication programs for exogenous ALV. This marked the beginning of a concerted effort by the breeding industry towards ALV control through eradication. The industry strongly opposed any governmental control and favored reduction programs over eradication.

Lymphoid Leukosis Workshop. On January 10, 1985, Hy-Line International, a commercial breeder of layer chickens, engaged the Laboratory in a discussion on the company's concerns regarding the role of SB-1 vaccine and slow-feathering in LL continuing mortality in certain chicken lines. The deliberations launched studies on enhancement of LL by serotype 1 MD vaccines and stimulated further work on slow-feathering and endogenous viruses – both of which were important and productive directions for the Laboratory. The issues raised and the ensuing collaborations with the Laboratory stimulated the company to complete the eradication of exogenous ALVs, which solved the problem and established a model for the poultry industry.

HEV Workshop. A meeting with representatives of several commercial vaccine companies was held on January 18, 1985 to explore interest in commercialization of the cell culture propagated vaccine for hemorrhagic enteritis of turkeys previously developed at the Laboratory.

Visioning and Action Planning Workshop. A retreat, initiated by the Laboratory and perhaps the most extensive program review in its history, was convened at the Sauk Valley Resort, Brooklyn, Michigan on May 16-18, 1988. The purpose was to prepare a long range plan for research programs, staffing and facilities of the Laboratory.

The conference consisted of 13 ADOL staff members and an equal number from government, Michigan State University, other institutions and poultry companies. The principal products were a mission statement, and recommendations that the research focus be narrowed, and that the physical plant be assessed and deficiencies corrected. Other findings were:

- The concept of research teams with significant soft-money funding to support graduate students and postdocs was affirmed, thus formalizing a trend that had already become evident in the Laboratory due to the availability of grant funds.

- The multidisciplinary focus was also reaffirmed, with a goal of two permanent scientists in each of five disciplines – genetics, molecular biology, immunology, virology and veterinary medicine.

- Finally, it was recognized that expansion of interactions with institutions and industry could greatly assist the Laboratory in accomplishing its mission.

Actions taken as a result of this conference were the phasing out of research on infectious bursal disease and hemorrhagic enteritis and the initiation of efforts to secure a substantive upgrade in the physical plant, a project which would consume much of the Laboratory's energy during the ensuing decade. These discussions also directly prompted consideration of alternate names for the Laboratory.

In addition, a mission statement was produced in an effort to document the vision and purpose of the Laboratory. This statement was useful but would soon be revised (see later).

The Laboratory also formed a long range planning committee that developed its own set of priorities, many of which were designed to implement the recommendations of this workshop.

50th Anniversary. The Laboratory celebrated its 50th Anniversary on June 16, 1989. Peter Biggs, a colleague from the Houghton Poultry Research Laboratory in England, and Dean Plowman, Administrator of ARS, joined laboratory staff and other dignitaries for the event. A brochure was produced and the public was invited to tour the Laboratory.

Broiler Breeder Workshop. On May 10, 1994, a workshop was organized by the Laboratory for representatives from 7 broiler breeder companies. The discussions focused on methods needed for ALV-J eradication including tests to distinguish exogenous from

endogenous avian leukosis virus. This also marked the beginning of a major effort by the Laboratory to assist the poultry industry in resolving this newly recognized disease problem.

ADOL Retreat. On October 6-7, 1994, the senior staff of the Laboratory met at the Kellogg Biological Station, Hickory Corners, MI to discuss vision issues and possible programmatic changes. Part of the discussion, led by Larry Bacon, focused on development of a revised mission statement. John Welser, from The Upjohn Company, was the featured speaker.

ADOL Mission Statement
1994
The mission of the ADOL is to provide leadership in solving current and future problems in neoplastic and other viral diseases of poultry using basic and applied multidisciplinary, team approaches thereby benefiting the poultry industry and consumers.

MD Symposium. The Laboratory hosted the 5th International Symposium on Marek's Disease in East Lansing on September, 1996. Over 250 persons attended a meeting with many special features. This included a unique historical focus entitled "The Legacy of the 1960s" to celebrate the accomplishments surrounding identification of the MDV and development of the HVT vaccine. Forty-five persons who contributed to MD research in the 1960s were invited as part of a panel discussion led by Dick Witter and Robin Morgan. A video was produced that documented the panel and some associated interviews.

This was a major group effort that involved most of the Laboratory staff. Leland Velicer, a colleague from Michigan State University, assisted substantially with the planning. A comprehensive videotape was produced to record the panel discussion, interviews, and other events of historical importance. The videotape was marketed by the AAAP and exists, along with full length supporting materials, in the historical archives of the AAAP.

Selected Research Advances

MD susceptible chickens. Although line 7 chickens were highly susceptible to MD, a cross ($15I_5x7_1$) was found suitably susceptible with improved hatchability and vitality. This cross, commonly known as 15x7, became the standard for many MD experiments starting in the 1970s. By the early 1980s, a need for chickens with MD maternal antibodies had developed and was met by establishing line 7 breeding populations on the East side of the farm that were vaccinated with MD serotypes 1, 2 and 3.

MHC congenic lines. Chicken lines that differed only for the MHC (B) locus led to the cloning and DNA sequencing of nine important MHC class I and class II haplotypes. Expression of these class I haplotypes firmly established the function of the different alleles and enabled the identification of thousands of potential MDV peptide antigens presented by the historically resistant B21 haplotype compared to twenty or less MDV peptide antigens presented by more susceptible MHC haplotypes. The expressed cells were injected into appropriate chickens to develop highly specific antisera that were helpful in blood typing. Additional research identified mechanisms used by MDV to evade the chicken's antigen presenting system.

Additional chicken lines. Nineteen recombinant congenic strains were developed that genetically dissected MD susceptibility. A specific cross resulted in the first chicken line (0) that had no endogenous virus genes (EV) and was resistant to EV at the receptor level. An additional line contained the EV21 locus, which was linked to the sex-linked slow feathering gene (K). Given the importance of these genetic resources, over 20 lines developed by the Laboratory were recognized as the first ones in the National Registry.

Eradication of Exogenous ALV. Efforts directed at eradication of ALV in commercial chickens commenced in the late 1970s. The key was the discovery by a visiting scientist, Lloyd Spencer, of viral gs antigen in the albumen of eggs, which could be utilized to detect shedder hens. Another key was the development by Gene Smith of simple ELISA tests to detect gs antigen and antibody, thus, providing the necessary tools for eradication

programs, and which are still in use worldwide. The Laboratory worked closely with a number of commercial White Leghorn breeders to transfer technology needed for success. The key moment was probably in 1978 when the first large layer breeding companies made the decision to launch eradication programs. By the mid 1980s LL in commercial stocks had ceased to be a problem in the US and flocks were sustaining improved egg production.

***In ovo* vaccination.** A technology was developed in the early 1980s for administration of MD vaccine by inoculation to chicken embryos at the 18th day of incubation. Originally conceived as a method to improve vaccine efficacy, the technology was licensed by a commercial company who developed sophisticated machines to inoculate large numbers of embryos both quickly and accurately. This technology has been widely used by the broiler industry since the mid 1990s for the delivery of MD and other vaccines (and other products), which results in improved administration of vaccines at lower costs, essentially creating a new industry to support the poultry industry. (See research program section for additional background)

Synergism and bivalent vaccines. After a hiatus of several years, the Laboratory reentered the MD vaccine arena in the late 1970s, in response to reports of suboptimal protection with HVT vaccine alone. The key finding was the synergism between vaccines of serotypes 2 and 3, which resulted in better protection with the bivalent vaccine than with either single vaccine. Bivalent vaccines were widely used by the poultry industry beginning in the mid 1980s.

Reticuloendotheliosis virus (REV). Inoculation of chickens with REV strains revealed their ability to induce, after long latency, either B-cell tumors that closely resembled lymphoid leukosis or, under different conditions, T-cell tumors that closely resembled MD. It was now clear that this class of avian retrovirus would need to be considered as a primary pathogen, as a vaccine contaminant, and as an important consideration in the differential diagnosis of tumors.

Insertional mutagenesis of herpesvirus by retrovirus. An accident involving REV also paved the way to a discovery in fundamental science. One strain of MDV, during serial passage at the Laboratory, became contaminated with REV. Our collaborator, Hsing-Jien Kung, discovered that REV sequences had inserted into the genome of the MD herpesvirus. This result was reproduced in subsequent experiments where both viruses were grown together in the same culture. This led to the discovery that retroviruses can insert into the genomes of large DNA viruses, including herpesvirus and pox viruses, a finding of importance in fundamental virology. Insertion of REVs into the genome of fowlpox virus has also proved to be important in the epidemiology of REVs in nature.

Efforts toward new MD vaccines. The development of improved MD vaccines was a primary objective of the Laboratory through the 1980s and 1990s, but success was elusive. The bivalent vaccine was a success (see previous) but by 1990, its efficacy had started to wane. The Laboratory determined that vaccine strain CVI988, originally developed by Rispens in The Netherlands, was the most protective against challenge with very virulent MDV strains. This data helped speed the introduction of this strain to the US where it continues to perform well.

Several other vaccine candidates were developed, including recombinant fowl pox virus expressing various MDV genes, but none was an improvement over CVI988 and some had residual pathogenicity for antibody-free chickens, which would preclude licensing. By the end of this period, additional recombinant DNA vaccines based on deletion of MDV genes using cosmid or BAC clone technology were just beginning to be available, and will be discussed in the next section.

Evolution of virulence. Throughout the 1980s and 1990s, field strains of MDV were isolated and pathotyped in the course of studies by the Laboratory. Eventually, it became clear that the virulence of field strains was increasing and that this phenomenon was responsible for the reduced efficacy of HVT and bivalent vaccines. The implications were obvious. If this evolutionary trend continued, no vaccine would provide acceptable protection. Recognition of this phenomenon has generated significant concern and a number of follow-on studies.

Monoclonal antibodies. Beginning in 1979, the Laboratory launched a major initiative to develop hybridoma technology for the production of monoclonal antibodies. A small mouse breeding colony was established but initial attempts on monoclonals for MHC antigens were discouraging. The fortuitous arrival in 1981 of Xiufan Liu, a Chinese scholar working under Lucy Lee, provided the brute force to yield success. Liu was the first in a series of scholars and students that worked on monoclonals at the Laboratory over the next 2 decades. Monoclonals for MD viral serotypes 1, 2 and 3 were first developed in 1983, and were followed other monoclonal antibodies against a variety of different viral antigens. These reagents proved to be invaluable for the Laboratory research program and similar programs around the world.

Meq. In collaboration with Hsing-Jien Kung and his student, Joanne Kivela, the Laboratory was directly involved with studies that identified the *meq* gene of MDV. The story is elaborated in Lucy Lee's biography (http://www.aaap.info/biographies). This gene proved important to the oncogenicity of the virus and has been the subject of many studies.

Blood typing. In collaboration with Elwood Briles and others, the Laboratory established a battery of specific sera to detect avian blood group antigens. This resulted in simple tests that were used by the Laboratory to ascertain the purity of its specialized lines as well as to initiate development of new B-congenic lines of chickens. Blood type antigens were shown to be linked to MD resistance and to the effectiveness of MD vaccines.

MDV genome sequence. Armed with a battery of monoclonal antibodies and the potential to make more, a systematic program was established to identify and sequence the genes of MDV, with the ultimate objective of obtaining the complete sequence of the viral genome – an almost unthinkable challenge in the 1980s when this started. It started with one gene and one protein at a time, with much help from students and scholars from China. The pp38 gene was identified in the early 1990s. The complete sequence of the GA strain was published in 2000 after more than 7 years of effort. This effort effectively launched the ability to create recombinant MDVs, a key to expanding basic knowledge and creation of new vaccines.

Hemorrhagic enteritis vaccine. In the late 1970s, the Laboratory developed ways to grow the virus of hemorrhagic enteritis virus, which causes an important disease of turkeys, in cell cultures. The resulting vaccine strain could be produced more easily than earlier products that utilized spleens of infected chickens. Importantly, it was highly protective. This technology was patented, licensed to several companies and remains in use within the turkey industry.

Transgenic chickens. Crittenden, with his extensive experience with endogenous viruses that integrated spontaneously into the chicken germline, reasoned that it would be possible to duplicate this event in the laboratory. With Don Salter's help and collaboration from Steve Hughes and others, fertile Line 0 eggs were inoculated with recombinant avian leukosis virus, hatched, and evaluated for germline inserts by mating viremic males or females to nonviremic partners. Virus from some of the viremic males was transmitted to progeny, which appeared in the form of integrated virus (clonal bands by Southern blots). Subsequent matings showed the integrated gene transmitted to progeny in the expected ratios. This was the first transgenic chicken. In total, 23 different transgenic lines were produced. One of these lines, ALV6, continues to be used in laboratory studies. The importance, however, was in establishment of the principle of transgenesis in chickens, raising the hope that this technology could be harnessed for genetic improvement.

Avian leukosis virus subgroup J (ALV-J). A new type of avian leukosis virus was discovered in England and quickly spread among broiler breeder companies worldwide in the 1990s where it caused losses in adult breeders from myeloid leukosis and other neoplasms. The Laboratory developed close cooperative relationships with several US broiler breeders, providing assistance and training, as they endeavored to mount eradication programs. Similar programs had been used for eradication of ALV in layer chickens a decade earlier, but several differences became apparent. Fortunately, the major broiler breeders in the US and elsewhere have now completed eradication of this newly discovered infection, a difficult and costly procedure that prevented a disaster in the industry. Although the Laboratory developed new

knowledge during the process, the distinguishing feature of this advance was the cooperative nature of the interactions between the Laboratory and breeder industry.

Chicken Genetic Map. With the rapid advances in molecular biology, Crittenden and Dodgson established the East Lansing reference panel. DNAs from this set of birds were distributed worldwide, which allowed for the generation of a genetic map comprised of DNA-based markers. Almost as important, it established the collaborative nature of the genomics field today while firmly placing the Laboratory as a very key player.

Synopsis

This period was characterized by change and by response to change. It was a time of excitement and activity, driven by evolving industry needs and advancing technologies. The Laboratory had a full staff and a clear vision of its mission. This was arguably one of the most productive periods during which the Laboratory contributed to eradication programs for ALV subgroups A and B and, later, subgroup J. It also contributed to advanced generations of MD vaccines, some of which became commonly used as adjuncts to the original HVT vaccine. It provided a vaccine for hemorrhagic enteritis of turkeys and a technology for administration of MD vaccines to the embryo. It also contributed to basic knowledge in many areas of tumor virus research and genetics.

It was during this period that the Laboratory's position as a preeminent contributor to knowledge in avian tumors and tumor viruses, already established in prior eras, became solidified. Also, the Laboratory and its staff demonstrated the ability to work closely with the poultry industry to assure application of its findings.

With much help from the poultry industry, the Laboratory started to plan for a long-term future in East Lansing with the launching of a major facility improvement initiative.

LEGACY OF THE 1960'S
Fifth International Symposium on Marek's Disease
East Lansing, Michigan, September 1996

This important symposium was hosted in East Lansing by ADOL. The individuals pictured here contributed to Marek's disease research during the decade of the 1960s. Six of these persons were from ADOL

The Fadly Years (1999-Present)

The Transition

In January 1998, Dick Witter stepped down as Laboratory Director and returned to the bench. Murray Bakst, Poultry Physiologist with ARS in Beltsville, MD, was immediately appointed as the acting director. Bakst arrived at the Laboratory on January 21, 1998 and served as acting director through June. Bob Silva then served as acting director July through September. In October, Aly Fadly was appointed as acting director. At that time, acting positions were normally limited to 3 months. The permanent director, appointed in January 1999, was Aly Fadly (pathology) who was an expert in retroviral diseases of chickens and had worked at the laboratory since 1976.

The poultry industry situation

In contrast to earlier periods, the level of concern about tumor virus problems in the poultry industry seemed less acute, although no less real for those who were thinking into the future. Predictions that MDV would again mutate to a yet more virulent pathotype, thus rendering CVI988 vaccines less effective, were common but MD losses remained at low levels in both broilers and layers throughout this period. No new MD vaccines were introduced despite continued research by this and other laboratories to develop new products.

Broiler breeders were completing the effort to eradicate ALV-J from their primary breeding stock. This was a costly job that was largely complete in the early part of this period, and essentially removed myeloid leukosis from the list of urgent and critical problems. The absence of ALV-J, however, did not completely eliminate lymphoid tumors and towards the end of this period, a new concern was directed towards so-called "spontaneous lymphoid tumors," which did not appear to be associated with exogenous retrovirus infections.

The industry was far from complacent, however, recognizing the propensity of both MDV and retroviruses to mutate and the potential of viral tumors to emerge again as a major concern. The poultry breeding industry also showed an intense interest in adopting molecular techniques for genetic selection.

Staffing

Like the previous eras, this period saw its share of change in personnel. Sanjay Reddy (with his wife, Blanca Lupiani) left in 2001. Both Witter and Bacon retired in 2002.

New hires included two support scientists, Raj Kulkarni (veterinarian and farm manager) in 1999, and Jody Mays (microbiologist) in 2000; and two principal investigators, Huanmin Zhang (geneticist) in 2002, and Mohammad Heidari (virologist) in 2004. In 2013, Alexis Black-Pyrkocz, a computational biologist, was appointed as a support scientist.

Efforts to recruit a veterinarian for the Witter position were not immediately successful so in 2004 Fadly made use of the new ARS Veterinary Medicine Doctoral Program to hire John Dunn (DVM, MS) in a temporary position and provide him the opportunity to earn his PhD with a guaranteed ARS appointment in the future. Dunn's graduate program, mentored by Dick Witter, who was now a collaborator, was completed in 2009 and he received his permanent appointment in 2010.

Lucy Lee retired in 2011 after 43 years of service on the professional staff of the Laboratory. All three retirees, Witter, Bacon and Lee, were appointed after retirement as collaborators (at their request), a position without salary and renewable yearly at the discretion of the Laboratory.

This was also a period when a number of senior technicians left the laboratory, along with their considerable institutional knowledge. Replacement was made difficult because of new restrictions on permanent appointments.

Facilities

The final chapter of the Laboratory plans for a major laboratory renovation came to a close in 2002, 14 years after the initial discussions during the 1988 meeting at Sauk Valley. The earlier events of this saga are in the previous chapter. Following on the two Congressional appropriations in FY92 and FY93, the Laboratory received an additional $1.8 million in FY98 for preparation of final plans for the project that was now estimated at >$20 million and involved a new lab addition and several new poultry buildings to largely replace all other structures on the farm (photo album). Starting about 1999, the Laboratory became, once again, fully engaged in development of plans. Silva led a committee on the laboratory modifications, and Bacon led a separate committee on the two proposed farm structures (to replace essentially all the existing buildings). The completion of this design phase was scheduled for 2002.

However, in 2001 ARS submitted a report to Congress proposing that steps be taken to combine the East Lansing program with that of the Southeast Poultry Research Laboratory located in Athens, GA., a sister ARS laboratory dedicated to respiratory and enteric diseases of poultry. The Georgia laboratory was also pursuing an $80 million renovation and a consolidation would result in cost savings.

Fadly recalls a visit by the Undersecretary of Agriculture in 2002 to review the East Lansing situation, indicating that the issue was receiving attention at the highest level. The FY03 budget, announced in February, 2002, called for (1) the transfer of MD research from the Laboratory to Georgia, (2) the transfer of genetics research to Beltsville and (3) the elimination of retroviral research. These program initiatives were opposed by the poultry industry and were not approved by Congress, but the die was cast. The idea that the Laboratory should ultimately be closed and the programs transferred was gaining traction.

The idea of a future consolidation was solidified during a 2005 meeting of ARS and industry representatives in Florida. Industry now accepted the idea of a consolidation providing that the East Lansing program would be kept intact to the extent possible. The immediate concern was that the substantial expertise and resources available at the Laboratory would be seriously depleted during a transfer and, consequently, would not be available for addressing current and future industry needs for a robust program in avian tumor virus research.

Starting with the President's FY11 budget, continuing in subsequent budgets, and articulated most recently in the FY15 budget, there have been proposals by ARS to effect this consolidation. That the consolidation has not already happened derives mainly from the lack of key facilities at the Georgia laboratory.

But this obstacle may soon be diminished as the Georgia laboratory has received funding for a new building to house East Lansing chickens. Certain Laboratory lines have been shipped to Georgia on a trial basis as it is important that the new facilities be capable of maintaining the specialized lines, many of which require special procedures or considerations for hatching, rearing, and reproduction.

Thus, the idea of moving the Laboratory to ARS facilities in Georgia seems ever closer to reality, although the concept has not been finalized, money has not been appropriated, and the date is not set. Furthermore, Congress has not yet approved such a move.

Aly Fadly recognized advantages accruing from a move in that the Laboratory would then be located in a state with a strong poultry industry and significant political influence. It is likely that poultry disease programs would be well supported. On the other hand, the Laboratory would cease to exist as an entity, its personnel and resources absorbed into an existing structure.

With the above scenario, there was little incentive (or money) for major new construction or renovations in the Fadly era. However, a crisis was met when the municipal sewer utility threatened to shut down the Laboratory farm because of feather contamination. This was solved through the development and installation of sophisticated feather traps for poultry buildings on both sides of the farm. Once again, the Laboratory used its own house knowledge and creativity in solving problems in poultry husbandry.

Operational efficiencies on the farm were achieved by management changes, resulting in the closing of several

buildings and a reduction in caretaker and maintenance staff. This change was prompted by the need for greater cost savings and the recognition that the current practice of vaccination of the breeder population with HVT vaccine was not likely to be effective against the more virulent MDV strains under study at the Laboratory. Thus in 2008, vaccination was stopped, 3 of 6 buildings on the west side of the farm were closed, and the breeding population was reared in strictly isolated (but not FAPP) environments. Results to date have been excellent – the chickens have remained free of extraneous infections, including MD, and considerable cost savings have been realized.

Research program and administration

This era saw its share of program reorganization and consolidation. In 2000, the four CRIS projects (Genome Mapping, Host Genetics, Marek's disease and Retrovirus research) were consolidated into three units (Marek's disease, Retrovirus, and Genomics/ Immunogenetics). In 2006, the Marek's disease and Retrovirus research units were combined into a single avian tumor viruses unit.

Four program increases were received by the Laboratory benefiting avian leukosis (2001), genomics (2001), Marek's disease (2004), and genomics (2014). The total budget in FY13 was about $3.8 million of which 14% was derived from soft funds. Thus grants and agreements continue to provide critical support for Laboratory programs. Indeed, this period was the most productive in the history of the Laboratory in the acquisition of soft funding, most of which was directed to the genomics program under the leadership of Hans Cheng. A research agreement with a breeder company provided funding for work on spontaneous tumors.

One program increase in FY03 to boost efforts in Marek's disease research was originally identified for East Lansing, but in the approved budget, the funds were assigned to "Athens, GA," clearly a last-minute change. With this money, the Georgia laboratory established in 2004 a one-person research unit on MD, the only other ARS program on avian tumor viruses outside of East Lansing.

Fadly continued his efforts to secure needed support for the Laboratory. He successfully demonstrated to industry and ARS the critical need for a program increase for maintaining a viable research program in Marek's disease; this resulted in a new program increase of $250,000 in Marek's disease that was assigned to East Lansing in FY04.

Input from stakeholders in the poultry industry has been actively sought out. In 2011, the ADOL Poultry Industry Coalition (APIC) was established as an advisory body, replacing the Users Liaison Group of the Witter era. This group was co-chaired by A. Gregorio Rosales and Janet Fulton and consisted of over 20 persons representing all aspects of the poultry industry relevant to Laboratory programs. The group met in East Lansing in 2011 and continues to advise the Laboratory on an ongoing basis.

Substantial efforts by Fadly resulted in the Laboratory's designation in 2006 as an OIE Reference Laboratory for Marek's Disease. Laboratories designated by the World Organization for Animal Health (OIE) as reference centers are typically the best and most capable in the field. This designation has permitted the Laboratory to receive specimens for testing from other countries, and to exchange reagents with foreign laboratories, thus advancing the in-house research program. This also required the availability of biosafety level-3 containment and rendered the Laboratory subject to periodic USDA inspections.

There was also a major uptick in the number of Material Transfer Agreements executed, indicating the Laboratory's continuing role in providing reagents and materials to other laboratories.

A major initiative during this period was the expansion of the genomics program, fueled by substantial soft funding and an enthusiastic cadre of young scientists.

The research directions by the end of this era were focused on 4 goals:

- host or viral genetic determinants that control pathogenicity, transmission and evolution of new strains
- diagnostics for new viral strains

- genetic determinants that influence immune responses and resistance to MD
- safe and effective vaccine platforms for MD

Despite the many distractions, the program remained clearly focused and was well positioned for the next decade. There are clearly many important questions concerning avian tumors and tumor viruses yet to be answered.

Although summer intern programs had existed for some years at the Laboratory, a special program to provide a summer research experience for veterinary students at Michigan State University was inaugurated in 2005. This program received a boost with an endowed gift from an outside donor in 2005 which provided, in perpetuity, a stipend for a student selected to work at the Laboratory. To date, at least 9 students have participated in this program, most of them working with John Dunn.

Key conferences

MD symposium. As this history is being written, the Laboratory is busy preparing to host the 10th International Symposium on Marek's Disease and Avian Herpesviruses, scheduled for July 20-23, 2014, in East Lansing. This symposium will also focus on historical aspects of herpesvirus research, continuing a theme established in the 5th Symposium (1996), also hosted by ADOL. The program will also include a celebration of the 75th anniversary of ADOL, of which this book will be a part.

Selected Research Advances

Genome map. The Laboratory developed the first high-utility map of the chicken genome, followed by several improved versions. This effort initially focused on microsatellites, ultimately switching to SNPs, genetic markers that are readily transferable to and informative in other chickens. The East Lansing chicken map has been incorporated with three other genetic maps to create a consensus map containing 9,200+ markers and forms the basis for the chicken genome assembly. These maps are being used by the entire poultry community to identify genes for simple and complex traits, and as tools to improve genomic selection, which is revolutionizing animal breeding.

Recombinant MD vaccine. The Laboratory has developed an attenuated serotype 1 MD vaccine through the deletion of the *meq* gene, which is responsible for the oncogenicity of the virus. This vaccine demonstrates a novel and elegant method of molecular attenuation but has not yet been approved for commercial development because of the propensity to induce lymphoid organ atrophy in antibody-free chickens. Other candidate attenuated vaccine strains have also been studied and evaluated in comparative efficacy tests, some of which were conducted in a commercial exposure facility.

Epidemiology of ALV-J. The Laboratory continued its in depth study of ALV subgroup J in broiler breeder flocks, documenting infection profiles and information on how to develop flocks free of infection. Monoclonal antibodies were also developed and used as the basis for antibody test kits. Responses of White Leghorn chickens were characterized, along with effects of various B-haplotypes.

ALV contamination of vaccines. The Laboratory has clarified the procedures needed to detect ALV contaminants in MD and other vaccines, resulting in a modification of the official Supplemental Assay Method issued by USDA-APHIS-CVB.

Genetic Resistance to ALV. The Laboratory has developed a DNA-based technology that is being adapted by poultry breeders to assess the genetic resistance or susceptibility of their lines to ALV. Some breeding companies, and vaccine manufacturers, have replaced one or more susceptible lines of chickens in crossing schemes to improve genetic resistance of their production lines based on the DNA test results. The unique merits of the DNA-based test are quick, repeatable, reliable, selectable, and free of viral challenge.

Differential diagnosis. Through publication of slide study sets and a new Tumor Diagnosis Manual, the Laboratory has provided updated information on the differential diagnosis of the various viral neoplasms of chickens. This replaces and updates prior guidelines published by the Laboratory in 1970. Even more recently, a PCR-based test for the detection of MDV and

REV sequences in histological sections of tissue has been described.

MDV pathotyping. A technique for classification of MDV serotype 1 strains by pathotype has been developed for use by laboratories that do not have access to the specific chicken strains used by ADOL in the traditional pathotyping assay. Use of this procedure should result in more standardized assessments of pathotype among different laboratories.

MDV evolution. Factors important to Marek's disease virus evolution have been identified. Competition between different viral strains infecting the same chicken was found to influence the outcome of co-infection under simulated field conditions, including the potential emergence or evolution of more virulent strains. Co-infection studies were conducted to demonstrate that both similar and dissimilar MDVs are able to compete for dominance within a chicken, but the time interval between infections has a much larger effect on competition than virulence – in other words, the first virus to infect a chicken has a distinct advantage.

New MD vaccines. Advances in recombinant DNA technology at the Laboratory in the late 1990s allowed the generation of several new candidate vaccines. Most involved deletion of the *meq* gene, that is associated with viral oncogenicity. Two different *meq*-deleted MDVs provided improved protection against MDV challenge compared to the CVI988 strain, However, these viruses also induced lymphoid organ atrophy in chicks without maternal antibodies to MDV and do not appear suitable for commercial use. Another recombinant DNA vaccine (designated CVRM2), originating with work by Sanjay Reddy at the Laboratory and continued by Reddy at Texas A&M University, also provides high levels of protection. This new vaccine has been transferred to a commercial company for evaluation and potential development.

Genomic selection. The Laboratory led an international effort to empirically evaluate newly developed molecular techniques for selection of breeding stocks in 2 commercial broiler and 3 layer lines. Based on the broiler results that are now complete, the relatively accuracy of genomic selection is about 33% higher than previous methods. This difference persisted for all generations in both parent lines indicating there is no loss over time. Based in large part on these results, genomic selection has been adopted by the commercial companies involved in the trial and is now being evaluated by the rest of the poultry industry.

Chicken lines. The Laboratory's inventory of specialized chicken lines began and ended the period at 35, including 19 recombinant congenic lines, although some changes occurred. A new line, designated RFS, was developed that lacks all endogenous virus genes and is susceptible to exogenous and endogenous avian leukosis viruses. This continues to be the largest and most important collection of germplasm relevant to avian tumor virus research in the world and is also indispensable for the Laboratory's in-house research programs. In 2002, the value of these specialized chicken lines was recognized by the National Animal Germplasm Program of the USDA. Many of these lines are included in The National Registry of Genetically Unique Animal Populations.

Synopsis

This is the first period of the history of the Laboratory not characterized by an urgent neoplastic disease crisis in the poultry industry. But this was not a quiet period.

The research program continued to be productive. The number of peer reviewed publications remained constant and a number of important discoveries were reported. The genomics program expanded and solidified its place as an international leader in the field. ADOL continues to conduct research and provide services that are relevant and critical to the poultry industry. If and when ADOL is relocated in Athens, GA, the ADOL programs will continue to fulfill the USDA/ARS mission to support one of the largest US agricultural industries.

Reflections

Research Initiatives

A number of important research initiatives spanned multiple eras. A few of these are presented here in order to capture a more comprehensive perspective.

Tumor diagnosis. One of the very first issues to be addressed by the Laboratory in the early 1940s was the methodology and criteria for the differential diagnosis of tumors. This issue continued to be important throughout the history of the Laboratory. The Siccardi and Burmester monograph (7) of 1970 focused on bursal tumors as a diagnostic criterion. This approach was considered useful in practice, but soon became outdated because the discovery of reticuloendotheliosis viruses and their tumors required new techniques to enable their differentiation from LL and MD. Myeloid leukosis in the 1990s, caused by ALV subgroup J, also required differentiation.

The Laboratory launched a comprehensive effort in the early 1990s involving at least 4 different staff members to further improve technology for tumor diagnosis. A trip was made to the laboratory of Max Cooper and Chen-lo Chen to learn immunohistochemical techniques to detect lymphocyte antigens on tumor cells. But attempts to bring this project to completion floundered. Finally, in 2010, upon the urging of industry colleagues, Witter and others compiled current information into a Tumor Diagnosis Manual (13), published by the American Association of Avian Pathologists, which seemed the end of this story. However, new techniques and criteria continue to emerge from research by the Laboratory and elsewhere. This issue will surely continue to be relevant into the future.

SPF chickens. An original objective of the Laboratory breeding program was the production of chickens free of tumors. Chickens of this type were necessary for the experimental work. The creation in 1942 of a strictly isolated flock (line 15I) was a good start but this flock was not totally free of tumors and was probably exposed sporadically to both ALV and MD. The true infection status of this flock could not be determined until the 1960s when more sophisticated tests proved its freedom from ALV infection (but not MDV).

In the 1970s, FAPP isolators permitted the rearing of breeder chickens free of MDV by offering protection against aerosol exposures from the environment. But these facilities were used mainly for line 7 chickens, which were more useful in MD research. Other strains, including 15I, were also SPF but were maintained in less strict isolation and were vaccinated with HVT as a safeguard against MDV exposure. Interestingly, such exposure was never detected over a period of many years.

This system was continued at the Laboratory until the 2000s when vaccination was stopped and all breeder chickens were reared in conventional housing without filtered air. This experiment has been a success as no evidence of exposure to MDV has been identified.

The more than 30-year absence of inadvertent infection with MDV on the west side of the Laboratory farm is amazing, considering the use of highly virulent MDV strains on the east side of the farm, in buildings only a few hundred yards distant. Efforts to contain infection from experimentally infected chickens through the use of exhaust air filtration and other procedures have obviously been effective.

Genetic resistance. Another objective of the original Laboratory breeding program was to create chickens selectively resistant to tumors (along with others that were susceptible) to enable Laboratory studies on underlying mechanisms. It was expected that such genetic resistance would be used by commercial breeders for line improvement. Although resistance against both MD and ALV in chickens was ultimately defined, the commercial breeding industry has been slow to give such genes much priority in selection programs.

Some companies used Laboratory data to select on the basis of B blood group antigens, as this locus was related to MD susceptibility and also to the efficacy of various MD vaccines. But this effort was limited at best.

However, in more recent times, the Laboratory's efforts to develop molecular markers for genetic traits of economic importance has started to be accepted and utilized by the

poultry breeding industry, bringing the original promise of practical application a bit closer to reality.

MD vaccines. Following the development of the HVT vaccine for MD in 1969, the Laboratory has continued efforts to develop improved vaccines for MD. The Laboratory contributed to the development of bivalent vaccines in the 1980s and helped defined the utility of CVI988 vaccine in the 1990s, paving the way for its licensing in the US. But other vaccines have been elusive.

Much work was done by the Laboratory in the 1980s and 1990s on various attenuated serotype 1 MD vaccines, some of which were reasonably effective, but none have been licensed. More recently, there have been efforts to develop recombinant DNA vaccines, but none of these have yet been licensed either. In essence, there has not been a successful new MD vaccine developed in the world, by this Laboratory or any other, during the last 30 years. This has been an unexpectedly daunting task, which will no doubt continue.

Staff Creativity

The ADOL staff has demonstrated creativity in a number of ways other than research in order to accomplish the mission of the unit. Here are a few examples.

Engineering expertise. As discussed in prior chapters, the Laboratory has developed many original designs for equipment and isolators. Burmester designed several isolator systems in the 1960s. In the 1980s, the maintenance staff developed a fiberglass isolator (see previous) and, importantly, a 3-egg inoculation device that was the forerunner of very elaborate machines later designed by Embrex, Inc. for administering inoculations to chicken embryos prior to hatch (photo album).

Date calculator. Sometime in the 1960s, Lyman Crittenden developed a simple plastic device for calculating the number of days between two known dates. A small number were produced and distributed to colleagues, including this author. In the days prior to computers, this device was frequently used by this author to calculate the date intervals that were such an important part of data analysis in chicken experiments (photo album).

Other issues

Administrative structure. At some point during the Winton era, ARS established a system of administrative officers to be located at the Laboratory. Administrative officers, who reported to ARS officials in Peoria, IL, typically supervised up to two staff persons to take care of purchasing and personnel issues. This office not only supported the Laboratory and its Director, but also provided service to other ARS units located at Michigan State University. It was an important part of the mix. At least some of the administrative officers in order of succession were William Lantzy, Alan Lundberg, James Harbin, Cynthia Glasscock, and Kris Foight. In 1993, Florence Trevino was assigned to the Laboratory as Cluster Environmental Protection Officer, and helped with safety programs for a number of years.

Science leadership. At the beginning, the professional staff was a combination of scientists with differing levels of experience and capabilities. Whereas a few assumed leadership of defined areas of research, others were more typically team members. This started to change in the Burmester era when staff such as Crittenden, Purchase, Witter and Nazerian were recruited to lead defined areas of work. On the other hand, Burmester also recruited a number of scientists in quasi-support roles.

This changed further in the Witter era during which few support scientists were hired and most scientists were in charge of defined areas and reported to the Director. This was solidified in the 1980s as scientists received outside funds and hired their own team of postdocs and students. ARS designated scientists in charge of projects as “lead scientists.”

True support scientists are still an important part of the Laboratory staff, but are less common than at the beginning. The point of the above is that the present hierarchy of scientists evolved with time, administrative policy and other factors – mirroring the change in research laboratory organization that occurred generally in science during this period.

Standard forms. In Government, standard forms are no surprise. But from the very first years, the Laboratory developed house forms for many tasks in research. There

was a 3x5" necropsy card with boxes to tick off when a lesion was observed, an inoculation sheet, and sheets to record mortality during experiments. Forms such as these were printed in bulk, adopted as standards by most principal investigators at the laboratory and used regularly for many years until well into the computer age.

Clerical staff. The clerical staff typically consisted of a lead secretary and several clerk typists. As computers replaced the need for manuscript typing in the 1990s, the number of support staff was reduced but there was always a lead secretary who wielded considerable influence on laboratory operations while providing assistance to the Director. At least some of the lead secretaries over the years were Maybelle Lott, Alicia Rhoades, Marcia Griffith, Lois Joehlin, Karen VanAtta, Lee Coburn, Dora Post (Westbrook), Mike Skowneski and Rebecca Horn.

Technical staff. For much of its history, senior investigators at the Laboratory had available one or more biological laboratory technicians to assist in the conduct of the experiments. The value of these individuals has been substantial and goes far beyond physical help. It is not possible to list here all the technicians who have contributed, nor is it reasonable to single out those who have contributed more than others. Suffice it to say that this group of employees *is* the institutional knowledge base and forms the soul of the Laboratory.

Industry liaison. From the initial plea to the Federal Government for help in the form of a new laboratory, the US poultry industry has strongly supported the research programs. Don Turnbull of the International Baby Chick Association was instrumental in securing a new building in 1950. Hiram Lasher, Maurice Hilleman, and others from the vaccine industry supported the Laboratory's launch of HVT vaccination in the 1970s. Jim Arthur and Bill Chase of Hy-Line International led the way in promoting eradication of exogenous ALVs from their stock, with considerable input for the Laboratory. Greg Rosales (Aviagen), Robert Owen (Hubbard) and others collaborated on ALV-J eradication from the broiler breeder industry in the 1990s. In the 2000s, Kenton Kreager (Hy-Line) provided material assistance on vaccine evaluation and Rosales stimulated the Laboratory to complete the Tumor Diagnosis Manual. On a continuing basis, the industry has provided access to biologic specimens and disease frequency data that have guided many Laboratory programs. These are only a few examples of the many critical roles played by the industry in the research of the Laboratory.

The poultry industry has also helped substantially with future planning, as is detailed elsewhere herein. No doubt the industry would agree the relationship has had mutual benefits, just as was envisioned by the founding fathers.

Diversity. The original Laboratory staff displayed little ethnic and cultural diversity but by the 1960s, this had changed. In the space of a few years, there were scientists of Japanese, Iranian, South African (English), and Chinese heritage. This group was joined by scientists from India and Egypt in the 1970s. Most of the graduate students and visiting scientists over the years hailed from countries outside the US. In this way, a truly cross-cultural environment was created. Although this probably reflected general trends in science at the time, it was (and is) an important and exciting component of Laboratory life, and may have contributed to productivity.

A Family Affair. Over the years, the Laboratory has accounted for at least four marriages among its various employees. These partnerships included Mary Fast and Bob Lowe, Brenda Irish and Chris Beisel, Cheryl Rowe and Carlos Romero, and Isabel Gimeno and Arun Pandiri. There were also two husband-wife teams: Curtis and Myrtle Bartlett, and Sanjay Reddy and Blanca Lupiani. There was also one brother-sister team: Tim Caswell and Cecyl Fischer. There were two father-daughter combos, Bill and Dorothy Okazaki and Zhizhong and Xiaoping Cui. There are undoubtedly others.

Conclusions

From this author's perspective, the Laboratory has been a special place and has assumed a unique role in the field of avian tumor virus research and avian genetics. In addition, it has transformed paradigms in science and agriculture. It has also influenced lives of persons important to the poultry industry and this field of science.

It is tempting to view the Laboratory as something a little different from most others of the era. Some of this is due to its physical identity as a stand-alone unit, unlike most University research units or large Government research centers. But there were unique philosophical, structural and operational features as well. Surely, this institution is one-of-a-kind.

The stature of the Laboratory accrues in some proportion from the accomplishments and the stature of its individual scientists. This report has intentionally subordinated individual contributions, but this does not diminish their importance. The permanent scientific staff of the Laboratory has collectively accumulated many individual recognitions and awards. Among these are 8 Levine awards for best paper in Avian Diseases and 2 Rispens awards for the best paper in Avian Pathology. This group has authored or co-authored 19 chapters in the textbook Diseases of Poultry (considered to be the "bible" of the profession) from the 5th to 13th editions – authorship usually indicative of the top scientists in a particular field. In addition, Fadly served as an associate editor. Three Laboratory scientists have been elected to the Poultry Hall of Fame (American Poultry Historical Society) and two to the ARS Hall of Fame. Two have been elected to National Academies of Science (Germany and US). Laboratory scientists have published more than 1000 technical reports and are authors on 20 patents.

The success of the Laboratory over the past 75 years is undoubtedly due to a combination of factors. One of these is timing. Nothing is better than working on the right diseases at the right time. It also helps when the diseases are of high importance to the poultry industry. The fact that the avian viral tumors were of interest to the field of comparative oncology and human cancer biology was also important.

Two other points should be considered. First, from the beginning the Laboratory established functional animal models for the study of neoplastic diseases. There was access to chickens, viruses and suitable housing. Animal experiments could be conducted easily and on a large scale. This greatly facilitated the work and also encouraged outside collaborators to join with us, as such extensive animal resources were exceedingly rare.

In addition, the Laboratory accumulated impressive collections of virus strains, cell lines, and monoclonal antibodies. Combined with the many genetic resources, these assets were (and are) unique to the field and have greatly facilitated research at the Laboratory and elsewhere.

As a result the Laboratory embraced collaboration with a succession of world-class scientists who collectively made serious impacts on its success. Starting with inputs from Erwin Jungherr and Fred Hutt, the Laboratory has attracted the interest and cooperation of many of the best scientists in the fields of avian tumor viruses, immunology and genetics as well as in adjoining fields.

The second point is that the Laboratory structure fostered internal collaboration. With 6 to 9 senior scientists in the building, each with a different set of skills and interests, there was an expectation that these scientists and their teams would work together. Consequently, collaborations among the professional staff occurred frequently and clearly strengthened the research program. This model was unlike that found in University departments where collaborations were usually driven by grant funding.

How the Laboratory is viewed as an institution and how it has served the poultry industry and scientific community may be best expressed through the statements of our colleagues:

For over 70 years, ADOL has been the world's leading institution on avian tumor virus research and diagnosis. ADOL's research programs and services are vital for the future well-being of the commercial egg laying, broiler, turkey, and allied industries. We at Aviagen have been very appreciative of ADOL's scientific achievements, their responsiveness to industry's needs, and have been honored by the kindness and willingness of its leading scientists to educate and train our veterinarians, geneticists and microbiologists. (Dr. Gregorio Rosales, Aviagen North America)

In the early years, ADOL was primarily involved with the leukoses where it made unique and important contributions. Since the mid 1960s it concentrated on Marek's disease where the distinguished staff made seminal contributions to the knowledge and control of this devastating disease. The importance of its research and its willingness to share experiences meant that I visited ADOL on numerous occasions when exciting and fruitful discussions took place. My laboratory valued highly the collaboration we had with ADOL over the years. (Dr. Peter Biggs, former Director, Houghton Poultry Research Laboratory)

The exterior of ADOL is deceiving with regard to the research done inside the building, and yet the outside appearance reflects reverence for what has occurred within the laboratory walls over many decades. Innumerable major discoveries are rooted in ADOL's experiments, conversations, collaborations, and quiet moments. Particularly for Marek's disease and avian leucosis, one will not venture far into the literature or explore current research efforts without intersecting science at ADOL. The people who have comprised ADOL over the decades have shared a genuine desire to mesh basic and applied research. While dedicating their careers to solving real and practical problems, they have affirmed that the best solutions are grounded in understanding basic fundamental biological mechanisms. Steadfast and enduring, ADOL has earned its reputation as a giant among the world's great poultry research laboratories. (Dr. Robin Morgan, University of Delaware)

ADOL has played a unique role in the field of avian medicine because of its highly focused basic and applied research on avian leukotic tumors. It was a pioneer in establishing an early understanding of avian leukosis. Studies on Marek's disease at the laboratory have been of tremendous theoretical and practical importance. The discovery and application of a turkey herpesvirus as an MD vaccine served the industry extremely well. Especially significant have been the molecular characterization of the offending herpesvirus and studies on its oncogenic properties. (Dr. Bruce Calnek, Cornell University)

I first became aware of ADOL through Hsing-Jien Kung's collaboration with Lyman Crittenden on c-myc activation by ALV. A few years later, I began working with Larry Bacon and, subsequently, with Critt, and my understanding of the unique personnel and infrastructure resources at ADOL expanded greatly. Later, as department chairperson, I learned of the long history of MSU/ADOL collaboration going back to Henrik Stafseth, Ben Burmester, Charlie Cunningham, Lee Velicer and others. Today, at a time when few, if any, Land Grant universities can support a focused analysis of major poultry diseases, ADOL remains a singular resource whose role should only expand in the future. (Dr. Jerry Dodgson, Michigan State University)

ADOL has emerged not only as a national but also as a global leader in solving economically important poultry health issues resulting from avian retrovirus and Marek's disease herpesvirus infections, and determining the impact of single genes or groups of genes on resistance or susceptibility to tumor induction. Such contributions have led to ADOL's recognition by the World Organization for Animal Health (e.g. OIE) as an international Reference Laboratory for Marek's Disease. These competences will continue as a research critical core in the development of the Agricultural Research Service's national poultry health laboratory. (Dr. David Swayne, Director, USDA/ARS Southeast Poultry Research Laboratory)

Perhaps the most lasting contribution of the Laboratory is through the people whose careers have been influenced by time spent at the Laboratory or by collaboration with Laboratory scientists. This included our visitors, postdocs, graduate students and many others who are continuing to push boundaries of science in a variety of disciplines. Some of these persons are listed in the appendix or pictured in the photo album. But the reach of this institution extends beyond such lists as the torch continues to be passed.

The future of the Laboratory is, at this writing, unclear. It seems certain that scientific expertise capable of solving future problems with chicken tumors will be needed as the presently recognized etiological agents continue to evolve and new ones are identified. One may

hope that the contributions of the Laboratory during its first 75 years will have provided a solid footing for meeting the challenges that lie ahead, and that the recording of this history will provide a useful reference point for those looking back on veterinary research laboratories in the 20th and 21st centuries.

Photo Album

The research accomplishments of ADOL are a direct reflection of the many people who have worked at this institution over the years. As this book is designed to record the history of the Laboratory, it is fitting that we also include a photographic tribute to our leaders, scientists, employees, students, visitors and collaborators who have made this history what it is.

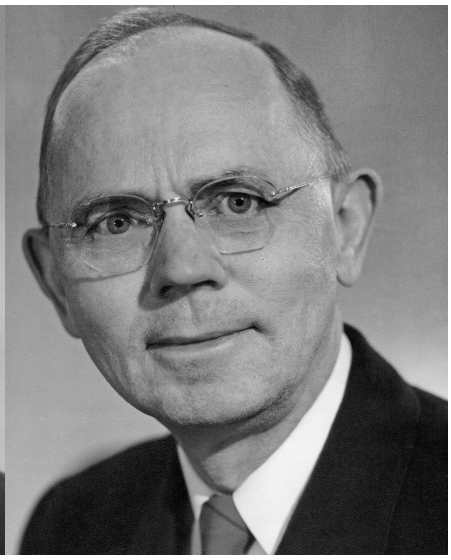
Also included are photos documenting the evolution of the physical features of the laboratory over the years including some of its structures and signage, A few items of memorabilia are also included.

The photos in this section are derived from various collections and sources. Berley Winton left a valuable personal photo album with photos from the early years. Dick Witter maintained an album with photos of most employees during his years as Director. Other employees have done likewise. Photos have been taken at celebrations and social gatherings. Photos have been taken for popular research articles. It is quite a collection.

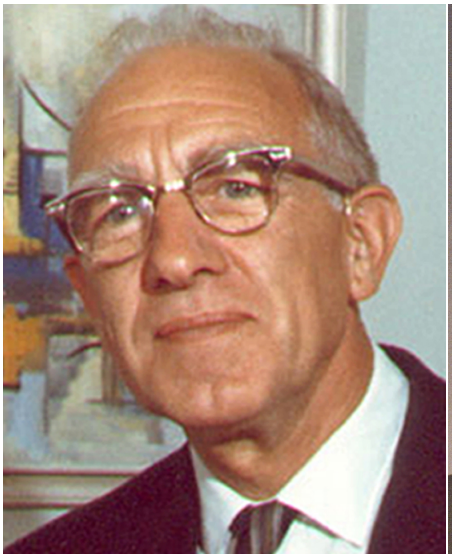
This section includes photos of the five Directors and as many as possible of the over 50 persons who served as senior investigators over the years. Other photographs representing postdocs, graduate students, technicians, visitors, secretaries, support scientists, caretakers and other support staff are included on an "as available" basis. A few of our many collaborators are also included. It was not possible to represent all who have contributed to the Laboratory because of limitations of space, time and availability of photos. However, we have assembled a generous collection that is designed to give the flavor of the many persons who have made the Laboratory what it is and are responsible for its productivity.

Laboratory Directors

J. Holmes Martin



Berley Winton



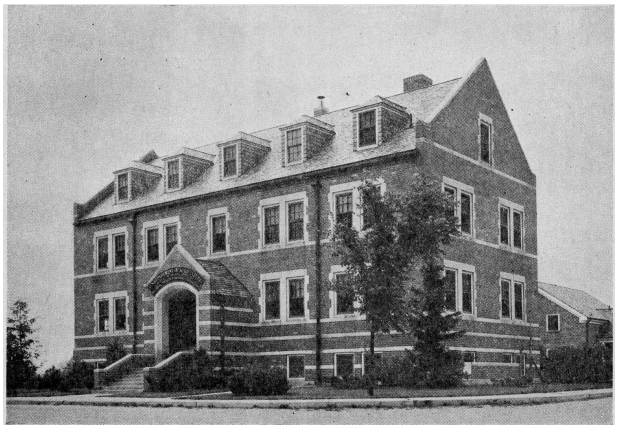
Ben R. Burmester

Richard L. Witter

Aly M. Fadly

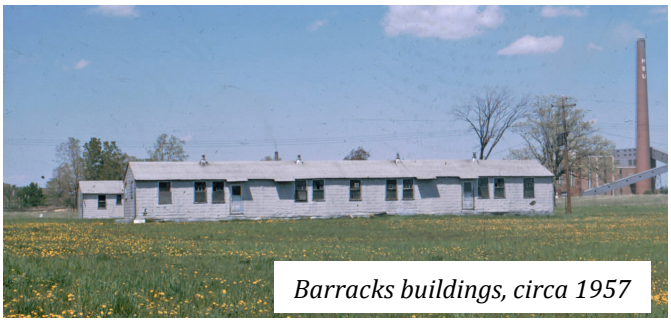
ADOL, 2012

Laboratory building and signs

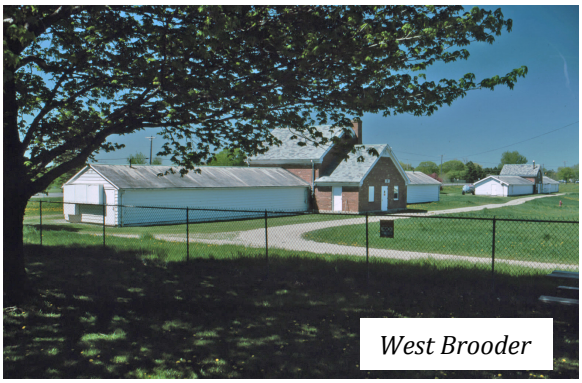


Farm Buildings

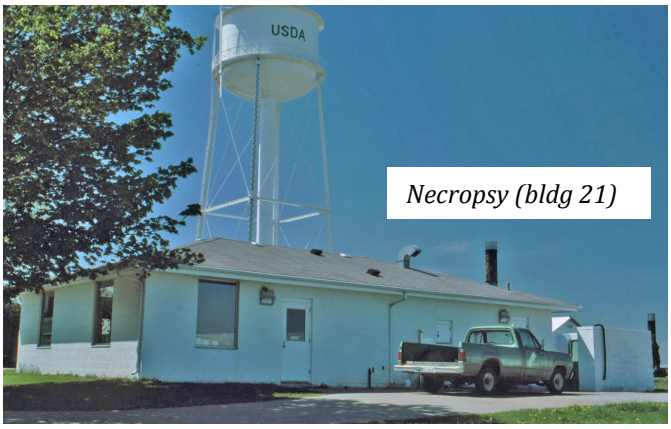
Panorama of west farm, circa 1940



Barracks buildings, circa 1957



West Brooder



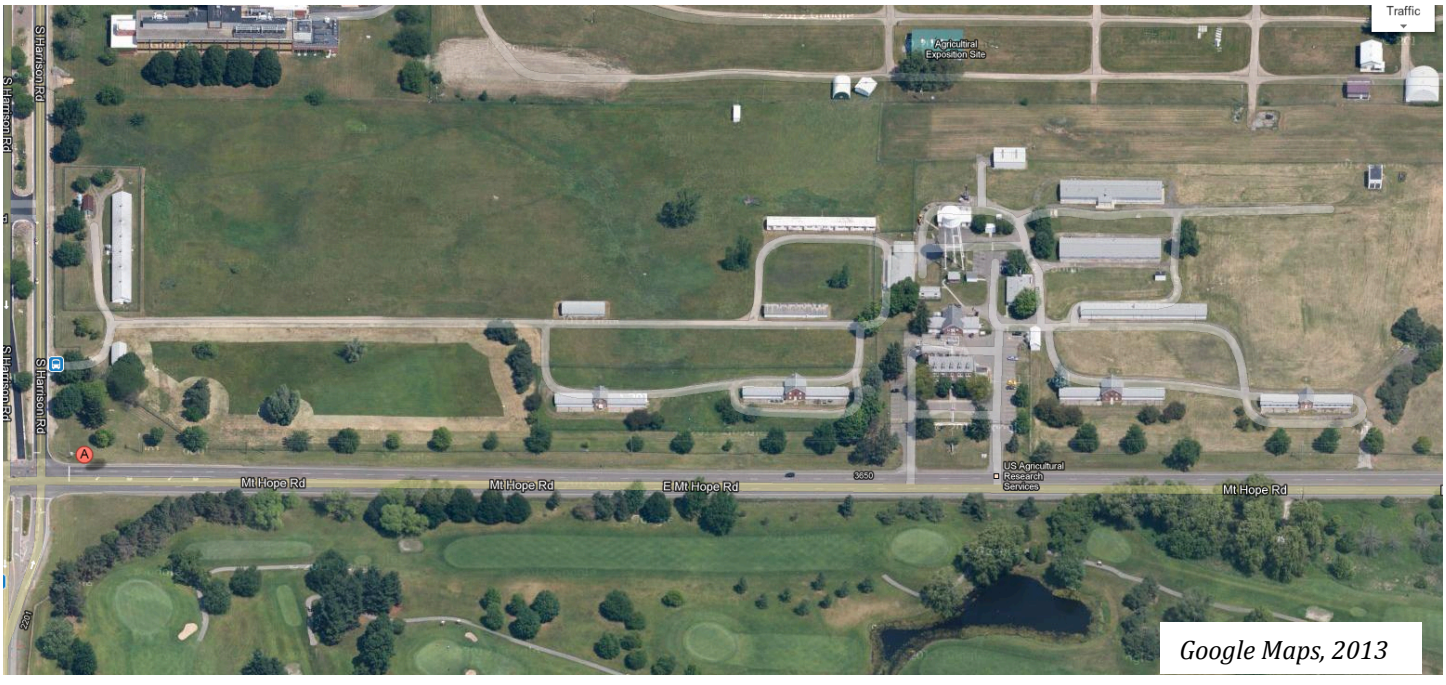
Necropsy (bldg 21)

East Layer

Building 22

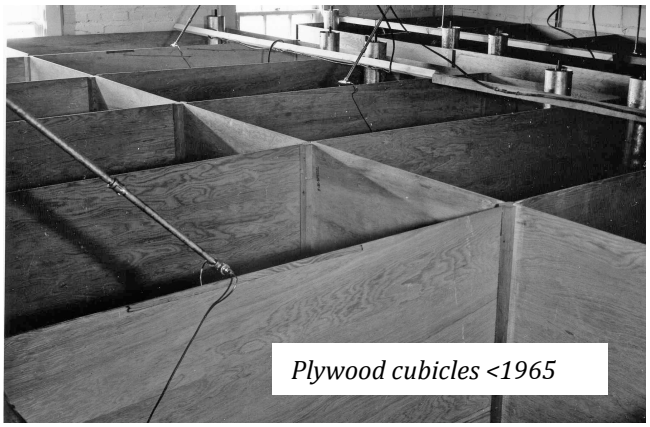
Wastewater treatment

Aerial view, 1942

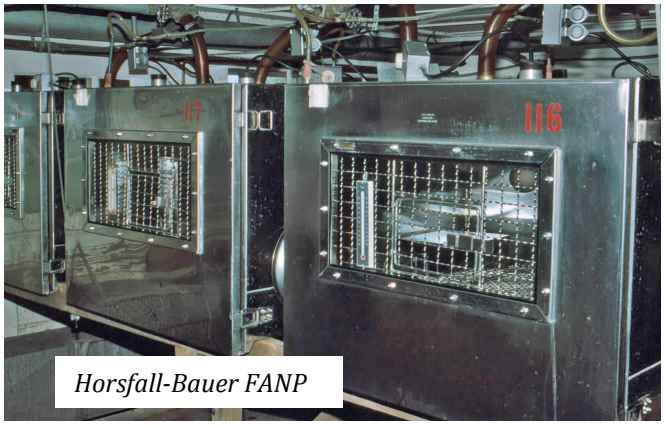


Google Maps, 2013

Isolators and Pens

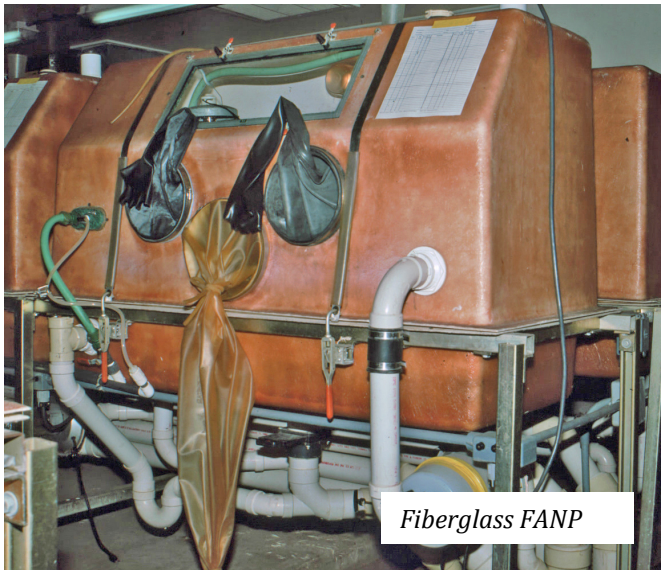


Plywood cubicles <1965



Horsfall-Bauer FANP

Stainless FANP



Fiberglass FANP

New Fiberglass FANP

Vinyl canopy FAPP

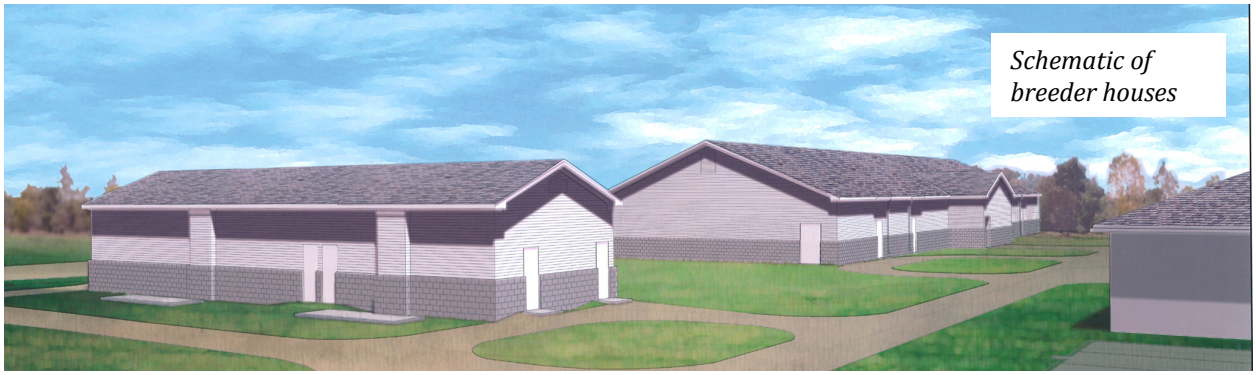
Building 22 cages

IBCA cages

Proposed laboratory design 1998

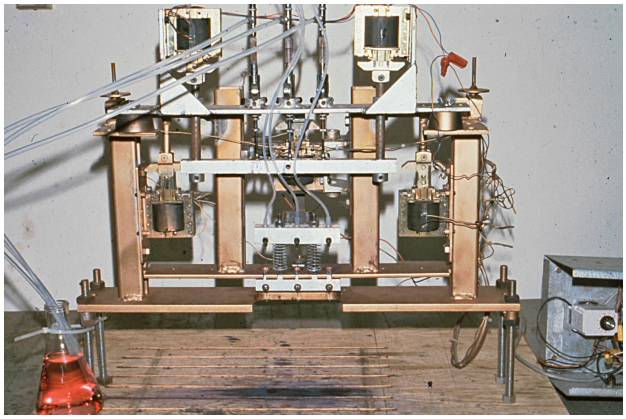
New lab schematic

Experimental bldg schematic



Schematic of breeder houses

Memorabilia



Inoculation machine, circa 1981

Age calculator, circa 1965

Biosecurity, circa 1940

Lab Award, 1972

Appendix

This section includes a listing by name and approximate dates of senior and support scientists, postdocs, graduate students and visiting scientists who have had substantial tenure with the Laboratory. Many of these persons have established notable careers in science and their tenure at the Laboratory may well be of interest to the larger scientific community.

It was not possible to include a similar listing of other employees because the numbers are very large and records were not available to this author. The support staff of the Laboratory has been the backbone of our program from the very first days, and deserves much credit for its many accomplishments. A tribute to all of our support staff is provided in the Photo Album where every effort has been made to include available photographs of our dedicated employees.

A more comprehensive listing of those associated with the scientific productivity of the Laboratory may be found in the authorship (and acknowledgments) of the more than 1000 publications of the Laboratory. These publications are not listed here but can be accessed from other sources. The list of publications contains much of the history of the Laboratory and would be a valuable resource for historians.

Senior and Support Scientists*

1939-40	J. Holmes Martin		1961-74	H. Graham Purchase
1939-60	Nelson Waters		1963-64	Ronald Hinz
1939-45	Carl A. Brandly		1963-77	John J. Solomon
1939-45	Norman M. Nelson		1964-02	Richard L. Witter
1939-47	James H. Bywaters		1964-65	Ralph L. Muhm
1939-53	George E. Cottral		1964-71	G. H. Burgoyne***
1940-63	Berley Winton		1965-68	Philip A. Long
1940-74	Ben R. Burmester		1966-76	Howard A. Stone
1940-42	Frank Thorp, Jr.		1966-94	Keyvan Nazerian
1942-45	Cavett O. Prickett		1967-69	Frank J. Siccardi
1942-61	Effie M. Dennington***		1968-11	Lucy F. Lee
1943-47	Harris D. Webster		1968-80	E. Ann Stephens (Holly)***
1944-45	Theodore C. Belding		1971-88	Jagdev M. Sharma
1944-63	Alfred M. Lucas		1975-96	John V. Motta***
1946-47	Gibson D. Dibble		1975-97	Eugene J. Smith
1947-49	Ralph C. Belding		1976-pres	Aly M. Fadly
1948-50	Eugene F. Oakberg		1978-02	Larry D. Bacon
1950-53	Robert F. Gentry		1983-09	Robert F. Silva
1951-52	Samuel W. Lesher		1991-pres	Henry D. Hunt
1952-53	Theodore A. Maag		1992-pres	Hans H. Cheng
1955-60	W. G. Walter		1997-01	Sanjay M. Reddy
1956-60	Anthony K. Fontes		1998-98	Murray R. Bakst****
1956-61	M. Adrian Gross		1999-pres	Raj Kulkarni***
1960-62	Frank Piraino		2000-pres	Jody Mays (Dybing)***
1960-63	T. Norman Frederickson		2002-pres	Huanmin Zhang
1960-82	William Okazaki		2004-pres	Mohammad Heidari
1960-89**	Lyman B. Crittenden		2010-pres	John R. Dunn
1961-67	Richard H. Reamer***		2013-pres	Alexis Black-Pyrkocz***

* Dates are approximate

** Includes years spent with ARS in Beltsville (1965-75) and as ADOL collaborator (1989-95)

*** Support scientist **** Acting Director only

Postdoctoral Research Associates*

1981-82	Patrick Shen		1992-94	Eileen Thacker
1982-87	Donald Salter		1995-97	Masahiro Niikura
1984-86	Tom L. Fredericksen		1995-97	Roger Vallejo
1984-87	Jeanne Carter		1996-98	Nissim Yonash
1985-88	Chris Beisel		1996-XX	Herng Tsai
1987-88	Mark Federspiel		1997-01	Blanca Lupiani
1987-89	Dolores P. Lana		1998-00	Christiane Hansen
1987-89	Shree Dhwale		2000-01	Maoxiang Li
1988-89	Ann Finkelstein		2000-03	Hsiao-Ching Liu
1988-90	Todd Pharr		2000-05	Isabel Gimeno
1988-91	Ilan Levin		2001-07	Masahiro Niikura
1989-91	J-L Liu		2001-08	TaeJoong Kim
1989-92	David Reilly		2004-07	Kyle MacLea
1990-92	Dana Marshall		2007-09	Sean MacEachern
1990-92	Judy Marsh		2010-pres	Sudeep Perumbakkam
1990-93	Jay Calvert		2011-12	Shaung Chang
1991-96	Janet Fulton		2011-13	Alexis Black-Pyrkocz
1992-94	Fuad Iraqi			

* This list may be incomplete. Dates are approximate.

Graduate Students*

1948-50	Ahmed El Dardiri		1991-96	Delin Ren
1948-50	George Cottral**		1992-97	Ping Wu
1950-52	Robert Gentry		1993-97	Carol Cardona
1960-63	Vance L. Sanger		1994-95	Yaopeng Mao
1961-65	H. Graham Purchase**		1995-03	Hsiao-Ching Liu
1964-67	Richard H. Reamer**		1995-96	Basheer Ahamed
1965-67	Min Chung		1995-01	Susan Williams
1967-70	H. Graham Purchase**		1996-00	Arun Pandiri
1968-72	George Harvey Burgoyne**		1996-97	Phil Jones
1971-72	Ji Hshiung Chen		1997-99	Isabel M. Gimeno
1971-74	Inguna S. Fauser		1998-00	Bilge Yondem
1972-77	Carlos Romero		1999-01	Tim D. Tesmer
1973-76	Ann Stephens**		1999-04	Xiaoping Cui
1974-75	Kathi Dunn		2003-09	Ghida Banet
1978-79	Abdel R. K. Elmubarak		2004-07	John Dunn
1981-85	Patricia Wakenell		2004-09	Weifeng Mao
1983-85	Nadir Ismail		2006-07	Muhammet Kaya
1984-87	Joanne Kivela (Tillotson)		2007-10	Shaung Chang
1984-90	Zhizhong Cui		2007-13	Suga Subramaniam
1987-92	Ding Yang		2008-pres	Evin Hildebrandt
1988-96	Margo Holland		2012-pres	Cari Hearn
1989-93	Heidi S. Camp		2013-pres	Alec Steep
1990-92	Yi Li		2013-pres	Supawadee Umthong
1990-93	Eric Kufour-Mensah			

* Students who did their thesis work at the Laboratory and earned M.S. or Ph.D. degrees. This list may be incomplete. Dates are approximate.

** Permanent ADOL employee at time of graduate study

Visiting Scientists*

1965-66	L.N. (Jim) Payne (England)		1990-93	Mona Aly (Egypt)
1966-66	Jochen Speck (Germany)		1990-94	Noboro Yanagida (Japan)
1968-68	Bart Rispens (Netherlands)		1991-93	Shigeto Yoshida (Japan)
1968-68	Alex Schudel (Argentina)		1991-94	Dexin Sui (PR China)
1968-69	Marius Ianconescu (Israel)		1992-94	Xiufan Liu (PR China)
1970-70	Hermann Schettler (Germany)		1995-96	Wumin Li (PR China)
1970, var	Daniel Gaudry (France)		1996-96	Ping Wei (PR China)
1973-74	Celedonio Garrido (Mexico)		1999-01	Aijian Qin (PR China)
1975-76	Jagoda Ignatovic (Yugoslavia)		1999-99	Leonid Dudnikov (Russia)
1975-76	Lloyd Spencer (Canada)		2000, var	Celina Buscaglia (Argentina)
1977-78	Uli Neumann (Germany)		2000-XX	Caroline Banet (Israel)
1981-82	Xiufan Liu (PR China)		2004-04	Suryakant Mishra (India)
1981-82	Patrick Shen (Taiwan)		2006-07	A.E. El-Gohary (Egypt)
1982-82	Sangao Liu (PR China)		2008-08	Suryakant Mishra (India)
1983-83	Marius Ianconescu (Israel)		2008-08	Luka Jwander (Nigeria)
1983-83	Youquan Cheng (PR China)		2009-10	Hasan Meydan (Turkey)
1983-84	Uli Neumann (Germany)		2009-11	Ming Xu (PR China)
1984-86	Puyan Chen (PR China)		2011-12	Muhammet Kaya (Turkey)
1986-87	Houda Li (PR China)		2011-12	Qingmei Xie (PR China)
1987-88	Yong-Ming Li (PR China)		2012-13	Santosh Haunshi (India)
1987-88	Tom Mickle (USA)		2012-14	Shuhong Sun (PR China)
1990-92	Ryohei Ogawa (Japan)		2012-13	Weisheng Cao (PR China)

* Visitors who spent at least 3 months doing research at the Laboratory. This list may be incomplete. Dates are approximate.

Laboratory Site Plan 2014

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