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SPECIAL ISSUE

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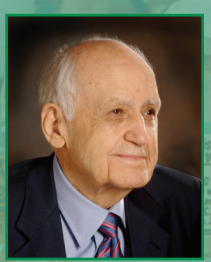
VALUE BEYOND THE LABEL

A look at

Marek's Disease

and four researchers who were significant in the development of critical vaccines

In this issue:



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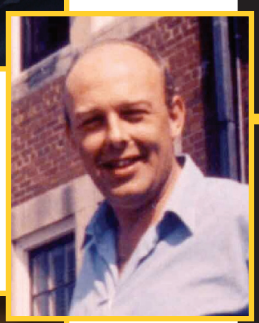
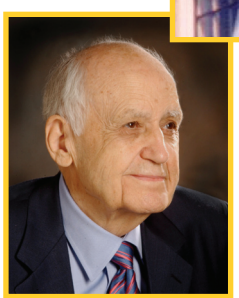
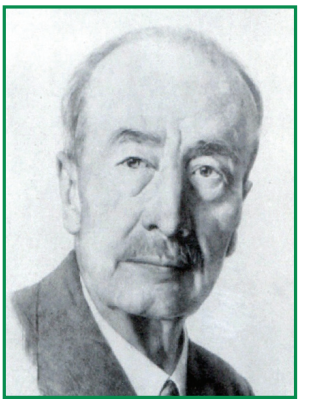




Marek's Disease: Poised for a comeback?



Josef Marek

Marek's disease (MD) was once a devastating virus that decimated chicken flocks and destroyed the fortunes of many a poultry producer in the US and across the world. The virus started gaining notoriety in the first decades of the 1900s, when Josef Marek in Hungary and other researchers in the US began describing a virulent poultry disease causing tumors, paralysis, and even death.

Thanks to the hard work of hundreds of dedicated researchers, we now know much more about the disease, how it spreads and how it can be controlled. Several of these researchers, including Bart Rispens, Maurice Hilleman, Dick Witter and Ton Schat, worked to create vaccines that saved the lives of millions of chickens around the world, and stabilized the cost of important protein for the average consumer. Hilleman's vaccine was the first to prevent a viral cancer in any species, and the work of these researchers has improved not only avian health, but the health of countless humans.

In the 1960s, Marek's disease had destroyed such a huge percentage of flocks that the future looked grim for poultry. Now, our increased understanding has led to a reduced infection rate that might even lull producers into thinking the disease has disappeared. That kind of thinking could create a perfect situation for Marek's disease to make a full-scale comeback, because the virus is anything but gone. In fact, it is almost everywhere, especially in large-scale chicken populations.

The virus has a lot of factors working in its favor: it moves very easily from one bird to another, and the high-density living conditions of commercial chickens create an optimal environment for disease spread. Even if a chicken is immunized, it will become a carrier. Once a chicken is infected, it will continue to harbor and potentially shed the virus for the rest of its life.

"Thanks to the hard work of hundreds of dedicated researchers, we now know much more about the disease, how it spreads and how it can be controlled."

Scientists fight back

When Marek's disease was crippling the poultry industry in the middle of the last century, poultry scientists searched for ways to fight back. They found two major paths of resistance: genetics and immunizations. In 1935, F.B. Hutt began working on a program to breed for resistance to Marek's disease. Their project continued into the 1960s, and showed that the ability to resist the disease did have a genetic basis. Other scientists continued to build on Hutt's work, and this study continues today, using advanced genetic research tools that were unavailable back in the early days of the disease. In addition to breeding a MD-resistant chicken, it may even be possible to "borrow" genes from a resistant bird and give them to another—this research is still ongoing.

While genetic study continues, immunizations have become the backbone of the poultry industry's fight against Marek's disease. Poultry farms the world over immunize their chickens, usually at one day of age. These vaccines have outperformed many other kinds of veterinary vaccines: the number of chickens condemned for MD has decreased about 99% since 1970. Marek's disease seems to be out of sight, out of mind. But it has certainly not disappeared.

Vaccinations, while extraordinarily

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Our thanks and appreciation

Special recognition goes to the following individuals for their help in preparing this issue of *Merial Selections*:

- Dr. Henk Maas for the CVI 988 information and the memorial document for Dr. Bart Rispens.
- Dr. Richard Witter for the introduction-materials and his suggestions and help with the concluding remarks.
- Dr. Sanjay Reddy for developing and writing the concluding remarks.
- Dr. Ton Schat for his photographs, materials and editing of the Bart Rispens article as well as his photograph of Josef Marek.
- American Association of Avian Pathologists for their contributions of materials.

Due to space & time limitations we could not feature all of the individuals that made significant contributions to the successful development of Marek's disease vaccines. A great undertaking by many individuals to solve the Marek's disease puzzle.

See for yourself!

To watch an edited version of "Legacy of the 1960's... a decade of progress in Marek's disease" video, please visit http://www.wattagnet.com/merial10.aspx

This video was made available courtesy of the American Association of Avian Pathologist, Inc. If you would like the complete version consisting of forty-two minutes, it is available on the AAAP website at www.aaap.info .

helpful, continue to leave opportunities for the virus. Chicks do not develop immunity immediately after *in ovo* or day-of-age vaccination and they are often exposed to the virus during the time before full immunity develops. Some chicks are now vaccinated even before they hatch, which buys them more time to develop immunity before they are exposed to the virus outside the egg. But that immunity will not keep the chick from spreading the disease to others.

The conditions in which the modern chicken lives makes it easier for the virus to move from bird to bird, but for most producers, the cost of implementing the kinds

"It seems that the worst choice the industry can make about Marek's is to underestimate its possibilities."

of measures that would reduce the spread of disease (filtered air, positive-air-pressure bird houses, improved litter management systems and a different arrangement of cages) far outweighs the perceived potential losses from MD. There is a possibility that further research could help pinpoint a particular blend of vaccines that would cut back the amount of virus cells shed by an immunized chicken, which would help keep the disease from contaminating the air and litter, reducing transmission to others.

The fact that the chicken can still contract Marek's disease also provides an opportunity for new strains of the virus to develop. The strain of the virus that is able to work around the immunization

would prosper, and could even be a more deadly version than the original. Marek's disease has already mutated several times in its known history: once in the 1960s, then after the introduction of HVT, and after HVT+ SB-1. There is no proven link between the introduction of the vaccines and the appearance of the mutant strains, but the timing does suggest a connection.

Complacency

It seems that the worst choice the industry can make about Marek's is to underestimate its possibilities. People may look at the reduced numbers of losses in the past few decades and begin to think of MD as a thing of the past, like typewriters and rotary phones. But the virus is alive and well in the U.S. Perhaps it would be better to think of it as something more like the flu virus in humans. For the most part, the flu is a minor inconvenience, but every so often, it experiences a major shift that results in an epidemic and a disastrous loss of life. Marek's disease virus has shown over and over again that it is capable of changing and adapting. The continued study of the virus becomes even more critical as those who lived through its reign of terror retire from the industry and take all their knowledge with them. Although there may be higher-profile issues in veterinary medicine, we still have a lot to learn about Marek's disease, and the disease has a lot to teach us.

Many individuals contributed significant time, energy and research to develop the Marek's disease vaccines that we utilize today. These vaccines have served our industry extremely well and have controlled the disease since the early 1970s. We will now give you a brief look at just four of these great researchers; a look at their lives and careers. **ms**

> **The continued study of Marek's becomes even more critical as those who lived through its reign of terror retire from the industry and take all their knowledge with them.**

HVT: Dr. Richard L. Witter

The Renaissance Man

Dr. Witter started playing the piano when he was around seven, and it remains a passion to this day. He plays for his own enjoyment, for singing at the local Kiwanis club and for his church.

Dr. Richard L. Witter is a quiet, complex man who is clearly more comfortable discussing the history and current issues of avian oncological research in general rather than the specifics of his career and accomplishments, and definitely happiest when the camera is off. He gives a generous nod to good fortune when discussing his exceptional professional achievements. In the autobiography he prepared for the historical archives of the American Association of Avian Pathologists (AAAP), he states, "My career benefitted from the fortuitous convergence of my entry to the job market with the emergence of a major viral disease which was amenable to study. I was surely at the right place at the right time, through no particular planning on my part. All scientists should be so fortunate."

Early years, and steps on the path

Richard Lawrence Witter was born on September 10, 1936, in Bangor, Maine, the only child of John Franklin Witter and Verna Harriet Church. He grew up in nearby Orono, and when the time came to further his education, it was his respect and admiration for his veterinarian father and interest in science and academics that propelled him to pursue a veterinary degree. As had both his father and mother before him, he attended Michigan State University, gaining his undergraduate degree in 1958 and his Doctor of Veterinary Medicine in 1960, with high honors. Again following in the footsteps of his father, Dr. Witter also met the woman he would ultimately marry, Joan Denny, while attending Michigan State. After his graduation in 1960, he passed the state boards in both Michigan and Maine, and then began applying to graduate programs, ultimately accepting a spot with Doctors P.P. Levine and Julius Fabricant at Cornell University in New York.

Though he did not know it at the time, his decision to study virology for his master's work at Cornell to round out his training was pivotal. "In the 1950s, the knowledge about viruses was limited, in poultry or in any other species. It was a newly emerging area, and I got just a minimal exposure to that in my formal courses going through veterinary school…I had no idea that would be my life's work." After completing his master's work, he continued on at Cornell for his Ph.D., choosing as his research project to define the role of maternal antibodies on the epizootiology of avian leukosis viral infections. During the course of his thesis work, Dr. Witter first encountered what he

referred to as "non-RIF lymphomatosis" in his paper, which he would come to know later in his career as Marek's Disease, or MD.

These specific academic pursuits made him well-positioned to accept a position back in East Lansing when a Cornell grant application fell through. In September of 1964, Dr. Witter started work at the ADOL (known at that time as the Regional Poultry Research Laboratory, or RPRL).

The researcher

Marek's disease (termed "acute leukosis" at that time), a new form of lymphoid tumors in chickens, began to emerge as a problem in the poultry industry at about the same time Dr. Witter started in his position at ADOL. In October of 1964, Dr. Witter began his first experiments into the etiology of MD.

In early 1967, breakthroughs in the work of Dr. Witter and his fellow researchers suggested that MD was caused by a herpesvirus. In his AAAP biography, Dr. Witter recalls a watershed moment: "I remember well the moment when I visited the isolator and was amazed to see every inoculated chicken with advanced clinical MD – a dramatic sight with obvious significance."

In the fall of 1968, he began a major study on the epizootiology of MD in chickens, and his decision to also study a turkey flock with a history of what resembled MD was another pivotal moment. He and his colleagues subsequently isolated and identified turkey herpesvirus, or HVT. When the HVT cultures were injected into chickens or turkeys, the researchers discovered that while none of the animals developed MD, the serum from the chickens did contain antibodies against MD virus. Shortly following this, associates of Dr. Witter, Bill Okazaki and Graham Purchase, had established a system to attempt to develop a vaccine. Dr. Witter recalls, "It seemed natural to me at the time to offer our FC126 [HVT] isolate to Okazaki for testing as a vaccine in his established system. He did, and the rest is history."

This fairly dry recounting of these events fails to capture the excitement that these findings generated in the avian research field and in the scientific community at large. The development of a vaccine for MD had a tremendous impact on the poultry industry, and was hailed as a near miracle and outstanding achievement.

When he speaks of these events, Dr. Witter is careful to reiterate, several times, that he was part of a *team* in these groundbreaking discoveries. The quintessentially thorough scientist, he points out the many contributions of colleagues, lists serendipitous situations with equipment and supplies, and gives a nod to Lady Luck for timing.

The administrator

In 1975, Dr. Witter was selected as the director of ADOL. As a leader in his own facility and in the research community, Dr. Witter and his colleagues were responsible for fostering a spirit of open communication that characterized the avian research community world-wide during those years. Dr. Witter's generation of researchers made rapid and very effective strides in dealing with avian diseases that had far-reaching health and economic benefits, strides that might not have been possible today in our more proprietary scientific culture.

Dr. Witter speaks rather wryly about his early experiences as an administrator, noting that as is often the case, he had no mentor to help him learn how to cope with the multiple roles now expected of him. He says he took various management training courses after he was in the position and rapidly realized that he needed help, but most of his duties as an administrator were learned on the job. He says, simply, "I tried hard. It became a priority for me."

Under his leadership, close ties were established between the poultry industry and the research community at ADOL. "That was not by accident," he points out. "We worked very hard from our end to make sure that those contacts were in place. We looked at the industry as the real reason that we're here…It worked very well for us. I think we reached out, made the contacts,

Top: Dr. Witter points out that he was part of a team in his discoveries and never forgets to mention the contributions of his colleagues.

Above: Dr. WItter poses with Barbara Riegle, Dr. Witter's technician for more than 20 years. Riegle was responsible for keeping Dr. Witter's research going through most of his administrative years.

Perspective: Looking Beyond the Horizon

In previous columns, I have talked to you about new opportunities that Merial is pursuing and what those mean to you, our customers. No doubt many of us will view 2009 as a challenging year for both the poultry industry and the US in general. But, as we look to 2010, I think we should strive to put some things in perspective.

To help illustrate this, I look to the example of my grandmother, who will soon be 105 years old! Think how different the world she lives in today is from the one that existed when she was born in 1905. Think about the historical events that have occurred in her lifetime. Two World Wars, the Great Depression, the rise and fall of communism, man walking on the Moon, and many other events.

Keith Pritchard, Executive Director, US Business Operations, Avian

Not only have there been dramatic changes in technology over Grandmother's lifespan, there have also been fundamental changes in the makeup of American society. The population of the US in 1900 was 76 million people. Today, the population is more than 300 million, an increase of almost 300 percent.

So how do we go about feeding that population? In 1900, 10 million people listed their occupation as agriculture. This represented 34 percent of the workforce and 13 percent of the total population. The 2007 Census of Agriculture reported 2.2 million principal farm operators. That's less than 1 percent of the current US population. So what does this mean for the future, and what should we do?

The first thing that we have to do is be more vigorous in recruiting young people to agriculture. I encourage each of you to take every opportunity, whether through organizations such as FFA or on an individual basis, to promote the poultry industry to young people.

The second thing that I see as important to the future of the poultry industry is to continue our outstanding record of improved efficiency. To successfully compete with other meat sources here in the US as well as with poultry producers in other countries, we will have to continue to gain every efficiency possible. This will take the concerted efforts of not only poultry producers, but also those of us in allied industry as well.

Finally, in these tough economic times, we all face challenges in operating our businesses. We must have the right business model to bring added value to our customers. At Merial, we will continue to commit the resources necessary to provide the high level of service and support for which we are known. Whether through the work of our Veterinary Services team or through the vaccine delivery and hatchery support provided by our Area Sales and Service teams, Merial will seek to bring added value that enhances the performance of your business. As we move into 2010 and beyond, we will continue to seek and find ways to live our vision of providing you Value Beyond The Label.

As we enter this New Year, I want to thank you for the opportunity to support your business in the past, and I look forward to helping you face the challenges and opportunities that the future holds.

Keith's Komments Video link

http://www.wattagnet.com/Merial9.aspx

try industry wanted to know. What kind of service or new knowledge should we be working to acquire, and we did the best we could along those lines.

I certainly made this a priority, to reach out, and make sure that our colleagues and friends in the poultry industry felt like we were a part of their team. They certainly became part of our team as well, because if it were not for the ideas and the raw materials that came from industry, we would not have been able to do what we did."

Dr. Witter served as director of ADOL for 23 years, stepping down in 1997 to return to the bench full time.

Associations and honors

Though he is a member of many professional and academic organizations, Dr. Witter most often refers to his association with the American Association of Avian Pathologists (AAAP). He joined the AAAP in 1963 and he remains an active member to this day. In 1998, the AAAP honored his efforts with a Special Service Award, and in 2007 he was awarded Life Membership.

In 1998, Dr. Witter was elected to the National Academy of Sciences, one of the highest honors that can be awarded to a scientist. When speaking of his election in his biography, Dr. Witter notes that, "As one of seven veterinary members (in 2007), only four of whom are involved with agricultural research, I have been presented with a unique opportunity to serve as a spokesperson for veterinarian scientists everywhere. I do not intend to shirk that responsibility."

Control of Marek's Disease in the Future

Inevitably, the discussion shifts to what might be coming in the future of avian disease control. Dr. Witter has

Watch the interview with Dr. Witter!
http://www.wattagnet.com/Merial8.aspx

observed that the poultry industry's stance on the benefits of research seems to have shifted, and not for the better. Dr. Witter notes that the companies seem to be more focused on short term issues and goals, rather than the long term view. The poultry breeding industry is the exception to this trend, and may set an example to lead the poultry industry as a whole back to the long-term planning that served Dr. Witter and his colleagues so well.

"Control of disease is a long term issue. With some of our viruses, we know that in the long term they may rear their ugly heads once again. It is just a hard job to sell that, in terms of getting a lot of research funding at the present time."

Late in his research career, Dr. Witter conducted studies on the evolution of virulence of viruses, with sobering results. "These individual infectious organisms have been undergoing an evolutionary change for a long time. In the past 100 years, we've put a lot of obstacles in the path of some of these organisms that has probably encouraged a more rapid and more obvious activity on the part of the organisms to work around these obstacles."

He also noted that the history of the evolution of the virus that causes Marek's Disease makes it "important and even prudent to be looking hard for further evolutionary changes, and that will continue to be true."

A current problem in the poultry industry is the "cutting" of vaccines, which is the improper dilution of the vaccine in an effort to "stretch" a single dose into many. When asked how that might affect the longevity of a particular vaccine, or whether or not this might be a factor in the cycles of increased virulence, Dr. Witter expressed his concern with this controversial practice.

"It does concern me quite a bit. There is certainly some experimental data with other organisms to show that the rate of mutations, the chances for evolutionary change may increase if you reduce the dose of a particular vaccine or other therapeutic compound. This is just one of the challenges, and this, I think, is an example of what I call the short term view. People saying, what is the cheapest way I can administer this vaccine to meet my particular situation right today, without much thought as to whether this will have a longer term impact. Those of us in science have spoken on this subject, even perhaps preached on it a little, and I don't think it has had much of an impact, as far as industry is concerned. I think we realized that industry is going to make its own decisions, and we're just going to have to live with the consequences."

Life beyond the bench

Dr. Witter married Joan Elizabeth Denny on June 30, 1962, and they have two children, a son and daughter, both of whom live in Colorado. Additionally, Dr. Witter says, "We have three grandchildren, and they form a big part of our lives."

> **"Control of disease is a long term issue. With some of our viruses, we know that in the long term they may rear their ugly heads once again. It is just a hard job to sell that, in terms of getting a lot of research funding at the present time."**

An avid outdoorsman all his life, he and his family own land with a cabin in Maine. "These cabins become a family treasure. Our place in Maine serves that function for us. It is a place that my dad built when I was still in school, and we still maintain that. Now our kids and grandkids are going out there… It is just a wonderful place – I only wish there were more chances to go."

He enjoys the chance to go fishing, though he does not spend as much time at it as he used to. "Probably fly fishing in streams is about as much fun as it comes, though I've taken to catching bass on flies out on my lake up in the state of Maine, and I've done my share of steel head fishing with flies here in the state of Michigan."

Dr. Witter really enjoys hunting, both turkey and deer. He does most of his gun hunting in Michigan's Upper Peninsula with a small group of friends he's been hunting with for many years. "I take that pretty seriously, too, more seriously than most of my friends do, and as a result, I usually have some venison in the freezer." He hunts with both bow and gun, and in this, too, he is a Renaissance man. He uses the rifle that was owned by his grandfather, and then by his father, a Winchester 33 caliber, model 1886.

As so many children do, Dr. Witter started playing the piano when he was around seven, and it remains a passion to this day. He plays both for his own enjoyment and for the singing at the local Kiwanis club and for his church. A beautiful baby grand piano, a gift from his mother, graces the living room in his home, and as the interview winds to a close, he sits down and begins to play an old, sweet song. Researcher, leader, historian, outdoorsman, photographer… and now, executed with consummate skill, Dr. Witter offers his finale for the day with "Georgia on My Mind." **ms**

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1 Merial Study 05-176MS, data on file
2 Merial Studies rBD/MD-04-97, rBD/MD-05-98, rBD/MD-06-98, rBD/MD-07-98, rBD/MD-10-98, rBD/MD-11-98, rBD/MD-12-98, rBD/MD-13-98, rBD/MD-04-99, rBD/MD-05-99, 98.319, data on file

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SB-1: Dr. Ton Schat

Researcher, author, international cooperator

Dr. Karel Antoni Schat, known as Ton to his friends and colleagues, always wanted to become a veterinarian. Luckily for the poultry industry, he did just that and became a research scientist in avian diseases. Among other accomplishments, Schat isolated the SB-1 strain of the chicken herpes virus, which led to the commercially important SB-1 Marek's disease vaccine. He is currently professor and unit director for avian facilities and research of the Department of Microbiology and Immunology at Cornell University, where his specialty is virology and immunology.

> **If I can instill anything in my graduate students and my DVM students, it's that cooperation yields much more than fighting for your own little turf.**

Throughout his career, Schat has studied avian virology and especially Marek's disease and recently chicken infectious anemia virus. Since 2006, he has studied the pathogenesis of infection with highly pathogenic avian influenza H5N1 strains in a joint project between the Australian Animal Health Laboratory and the CSIRO Livestock Industries, the CDC, and the College of Veterinary Medicine.

Schat was born and reared in The Netherlands, lived near a veterinarian as a youth and on free afternoons would join him on visits to farms. Schat did not have a farm background but decided he would become a vet based on those visits. "I wanted to become a large animal practitioner in the dairy industry in The Netherlands, never thinking that it would end up in Ithaca, New York," he says.

Bitten by the research bug

While getting his DVM from the State University of Utrecht, Schat found that this very practical degree had almost no emphasis on research. "In the 60s, the curriculum of the vet school in Utrecht was how to get a calf out of a cow," he says.

However, when he received a fellowship to spend five months in northern Nigeria, he was bitten by the research bug. The fellowship allowed him the opportunity to study the causes of infertility in Fulani cattle. "I didn't find any causes, but it certainly got me interested in research," he says.

During his practical year of his DVM studies, Schat attended a lecture by Dr. Bart Rispens on his work with Marek's disease (the Rispens vaccine). "I said, 'Gee, what he's doing is interesting,' not knowing that I would become his associate a couple of years later," Schat says.

Getting a start internationally

Schat decided to work in a developing country before doing graduate work. He landed a job for the Dutch government to work on Marek's disease in Mexico. His task was to set up a lab in Mexico, train people in basic research on Marek's disease and work towards the development of a vaccine. "So I went back to Bart

Rispens. I trained with him for five to six months," Schat says. "I didn't know anything about cell culture; I didn't know anything about growing viruses." He took six weeks of Spanish, five months of cell culture, and a two-week course on how to work in a developing country.

The first report on his work that he gave in Mexico was memorable because he gave it in Spanish. "I got up to give it and everyone put on headphones, thinking it would be translated into Spanish. But I gave it in Spanish. Four years later at my farewell party, they told me they were still talking about that," he says. "That was the best thing I could have done to introduce myself. My Spanish was not perfect, but none of my languages are perfect."

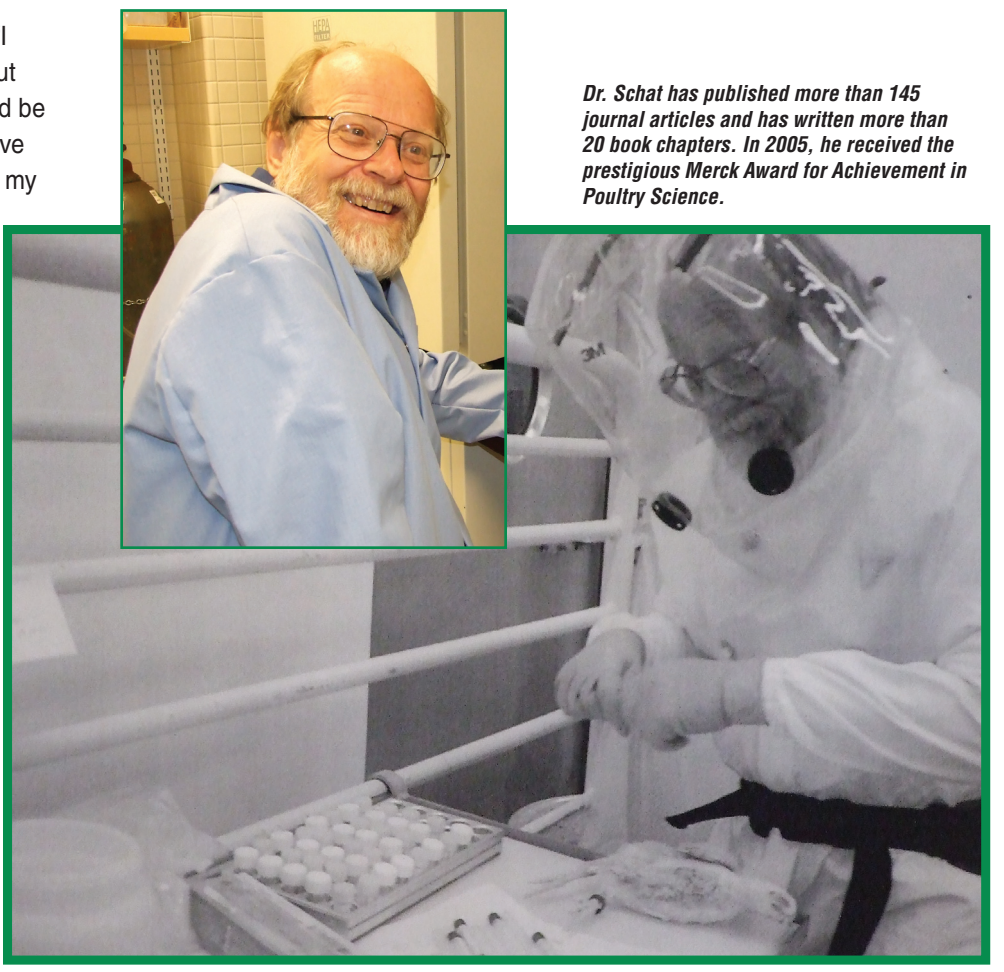
Thirty years later, he has no regrets about his experience in Mexico. "I would do all of it again. I would again go internationally, first. Scientifically, it did not advance my career in the sense of a post doc in a good lab, but I learned a lot culturally, about myself, and also troubleshooting," he says. "I had to do everything. At certain times we did not have gas because the gas bill was not paid by the Institute and we had experiments going on. We hooked up gas illegally with a line through the window to the roof to keep work going!"

Working with Dr. Calnek and others

After his time in Mexico, Schat wanted to begin graduate work. "In 1974, I met Bruce Calnek. I had planned to do my Ph.D. with Bart Rispens but he had passed away with cancer," he says. "He [Calnek] asked me to be his graduate assistant." Schat liked the idea of living in a town the size of Ithaca. "After four years in Mexico City, big city life was not for me."

Schat tells a funny story about his first memory of poultry legend Dr. Julius Fabricant, who had (and still has!) a reputation for asking presenters tough questions at conferences. Schat was making one of his first presentations at a poultry conference. "I saw Julius going after all those grad students and post-docs," he says. "And I gave my lecture and he didn't ask a single thing." So years later, he asked Dr. Fabricant why he hadn't asked him any questions about his presenta-

> **DVMs have a wider perspective on disease which filters into our scientific research interests, and we can see the field. I can talk to a poultry farmer and not make a fool of myself. I can talk to a molecular biologist at the most advanced level, on herpesvirus, and not make a complete fool of myself either.**



Dr. Schat has published more than 145 journal articles and has written more than 20 book chapters. In 2005, he received the prestigious Merck Award for Achievement in Poultry Science.

Watch the interview with Dr. Schat!
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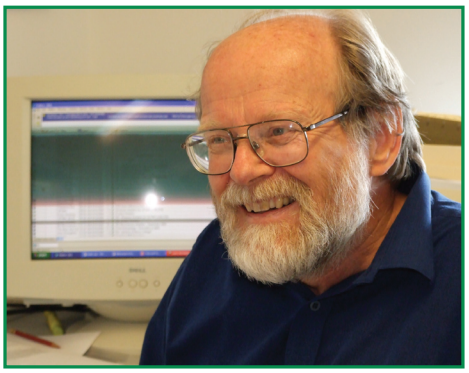
tion. "He said, 'Yeah, but I knew you would be a graduate student of Cornell, and I would have at least three years time to educate you.' And he still tries to educate me!" he says.

Schat attributes much of his success at Cornell to his mentor Bruce Calnek's working style. "There was something really unique between Bruce and me. We never were in any conflict there. And that was so great and so different than in many academic departments or research institutes," he says. "And if I can instill anything in my graduate students and my DVM students, it's that cooperation yields much more than fighting for your own little turf."

Isolating SB-1 strain

While he worked on his Ph.D. from 1975 to 1978, he isolated the SB-1 strain of chicken herpes virus, which led to the SB-1 Marek's disease vaccine. In 1980, he received a position as an assistant professor at Cornell. "For a young assistant professor, it was very heavy stuff, all the industry folks came to my lab to learn how to grow SB-1," he says. "So I had to manage with first eight small rollers and then later 16 small rollers to show all the people who worked with large numbers of rollers and large flasks how to grow SB-1. It was a very interesting time, again not scientifically, per se, but certainly in the interaction with the industry, with the vaccine industry. It was fascinating." It is amazing to him that SB-1 is still doing so well on the market.

Schat has attended every Marek's symposium and has been instrumental in organizing several of them, including ones in Montreal and Ithaca. The first Marek's symposium ever held was in Berlin in 1978, and it was a great experience in his budding career. "It was incredibly exciting for me. I met all the big names there," he says. "I gave my own presentation. To start your career and to be at that meeting or any of those Marek's symposiums afterwards, for a young scientist was extremely important."



Dr. Schat has attended every Marek's symposium and has been instrumental in organizing several of them.

Perspective on the future

These days, Schat rides his bicycle to work (school), brings his lunch in a plastic container, wears Birkenstocks, and walks up and down stairs rather than using the elevator. He recently co-edited the book Avian Immunology, which was published in February 2008. He has published more than 145 journal articles and has written more than 20 book chapters. In 2005, he received the prestigious Merck Award for Achievement in Poultry Science for distinctive contributions to the advancement of poultry science. He has also recently been spending part of each year doing research in Australia.

Schat believes that one great thing about being a DVM scientist in poultry is a broad perspective. "DVMs have a wider perspective on disease which filters into our scientific research interests, and we can see the field," he says. "I can talk to a poultry farmer and not make a fool of myself. I can talk to a molecular biologist at the most advanced level, on herpesvirus, and not make a complete fool of myself either."

A looming problem in the future of the poultry industry that concerns him is lack of interest on the part of vet schools and land grant institutions for poultry. This lack of interest makes no sense to him. "Poultry is a big commodity in the United States, a big commodity worldwide," he says. "Everybody eats poultry unless you are vegetarian. There is no religious restriction on poultry, and yet we don't get the message, we don't stimulate it in general."

> **"Poultry is a big commodity in the United States, a big commodity worldwide. Everybody eats poultry unless you are vegetarian. There is no religious restriction on poultry, and yet we don't get the message, we don't stimulate it in general."**

Schat is hopeful, however, because the department has sent four students to a course in Canada for a clinical phase, and next year four more students are going to Guelph. "That is exceptional for a student population of 86," he says. "They may not end up in poultry but at least they have an interest," he says. **ms**

CVI 988: Dr. Bart Rispens

Researcher and developer of the CVI 988 Rispens vaccine

Bart Rispens had a knack for finding the best way to apply vaccines and other disease prevention measures. In the late 1960s Marek's disease was ravaging the poultry industry in The Netherlands and elsewhere until he developed the CVI 988 or Rispens vaccine, which is still used today and considered the "gold standard' for monovalent MD vaccines..

> **Rispens' influence on vaccines and disease prevention was evident early during his scientific career.**

Passion for learning

Born in 1929 in Deventer, The Netherlands, Rispens grew up in a home that valued learning. His father, Albert Rispens, had a PhD in Dutch and philosophy, and published several books. Albert's passion for learning had an early influence on the young scholar, who spent his career contributing to humanity's collective knowledge base.

Rispens graduated from the College for Tropical Agriculture in Deventer and went on to study Veterinary Medicine at the State University of Utrecht. He completed his DVM in 1956. While in Utrecht, Rispens met his future wife, Wilhelmina Johanna Adriana Agerbeek. The two married in 1959, and their family eventually grew to include two children.

Rispens' influence on vaccines and disease prevention was evident early during his scientific career. His PhD thesis, "*Prevention of Duck Hepatitis in Ducklings*" demonstrated that hepatitis prevention is possible through maternal antibodies. This finding was of crucial importance for the duck industry and helped duck producers modify their practices to increase efficiency.

As Rispens' research evolved, he focused on improving poultry vaccines. He wrote several articles that the scientific community referenced many years after their publication.

CVI 988 vaccine

The accomplishment for which Rispens may be most remembered is his creation of the CVI 988 vaccine against Marek's disease in 1970. The acute form of Marek's disease affects younger chickens and has a mortality rate of almost 60 percent. The disease was considered a pandemic at the time, and had affected every country with a major poultry industry.

Rispens first became involved with Marek's disease in 1966 while on sabbatical at the Avian Disease and Oncology Laboratory (ADOL) in East Lansing, Michigan, where he was working on methods to detect avian leukosis virus for potential eradication approaches. During his sabbatical he became very familiar with the Marek's disease research program at ADOL. He returned to the Netherlands with many ideas to begin his own research program on Marek's disease.

Beginning in 1967, Rispens and a team of researchers went to work on isolating strains of the virus and understanding the factors that seemed to protect some flocks from the disease. After years of work, Rispens and his team eventually developed a vaccine. The early findings were so encouraging that poultry producers lobbied the government to let them have access to it, because Marek's disease continued to decimate their flocks.

Eventually, the Dutch Ministry for Agriculture and Fisheries allowed an experimental, nationwide vaccination campaign. Between August 1970 and April 1971, workers vaccinated nearly

4.5 million day-old chickens.

When the Rispens vaccine was introduced in 1970, flock losses dropped dramatically, saving the Dutch poultry industry's export market share. Poultry producers and scientists alike recognized Rispens' contribution. In 1971, a committee of professors of the College of Veterinary Medicine in Utrecht awarded Rispens the Schimmel-Viruly Award, which is presented every five years to a Dutch researcher who has contributed the most to the enhancement of veterinary medicine.

An ongoing legacy

After Rispens' early successes, scientists around the world were looking forward to more research from the Dutch scholar. However, Rispens' life was cut unexpectedly short. He became ill shortly after the release of the CVI 988 vaccine, and passed away in 1973. During the last few years of his life, Rispens doubled his research efforts to complete as much work as he could in the time he had remaining.

Although the research community lost a great asset, Rispens' legacy continues with the Dr. Bart Rispens Award, which is given every two years by the World Veterinary Poultry Association to the first author of the best publication in Avian Pathology during the preceding two years. Even today, the Rispens vaccine protects chickens in every country with a major poultry industry. Combined with the other Marek's disease vaccines, CVI 988 vaccine has contributed to keeping this devastating disease at bay for more than 30 years. **ms**

> **When the Rispens vaccine was introduced in 1970, flock losses dropped dramatically, saving the Dutch poultry industry's export market share.**

The Rispens CVI 988 vaccine continues to protect poultry across the globe.

MMR:
Dr. Maurice Hilleman

Creator of vaccines that saved countless human and avian lives

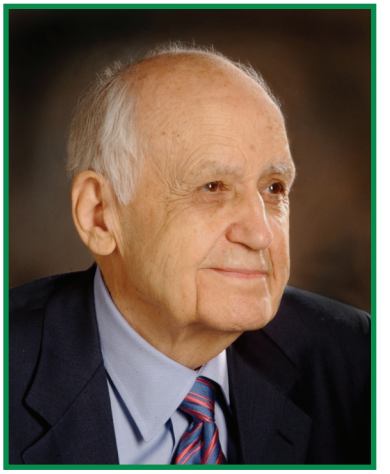


Photo courtesy of Merck & Co.

In many ways, Maurice Hilleman is a giant among vaccinologists. He is best known for developing dozens of vaccines used today. To those who knew him personally he was a plain-spoken researcher from out West, a man whose assertiveness and dedication led to the development of not only human vaccines, but also to one very important avian vaccine against Marek's disease.

Humble beginnings

Born in 1919 in Miles City, Montana, Hilleman was the youngest of eight children. His mother and twin sister both passed away at his birth. Hilleman's father, left to raise eight children on his own, sent several of them to live with relatives on a farm about 100 miles away. The life of a frontier farmer during the Great Depression involved intense labor, and taught Hilleman the value of hard work. It also provided him with the opportunity to observe genetics and disease in action every day.

At the farm, Hilleman eventually took on the task of chief chicken caretaker. He once said, "Coming from a farm, I always had a good friend called the chicken." This friendship would end up benefiting not just the man and his flock, but the worldwide population of humans and chickens.

Hilleman said he grew "fond and respectful of chickens and they provided me many good returns during my research career in which they served as volunteers."

Educating the man

After Hilleman graduated high school, he took a job as a clerk at J.C. Penney, where he could have spent his days successfully selling bathrobes and slippers — but one of his older brothers convinced the family to send him to college. As the youngest in a family of eight, the cost seemed astronomical. Fortunately, Hilleman received a scholarship from Montana State. After completing his Bachelor's degree, Hilleman went on to complete a PhD in microbiology and virology from the University of Chicago in 1944.

With his choice of virology, Hilleman's early farm life merged into his laboratory work. The chickens that had schooled him as a young boy would now provide the eggs in which he grew his vaccines.

Vaccinating the world

Hilleman's vaccines are the accomplishment for which he is most well-known. Many once-common childhood diseases are now nearly eradicated because of his work. Measles, mumps, rubella, chickenpox, bacterial meningitis, and hepatitis B are a few of his most famous immunizations.

> **Measles, mumps, rubella, chickenpox, bacterial meningitis, and hepatitis B are a few of Hilleman's most famous immunizations.**

The mumps vaccine is actually named after Hilleman's daughter, Jeryl-Lynn, and is still called by the same name. The girl woke up

one night with a sore throat and swollen glands. Hilleman, who was headed out of town the next day, drove to his lab to get some swabs so he could take a throat culture. He preserved the virus in a little beef broth in the freezer and ended up developing from that swab the mumps vaccine that is now standard for all children.

Hilleman also figured out how to effectively combine several different vaccines into one shot, like the ubiquitous Measles, Mumps and Rubella shot-plus-booster (MMR).

Saving lives through research

In 1957, Hilleman began working as director of virus and cell biology research for the pharmaceutical company Merck & Company, Inc. Merck is where he spent the majority of his professional career. When he retired in 1984, Hilleman was a vice president.

> **Hilleman and his team curtailed what was predicted to exceed the 1918 flu pandemic that killed 600,000 US citizens.**

While at Merck, Hilleman made major contributions to flu research. He documented the two kinds of changes in the influenza virus: drifts and shifts. Drifts are the minor changes in the virus that necessitate making a new vaccine every year. Shifts are major genetic mutations in the virus that produce a completely different strain to which no one has any immunity. A shift in the flu is likely to cause a major pandemic and loss of life.

In 1957, Hilleman detected a major shift in the virus. He and his team went to work on it immediately, isolating the strain and developing a weakened version of the disease in fertilized chicken eggs. At the time, Merck was reported to have gone through 150,000 eggs each day. After a marathon of inoculation-brewing, 40 million doses of the vaccine were ready to go the following flu season.

Hilleman and his team curtailed an outbreak that was predicted to exceed the 1918 flu pandemic that killed 600,000 US citizens. The new 1957 flu strain, which was expected to take more than a million US lives, claimed only 69,000.

Although Hilleman was known for being assertive and vocal, he was also known for giving credit to his research team who pulled together and made these accomplishments possible.

He even gave credit to the chickens, whose eggs he depended on. He found a way to protect them from Marek's disease, a lymphoma virus that plagued the poultry industry and devastated flocks.

Hilleman wrote in 1996 that he remembered from his first job on the farm, "The great festoons of electrostatically charged chicken dandruff that hung from the ceilings and walls, and the deaths from range paralysis we couldn't do a damn thing about."

Creating a Marek's disease vaccine

The opportunity to do something about the disease finally came in the late 1960s and early 1970s. Hilleman and other scientists noticed a link between a turkey herpes virus (HVT) and protection against Marek's disease in chickens. Hilleman and the other scientists jumped on the project and began research. In 1971, Hilleman and his team of researchers produced one of the first commercial vaccines to protect against Marek's disease. This was also the first vaccine against a viral cancer for any species.

Hilleman wrote that the newly introduced Marek's vaccine had, "such an immediate impact on chicken efficiency that eggs went for a nickel a dozen and broilers sold for two bits each."

Not only did the vaccine save millions of dollars for poultry farmers and increase the food supply both in the U.S. and all over the world, but it also saved countless chickens and spared the animals from a debilitating disease. When asked about his accomplishment, he would say, "I figured I owed it to the chickens." **ms**

Concluding Remarks

by Dr. Sanjay Reddy, Associate Professor, Dept. of Pathobiology at the College of Veterinary Medicine, TAMU.

Condemnation losses at slaughter due to Marek's disease (MD) have decreased about 99% since the successful introduction of vaccines in 1970. However, it is important to note that MD vaccines prevent tumor development, but not infection; hence, the virus present in all commercial poultry facilities will infect chicks soon after hatch, will persist in the host and will be shed throughout the life of the chicken. Thus, MD could make a full-scale comeback if currently available vaccines are no longer able to protect against highly virulent field challenges.

The reduced incidence of MD associated losses might have contributed to producers cutting vaccine dose and to changes in management practices to improve profitability. We currently do not understand the impact sub-optimal dose and management practices have on the evolution of more virulent strains; however, it is clear that MD virus has continued to increase in virulence. The future may be bleak if the current trend continues and field isolates are able to break through vaccine immunity.

The Avian Disease and Oncology Laboratory (ADOL, formerly known as Regional Poultry Research laboratory) was established 70 years ago to solve viral neoplastic diseases of poultry. This laboratory has been a leader in MD research and developed the HVT vaccine that helps control this devastating disease today. Their facilities and funding have not kept pace with the growth of the poultry industry and there has been discussion of closure or realignment. During the 1970s (at the time of discovery of HVT vaccine), the ADOL laboratory employed 9 scientists, 5 of them veterinarians. Currently the staff has been reduced to 7 scientists and only 1 veterinarian. This could negatively impact vaccine research going forward, as it is important to train the next generation of veterinarians and research scientists conducting MD research.

MD research is also conducted at various universities in the United States. One funding stream for this research is provided in the form of competitively awarded grants administered by the USDA's National Institute of Food and Agriculture (NIFA), formerly the Cooperative State Research, Education and Extension Service (CSREES). Research at universities is severely constrained due to a lack of adequate animal housing facilities and reduced funding available through grant programs. For example, the USDA-NIFA animal health research funding has continued to decline over the past 10 years. In fiscal year 2004, the agency's total budget for animal disease research (excluding external and internal parasites) was $34.6 million compared to $25.3 million in fiscal year 2007. These totals include competitive grants, formula funds and congressionally-directed appropriations.

> **"The reduced incidence of MD associated losses might have contributed to producers cutting vaccine dose and to changes in management practices to improve profitability."**

Many universities across the US are reducing or closing their avian research facilities along with their Poultry Science departments due to funding constraints, consolidation

and declining student enrollment.

It is important to realize that research support has drastically declined but the need for research has not gone away. Successful research on MD depends on infrastructure, including specialized knowledge, genetically defined chicken lines, facilities and reagents. This is especially true for MD more than any other infectious disease of animals because of the complexity of the MD system. Once this infrastructure is lost, it would be very difficult to reestablish it on a short notice (if at all).

The poultry industry should realize that MD associated losses may be at an all-time low, but prevalence of virulent MD virus maybe at an all-time high and it can come back anytime; therefore, there is a great need for continued support for research and development. The fight with MD is a protracted battle that started over 100 years ago when the disease was first identified. The research conducted by the scientists featured in this edition as well as many others has aided the poultry industry to manage losses associated with this disease. However, this battle could easily be lost if the current trends continue. In summary, MD research needs enthusiastic support from the poultry industry, universities and USDA for continued avian research and investments in future scientists. **ms**

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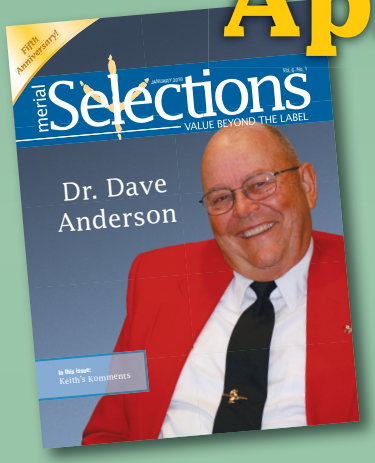

In this issue, Dr. Dave Anderson talks about his distinguished career – as a pioneer in Marek's research and in academia. He reflects on a career which includes heading up the Poultry Diagnostic and Research Center, and more than two decades as dean of the prestigious University of Georgia College of Veterinary Medicine.

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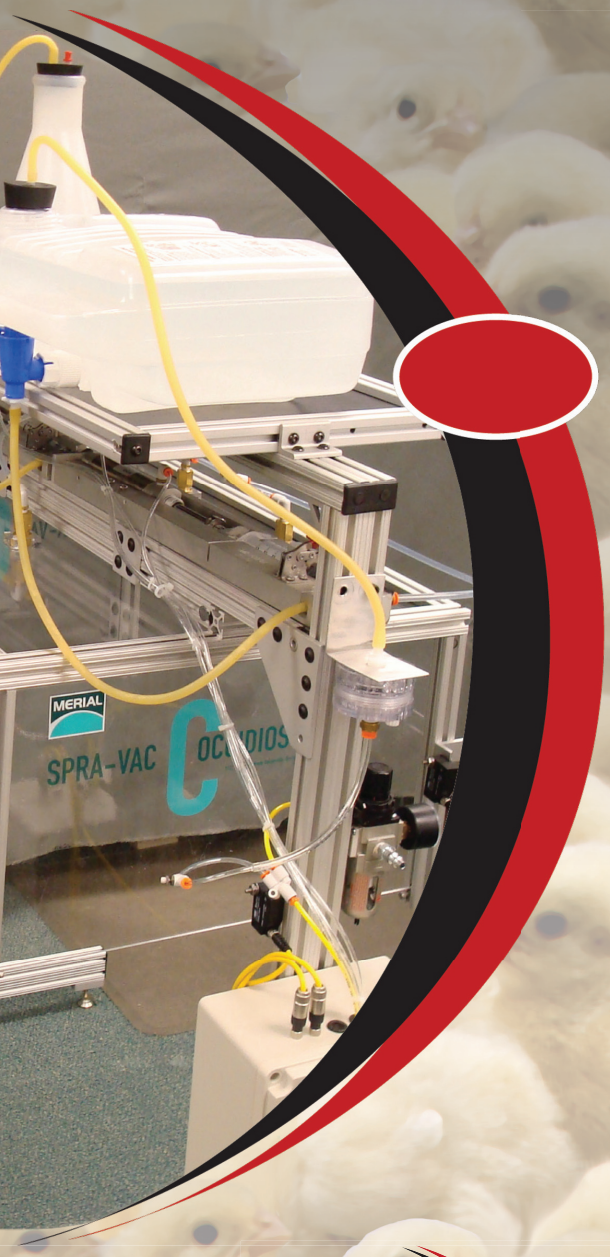

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