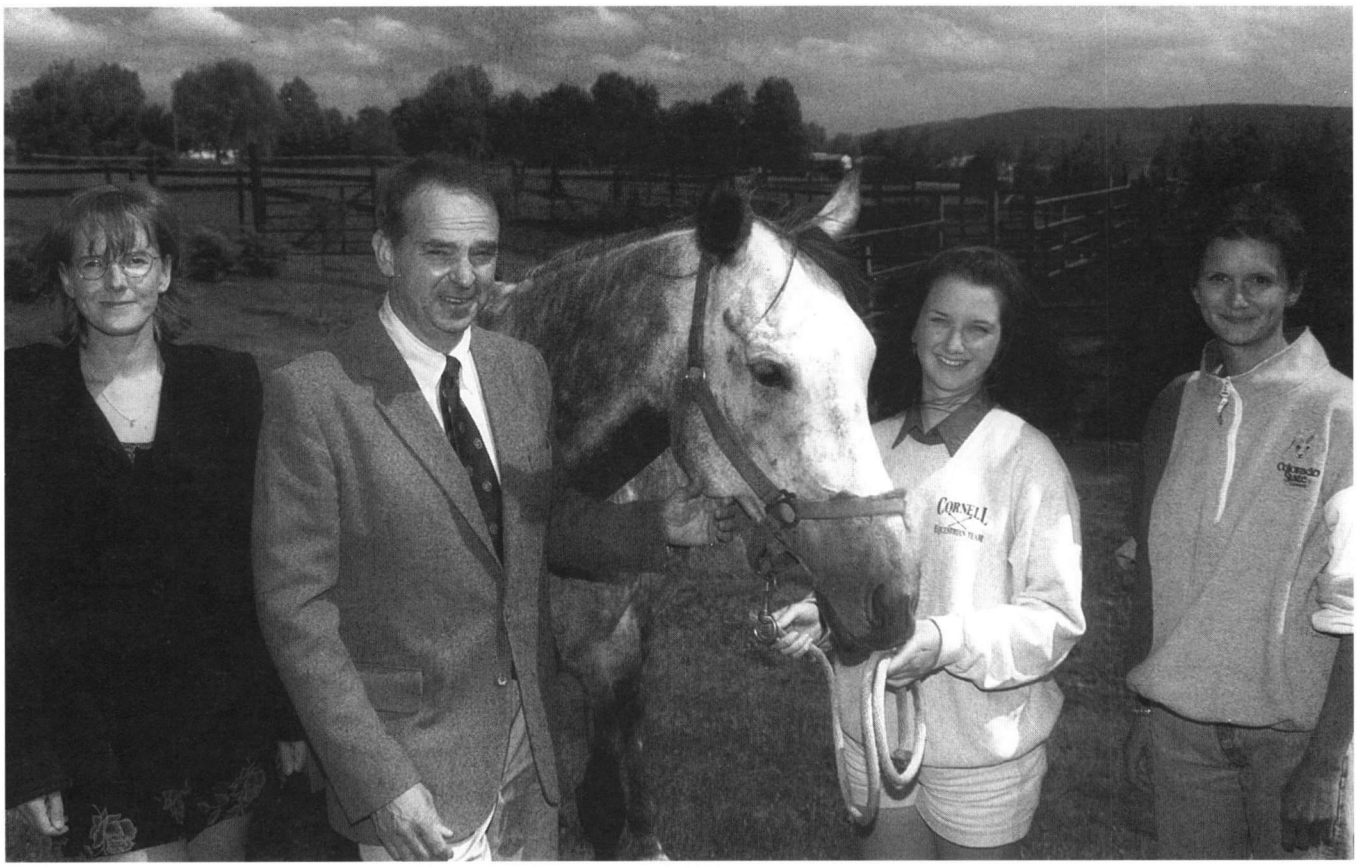
Zweig

Memorial Fund News Capsule

A report from the Harry M. Zweig Memorial Fund for Equine Research at the College of Veterinary Medicine at Cornell University

No. 25 June 1998

ROBERT BARKER



Horse Genome Project leader Doug Antczak with (l. to r.) project assistants Tatja Hopman, Leah Ruth, and Kitren Nickerson.

INSIDE

Zweig Support Helps Gene Jockeys Map the Horse Genome

The term "gene jockey" is bandied about a great deal these days. It was originally coined to refer to biologists who rely heavily on the tools of modern molecular biology for their research. But according to Doug Antczak, D.V.M., Ph.D., director of the James A. Baker Institute for Animal Health at Cornell's College of Veterinary Medicine, it has recently taken on a new meaning in the context of an ongoing international collaborative effort to map the genome of the horse.

The Horse Genome Project began officially in October 1995 when, with ▶

Horse Genome *continued from page 1*

support from the Dorothy Russell Havemeyer Foundation, Inc., the world's finest horse geneticists met in Lexington, Kentucky, at the First International Equine Gene Mapping Workshop. There, they divided their workload and agreed to share and integrate their data. The Havemeyer Foundation has continued to provide the umbrella organization under which laboratories from Cornell, California, Kentucky, Texas, England, France, Sweden, Switzerland, and Japan collaborate in this gene mapping effort.

The equine geneticists had their second meeting earlier this spring at the prestigious Cold Spring Harbor Laboratory on Long Island. The reputation of Cold Spring Harbor as a site for important conferences in genetics was built by the former director, Dr. James Watson, who, with Dr. Francis Crick, was awarded the 1962 Nobel Prize for the elucidation of the structure of DNA. The meeting on the genetics of performance in racehorses, convened by the Havemeyer Foundation, was the first equine meeting to be held at Cold Spring Harbor. It attracted not only equine scientists, but also human geneticists, equine clinicians and physiologists, and racehorse owners and breeders.

"This indicates the high level of interest in equine gene mapping in the scientific community and in the horse industry," says Antczak, who organized the meeting with Dr. Ernie Bailey of the University of Kentucky. "Since the initial meeting in Kentucky, there has been enormous progress in gene mapping in horses, and that progress continues at a terrific rate."

Although the mapping of human genes is way ahead of comparable efforts in horses, the horse's slow start in the genetics race has provided unexpected benefits to the horse gene mappers. This benefit comes in the form of *comparative gene mapping*, the aspect of genome studies which compares the organization of genes on chromosomes between and among species.

Antczak reports that a stunning discovery in Sweden two years ago gave the horse genome project a fantastic boost. Whereas patterns of gene order on human chromosomes tend to be very different from those of most other species (except for primates), researchers discovered that the patterns between humans and horses are wonderfully close.

"In other words, there is a very strong conservation of gene order on the chromosomes between the two species," explains Antczak, who is also the Dorothy Havemeyer McConville Professor of Equine Medicine at Cornell. "That means that much of the progress that has been made in mapping human genes can be—and is being—applied to horses. This is a huge boon for equine researchers, saving millions of dollars in time and energy and allowing equine research to forge ahead at an unprecedented rate."

Gene mapping is the decoding of the thousands of genes that line up on the 32 pairs of rod-shaped chromosomes within the nucleus of each equine body cell. The genes determine all the traits and characteristics that are passed down from parents to offspring, such as coat color, running ability, conformation, courage, or genetic defects that trigger inherited diseases.

By having a good comparative map between humans and horses, researchers now know, for example, that many of the genes that are located on human chromosome 6 are on horse chromosome 20. By knowing which genes on which chromosome are linked to muscular or immune diseases in humans, equine researchers can go directly to the corresponding chromosome in horses to look for the disease-causing gene in question.

Although the Horse Genome Project was launched just a few years ago, researchers already have been able to develop genetic tests to identify carriers of three enormously important equine diseases: severe combined immunodeficiency disease (SCID) that runs in Arabians; hyperkalemic periodic paralysis (HYPP) that can devastate quarter horses; and most recently, lethal white disease that can afflict the offspring of overo paint horses.

Cornell's focus, which is supported primarily by the Zweig Memorial Fund, is to contribute to the development of a linkage map for the horse. To develop linkage maps, Antczak and his colleagues are working to first identify as many so-called *microsatellites* as possible. Microsatellites are anonymous but variable bits of DNA that can be used as markers to identify regions on chromosomes that contain important genes that control traits or functions. They can be thought of as similar to the X and Y coordinates that frame a road map. For example, the coordinates A6 or B19 have no intrinsic meaning on a map of New York State. But they can be very useful in locating specific cities like Syracuse or Albany. Similarly, the equine linkage map can be used to pinpoint particular regions on a chromosome that carry genes for particular traits, such as running speed or disease susceptibility.

As of January 1998, after two years on the project, Antczak's laboratory had identified 145 new microsatellites in the horse genome. When added to those described previously by other horse geneticists, these new markers double the total number of equine microsatellites. Through collaboration with the equine genetics laboratory at the University of California at Davis, 55 of the Cornell microsatellites have already been assigned to locations on horse chromosomes. In addition, 20 are under test at the Animal Health Trust Laboratory in Newmarket, U.K., on a unique family of full sibling horses produced for linkage mapping by Professor W. R. Allen's Equine Fertility Unit at the University of Cambridge. Such international cooperation is very rare

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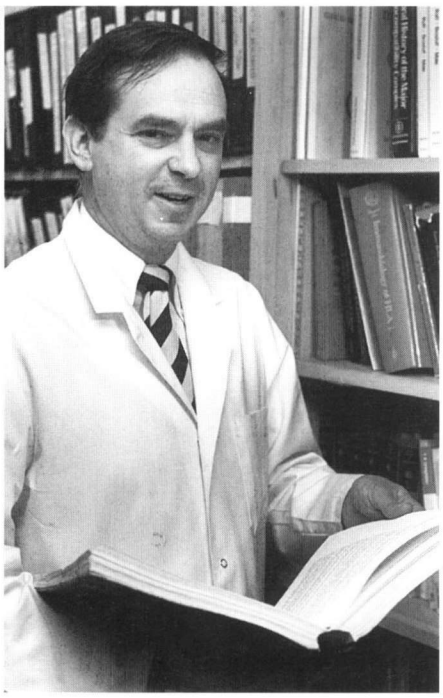
CHARLES HARRINGTON



Doug Antczak

among scientists, who are often competitive by nature.

"This cooperation is one of the most satisfying aspects of the Horse Genome Project," says Antczak, whose laboratory exchanges DNA probes and e-mail messages with half a dozen labs around the world each week as part of the project.

Although the horse genome contains thousands of microsatellites, just a few hundred can provide a wealth of information. Already, with just a few years of gene mapping, breeders can use genetic tests to prevent stallion-mare pairings that would result in HYPP or SCID in the offspring. Soon, scientists hope to be able to determine the genetic contribution to conditions such as "heaves" (chronic obstructive pulmonary disease) or "wobbles" (a defect in cervical vertebral formation) and to be able to offer better methods for diagnosis and management.

With gene mapping data, researchers are also learning how multiple genes act together. In the not-too-distant future, this information should allow breeders to not only select for particular traits that are linked to single genes, such as coat color, but also to multiple genes, such as fertility and performance. The microsatellite markers already can be used to provide more precise estimates of inbreeding in horses. This can be particularly useful for choosing matings in certain horse families or in breeds where the total number of individuals is limited. Microsatellites are also being used to study the evolutionary relationships between horses and their close relatives, the donkeys and zebras.

With molecular tests now in hand for three of the most serious genetic diseases that have plagued equine veterinarians and horse owners for years, applications of the Horse Genome Project are not futuristic: they are already off and running with the gene jockeys firmly in the saddle. ■

Harry M. Zweig Memorial Fund for Equine Research—1998 Research Awards

Renewals

$40,000 to Dr. Douglas Antczak for "The Horse Genome Project."

$80,000 to Dr. Y-F Chang for "Vaccination Against Lyme Disease in the Horse, Part II. Immunization of Horses Against Lyme Disease."

$11,100 to Dr. Patrick Concannon and Dr. Peter Daels for "Induction of Reproductive Function in Anestrous Mares Using a Dopamine Antagonist: A Field Study."

$7,725 to Dr. Douglas McGregor for "Career Development Training for Equine Research Scientists."

New

$26,000 to Dr. Stephen Barr for "Endoproteases of *Sarcocystis neurona*: Drug and Vaccine Targets."

$48,000 to Dr. Alan Nixon for "Growth Factor Gene Therapy Approaches to Equine Cartilage Repair."

Revised

$45,000 to Dr. Dorothy Ainsworth for "Immunotherapy for the Treatment of Chronic Obstructive Pulmonary Disease (COPDS) in Athletic Horses."

$30,000 to Dr. Peter Daels for "Ontogeny of Luteal and Fetal Steroidogenisis During Early Pregnancy in Mares."

Total Zweig Funds Awarded–$287,825

Zweig Research Improving Equine Health

Dr. Stephen Barr Battles the EPM Parasite

When a horse begins to wobble, becomes weak and uncoordinated, or has trouble standing or balancing, chances are it is a victim of equine protozoal myeloencephalitis (EPM). EPM is the most common neural disease in horses and accounts for more than one-third of all equine spinal cord disease in the United States.

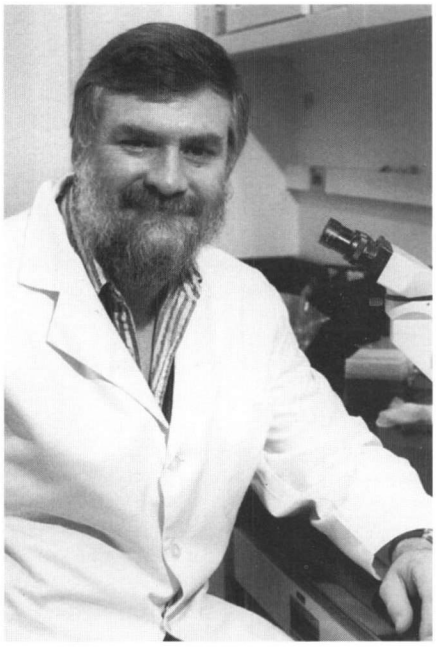
"EPM is the most important infectious disease facing the equine industry today," says Stephen Barr, a New Zealand immunoparasitologist, protozoologist, and small-animal internist at Cornell who has been awarded a new Zweig grant to study the cause of the disease in detail. "It is fairly common and tends to affect certain farms."

Scientists first clinically recognized EPM in New York, Ohio, Illinois, and Pennsylvania during the 1970s. Since then, it has also been detected in Florida, Texas, Kentucky, and California and as far away as Central and South America. Usually afflicting young adult horses, the disease is especially prevalent in yearlings in training or in young racehorses. Veterinarians still don't know how long it takes for a horse to show clinical signs once it's been infected, although many assume the animals are infected early in life. Some veterinarians believe that clinical signs may be triggered by the stress of racing or even somehow by the administration of corticosteroids.

Without reliable diagnostic tests, veterinarians don't really know just how common the disease is, although at least 100 cases are diagnosed each year in just Florida, Texas, and Ohio. Once a horse has the disease, it is no longer useful for work or riding.

"There are no drugs currently known that will kill the parasite, so once a horse has the disease, it's very difficult to treat," says Barr. "There are no vaccines for it either."

Scientists were able to link the disease to a protozoan about 20 years ago. But it wasn't until the early 1990s that the parasite, *Sarcocystis neurona*, was isolated from horse tissues. Previous Zweig funding helped support research to identify the parasite involved.



FRANK DIMEO

"Although no one really knows how or why horses become infected, we assume the infection is picked up by horses eating the parasite in the feces of opossums [spread on pasture], and that the parasite then makes its way from the horse's gut to the brain and spinal cord where it damages cells," says Barr.

His ultimate goal is to develop a drug or vaccine against the protozoan parasite.

"We are trying to identify important molecules, such as certain enzymes, in the parasite that have important functions and are essential for its survival and the progression of its life cycle," he explains. "If the function of a particular enzyme, for example, is removed or inhibited by the action of drugs or a vaccine, the parasite would die."

Because certain enzymes, or proteases, that are present in protozoan parasites are known to contribute to other diseases, such as AIDS in humans, protozoologists like Barr already know a great deal about the function and structure of many proteases. He is using this knowledge to help find similar proteases in the protozoa known to cause EPM.

He has already determined that the merozoites—the life stage of *S. neurona* that is responsible for the damage to the brain—contain a gene that expresses a type of protease (an aspartic protease) that previously had been shown to be important in allowing the HIV virus to enter cells. He also has identified major parts of two genes that he believes encode for two other proteases, one or both of which he suspects will be important for the survival of the protozoa in EPM.

"Once we're able to identify the entire gene, we not only will be able to determine how the protease will look and act, but also what its function is. If it is essential for survival, we will go ahead and make large amounts of it. Once made, we can use the protease to design drugs that inhibit the protease, and also use it as a basis to make a vaccine against it."

The parasite, however, has been particularly difficult to work with and to gather large amounts of genetic material from, says Barr. He is growing in his laboratory both the *S. neurona* parasite and *S. falcatula*, a very similar parasite which does not cause disease.

"We're feverishly trying to find genes in one that are not in the other. That way, we might be able to identify the gene that causes the disease," he says.

Barr is not only isolating and characterizing genes that express the enzymes he thinks will end up being important for EPM, he's also working with other genes he and his colleagues find. He feels that many could prove useful in drug testing and in the development of vaccines for other diseases in horses or other animals. ■

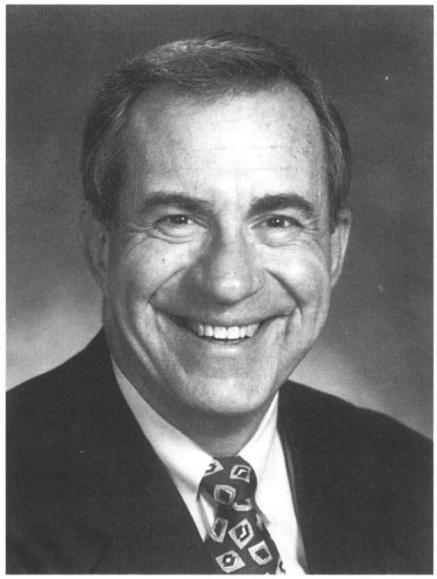
A lawyer, ex-racehorse owner, and former elected public servant for 20 years, Michael J. Hoblock Jr. is the new chairman and chief executive officer of the New York State Racing and Wagering Board. As such, he is also the newest member of the Harry M. Zweig Memorial Fund Committee. He joined the committee in May 1997, succeeding Jerry Bilinski.

As chair of the Racing and Wagering Board, Hoblock has responsibility for regulating all legal betting except the lottery in New York State. His office oversees ten racetracks, six harness and four thoroughbred off-track betting corporations as well as scores of branches; bingo, raffles, bell jars, and Las Vegas nights that run every year at thousands of organizations throughout the state; and one casino on the Oneida Indian Reservation and another that's about to be opened by the Mohawk Indian tribe on the St. Regis Reservation. All told, the Board issues about 15,000 licenses a year and the operations account for $7 billion to $9 billion in legal wagering. These activities provide jobs for thousands of New York State citizens and generate tens of millions of dollars in revenues for local and state government.

Hoblock notes that all these forms of legal wagering have taken a toll on horse racing. Fifteen years ago, he says, the pari-mutual tax collected from the state's race tracks brought in some $85 million a year. These days, the tax yields only about $20 million.

"It's a fact of life that horse racing nationally, because of competition, is not what it used to be. We didn't have casinos or state lotteries 15 or 20 years ago," Hoblock says. He adds that the state has responded by taxing the racing industry less and less so that now the tax on standardbred racing, for example, is down to almost zero.

Hoblock, 55, was born and raised in the Albany area. After attending a military high school, he earned a bachelor of business degree at Siena College and a law degree at Albany Law School. He then served in the U.S. Marine Corps in Vietnam, where he



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was awarded the Bronze Star. Leaving the Marines in 1971, he joined the law firm of Zubres, D'Agostino, Hoblock, & Greisler, eventually becoming a partner. He specializes in civil litigation, family and domestic law, real estate, and commercial business law.

Although Hoblock had ridden as a boy, having grown up around horses that lived on neighboring farms, he became much more involved with them in the mid-1970s when he bought two standardbred pacers. He raced them until 1978, when his election to the New York State Assembly required that he sell them to avoid potential conflicts of interest. In 1985, after three terms in the assembly, he was elected to the Colonie Town Board, where he served for six years before being elected to the full time job as Albany County Executive. In 1994, he was elected to the New York State Senate. A re-election bid in 1996 failed.

"I come from a family that's always been very active in public service and politics," says Hoblock, who estimates that he put in 80- to 90-hour weeks practicing law and serving in public office at the same time. "Both my father and uncle were involved so it was natural for me at some point to get involved as well. I enjoyed public service very much, but like all things, it came to an end."

When he was defeated in 1996, Hoblock expressed interest to the governor that he would be interested in the position of chair of the Racing and Wagering Board, which was due to become vacant, and he was appointed in May 1998. By statute, Hoblock not only serves as a member of the Zweig Committee, he also serves as vice chair of both the Thoroughbred Capital Improvement Board and the Thoroughbred Breeding Board, and as chair of the Harness Breeding Board.

"Although I've only been to one Zweig meeting so far, I'd like to become much more knowledgeable and involved with the research projects and other activities of the board so I can develop my own opinions about the value of potential projects to the thoroughbred and harness industry," he says. "As a lay person, I must now rely heavily on the veterinarians and other scientists on the committee. But even in this short time, I've learned an enormous amount."

When not on the job, Hoblock can often be found working in the community. He's a member of the board of the Northeastern Urban League, a member of the local senior citizens service center, director and vice president of the local Boy Scout Council, a local advisory board member with Key Bank, a member of the New York State Commission on Restoration of the State Capital, and a major with the New York State Naval Militia.

In whatever few leisure moments are left, he might be found relaxing with his wife, Karen, skiing, or playing golf or handball. ■

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The Harry M. Zweig Memorial Fund for Equine Research honors the late Dr. Harry M. Zweig, a distinguished veterinarian, and his numerous contributions to the state's equine industry. In 1979, by amendment to the parimutuel revenue laws, the New York State legislature created the Harry M. Zweig Memorial Fund to promote equine research at the College of Veterinary Medicine, Cornell University. The Harry M. Zweig Committee is established for the purpose of administering the fund and is composed of individuals in specified state agencies and equine industry positions and others who represent equine breeders, owners, trainers, and veterinarians.

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