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

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DAVID LYNCH-BENJAMIN

Zweig support is helping Dr. James MacLeod understand how steroids change the biology of joint tissues.

INSIDE

Examining the Effects of Steroids on Joint Tissue

During a race, thoroughbred horses pound the track with such force that 12,000 pounds of pressure is exerted on the cannon bone alone. "Such physical exertion and musculoskeletal stress predisposes most race horses to joint disease that sooner or later compromises their careers," says Dr. James MacLeod, a veterinary molecular geneticist at Cornell's College of Veterinary Medicine.

In recent years, however, many people have become concerned that the number of racehorses suffering catastrophic breakdowns while racing and training is increasing. Some veterinarians blame the widespread

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use—some would even say abuse—of corticosteroids.

Steroids are a family of molecules that are chemically related to cholesterol. They act by changing the rate at which certain genes are transcribed, or coded, into RNA. This, in turn, alters which proteins are produced by the cells. Anabolic steroids, such as testosterone, are used by weight lifters and other athletes to enhance muscle growth and are the subject of great concern in amateur and professional sports. Corticosteroids, such as hydrocortisone and dexamethasone, are popular for their anti-inflammatory effects.

Corticosteroids are widely used in race horses for a very good reason—they are the most powerful anti-inflammatory agents available to veterinarians and are extremely effective in controlling joint pain and lameness. Human athletes such as baseball pitchers, tennis players, and long-distance runners also commonly use steroids to reduce pain and joint swelling. However, these medications carry the serious side effect of weakening cartilage and ligaments in damaged joints and may even promote degenerative joint changes such as arthritis.

A highly publicized case in point was the race horse Prairie Bayou, who last year won the Preakness and finished second in the Kentucky Derby before being euthenized after his left foreleg shattered during the Belmont Stakes. Two Cornell veterinarians who performed an autopsy on the young gelding concluded that steroids injected into the horse's left fetlock joint had gradually degraded a critical ligament until it finally broke.

Although the owners of Prairie Bayou and many veterinarians aggressively disputed this Cornell conclusion, University of Minnesota researchers have reported that 840 horses suffered fatal racing breakdowns and another 3,566 suffered nonfatal racing breakdowns in the U.S. in 1992 alone. Not included are the additional breakdowns that occurred during training. It has been argued that widespread corticosteroid use was an important causative factor in many of these injuries.

MacLeod, in collaboration with veterinary surgeon Susan Fubini, hopes to better understand how steroids change the biology of joint tissues and learn how to minimize the drugs' deleterious effects. Up to this point, there have been few molecular studies on horse diseases, particularly those that affect joint cartilage.

"Our objective is not to generate data that condemns steroid use, but rather to learn how steroids change joint tissue physiology so that their beneficial effects can be optimized while their deleterious effects are minimized."

"Understanding the basic mechanisms of a disease process first and foremost offers the potential for prevention," MacLeod explains. "By understanding what changes occur as disease develops, veterinarians may be able to target treatment to the actual pathology and minimize the potential of damaging the joint cartilage."

So far, MacLeod has isolated (or cloned) several equine-specific gene fragments that have allowed him to use powerful new methods to study equine joint disease. Specifically, he has isolated pieces of horse DNA from genes that encode important cartilage proteins.

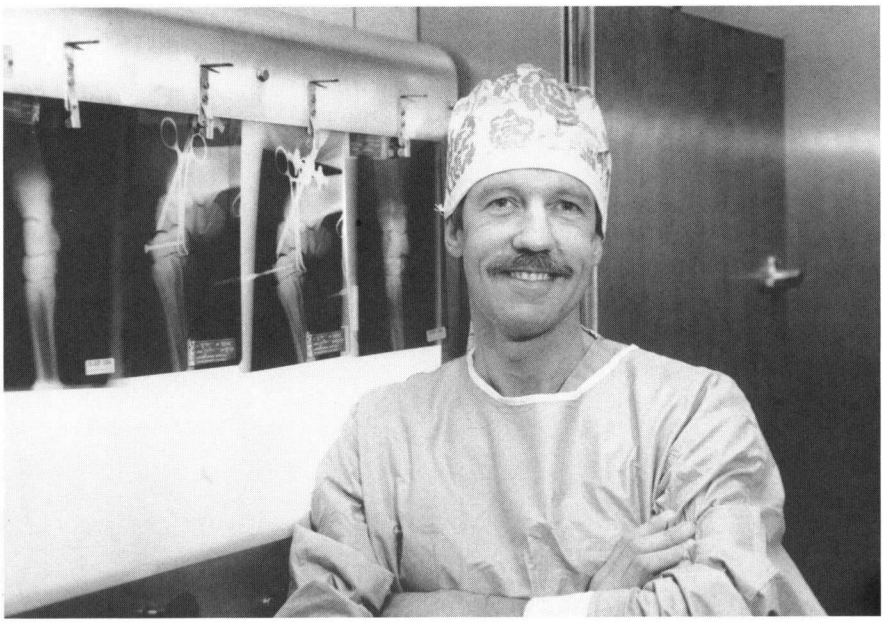
"Once isolated, the DNA segments are used to measure the rate at which these genes are transcribed into RNA," says MacLeod. "After transcription, the RNA is transported to the cell's cytoplasm (outside the nucleus) and translated into proteins. By changing gene transcription, steroids alter which proteins are made by the cells. For any given gene, transcription can be increased, decreased, or unaffected by steroid treatment."

MacLeod is now working to uncover how the expression of the isolated genes influences cartilage biology and the onset and progression of joint diseases such as arthritis. He hopes to learn how the genes are expressed in different areas of healthy cartilage, in arthritic cartilage, and in both normal and inflamed joints that have been treated with steroids. In addition, he will continue isolating genes that are involved in cartilage biology by cloning four more equine-specific DNA segments.

"We would like to distinguish between cartilage changes caused by joint inflammation, or the disease process, as opposed to those induced by steroid therapy. We also want to better understand how steroids might actually protect cartilage from degradation by reducing the expression of protein-degrading enzymes that are released during inflammation."

Ultimately, MacLeod hopes to determine the negative and positive effects of steroids at the genetic level so that the positive effects may somehow be optimized, perhaps through the development of new steroids, and the negative effects minimized or compensated for.

"For the well-being of race horses, the racing industry, and the people who love the sport of racing, we need to learn more about how corticosteroids change the biology of joint tissues. Our objective is not to generate data that condemns steroid use, but rather to learn how steroids change joint tissue physiology so that their beneficial effects can be optimized while their deleterious effects are minimized." ■



Equine orthopedic surgeon Alan Nixon's successful cartilage grafting techniques may have potential for use in humans as well as in horses.

Almost weekly, Dr. Alan Nixon boards a plane for some distant clinic to perform his highly specialized surgical techniques on horses. The College of Veterinary Medicine professor is one of the few equine orthopedic surgeons in the world who performs a particular procedure that cures a "wobbler," a horse with pinched nerves in its spinal cord.

And he's the world's *only* equine orthopedic surgeon using special grafting methods he developed to resurface cartilage defects such as fractures before arthritis sets in. The technique, developed over the past four years with Zweig funding, has been so successful that its potential application to human joint repairs was published in the September, 1994 issue of *Journal of Orthopedic Research.*

"Our main interests are the wear and tear that occur in race and performance horses and catching problems early enough to prevent arthritis. But if our techniques and knowledge can be adapted to humans, so much the better," he says.

Nixon is accustomed to being a pioneer in equine orthopedics. He and his colleagues were also the first to develop arthroscopic hip, elbow, shoulder, and tendon surgeries in the horse.

Nixon's career took root more than 30 years ago on his family's farm, which covers more than 10,000 acres in southeastern Australia. Growing up, he and his two brothers worked cattle, horses, and sheep on the farm. While his brothers continued farming and run the family farm to this day, Nixon knew as a young teen that he was interested in pursuing a career in veterinary science. He asked a local veterinarian if he could ride with him for several weeks to get a feel for what vets really do. He liked the feeling.

At 17, Nixon went right from high school to veterinary college at the University of Sydney in Australia. To pursue more specialized training, he continued on to Colorado State University to do a residency in equine surgery and earned his masters in 1983. After several years at the University of Florida College of Veterinary Medicine in Gainesville, he came to Cornell.

"I chose orthopedics because I consider this field the most challenging and exciting, and I came to New York for the quality of the horses and racing here," says Nixon. "The College of Veterinary Medicine at Cornell, however, was the major draw. I consider this the most attractive school in the world for its rich academic, clinical, and research programs."

His passion, Nixon admits, is his work. He can frequently be found in his research labs late at night after a busy day of surgery. His other interests include downhill skiing, hiking, sailing, windsurfing, and keeping tabs on the brood mare and two geldings he left in Colorado.

At Cornell, Nixon spends about half his time in the Large Animal Clinic, performing routine lameness workups and general joint and reconstructive surgeries such as knee and fetlock chip removals, removing flaps in horses with OCD (osteochondritis dissecans, an abnormal cartilage growth), and his newly developed cartilage graft procedure. The rest of his time is spent teaching orthopedics and conducting research on cartilage grafts, tendon metabolism in horses, and innervation in equine bones.

His next frontier is molecular biology research in cartilage defects and healing and studying how changes in genetic expression occur after insult to a joint. With vet school colleague Dr. James MacLeod and researchers at the University of Washington, Nixon is exploring growth factor genetic expression in damaged cartilage, such as osteoarthritic cartilage, to learn what can be done to improve damaged joints.

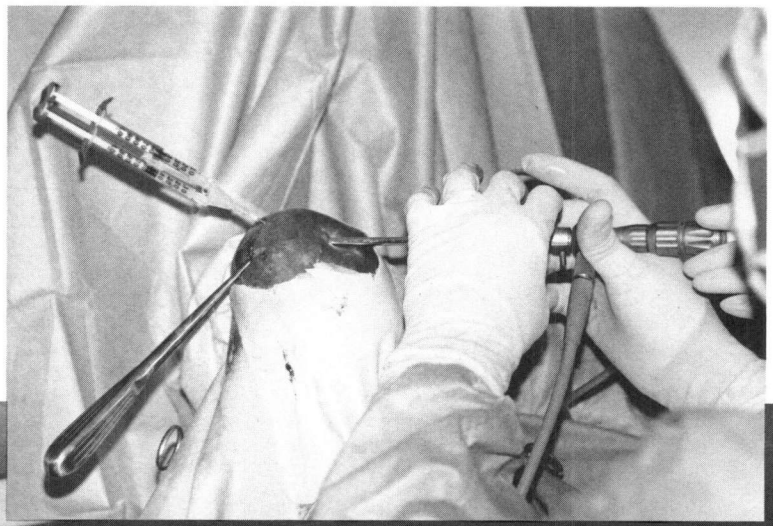
"We hope to learn how to minimize damage and perhaps develop better doses of external growth factor and better timing of cartilage grafts to improve the situation," he says.

Will Nixon eventually return to Australia? "Maybe to retire," he says. "There's so much going on here in this country it's phenomenal. I believe it's unsurpassed anywhere in the world—and I love it." ■

Zweig-funded Research Helps Extend a Racing Career

A large part of orthopedic surgeon Alan Nixon's day is spent in the operating room. One recent day found him performing a procedure to correct damage to the carpus, or knee joint, of a three-year old racehorse. After inserting a screw to repair the injury, he injected a matrix containing cartilage cells and growth factor to help the cartilage regenerate. The technique, which Nixon developed with Zweig support, will help prevent arthritis from forming in the joint. The operation was successful and Nixon predicted the filly would soon return to the track to finish her racing career. ■

Three incisions in the horse's knee allow the insertion of an arthroscope, surgical instruments, and a double syringe containing the cartilage cell matrix.



Nixon checks the television monitor to assess the distribution of the cartilage cell matrix.

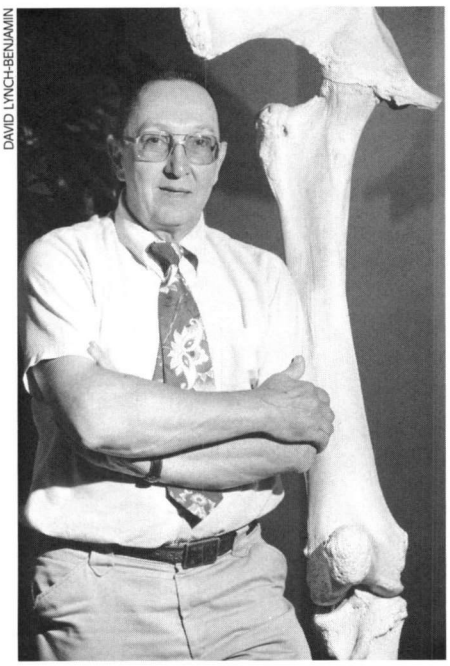
Photographs by David Lynch-Benjamin

X-rays taken during the procedure show the screw Nixon has inserted into the knee as well as the arthroscope and surgical tools.

Moving the sedated horse from a gurney to the padded floor of the recovery room takes the coordinated efforts of nine people.

Waiting for the anesthesia to wear off, veterinary student Charles Brockett and anesthesiology technician Joan Ballenstedt monitor the horse in the recovery room. In a few hours, she'll be up and around.

New Urine Test Helps Detect Bone Weakness



DAVID LYNCH-BENJAMIN

Ronald R. Minor, D.V.M., Ph.D.

Breakdown injuries of the bone, such as "bucked shins," saucer fractures of the cannon bone, and other types of fractures commonly cut short the careers of race horses. Weakened bone may contribute to these musculoskeletal injuries. While the normal process of bone growth involves some bone degradation and replacement, called "bone turnover," bone becomes weaker when there is more degradation than production of bone matrix. Yet, current equine sports medicine lacks a simple way to measure such bone breakdown.

Recently, however, a quick and inexpensive urine test for humans that measures bone turnover was developed by Dr. David Erye at the University of Washington School of Medicine. The test can determine if the delicate balance between normal bone growth and degradation has become disrupted. Using funds from the Harry M. Zweig Memorial Fund, Ronald R. Minor, Ph.D., V.M.D., an experimental pathologist at Cornell's College of Veterinary Medicine, and his colleagues are adapting the procedure for equine urine to identify and quantify bone resorption in horses.

To learn the specific techniques needed, such as amino acid sequencing and collagen cross-link analysis, Minor spent a month in Washington with Dr. Erye and enlisted him as a consultant for the equine project. With fellow veterinary scientists Drs. Fernando de Noronha, Lennart Krook, and Susan Fubini, Minor has successfully developed a biochemical test for equine urine that provides the needed information on bone growth and degradation. To do so, they tested the two commercially available human tests with horses. One of the kits strongly reacted with the horse urine and allowed the researchers to isolate certain linked amino acids, the building blocks of the protein. Unlike most amino acids, the isolated amino acids are not reutilized in bone production but are excreted in the urine. They are specific to collagen, the major protein of bone.

> "Our hope is to be able to inexpensively identify athletic horses at risk for many traumatic and life-threatening injuries."

"Collagen is the glue that holds everything in the body together," explains Minor, who has spent more than 20 years studying collagen in several species, including an 11,000 year-old mammoth whose bones were discovered in Utah in 1988. "Collagen, in fact, makes up more than one-third of the total protein in all species and constitutes the major framework that is mineralized to form bone. Whenever bone is degraded, collagen molecules are broken up into free amino acids that are either reutilized or excreted in the urine."

Using the test, a chemical assay they modified from the methods developed for humans, the veterinary scientists are currently developing baselines of normal values for horses at different ages. They have found, for example, that the values for the bone-specific "cross-linked" (covalently linked) amino acids in the foal are three to five times higher than in the mature horse. This difference might be expected, since the foal is growing bone much more rapidly and therefore experiences much more bone turnover.

Next year, after the researchers have completed the normal range of values for horses of different ages, they will test athletic horses of two and three years of age and compare the values with those of younger and older horses. They plan to test horses that show no indication of bone breakdown and use the values obtained as baselines. They will then compare those values with values derived from horses that have experienced bone fractures during racing.

"Our hope is to be able to inexpensively identify athletic horses at risk for many traumatic and life-threatening injuries," says Minor. "As the method of quantifying bone turnover becomes more sophisticated, we hope to be able to analyze the urine of colts and fillies receiving different diets (such as excessive or incorrect dietary supplements), experiencing different growth rates, and being given various drug therapies (such as corticosteroids and anabolic steroids). Then we might be able to determine if any of these factors are changing the collagen degradation values in urine. Such a test would also allow us to identify abnormalities in bone growth in the young horse. With a better understanding of the signs of bone turnover, horse owners and trainers, in consultation with veterinarians, could then make informed decisions concerning the effects of diet, training, and racing management based on the effects of their regimens." ■

William H. Welch

William H. Welch, 54, a Zweig Committee member and executive administrator of the New York Thoroughbred Breeding and Development Fund, "practically grew up on a horse" in the Genesee Valley. He was steeplechase racing and fox hunting by age 9, and later went to Cornell University thinking he'd become a veterinarian. He got sidetracked, however, and graduated in 1962 with a major in economics.

Unsure of what he wanted to do, Welch became a deputy sheriff in Livingston County for several years and during that time, decided to make horses the focus of his career. After attending the Jockey Club School for racing officials, he worked for several years as a part-time sheriff and part-time placing and patrol judge at Aqueduct and the then newly-opened Finger Lakes Race Track in Canandaigua.

In 1967, Welch moved to New York City to take the position of assistant director of the New York Breeders Bureau. Named director in 1971, he was one of the driving forces in the passage of the breeding and development law, which, after two vetoes, the governor finally signed into law in 1973. The law changed the name of the Breeders Bureau to the New York State Thoroughbred Breeding and Development Fund Corporation and mandated that the corporation would receive one-half of one percent of the on and off track handle—approximately

William H. Welch

$12 million a year—for incentive and development programs for New York bred horses. The fund supports races for New York breds and bestows almost 1,500 awards to breeders, stallion owners, and owners of winning horses as well as purse enrichments to New York bred restricted races. In addition, the fund gives two percent of its resources to the Harry M. Zweig Memorial Fund for Equine Research at the New York State College of Veterinary Medicine at Cornell.

"I believe our fund has been one of the most successful programs in the state in terms of lighting a spark in agriculture and the economy while also promoting research through the Zweig Fund."

"The thoroughbred business is going through a shake up with new tax laws that are no longer as favorable to horse breeders," said Welch during an August interview while he was at Saratoga for the races. "We're trying to change with the times and find ways to encourage people to continue breeding."

This past year has been one of the fund's most successful. New York bred horses broke their record for winning graded or group races, the most prestigious races in the industry. Seventeen New York breds won 19 such races, two more than the previous record set in 1992. Some $900,000 of the $40 million in purses in 1993 was won by thoroughbreds bred in New York, once again placing the state among the nation's leaders.

"In addition to the $12 million we put back into the economy, more than $200 million has been spent renovating former dairy farms into vital horse farms," Welch says. "All told, the breeding industry contributes $2 billion to the overall economy of New York. For fear of boasting, I believe our fund has been one of the most successful programs in the state in terms of lighting a spark in agriculture and the economy while also promoting research through the Zweig Fund."

Welch, a bachelor, is an avid deep sea fisherman, going after tuna, shark, and marlin in particular. But his love of riding has never left him, and he still likes to climb on a horse when he can. ■

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 pari-mutuel 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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