

# **HYPP**

**HYPERKALEMIC PERIODIC PARALYSIS**

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*A Comprehensive Brochure to Inform & Educate  
American Quarter Horse Enthusiasts*

P.O. Box 200, Amarillo, TX 79168

AMERICAN  
QUARTER  
HORSE  
ASSOCIATION



Dear American Quarter Horse Enthusiast,

For some time now, you have probably heard, or had first-hand knowledge, of the condition known as hyperkalemic periodic paralysis (HYPP). This condition is characterized by intermittent episodes of muscle tremors (shaking or trembling, weaknesses and /or collapse).

At the 1996 AQHA Convention in Seattle, Washington, the AQHA Board of Directors approved some rules which will have substantial effects on the future of the registry. These rule changes were recommended by the AQHA Stud Book and Registration Committee and approved by the Board of Directors. Among the changes was a rule requiring disclosure of HYPP status on the registration certificates of foals born on or after January 1, 1998, which descend from any bloodline determined to carry the HYPP gene.

Beginning with the 1997 AQHA *Official Handbook*, HYPP will be listed in rule 205 among conditions commonly considered undesirable traits or genetic defects, such as parrot mouth and cryptorchidism. These conditions do not prevent a horse from being used as breeding stock or from participating in AQHA-approved events, subject to rules of the individual event.

Beginning with 1998 foals, the rule requires the following notification to be placed on the registration certificates of foals descending from any bloodline determined to carry the HYPP gene:

“This horse has an ancestor known to carry HYPP, designated under AQHA rules as a genetic defect. AQHA recommends testing to confirm presence or absence of this gene.”

Facts about HYPP have been gained through research projects funded in part by AQHA, through the University of California, Davis and the University of Pennsylvania. The first report, from Drs. Sharon Spier and Gary Carlson of U.C. Davis, was delivered to AQHA in the summer of 1992, and published in-full in the September 1992 issue of *The Quarter Horse Journal*. As additional information has been made available, AQHA has promptly published it. I invite you to refer to the last page of this brochure for a list of AQHA publications and others which contain information about HYPP.

AQHA has a duty to its members and American Quarter Horse owners to keep them abreast of current information on HYPP, and indeed, all health matters, so that they may make informed decisions concerning their equine programs. In furtherance of these objectives, AQHA has published this brochure, “HYPP: A Comprehensive Brochure to Inform & Educate American Quarter Horse Enthusiasts.”

Respectfully,

A handwritten signature in cursive script that reads "Bill Brewer".

Bill Brewer  
AQHA Executive Vice President

# Hyperkalemic Periodic Paralysis FACT SHEET

Prepared by the American Quarter Horse Association, September 1996

- ▶ Hyperkalemic periodic paralysis (HYPP) is an inherited disease that leads to uncontrolled muscle twitching or profound muscle weakness, and in severe cases, may lead to collapse and/or death.
- ▶ HYPP is listed as a genetic defect in AQHA's rules, along with Parrot Mouth and Cryptorchid conditions.
- ▶ To date, HYPP only has been traced to descendants of IMPRESSIVE, #0767246.
- ▶ Having negative (N/N) results on file may prevent a horse's offspring from being tested.
- ▶ Foals born in 1998 and later and tracing to IMPRESSIVE will have a statement placed on their Certificates of Registration that recommends testing for the condition unless test results indicating the foal is negative (N/N) are on file with AQHA.
- ▶ AQHA will test any foals who are required to be parentage verified and who trace to IMPRESSIVE for HYPP prior to them being registered. This testing will be performed with the same DNA sample submitted to the laboratory for parentage verification.
- ▶ AQHA will accept HYPP test results only if performed through a licensed laboratory.
- ▶ Beginning with the 2007 foals, all Impressive progeny are required to be parentage verified and HYPP tested subject to the conditions listed in rule 205. Any that test H/H will not be eligible for registration.
- ▶ Possible results of HYPP testing are N/N, N/H and H/H.

HYPP is inherited as a dominant trait, which means a heterozygous (N/H) stallion or mare bred to a normal (N/N) horse will result in approximately half of the offspring being affected and half being normal. The rare homozygote (H/H) usually is severely affected with the disease and will pass the gene to its offspring 100 percent of the time.

- ▶ HYPP can be treated through diet and medication in most cases.
- ▶ AQHA Testing Kits can be ordered for \$35. (see back cover)

From AQHA's Official Handbook of Rules and Regulations

## RULE 205: GENETIC DEFECTS and UNDESIRABLE TRAITS

The conditions listed below and commonly considered undesirable traits or genetic defects by the Board of Directors shall be indicated on the registration certificate for horses foaled on or after the indicated date, once the condition is known. Upon discovery, the owner shall immediately report such condition to AQHA for marking its condition on the registration certificate as provided below. Failure to timely report these conditions may subject the owner to possible disciplinary action. One or more of these conditions does not prevent a horse from being used as breeding stock or from participating in AQHA-approved events, subject to rules of the individual event:

[a] *Parrot Mouth - either overshot or undershot, defined by the American Association of Equine Practitioners as "no occlusal contact between the upper and lower central incisors." Designation effective for foals born on or after January 1, 1992.*

[b] *Cryptorchid - meaning less than two visible testicles descended into the scrotum. Designation effective for foals born on or after January 1, 1992.*

[c] *Hyperkalemic Periodic Paralysis (HYPP) - designation effective for foals born on or after January 1, 1998. A muscular disease caused by a hereditary genetic defect that leads to uncontrolled muscle twitching or profound muscle weakness, and in severe cases, may lead to collapse and/or death. According to research, this condition exists in certain descendants of the stallion Impressive, AQHA registration number 0767246.*

[1] The following notification shall be placed on registration certificates of foals descending from the stallion Impressive or any other bloodline determined to carry the HYPP gene:

***"This horse has an ancestor known to carry HYPP, designated under AQHA rules as a genetic defect. AQHA recommends testing to confirm presence or absence of this gene."***

When the parent(s) tracing from the HYPP line has tested negative for HYPP with an appropriate designation appearing on their registration certificate, the above notification is not required, and will, instead, be substituted by the designation "N/N"; or, after testing negative for the gene, the notification may be substituted by the designation "N/N" upon request of the owner at his or her expense.

[2] Mandatory testing for HYPP. At such time as AQHA requires mandatory parentage verification of any foals to be registered in either the numbered or appendix registry, (see 202 (i)) any foal tracing to bloodlines known to carry the HYPP gene shall be tested for HYPP at the time the genetic testing for parentage is performed. The results will be designated on the registration certificate in lieu of the above notification. Such testing will not be necessary if the foal's closest ancestors, tracing to the HYPP line, have been tested negative and designated on their registration certificates, these foals will automatically be designated "N/N" on their registration certificate.

# HYPP

*Someone else's problem? By Lesli Groves.*

**Genetic testing allows horsemen to make informed breeding decisions.**

**H**YPP is the acronym for hyperkalemic periodic paralysis. As the first equine disease which can be identified by a DNA test, HYPP means much more than four simple letters can indicate.

Research showing HYPP tracing to the preeminent halter horse sire Impressive has generated a lot of publicity. But because only one segment of the global equine industry has been hit hard, other horsemen think of it as "someone else's" problem.

Most people don't have a lot of money or emotions bound up in a horse that "ties up" from muscle spasms related to a mutant gene. Nor do they ponder questions like, "Will he always be asymptomatic?" or "Can I afford not to breed this \$20,000 HYPP mare?"

Obviously it's affected the Quarter Horse halter industry. However, the issue is much broader in scope, and affects all members and horse owners.

It extends to the issues of artificial insemination, chilled and transported semen and embryo transfer. It's about sexing semen, cloning and other genetic engineering we have yet to imagine. It's about the repercussions, as well as any rewards, of trying to "fool" Mother Nature.

HYPP provokes thought about the role of breed associations, selection criteria in the show ring, and selection criteria for mating one horse to another.

It's about handling the next disease identified by a DNA test, and the one after that, and the one after that . . .

Consider the consequences if colic proves to be genetically linked. Researchers think it's possible.

Colic is much more widespread than HYPP,

and it, too, can be fatal. What if your best horse possesses a "colic gene?" How would that affect you when you want to sell or breed him? How would it affect your future buying decisions? How would it influence new owners coming into our breed?

"But my horses don't colic!" you say. A lot of horses with HYPP are asymptomatic.

"Besides, if you manage them right, it makes a world of difference!" Owners of horses with HYPP have learned that, too.

People manage horses with a variety of characteristics: cribbing, parrot mouth, OCD, cryptorchidism, mean tempers, short tails and crooked legs. Perhaps those conditions have a genetic link, too. They may or may not trace to one sire. Nor will anyone be as eager to fund the research.

The good news is that genetic testing allows horsemen to make informed breeding decisions. By not mating two HYPP-positive parents, breeders can stop producing the most severely afflicted group — homozygotes — right now. With selective breeding, HYPP could conceivably be eliminated completely, but that goes back to a lot of those other issues.

Researchers have identified a human breast cancer gene, as well as a "fat" gene, and interest in the subject is growing exponentially. Advances in human research trickle down to equines before long. The next breakthrough in genetic technology could point out some latent flaw in your own horse. It might even point out a genetic flaw in you.

So please read the available HYPP research, and realize that this is a multi-faceted issue which potentially affects the entire AQHA membership — for that matter, the entire horse industry.

## The Latest Research . . .

**A**QHA receives an annual progress report and a final report on every research project it funds. The following report was submitted by researchers at the conclusion of the most recent project addressing HYPP.

Excerpts have been highlighted, plus, in the sidebar, QHJ asked Dr. Sharon Spier to personally answer a few questions which might be of interest to horsemen.

**Hyperkalemic periodic paralysis in certain registered Quarter Horses:**

**Factors Affecting Expression of Clinical Symptomatology, Screening of Quarter Horse Bloodlines, and Improved Methods for Disease Control.**

**Investigators:** S.J. Spier, A.T. Bowling, E.P. Hoffman, S. Valberg, G. Byrns, J. Zhou, C.M. Drake; Department of Medicine and Epidemiology (Spier), the Veterinary Genetics Laboratory (Bowling, Byrns) and the Department of Statistics (Drake), University of California, Davis, and the Department of Molecular Genetics, Human Genetics and Pediatrics, University of Pennsylvania (Hoffman, Zhou).

**T**his report will update AQHA members on research that has been performed since DNA testing became widely used in the horse industry. Studies were performed to try to answer specific questions regarding this genetic disease: just how widespread the mutation was in the Quarter Horse breed and where the mutation originated were unknown. While the gene frequency in Quarter Horses was not known, at the time of identification of the genetic mutation, all affected horses traced to a common sire.

The reason(s) for the variation of clinical severity of symptoms, ranging from no apparent signs of disease to sudden death, were unclear and warranted investigation. There was also concern among horse owners about the possibility of episodes of paralysis occurring during exercise when an affected horse is ridden. A series of exercise studies were performed in effort to try to answer some of these questions.

Hyperkalemic periodic paralysis (HYPP) is an inherited disease of muscle which is caused by a genetic defect in the alpha-subunit of the adult muscle sodium channel gene. The disease is inherited as an autosomal dominant trait, which means that only one copy of the gene is required to produce the disease, and the disease occurs with equal frequency in both sexes (stallions, geldings or mares). The disease is strictly genetic (i.e., not infectious or contagious) and breeding of a heterozygote results in approximately 50 percent of the offspring that will not possess the mutation (normal) and 50 percent of the offspring that will possess the mutation (affected, heterozygote). The transmission is purely random, that is, much like flipping a coin.

Presence of the defective sodium channel makes the horse's muscle overly excitable (firing more readily than normal), making the horse susceptible to sporadic episodes of muscle tremors or paralysis that can last from minutes to hours. The majority of the time, affected horses appear clinically normal and many are highly successful show horses (both halter and pleasure), while others are used for pleasure and trail riding. The mutation can be identified from a DNA test and is available through the Veterinary Genetics Laboratory at the University of California at Davis.

### HYPP gene frequency study

More than 27,000 samples have been tested for the DNA mutation since October 1992. Of these, 63 percent were normal (N/N), 36 percent were heterozygous for HYPP (N/H) and 1 percent were homozygous affected (H/H).

For AQHA to provide satisfactory answers to questions about the frequency of the HYPP mutant gene among Quarter Horses, a random testing program not skewed to a single bloodline is needed. Responsible owners frequently ask for advice whether to incur the expense of testing horses that do not trace to Impressive, but do trace to his Thoroughbred or Quarter Horse parents or grandparents. At the time of the proposed study, we did not have adequate answers for these inquiries. Data summaries from an HYPP service testing program cannot provide the needed information since the samples tested are likely to be either from horses showing presumptive signs of the disease or from horses whose pedigrees trace to Impressive.

See glossary of difficult terms on page 59.

Please read the available HYPP research, and realize that this is a multi-faceted issue which potentially affects the entire AQHA membership — for that matter, the entire horse industry.

Stored blood samples from 6,000 horses, received between January 1989 and December 1991 in conjunction with blood-typing requirements of AQHA, were available at the Veterinary Genetics Laboratory for an HYPP frequency and bloodline study. All samples were from horses bred and foaled before the availability of a genetic test for HYPP. We used a computer program to choose at random 1,000 samples from the 6,000 available to test for the HYPP gene mutation. The samples were primarily from breeding stallions, but were otherwise not selected for bloodlines. Among the 1,000 samples, 22 were Thoroughbred (16 males and six females) and 978 were from Quarter Horses (882 males and 96 females). The foaling year with the largest number of tested horses was 1983 (109 horses).

Forty-three horses (42 males and one female) tested positive for a single copy of the HYPP gene (N/H). No homozygotes (H/H) were detected. All of the positive horses were Quarter Horses and all traced to the stallion Impressive as first, second or third generation descendants. The frequency of gene positive Quarter Horses in the sample set was 4.4 percent. This translates to an allelic frequency of 0.02 because the affected horses contained two alleles or copies for the given gene (one normal allele and one abnormal allele.) The first foaling year with an HYPP-positive horse was 1977. The foaling years with the highest frequency of HYPP positives occurred between 1984 and 1987, for which the average frequency of positives per year over those four years was 10 percent.

Among the 1,000 tested horses, 100 traced by pedigree to the stallion Impressive. All of the N/H horses were Quarter Horses and all traced to Impressive as first, second or third generation descendants. This information provides substantial evidence to confirm that Impressive is the major, if not only, pedigree source of the HYPP gene in Quarter Horses, as proposed in previous studies. Three horses traced to Impressive through both sire and dam.

Although clearly associated with muscle disease, the HYPP trait may be a source of phenotypic characteristics highly valued by Quarter Horse breeders, such as the appearance of muscle development. Prior to the availability of a reliable genetic test, breeders could not make informed mating decisions with respect to HYPP. Basic theories of trait inheritance and population genetics allow us to evaluate whether the frequency of HYPP-positive horses among offspring in this pedigree is higher than anticipated.

The overall frequency of HYPP positives among the Impressive subset was 43 percent. This frequency is much higher than expected if breeding stock is randomly selected with respect to HYPP from pedigrees tracing to Impressive. It is in the range of values expected, for example, from a set of matings in which one parent in every breeding pair was N/H. Since the majority of horses in this sample set that traced to Impressive were second or third generation descendants for which only 50 percent or 25 percent, respectively, of breeding pairs could be expected to have one parent positive for the trait, the frequency of HYPP positive horses is clearly higher than expected.

From these data we conclude the HYPP gene is infrequent among registered Quarter Horses, although its occurrence is substantially linked to pedigrees tracing to Impressive. Among horses bred prior to the availability of a gene test, a higher frequency of the HYPP trait than anticipated by random occurrence is evident among descendants of Impressive. A reliable gene test based on analysis of DNA sequence is available that allows breeders to select stock free from the gene and the muscle disease it produces. It is anticipated that the frequency of horses positive for the HYPP trait will substantially decrease among breeding stock during the next decade.

### Horse sodium channel research

There have been a few reports from horsemen and veterinarians that there are horses which are showing clinical signs of disease similar to HYPP, but have tested negative by the current assay. Some of the horses are descendants of Impressive, while others are unrelated. In humans, more than one mutation in the sodium channel gene have been identified with patients with HYPP. It is theoretically feasible that a different mutation in the same gene could produce a similar disease. It is also possible that these horses suffer from an entirely different muscle disease which may or may not be inherited. Thirteen horses were identified from the 27,000 sample submissions that tested negative for HYPP yet had a history of signs of muscle disease such as tremors or painful muscle cramping. Of these 13 horses, three were donated to UC Davis, and the remainder were evaluated by other veterinarians. Nine of 13 horses were found to have other neuromuscular diseases unrelated to HYPP, including exertional rhabdomyolysis or "tying-up," myotonic

dystrophy, polysaccharide storage myopathy and epilepsy. Four horses had a history of localized painful muscle cramping which occurred episodically, similar to HYPP, and muscle damage was not evident on biopsy. None of these horses had episodes of paralysis. Muscle samples from four of these horses were sent to Dr. Eric Hoffman and Dr. Dietrich Stephan for sodium channel sequencing. The normal horse sodium channel gene has been sequenced and submitted to GenBank (an international computer database for gene sequences of all organisms). We found no other mutations which alter the amino acid sequence of the alpha-subunit of the skeletal muscle sodium channel. Thus, we can exclude this gene as causing the symptoms observed in these few horses, and we now have the capability to screen other horses in the future for sodium channel mutations.

### **Causes of variable expression of clinical symptomatology**

#### **Homozygosity for the HYPP mutation**

There appears to be a wide range of clinical severity of disease among different horses carrying the same mutation, ranging from asymptomatic (no evidence of disease is observed by their owners) to those horses requiring medication on a daily basis to control episodes. Often, episodes are accompanied by increased respiratory rate and noisy breathing. The homozygote affected horse (carries both copies of the gene mutation, or H/H) displays more severe clinical symptoms and will exhibit noisy breathing even when not experiencing an episode of paralysis. Data were gathered on homozygote affected animals to further characterize this condition. A manuscript describing the findings in 69 homozygous affected horses has been submitted to the *Journal of the American Veterinary Medical Association*.

Both sire and dam of all homozygous horses were descendants of Impressive. The age of horses ranged from one month to seven years. Clinical episodes of muscle weakness or paralysis varied widely in severity of symptoms and frequency of episodes. Sixty-one of 67 horses were considered by their owners to display more prominent musculature than herdmates. Sixty-three of 68 (93 percent) of the horses were reported to have respiratory stridor or abnormal respiratory noise, which was associat-

ed with exercise, excitement, stress or episodes of muscle paralysis. Endoscopic evaluation of the upper airway or throat revealed upper airway obstruction resulting from spasms or paralysis of the muscles of the larynx and pharynx. Twenty-seven of 61 horses (44 percent) were receiving acetazolamide (2.2 mg/kg orally, every 12 hours) for control of respiratory noise and episodes of muscle paralysis. Sixty-four of 69 horses were still alive at the time of the survey, and of the five horses that were reported dead, four died or were euthanized due to problems related with breathing difficulty or recurring episodes of paralysis.

In summary, the homozygote (H/H) appears to be more severely affected than the heterozygote (N/H), as these horses show more pronounced myotonia (muscle spasms) and intermittent upper airway obstruction even between episodes of paralysis. Therapy with acetazolamide is felt to lessen clinical symptoms of disease in the homozygote.

#### **Horses with more severe clinical symptoms have a higher proportion of mutant sodium channels in skeletal muscle**

To investigate the causes for variation in clinical severity, samples from 28 horses of varied clinical severity were assayed for the proportion of mutant to normal mRNA in gluteal muscle samples. An assay was developed which quantifies the relative amounts of normal and mutant sodium channel gene expression in horse muscles. The muscle samples were provided from research horses from Dr. Spier and Dr. Jill Beech of the University of Pennsylvania. The assays were performed by Dr. Jianhua Zhou and Dr. Eric Hoffman of the University of Pittsburgh.

The results from this study were published in the journal, *Human Molecular Genetics*, 1994, Vol. 3, pages 1599-1603, entitled "Pathophysiology of sodium channelopathies: correlation of normal/mutant mRNA ratios with clinical phenotype in dominantly inherited periodic paralysis."

Horses that had more severe clinical symptoms were found to have a very small, but significantly higher proportion of mutant sodium channels in skeletal muscle biopsies than horses which were asymptomatic. The finding of fewer mutant sodium channels in skeletal muscle from asymptomatic horses is interesting, but should be considered tentative as there was considerable overlap of values between individ-

ual horses. The classification of severity of clinical signs and frequency of episodes is difficult as horses may experience episodes which are not witnessed. Nonetheless, these findings may reflect differences in the expression of the normal sodium channel gene or may indicate that unlinked genes modulate the expression or stability of the mutant mRNA or protein.

Environmental factors including dietary changes, fasting, general anesthesia, concurrent illness and exercise restriction may precipitate episodes of paralysis. It is our opinion that management factors remain an important cause for variation in clinical symptomatology among affected horses.

### **Fiber type distribution and mean fiber diameter in horses with HYPP**

It is subjectively well-recognized that many horses with HYPP have well-developed muscles, a desirable trait in the halter horse arena. It is possible that horses with HYPP were selected as breeding animals because the gene mutation had a direct effect on the size of muscle cells, also called muscle fibers. It has been hypothesized that the continuous electrical depolarizations that occur with HYPP may have a "weight training"-like effect on the muscle cells, causing them to hypertrophy or enlarge in size. It was suggested that horses with very large muscle fibers may be more severely affected with the disease. Large fiber diameter could affect the regulation of potassium across cell membranes. We examined these possibilities by measuring the percentage of slow-twitch type 1 and fast-twitch type 2 fibers in normal and HYPP horses, as well as the cross-sectional area of the fiber types. Gluteal muscle biopsies were analyzed for fiber type distribution (slow-twitch and fast-twitch) as well as mean fiber area (as a measure of muscle bulk) to see if these factors are associated with clinical severity. This study was performed by Dr. Stephanie Valberg on biopsies provided by Dr. Spier. Five normal Quarter Horses and nine horses heterozygous for HYPP were used for this study. The affected horses were classified as asymptomatic, mildly affected or moderately affected, based upon frequency of episodes of muscle tremors or collapse. Muscle biopsies of the middle gluteal muscle were obtained using a percutaneous needle biopsy. All samples were aligned in cross-section and frozen in isopentane suspended in liquid nitrogen. Myosin adenosine triphosphatase (ATPase) staining

was performed to distinguish fiber typing. The cross-sectional area of 25 fibers was measured for both fast-twitch and slow-twitch fibers and compared among normal and affected horses. Our results showed that the percentage of fast- and slow-twitch fibers was very similar between normal and HYPP horses. The muscle fiber sizes for HYPP horses were not larger than normal horses. In fact, the HYPP horse muscle fibers were actually slightly smaller than normal horses. Subjectively, both the normal and HYPP groups had individuals with pronounced muscle development. The larger muscled horses in each group did not have the largest muscle fiber sizes. It seems clear, therefore, that the heavy muscling in these animals is related more to possessing more muscle fibers in a given muscle than having large-sized muscle fibers (or cells) and is probably regulated by a separate series of genes. A study performed by Jonathan M. Naylor, which was published in the *Journal of the American Veterinary Medical Association*, Volume 204, Number 6, March 15, 1994, pages 926-928, showed evidence for selection of HYPP-affected horses as superior halter horses by show judges. As their muscle fiber diameter is not larger, it is speculated that they may have increased tone to the muscle as a result of the spontaneous activity which can be demonstrated by electromyography. There were no significant associations between muscle fiber size or fiber typing and clinical severity or symptoms of HYPP.

### **Exercise testing of horses with HYPP**

Many owners of affected horses ride in performance classes or for pleasure or trail riding and have expressed concerns about a horse having an episode while under saddle. Episodes of weakness or paralysis are unpredictable. Studies were designed to collect data that would give insight into the events which initiate an episode in affected horses. The effects of exercise and treatment with acetazolamide were studied in horses performing standardized exercise tests. Nine horses (five affected N/H and four normal N/N) completed four exercise trials using a high-speed treadmill at both aerobic and anaerobic intensities; with or without the use of acetazolamide therapy at the currently recommended dosage (2.2 mg/kg orally, q 12 hours). The near maximal exercise test consisted of a warm-up followed by two minutes of strenuous galloping. The submaximal exercise test consisted of 30 minutes of slow trotting at

60 percent maximal effort as determined by measurements of heart rate. Considerable care was taken to ensure that the work effort between horses and between exercise tests remained constant.

All of the horses performed the treadmill exercise studies without episodes of paralysis. Of the five affected horses, three were clinically asymptomatic for HYPP according to past histories, yet symptoms of muscle fasciculation or paralysis were inducible by oral administration of potassium chloride. Two of the horses classified as "asymptomatic" exhibited generalized muscle fasciculation in the rest period ranging from 45 minutes to three hours following submaximal exercise (30 minutes of trotting). One affected horse showed only slight muscle tremors five minutes after the exercise stopped and the horse was walking to cool down. Interestingly, the two affected horses which were classified as moderately affected with HYPP, based upon a clinical history of multiple episodes of paralysis, exhibited no abnormal clinical signs associated with exercise.

Near-maximal exercise in horses is normally associated with marked hyperkalemia (potassium concentrations of 7-10 mEq/L; normal potassium 3-4 mEq/L) at maximal heart rates of approximately 200 beats per minute. Of great interest, no HYPP horses exhibited any difficulties with the near maximal exercise test, in spite of marked hyperkalemia (potassium concentrations of 7.7-9.8 mEq/L). It is postulated that increased circulating catecholamines offer a protective effect against muscle weakness.

From this study, we can advise owners of affected horses that the chances of a paralytic episode occurring while the horse is being exercised appears unlikely. However, we did observe episodes of muscle tremors in the rest period after exercise. We recommend that only persons experienced with the symptoms handle and ride affected horses, and to use caution if any abnormal clinical signs are observed. Acetazolamide therapy decreased the appearance of clinical signs following exercise in two of the three horses which had episodes of muscle tremors during the rest period.

**I**n summary, we conclude that the HYPP gene is infrequent among Quarter Horses and its occurrence is substantially linked to pedigrees tracing to a common sire. The gene test is highly accurate and consistently segregates with the disease in this pedigree. Clinical episodes of muscle weakness or paralysis varied widely in severity of symptoms and frequency of episodes. The causes for variation in clinical symptomatology are multifactorial and include homozygosity for HYPP (H/H), diet and management factors and increased proportion of mutant sodium channels in some heterozygous (N/H) individuals.

Because the Impressive pedigree is so large (more than 100,000 horses), we are actually dealing with a population of horses rather than a family at this time. Other neuromuscular disorders which may have symptoms which overlap with the symptoms of HYPP (such as tying-up or other electrolyte disorders) can be observed in any horse (in this pedigree or others) and require a veterinary examination and diagnosis. No additional mutations of the sodium channel gene have been identified at this time. With the availability of an accurate gene test that allows breeders to select stock free from the gene, it is hopeful that the gene frequency will decrease among breeding stock during the next decade.

We still spend a considerable amount of time on the telephone with equine veterinarians and horse breeders, providing advice and genetic counseling. Our laboratory has distributed large volumes of literature, mostly in the form of scientific reprints in reply to numerous requests for information, ranging from science fair projects to graduate studies in molecular genetics, veterinary institutions and other members of the horse industry who seek education about this important equine disease. ♣

# HYPP

## Questions and Answers

**A**n interview with Dr. Sharon Spler, University of California at Davis, Department of Medicine and Epidemiology. Dr. Spler personally answers a few questions which might be of interest to horsemen.

### **Did Impressive's ancestors pass along HYPP to him?**

We are unable to answer this question because there are no living ancestors to test and we have no genetic material from these horses to test.

### **Why are most horses tested heterozygous rather than homozygous?**

This genetic disease is inherited as a dominant trait, which means that only one copy of the mutated gene must be inherited to possess the disease. Fifty percent of all offspring of heterozygotes will possess the disease. The mating of two heterozygotes will produce 25 percent homozygous-affected foals, 50 percent affected and 25 percent homozygous normal.

### **Isn't there a proportionately greater number of heterozygotes tested than homozygotes — proportionately meaning greater than what the statistics would indicate would exist within the population?**

There is a higher than expected number of heterozygotes in this pedigree. Theoretically, if breeding stock were selected at random with respect to HYPP, the gene frequency would decrease with each generation. The high frequency of HYPP positive that we found in our research suggests that more affected horses were maintained as breeding stock than normal horses. The most likely reason is that the trait has been selected for by breeders seeking phenotypic characteristics which may be linked to this gene.

### **Is there any relation between the number of times Impressive traces to one particular stallion**

### **[Three Bars (TB)] and this — or any — genetic mutation?**

No, there does not appear to be any association.

### **How would you respond to someone who said a horse had to be HYPP-positive to win at halter?**

We were curious as to what effect the gene would have on muscle mass, which is just one of the qualities that are selected for in halter horses. We studied muscle cell (muscle fiber) diameter and muscle fiber type distribution (slow twitch and fast twitch fibers) in HYPP positive and negative horses. We found no relationship between large muscle diameter and the gene mutation. There was no difference in muscle fiber types between HYPP-positive and HYPP-negative horses. While there may be some other effect the mutation has on the appearance of muscle that we could not measure (for example, an increase in muscle tone), the appearance of heavy muscling is regulated by a separate group of genes.

Impressive had numerous qualities, including excellent conformation, which gave him tremendous success in the halter ring. The DNA test allows breeders to preserve the other qualities of this bloodline yet select away from the genetic disease. Decreasing the incidence of HYPP is important for the long-term health of the Quarter Horse breed.

### **If a horse is HYPP-positive, but is asymptomatic, does it lower the chances of its offspring being HYPP-positive?**

No, the gene mutation is identical for those horses that are asymptomatic and those horses that require medication to control symptoms. The expression of clinical symptoms is quite variable, which is identical to what occurs in humans with HYPP and

*HYPP is the first equine disease which can be identified by a DNA test, but it will certainly not be the last.*

occurs with many other genetic diseases. Unfortunately, offspring of asymptomatic HYPP-positive horses have just as high a chance of inheriting the gene (50:50 chance) and just as high a chance of showing clinical symptoms as other offspring of HYPP-positive horses.

### **What other equine health problems could conceivably have a genetic link?**

There are numerous other equine health problems with a probable genetic basis. Many conditions are under intensive study in hopes to identify the casual genes. HYPP is the first equine disease which can be identified by a DNA test, but it will certainly not be the last. Some examples of other inherited defects of horses include parrot mouth, lethal white syndrome, combined immunodeficiency, cerebellar abiotrophy, epitheliogenesis imperfecta, hyperelastosis cutis, degenerative suspensory ligament desmitis, recurrent uveitis, polysaccharide storage myopathy, osteochondrosis and limb deformities.

### **Do you personally feel additional research on HYPP is needed?**

HYPP is just one of the many problems that can plague our horses. Research on other diseases of muscles is ongoing and needs additional support. Colic and laminitis remain the leading causes of death in horses and are major areas of research. While there are still many unanswered questions about HYPP, we do know a great deal. We know how to treat the symptoms and can control the disease in horses very well. We now have a useful tool to prevent the disease in future generations. Personally, while I do not wish to down-play other work that is being done with this disease, I feel that some of these questions are more of an academic interest only.

## **Glossary**

### **Sodium channel**

A membrane "pore" or channel in the muscle membrane which opens and closes allowing for exchange of the electrolyte sodium from outside to inside of the muscle cell. Proper function of the sodium channel is vital for electrical activity and contraction of the muscle fibers. There are two parts to the sodium channel, the larger alpha-subunit and the beta subunit. The HYPP mutation causes a change in the protein structure of the alpha-subunit.

### **Allele**

One copy of a pair of genes located at the same location in paired chromosomes. One allele is inherited from the sire, and one from the dam, for each gene.

### **Heterozygote**

An individual possessing different alleles for a given gene or trait. For example, the classification N/H is given to horses which contain one normal sodium channel allele and one altered allele.

### **Homozygote**

An individual possessing identical alleles for a given gene or trait. A horse may be homozygous normal as in the classification N/N, or homozygous affected H/H.

### **Myotonia**

Increased muscle irritability which results in sustained muscle contraction or delayed muscle relaxation. A muscle cramp or spasm where the muscle fails to relax normally.

### **mRNA**

Messenger RNA is the intermediate template providing the code to assemble amino acids into proteins.

# Current Facts about hyperkalemic periodic paralysis (HYPP)

A series of questions and answers released by the University of California, Davis

by Dr. Sharon J. Spier, DVM, PhD

Reprinted from The Quarter Horse Journal, April 1993

*Clinical signs of HYPP do vary widely among different horses.*

## What is HYPP?

Hyperkalemic Periodic Paralysis (HYPP) is a muscular disease that affects both horses and humans. It is caused by a hereditary genetic defect that disrupts a protein called a sodium ion channel, a tiny gateway in the membrane of muscle cells. The genetic defect disrupts the channel's normal opening and closing, such that uncontrolled sodium influxes occur. These influxes in turn change the voltage current of muscle cells, causing uncontrolled muscle twitching or profound muscle weakness. High levels of potassium in the blood usually are present when the disruptions in the ion channel occur.

## What are the effects of HYPP?

Horses with HYPP can experience unpredictable attacks of paralysis which, in severe cases, can lead to collapse and sudden death. The cause of death usually is cardiac arrest and/or respiratory failure. The disease is characterized by intermittent episodes of muscle tremors manifested by generalized or localized shaking, trembling and weakness. Occasionally, episodes are accompanied by respiratory noises resulting from paralysis of the muscles of the upper airway (larynx and pharynx). In cases of mild attacks, muscle tremors may be so subtle as to be detectable only by an experienced clinician performing EMG testing.

## Can symptoms of HYPP vary in severity?

Clinical signs of HYPP do vary widely among different horses. Homozygous horses are affected more severely than heterozygous horses. Under ideal management practices, the defective gene does not appear to have adverse effects, but stress and/or increased potassium in the serum can trigger clinical signs of muscle dysfunction. Why some horses manifest severe signs of the disease and others exhibit little or no signs is unknown, but currently under investigation. Unfortunately, a horse carrying the defective gene, but showing minimal signs, has the same chance of passing the gene to future generations as does the affected horse with severe signs.

## What is the origin of the genetic defect causing HYPP?

The original genetic defect causing HYPP was a natural mutation that occurred as part of the evolutionary process. The majority of such mutations, which are constantly occurring, are not compatible with survival. However, the genetic mutation causing

HYPP produced a functional, yet altered, sodium ion channel. This gene mutation is not a product of inbreeding. The gene mutation causing HYPP inadvertently became widespread when breeders sought to produce horses with heavy musculature.

## Is HYPP limited to a particular bloodline of horses?

HYPP is associated with horses of heavy musculature, but this does not mean that all horses with well-developed musculature are affiliated with the disease. The mutant gene causing HYPP presently has been identified in the descendants of the horse Impressive. Research has not yet been performed on other bloodlines to ascertain whether the same or similar genetic mutation existing in other bloodlines also may cause HYPP. Since Impressive descendants are so numerous, the genetic mutation in this bloodline is widespread. Theoretically, it is possible that other mutations causing HYPP in different bloodlines may be more difficult to identify because they are not so wide-spread.

HYPP is unique in that it is the first equine disease in which breeding and molecular genetics have yielded a specific genetic mutation identifiable with a named bloodline. It is only a matter of time before other heritable conditions in various bloodlines likewise can be identified.

## How is HYPP inherited in horses?

Based upon breeding trials conducted at the Equine Research Laboratory at the University of California at Davis, it was determined that HYPP is inherited as an autosomal dominant trait, which means it can occur in both males and females. The trait is inherited from generation to generation with equal frequency; it does not get "diluted" out. Breeding an affected heterozygous horse (N/H) to a normal horse (N/N) will result in approximately 50 percent normal offspring, while 50 percent will carry the defective gene (N/H). Breeding an affected homozygote (H/H) will result in all offspring carrying the gene mutation, regardless of the status of the other parent.

Normal (N/N) offspring can be safely bred without fear of HYPP being inherited. Selective breeding to normal (N/N) horses could entirely eliminate HYPP disease. As HYPP is inherited as a dominant condition, it can and is being spread to other breeds. It is to everyone's benefit to take the necessary steps to selectively breed HYPP out of existence before it becomes so widespread that this is impossible.

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## Can horses be tested for HYPP?

A DNA test now has been developed and presently is available at University of California at Davis to identify horses carrying the defective gene causing HYPP. This test detects the presence or absence of the specific genetic mutation which has been found in the extended pedigree of Impressive descendants. From a sample, a part of the gene coding for the horse muscle sodium channel is amplified, cut (using enzymes which cut specific DNA sequences), separated by electrophoresis, stained and read. Based on the number of DNA fragments observed, it can be determined whether the horse does not carry this specific mutation (a normal horse), or whether it carries one to two copies of this abnormal gene mutation (heterozygous or homozygous for HYPP, respectively).

## How accurate is the DNA test for HYPP?

The test is accurate and reliable based upon research studies. The presence of the genetic mutation has been found to be associated with the disease in more than 600 animals tested to date. In a prior publication (Nature Genetics 1992, Volume 2, p. 144-147), we reported upon our testing of 51 related horses which were diagnosed with HYPP based upon documented episodes of muscle fasciculations or paralysis not induced by exercise. All 51 horses were positive (for the sodium channel mutation) using this test. An equal number of related horses which were determined to be normal (based upon potassium challenge and/or free clinical signs of muscle disease) were negative for the gene mutation. We also tested 130 horses from five different breeds to determine if the mutation could be found with any frequency in the general horse population. The only horses to date which have shown the mutation have been descendants of Impressive but, theoretically, other mutations may exist for which we now have the tools to start looking. The test has proven to be repeatable, as we routinely re-run samples (every sixth sample is repeated as part of quality control) and we have not encountered any discrepancies in results following retesting.

## Are false negative or false positive HYPP test results possible?

“False” negatives: Of the 600 horses tested, we have encountered four horses which show various clinical signs of muscle disease but are negative for the specific gene mutation in the sodium channel. All are privately owned horses which we have been unable to study thoroughly. None of these horses have demonstrated increased blood potassium con-

centrations in association with abnormal clinical signs. Two of these horses had markedly high muscle enzyme measurements, and one horse had marked muscle damage evident on muscle biopsy. We feel at this time that these horses probably have another muscle disease and not HYPP. We are sequencing the sodium channel for these four horses to determine if a second mutation actually exists.

“False” positives: We have not identified any horses which carry the gene mutation and do not carry the disease. Of 142 samples we have received accompanied by clinical information, approximately 10 percent of the positive horses have not shown abnormal clinical signs (according to their owners). All have been young horses (age four or less). None of these horses have tested negative by other means (such as response to potassium challenge or electromyography).

No diagnostic test is 100 percent accurate. Errors feasibly could occur by several means. If the test results conflict with clinical data, then it is possible that the sample was mislabeled, or mishandled in the laboratory. Retesting should be performed. However, based on the results to date, we can say with confidence that the presence of the mutation is the cause of HYPP, and the test is accurate and reliable. The test is extremely specific, and is accurate for the gene sequence substitution which has been shown to cause HYPP in descendants of Impressive. Theoretically, it is feasible that a different horse bloodline could have a mutation in another portion of the sodium channel which might produce a similar form of muscle disease and not be detected by this test. If this occurs, careful documentation of the clinical signs and corresponding laboratory results (including serum potassium and muscle-derived enzyme concentrations) should be used to confirm the diagnosis.

## Which horses should be tested for HYPP?

As noted above, the DNA test for HYPP identifies the specific genetic mutation which we now know exists in descendants of Impressive. We presently do not know whether different genetic mutations in other bloodlines also cause HYPP, and the DNA test will not identify other such mutations. Further scientific research is required as to other bloodlines. We presently recommend that all descendants of Impressive be tested for diagnostic, treatment and breeding purposes.

## Are HYPP test results confidential?

Test results are treated as confidential at our facility. We notify owners or veterinarians (who request the test) of the results by mail.

*A DNA test now has been developed and presently is available... to identify horses carrying the defective gene causing HYPP.*



***HYPP in horses can be managed, and incidents of mortality significantly reduced, by proper diet and the administration of medication.***

## **Do horses outgrow HYPP?**

No, an affected horse is affected for life, but symptomatology does seem to decrease with age. The disease also appears to be associated with periods of stress, transport, concurrent diseases, initiation of training or intensive training, and dietary changes. It is possible that older horses do not experience the same degree of stress as young horses (i.e., they are not subject to the rigorous show schedules of younger horses, and their owners have discovered the best diet and management routines for these older horses).

## **Can effective treatment be rendered to HYPP afflicted horses?**

HYPP in horses can be managed, and incidents of mortality significantly reduced, by proper diet and the administration of medication. While further studies on the mortality rate of HYPP are required, it is important to put HYPP into perspective relative to the many other conditions afflicting horses. Horses afflicted with HYPP, if properly managed, can lead productive, useful lives, and bring their owners many hours of pleasure.

The first step towards effectively managing HYPP is to have the disease properly diagnosed. It can be confused with other conditions, such as “tying up.” It is essential that you consult with your veterinarian if you wish to ascertain whether your horse has HYPP. We recommend the DNA blood test as the most effective and reliable means of diagnosing HYPP.

## **What emergency treatment is recommended for acute attacks of HYPP?**

For a mild attack (when the horse is not down but has muscle tremors), one or more of the following emergency treatments are recommended:

- Exercise the horse, either by walking or lunging. Exercise stimulates adrenaline which helps replace potassium inside cells. However, use caution, as the horse could stumble and fall while sustaining muscle tremors.
- Feed grain (oats, dry corn-oats-barley or light Karo syrup for glucose supplement). Feeding carbohydrates supplies glucose which stimulates the release of insulin and promotes potassium uptake by cells.
- Administer acetazolamide orally (3 mg/kg). This is usually six to eight tablets if the tablets are 250 mg each. Acetazolamide increases potassium excretion from the kidney and also affects glucose metabolism.

For severe attacks, immediate veterinary attention is necessary. If the horse is down and unable to stand, have your veterinarian:

- Place intravenous (IV) catheter and administer 23 percent calcium gluconate (150 cc in one to two liters of five percent glucose/500 kg horse). The majority of horses respond immediately to this and stand up.
- If no response, follow with one L five percent sodium bicarbonate IV (dose is one meq/kg).
- Still no response, give three L five percent dextrose IV, and monitor potassium levels in blood.

All of these treatments help stabilize the muscle membranes and lower blood potassium. Your veterinarian should draw a blood sample prior to initiation of treatment in order to analyze the blood potassium and muscle enzyme concentrations. This is required to confirm that the horse was suffering an attack of HYPP and not something else (i.e., colic).

## **What management practices will help control HYPP?**

The following management practices will greatly assist in the control of HYPP:

- Establish a regular feeding and exercise schedule. Avoid fasting and water deprivation. Horses do better if allowed access to a paddock or pasture rather than strict stall confinement. Daily or nightly turnout is helpful.
- Adult horses do very well on grass or oat hay alone or pasture. If it is necessary to use alfalfa to balance the ration for growing horses, then mix alfalfa with grass hay or oat hay and grain (oats are best) to decrease potassium content of diet. Feed equal amounts of hay and grain two or three times daily. Avoid rapid changes in diet. Provide access to a white salt block or feed loose salt.
- Administer acetazolamide (Diamox), a diuretic (2 mg/kg orally twice a day). Many halter horse owners continue to feed alfalfa hay as the only roughage, but maintain their horses on this drug for all or most of their lives. Please note that this drug is a forbidden substance at horse shows under AQHA and AHSA regulations.
- Inform your veterinarian of HYPP condition prior to any general anesthesia, which may precipitate an episode of paralysis. Maintain acetazolamide therapy before and after surgery or anesthesia.
- Use common sense while hauling. Be sure to stop and water horses frequently (every two hours). Acetazolamide treatment is helpful to prevent problems.

## **What is AQHA's position on HYPP?**

AQHA recognizes that HYPP disease exists in the Quarter Horse breed and has contributed funds to our research to better understand its heritability

and to develop improved methods of diagnosis and control. The Association discussed HYPP at the 1993 AQHA Annual Convention and determined that AQHA will fund \$100,000 in additional research on HYPP, and continue to inform and educate AQHA members on the condition. In the future, the Association will determine what official policies, if any, will be adopted by the membership. Owners and breeders should possess all currently available facts about HYPP before making decisions about their breeding programs.

At this point in time, testing horses for HYPP is a voluntary procedure by concerned owners and breeders who wish to utilize the results to identify horses which may require dietary changes and medication, and to reduce the disease in subsequent generations. Important issues to be resolved by AQHA and its membership concerning HYPP include the development of blood test protocols; the promulgation of disclosure requirements for sellers, breeders and owners; regulations covering drugs (such as acetazolamide) used to control HYPP; foal registration requirements (if any); and related issues. Persons interested in these issues should contact AQHA.

#### **EDITOR'S NOTE:**

*Since the publication of this article in 1993, AQHA rules concerning the disclosure of HYPP have changed. Foals born on or after January 1, 1998, which descend from any bloodline determined to carry the HYPP gene will have the following notification placed on their registration certificate:*

*"This horse has an ancestor known to carry HYPP, designated under AQHA rules as a genetic defect. AQHA recommends testing to confirm presence or absence of this gene."*

*If the parent(s) tracing from the HYPP line tests negative for HYPP with an appropriate designation appearing on the registration certificate, the above notification is not required and will be substituted by the designation "N/N." In addition, once a foal has tested negative for the gene, owners can purchase a corrected registration certificate which substitutes the designation "N/N" for the notification.*

*Any foals required to be parentage verified before registration, who trace to bloodlines known to carry the HYPP gene, will be tested for the disease at the same time genetic testing is performed. The results will be designated on the registration certificate in lieu of the above notification. Beginning with the 2007 foals, all Impressive progeny are required to be parentage verified and HYPP tested subject to the conditions listed in rule 205. Any that test H/H will not be eligible for registration.*

**AQHA recognizes that HYPP disease exists in the Quarter Horse and has contributed funds to...better understand its heritability and to develop improved methods of diagnosis and control.**

## **HYPP: Another Look**

*Reprinted from The Quarter Horse Journal, May 1993*

During the past year, hyperkalemic periodic paralysis has become a major issue with the membership of the American Quarter Horse Association. The majority of the concern has centered around not knowing what the disease is or how it can be controlled. It was those same concerns that prompted the AQHA Research Committee, in 1989, to fund a project at the University of California, Davis. Another project on HYPP was funded in 1991, this one with the University of Pennsylvania.

The results of the University of California research project were printed in the September 1992 issue of *The Quarter Horse Journal*. During the next couple of months, concern, speculation and rumors about the condition abounded, prompting an official statement of position by AQHA. Published in the December issue of *The Quarter Horse Journal*, the statement noted that the disease affects only a small percentage of the

total horses registered by AQHA, and that it appeared to be limited to individuals from one bloodline. It also said that most of the individuals affected were bred for halter competition.

In the January 1993 issue of *The Quarter Horse Journal*, it was reported in "AQHA Update" that Dr. Sharon Spier of UC, Davis, had acknowledged that in her research, all horses found with the disease were descendants of the Quarter Horse stallion Impressive. Dr. Spier revealed the stallion's name while responding to questioning following a talk she presented on HYPP at the American Association of Equine Practitioners meeting on November 30, 1992.

Articles on HYPP have now appeared in every major horse publication, and in many daily newspapers, including the *New York Times*. Much of the information reported was in error, and has blown out of proportion the effect the

***Hyperkalemic periodic paralysis is a muscular disease caused by a hereditary genetic defect, which, simply put, affects the muscle cells' balance of sodium and potassium.***

disease is having on the American Quarter Horse breed. The Association has acknowledged the existence of HYPP and that so far the disease has been found only in one bloodline. However, at the 1993 AQHA Convention in March following a discussion with UC Davis', Dr. Spier, the Stud Book and Registration Committee felt that not enough was known about the disease for the Committee to make any recommendations either way, and asked the AQHA Executive Committee to fund further research into the disease at the University of California, Davis.

"It is important to put HYPP into perspective relative to the many other conditions affecting horses," said Dr. Spier. "Horses afflicted with HYPP, if properly managed, can lead productive, useful lives, and bring their owners many hours of pleasure."

### **What is Hyperkalemic Periodic Paralysis?**

Hyperkalemic periodic paralysis is a muscular disease caused by a hereditary genetic defect, which, simply put, affects the muscle cells' balance of sodium and potassium.

The genetic defect disrupts the normal opening and closing of a tiny passageway in the membrane of muscle cells, allowing sodium to flow in and potassium to flow out of the cell in an irregular manner. The influxes change the voltage current of muscle cells, causing uncontrolled muscle twitching or profound muscle weakness. High levels of potassium in the blood can be associated with an attack.

The genetic defect which causes HYPP was the result of a gene mutation. Gene mutations are constantly occurring, but the majority of those which prove to be detrimental to the species in which they occur are not compatible with survival. However, this mutation happened in an animal which was to become a popular type for halter competition, and it not only survived, it was continually reproduced.

In breeding trials at UC Davis, it was determined that HYPP is inherited as an autosomal dominant trait, which means that it is not sex-linked — it can occur in both males and females. The trait is inherited from generation to generation with equal frequency; it does not get "diluted" out.

Those carrying the defective gene are either heterozygous, which means that only one of the two sets of genes inherited from their parents is affected, or homozygous, where both sets of genes are affected. When a heterozygous individual is bred to a normal horse, approximately 50 percent

of the offspring will carry the defective gene. Breeding two heterozygous animals will result in 75 percent of the offspring being affected. One-fourth of the offspring of such a mating are homozygous for the defective gene, and one-fourth are normal.

Researchers at UC Davis have found only one percent of the horses they have tested to be homozygous affected. Breeding an affected homozygous animal will result in all offspring carrying the defective gene, regardless of the status of the other parent.

A DNA test is available at UC Davis, to identify horses carrying the defective gene. If a horse tests positive for the genetic mutation, the test will also determine whether it is heterozygous or homozygous. The foals from heterozygous matings that do not receive the defective gene can be bred without propagating HYPP. It is possible to totally eliminate HYPP resulting from this identified mutation by breeding only those individuals with negative blood tests. A similar condition exists in humans, where several different mutations have been found to cause the disease. The current test for horses is highly specific for one mutation which has been identified in association with HYPP.

### **Symptomatology of HYPP**

In most cases, symptoms of the disease include intermittent muscle tremors or twitching. In some instances, horses lose complete muscle control and collapse. Occasionally, episodes are accompanied by respiratory noises resulting from paralysis of the muscles of the larynx and pharynx.

In rare cases, death may occur, usually from cardiac arrest and/or respiratory failure.

Attacks of the disease may be associated with periods of stress, transportation, concurrent disease and training, or by a dietary change, in particular the ingestion of potassium in feed. Alfalfa hay is very high in potassium, as is molasses, a significant ingredient in most sweet feeds. High levels of potassium in the bloodstream are not only indicative of an attack of HYPP, but may also trigger attacks. Stress causes a release of potassium into the bloodstream, as does the ingestion of alfalfa or other feeds high in potassium.

### **Metabolic pathways of HYPP**

Hyperkalemic periodic paralysis is a muscular disease caused by a hereditary genetic defect which serves to disrupt the normal operation of the sodium ion channel in cells. The sodium ion channel is a tiny passageway in the membrane of muscle cells which controls the movement of sodium par-

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ticles in and out of the muscle cell.

There is normally a low concentration of sodium inside muscle cells, and a high concentration on the outside. This difference determines whether or not a muscle is relaxed or contracted. Naturally occurring electrical charges exist in all muscle cells, and sodium particles carry a charge that changes the voltage current of a muscle cell, allowing it to contract or relax. In horses affected with HYPP, the regulation of particles through the sodium channel occasionally fails, which disrupts the normal flow of ions in and out of the muscle cells. The result is uncontrollable muscle twitching or complete muscle weakness.

Potassium, too, plays a part in the defect. Every cell in the body contains potassium, as it is vital for maintaining the cells' volume and the "charge" in excitable tissues such as muscle cells. In an opposite relationship as that of sodium, the concentration of potassium on the inside of cells is much higher, up to 25 times, than on the outside. The "leaky" cell membranes in horses with HYPP, which allow sodium to pass through, also allow potassium to pass, resulting in a higher concentration of potassium in the blood than is normal.

Minor changes in voltage (depolarization) can occur due to increases in the potassium concentration outside of the cell, such as might occur following ingestion of large amounts of feed high in potassium - alfalfa hay for instance. As single muscle fibers depolarize, they communicate this charge to surrounding fibers, leading to visible muscle tremors. If enough fibers depolarize, muscle paralysis and collapse will occur. When the muscles depolarize, potassium from inside the muscle cells moves to the outside of the cells, leading to further increases in potassium concentration in the blood, which helps perpetuate the cycle.

### **If your horse has HYPP...**

"Having a positive test for the hyperkalemic periodic paralysis is not necessarily fatal," according to Dr. Spier. "HYPP in horses can be managed, and incidents of mortality significantly reduced, by proper diet and the administration of medication."

Mild attacks can normally be handled by the owner. Sometimes exercising the horse will cause the symptoms to disappear, and in other instances, the administration of acetazolamide, a mild diuretic that increases potassium excretion from the kidneys, will return the horse to normal. More serious attacks should be handled by veterinarians.

To be certain that the symptoms indicate the presence of HYPP, a veterinarian should draw a blood sample prior to initiation of treatment in order to analyze the blood potassium and muscle enzyme concentrations. Some cases

of colic have been confused with attacks of HYPP, and vice versa. According to Dr. Spier, "There may be some room for misdiagnosis, or over-diagnosis. Every horse that trembles or ties up does not have HYPP."

Owners with horses that have tested positive for the condition may want to have their horses on daily doses of acetazolamide as a preventative. They should be aware, however, that acetazolamide is a prohibited substance for any horse competing in an AQHA-approved event.

Several management practices may also help control the disease, including regular feeding schedules and continuous access to water. Horses on pasture do better than those confined to stalls, and rations should contain as little potassium as possible.

Roy Donn of Crosby Farms in Aubrey, Texas, has been dealing with HYPP since 1985, when a horse he had just purchased had an attack while being unloaded from a van. Since then he has handled a number of positive horses, and says that it does not pose too big of a problem.

"We have dealt with a lot of them and have never had one die," he said. "The reason is that if we see any symptom of HYPP, we start the horse on medication and never take him off of it."

Dr. Spier recommends a dosage of four to six 25-milligram acetazolamide tablets twice a day. Donn noted that for a large horse, he gives six tablets, twice a day, but that on some exceptionally large animals, he has given up to eight tablets.

"I don't think we've ever treated anything until after it was weaned," he said, "and very few of them. But you put them in a stressful situation and it will show up. With babies, we give two or three tablets, on up to six as they get older."

Donn says that he feeds his horses straight oats, which are low in potassium, but he also feeds alfalfa hay. He says that the acetazolamide controls the disease, even when the animals are on alfalfa.

### **What now?**

At the 1993 AQHA Convention in March, Dr. Spier appeared before the open session of the Stud Book and Registration Committee and answered numerous questions concerning HYPP. She also attended the closed meeting of the Committee, and pointed out that there were still a number of unanswered questions about the disease. The consensus of the Stud Book and Registration Committee was that further research was needed to better understand the disease, and perhaps, its control. At its April meeting, the AQHA Executive Committee approved the request for funding that research.

***"HYPP in horses can be managed, and incidents of mortality significantly reduced, by proper diet and administration of medication."***



**Several management practices may also help control the disease, including regular feeding schedules and continuous access to water.**

Dr. Spier said recently there were several areas that UC Davis was hoping to research, including trying to get as accurate a set of statistics as possible on the number of horses affected by the disease; why there are ranges in degree of severity of those affected, even among families; and why some horses appear to be asymptomatic, even though they have tested positive for the gene.

She said, "The disease is very complicated, because management, training and feed all play a big role in whether or not a horse shows symptoms."

Dr. Spier also noted that they were initiating a study on testing embryos and fetal cells for HYPP. That way, she said, if an embryo is determined to be positive, the owner has the option of aborting the mare and rebreeding her.

"We're also going to be looking at where the disease came from," she said. "No one here has ever said that the disease originated with Impressive, contrary to what has appeared in some of the media. All of the horses to date that we have found to have the disease did trace back to Impressive, but we are going to screen some related and non-related horses to see if we can find the condition existing in another bloodline. We hope to

screen at least 1,000 horses in this project."

Dr. Spier concluded by emphasizing that research takes time. It took years to find out what is now known, and any further discoveries will not happen overnight. However, if and when additional information is learned, it will be made available in order to allow owners the opportunity to make responsible decisions about their horses.

#### **EDITOR'S NOTE:**

*Since the publication of this article in 1993, researchers at the University of California, Davis, have completed a screen of 1,000 samples to test for HYPP gene frequency. The results from this research, as well as an update on other HYPP research, can be found in the article "HYPP: Someone else's problem" by Lesli Groves, which appears near the front of this brochure.*

*Since the publication of the articles appearing in this brochure, the preferred sample to perform an HYPP test at the University of California is a hair sample.*

## **For More Information...**

Many persons have requested a list of publications on HYPP. AQHA's official publications, including *The Quarter Horse Journal*, are excellent resources on issues affecting the American Quarter Horse breed and the industry. Subscription information can be found on the back cover of this brochure.

The following are publications/articles on equine hyperkalemic periodic paralysis:

- Cox, J.H., DeBowes, R.M. "Episodic weakness caused by hyperkalemic periodic paralysis in horses." *Comp Cont Educ Pract Vet (Equine)* 1990; 12:83-89.
- Naylor J.M., Robinson J.A., Bertone J. "Familial incidence of hyperkalemic periodic paralysis in Quarter Horses." *J Am Vet Med Assoc.* 1992; 3:340-343.
- Pickar J.G., Spier S.J., Snyder J.R., et al. "Altered ionic permeability in skeletal muscle from horses with hyperkalemic periodic paralysis." *Am J Physiol (Cell Physiol)* 1991; 260:C926-C933.
- Rudolf J.A., Spier S.J., Byrns G. Hoffman E.P. "Linkage of hyperkalemic periodic paralysis in Quarter Horses to the horse adult skeletal muscle sodium channel gene." *Animal Genetics* 1992, 23:241-250.
- Rudolf, J.A., Spier, S.J., Byrns, G. Et al. "Periodic paralysis in Quarter Horses: a sodium channel mutation disseminated by selective breeding." *Nature Genetics* 1992; 2:114-147.
- Spier S.J., Carlson, G.P. "Hyperkalemic periodic paralysis in certain registered Quarter Horses." *The Quarter Horse Journal*, September 1992, p.p. 68-69, 120.
- Spier, S.J. Carlson, G.P., Holliday, T.A, et al. "Hyperkalemic periodic paralysis in horses." *J Am Vet Med Association* 1990; 197:1009-1017.
- Steiss J.E., Naylor J.M. "Episodic muscle tremors in a Quarter Horse: Resemblance to hyperkalemic periodic paralysis." *Cn Vet J* 1986; 27:332-335.



## Funding for Equine Research Projects

Each year, the American Quarter Horse Association awards hundreds of thousands of dollars to college and university equine research programs to fund research that benefits all horses. That figure is a testament to the fact that AQHA is dedicated to a better understanding of the horse, as well as to his future enjoyment by everyone.

AQHA represents more than 332,000 Members and some one million owners of American Quarter Horses worldwide. With a registry of more than 4 million American Quarter Horses, AQHA recognizes the need for practical equine research and increased knowledge of equine health care and treatment.

AQHA's Equine Research Committee was founded in 1960 and comprises leading American Quarter Horse breeders, veterinarians and individuals well grounded in equine research methods. Each year this committee reviews specific research funding requests from many colleges and universities, selecting the most promising and appropriate projects to fund. Since 1960 AQHA has awarded more than \$4.5 million in research funds.

## What type of Equine Research does AQHA support?

For funding consideration AQHA places a premium on research projects that address problems of prime importance to the general horse population and to those people involved in the day-to-day management of horses. While any research that leads to a better understanding of equine disorders, diseases or nutrition can be beneficial, AQHA most readily supports research that addresses areas of primary relevance to the most common equine management issues and concerns.

## AQHA research priority lists:

- Diagnosis and treatment of acute gastro-intestinal disorders (colic, etc.)
- Diagnosis and treatment of musculoskeletal defects of nutritional origin (OCD, epiphysitis, etc.)
- Diagnosis and treatment of reproductive disorders (endometritis, etc.)
- Immunization of foals
- Diagnosis and treatment of infectious diseases of the gastro-intestinal tract (potomac fever, salmonella, etc.)
- Diagnosis and treatment of respiratory diseases (bleeders, pneumonia, etc.)
- Vesicular Stomatitis Virus (VSV)
- Equine Protozoal Myeloencephalitis (EPM)

This list indicates types of research projects of significant importance to horse owners and their priority in AQHA funding support. The research areas indicated on the list are only guidelines to the type of research AQHA feels is of most benefit and does not preclude the possibility that the AQHA Equine Research Committee would recommend approval of funding for any worthwhile areas of research.

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