Furosemide, the Prevention of Epistaxis and Related Considerations: A Preliminary Evaluation

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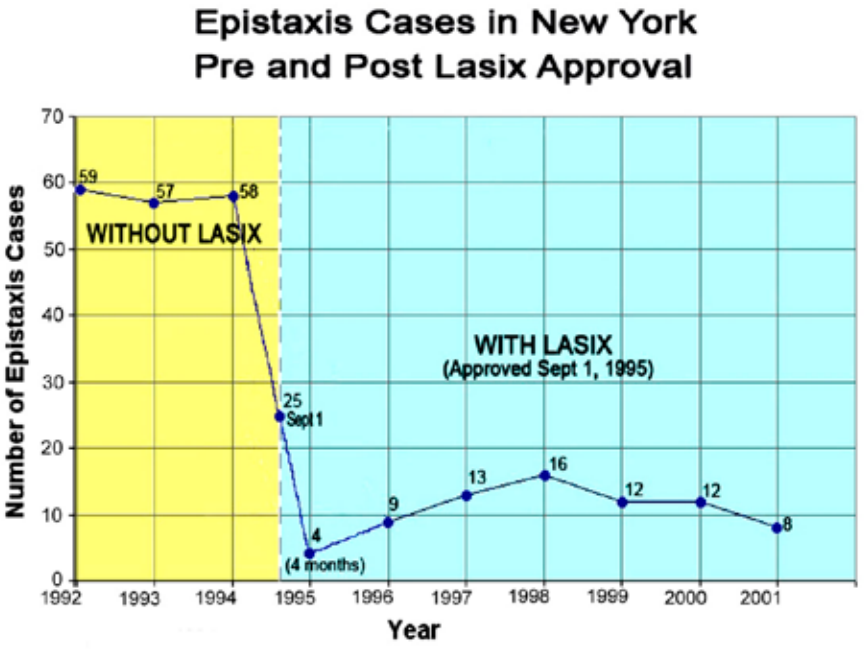
ABSTRACT

Furosemide is widely approved in the United States, Canada and elsewhere in the Americas for the prevention of Exercise Induced Pulmonary Hemorrhage [EIPH]. We review the scientific evidence for the efficacy of furosemide in reduction/ prevention of EIPH, including, presumably, EIPH related acute/sudden death in racing horses. We present evidence from the scientific literature and our own experience, clinical and otherwise [RHG, AMB, DVL, and TT], that EIPH driven acute/sudden death in racing horses has significant adverse health consequences for horses and jockeys. We then outline the adverse effects on equine and human [jockey] health and welfare to be expected when furosemide is not approved for use in racing horses or, where approved, if approval is withdrawn.

FINDINGS

Epistaxis, ie, bleeding from the nose in racing horses, has been observed by horsemen since at least the seventeenth century. [1] In the late 1960s, injectable furosemide (Lasix, Salix) became available in the United States and soon thereafter furosemide was

Figure 1 *Effect of Furosemide on Epistaxis Cases/Year in New York Racing*



being used in the prevention of epistaxis. This initial use of furosemide was based on clinical experience and, until recently, there was little scientific evidence concerning its efficacy in the prevention of epistaxis. On the other hand, most American racing states have long since approved the use of furosemide on race day for the prevention/alleviation of epistaxis, now known to be a component of Exercise-Induced Pulmonary Hemorrhage [EIPH]. Very recently, however, questions have been raised about whether or not the routine pre-race treatment of racing horses with furosemide for the prevention of epistaxis/EIPH passes "the smell test,"[2] which has led to renewed examination of the scientific basis for the pre-race use of furosemide in North American racing.

We now draw attention to some clinical evidence establishing, in large numbers of racing horses, the efficacy of furosemide in reducing the incidence of epistaxis. These data were first communicated by Mr. Bill Heller in his monograph on Lasix, "Run, Baby, Run,"[3] where these data have remained hidden in plain sight since the 2002 publication of this book. Reviewing this book as part of an overall review of the literature on furosemide in the horse, we noted, on pages 112 and 113, a table entitled "New York By The Numbers, Cases of Epistaxis," dated 1992 to 2001. Inspection of these data immediately clarifies the dramatic reduction in the incidence of EIPH in New York racing following the 1995 approval of furosemide. We now present this data in standard graphical format (Fig 1), which clarifies the remarkable efficacy of furosemide in reducing the incidence of epistaxis in horses racing in New York in the 6 years and 4 months immediately following approval of furosemide in New York racing.

In analyzing these data we note the following facts. The first is that epistaxis is, by definition, clearly observable bleeding ("dripping of blood") from the nose, sometimes defined as from both nostrils. Epistaxis is, however, only one manifestation of what is now known as Exercise-Induced Pulmonary Hemorrhage (EIPH).[4] It is also the only manifestation of EIPH observable without special equipment, and

as such, epistaxis has long been recorded in performance horses.[1,4] Epistaxis is thus the historical "low tech" manifestation of EIPH, with acute sudden death due to EIPH, only recently recognized by science, representing the most severe clinical outcome of this disease.[5 6,7]

All manifestations of EIPH other than epistaxis, including acute/sudden death due to EIPH, require scientific tools and expertise to identify as being EIPH related. [5] As such, the data represented in figure 1 reflect directly on the second most severe manifestation of EIPH, namely epistaxis, and these results speak directly and very compellingly to the efficacy of furosemide in reducing the incidence of both epistaxis and presumably the entire EIPH syndrome in all its various manifestations. The solid circles (O--O) show the total number of epistaxis cases in the previous 12 months of New York racing for 1992 to 2001, inclusive. Furosemide was approved in New York on Sept. 1, 1995, so the 1995 figures are split, with the number 25 representing cases prior to Sept. 1, and the number 4 representing cases from Sept. 1 to Dec. 31, 1995. The annual mean rate of EIPH cases prior to 1994 was 58 per year, and post Sept. 1, 1995, 11.6 per year. These data show that approval of furosemide for use in New York was associated with an immediate and well maintained essentially 80% reduction in the incidence of epistaxis in New York Racing. Data re-plotted from Heller, "Run, Baby, Run," 2002.[3]

With respect to the New York data, review of figure 1 shows that for the years 1992, 1993, and 1994 the numbers of epistaxis cases reported in New York racing were, respectively, 59, 57, and 58, a consistent average of about 58 epistaxis cases per year, which equates to approximately one case per week prior to approval of furosemide. Then, on September 1st, 1995, furosemide was approved for use in New York racing, and the number of epistaxis cases dropped immediately, to a total of 4 cases for the 4 remaining months, September to December, inclusive. In the following year, 1996, the total number of epistaxis cases was 9, followed by 13 in 1997, 16 in 1998, and 12 each in 1999 and 2000, and then a total of 8 cases in 2001, by which time the proportion of horses racing on furosemide in New York had increased to 88.3%. Overall, therefore, in the six calendar years starting on January 1, 1996 and continuing to December 31, 2001, there were a total of 70 epistaxis cases over 6 years, for an average of 11.6 epistaxis cases per year during the first 6 years of furosemide approval in New York.

We also note that this rate of about 11.6 cases of epistaxis per year was remarkably consistent, in that in the last 4 months of 1995, September 1st, 1995 to December 31st, 1995, the first 4 months during which New York raced on Lasix/Salix, there was a total of four cases of epistaxis reported, completely consistent with the subsequent overall average of 11.6 epistaxis cases per year for the following 6 years.

These data are very compelling, and the conclusion to be drawn is that approval of furosemide in racing horses in New York immediately, and we emphasize the word immediately, reduced the incidence of epistaxis by almost 80%. The effect was immediate because it was apparent within the first month of approval of furosemide, and the incidence of epistaxis remained, on average, at essentially the same reduced level in New York racing, 11.6 cases per year, or approximately one case per month, over the following six calendar years. We also note that this reduced rate of epistaxis represents a close to 80% reduction from the baseline 1992-1994 rate of approaching five epistaxis cases per month prior to the regulatory approval of furosemide for use in New York racing.

An unusual aspect of these data is that they have to our knowledge remained unrecognized in the scientific literature. New York was the last major U S racing state to permit use of furosemide, and as such, there was a clearly defined time point after which furosemide was permitted for use in New York. Given the reluctance of the authori-

ties to approve the use of furosemide in New York racing, it may be understandable that these data were not reported earlier. In any event, it is clear from these data that in the actual racing situation, furosemide is remarkably effective in reducing the incidence of epistaxis, and it would have been helpful if these data had been communicated earlier in the scientific literature.

The second point of interest is that these New York data almost certainly underestimate the true efficacy of furosemide in preventing epistaxis. Because New York did not allow the use of furosemide in racing horses, any New York area horses with a propensity to bleed were more likely to race in neighboring jurisdictions that permitted furosemide. Additionally, since EIPH is associated with reduced racing performance, this provided further incentive for horses with any tendency to EIPH to race outside of New York. As such, it is reasonable to assume that the baseline epistaxis rate of 58 per year reported for 1992-1994 actually underestimates the true baseline incidence of epistaxis in North American racing, because horses known to be EIPH prone would tend to have been raced outside of New York. These data, compelling as they are, showing an almost 80% reduction in the incidence of epistaxis after the introduction of furosemide, almost certainly underestimate the true clinical efficacy of furosemide in reducing the incidence of epistaxis.

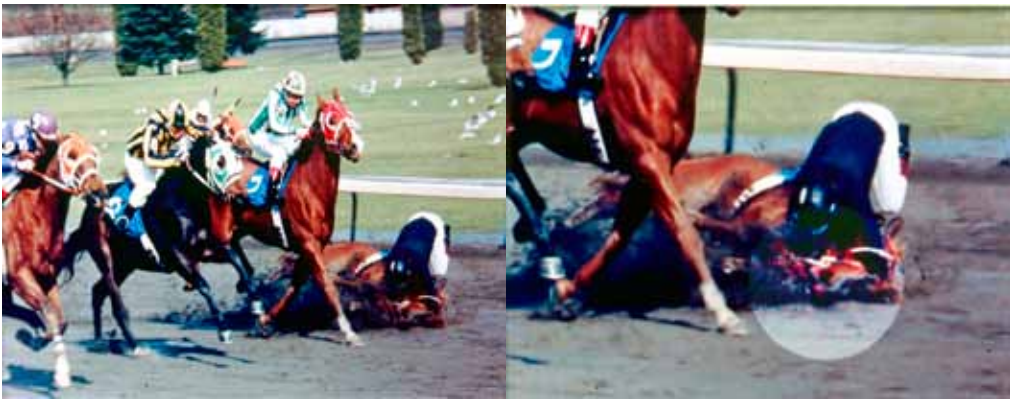
These data also speak to the lack of effective alternative therapies for epistaxis, non-race day therapies or otherwise.[8-10] Where use of furosemide in the prevention of epistaxis/EIPH is prohibited, the likelihood of use of alternative epistaxis prevention therapies increases. If we make the reasonable assumption that horsemen racing in New York were likely to use any legitimate alternative therapy for epistaxis available to them that did not contravene the rules of racing in New York, we must again assume that the 1992-1994 EIPH incidence figure represent the incidence of epistaxis in the presence of whatever alternative therapies were available to New York horsemen. Again, the demonstrated efficacy of furosemide likely represents the effect of furosemide over and above any possible baseline reducing effect of other available anti-epistaxis therapies.[11]

We must also note that the original clinical observations that furosemide reduced the incidence of epistaxis in racing horses were made in the late nineteen sixties and early nineteen seventies by equine veterinarians and horsemen soon after the introduction of injectable furosemide. These observations were made prior to the introduction of the fiberoptic endoscope and our resulting increased understanding of EIPH and its prevalence in racing horses. The observations reported here fully support these early insightful clinical observations and interpretations and the various decisions since then by equine veterinarians, horsemen and racing authorities to support the prerace use of furosemide in the prevention of epistaxis, as it was then understood, and the entire EIPH syndrome, as it is now understood. As such, these findings leave no reasonable room for doubt that furosemide will also reduce the incidence of acute/sudden deaths during racing due to EIPH.

As well as the data reported here, it is also appropriate for us to acknowledge the recent (2009) highly significant contribution by Hinchcliff, Morley, and Guthrie in this area.[12] These workers performed a classic randomized, blinded, placebo-controlled crossover study on the efficacy of furosemide in preventing EIPH in racing horses. This study established that pretreatment with furosemide reduced the incidence of EIPH in 167 thoroughbred horses under simulated racing conditions at Vaal Racecourse, Johannesburg, South Africa, at, we might note, an altitude of 4,671 ft.

While this study provides strong experimental evidence that pretreatment with furosemide reduces the intensity of EIPH in horses under racing conditions in South Africa, this study did not directly address the efficacy of furosemide in reducing the incidence of epistaxis. We respectfully sug-

Figures 2a and 2b: *Acute/Sudden Death due to EIPH as an Equine and Jockey Safety Hazard*



These photographs record an acute/sudden death EIPH incident in U S Quarter Horse Racing. The horses were moving at approaching 50 mph; the far horse is crashing to the track associated with an acute/sudden EIPH event, and the jockey is being thrown onto the track. The close-up, figure 2b, highlights the blood in the horse's exhalation, consistent with these events being triggered by an acute/sudden EIPH episode. Centennial Racetrack in Littleton, Colorado, altitude 5,389 ft., photographs courtesy of Dr. Richard H. Galley, Willow Park, Texas.

gest that the New York data presented here provides further evidence that is fully supportive of the results obtained by Hinchcliff and his colleagues in their South African study, and extends the clinical efficacy of furosemide to the very effective prevention of epistaxis. Together these studies, as well as approaching 40 years of accumulated clinical experience make an extremely strong scientific case for the use of furosemide in the prevention/alleviation of the EIPH group of syndromes, including the propensity of EIPH to produce acute/sudden death in racing horses.[5,13-17]

Acute/sudden deaths during racing due to EIPH occur when the hemorrhage is sufficiently voluminous to acutely interfere with respiration/blood oxygenation, such that the horse collapses and dies acutely on the racetrack. Although acute/sudden death during racing due to EIPH has long been known to equine practitioners, more recent work has shown that acute/sudden death from EIPH can occur without blood being visible at the nostrils, as shown by the work of Gunson and her colleagues [1988] and others[5], Morales et al [7] and work from our group.[17] Based on this work, it is now very clear that one of the outcomes of EIPH is acute/sudden death of a horse during racing with no obvious external signs of epistaxis. Review of the relevant literature, including the 1988 paper by Gunson and coworkers suggests that in the U S such acute deaths during racing and training occur approximately once per 1,500 Thoroughbred races, and that a substantial proportion, approximately 60% of acute deaths during racing are due to EIPH.[5] As such, the data presented here suggests that pretreatment with furosemide is likely to reduce the instance of such EIPH related sudden deaths during racing by approximately 80%, a very significant contribution to equine and human safety in racing.

Furthermore, we must also note that the Gunson analysis almost certainly underestimates the true incidence of EIPH related acute deaths in racing horses, since this study was carried out after use of furosemide had been approved in Pennsylvania racing (personal communication, Dr. Corinne Sweeney to TT, July 2011). As such, a true estimate of the incidence of EIPH related acute/sudden deaths in racing horses under U S conditions in the absence of furosemide is likely to be substantially greater than the once per 1,500 thoroughbred races reported by Gunson and coworkers, with the expected EIPH related acute sudden deaths figure in the absence of furosemide being between

four and five fold greater, based on the data of figure 1.

With respect to the matter of equine and human safety, the question then becomes what is the incidence of equine and human deaths in racing caused by the EIPH driven acute/sudden death syndrome? At this point, we definitively know from the experience of four of us [RHG, AMB, DVL, and TT] that such EIPH related acute death events occur in racing horses, and that these events also carry clear and highly significant risks for jockeys. The incident represented in figures 2a and 2b occurred at Centennial Racetrack in Littleton, Colorado, in the early to mid 1970's, shortly prior to approval of furosemide for use in Quarter Horse Racing in Colorado. One of us, RHG, was the treating veterinarian. The photograph was taken as the horses reached the finish line and fortunately, as may happen in Quarter Horse racing, there were no horses directly behind the horse that went down. The jockey in question was slightly injured, but the horse did not survive the incident. This photograph therefore records a not an atypical EIPH related acute/sudden death event in Quarter Horse racing, which incident resulted in one equine death and, in this particular case, minor injuries to the jockey. The incident presented in figure 3 represents another EIPH related sudden death incident in racing, this time, in Thoroughbred racing at Ruidoso Downs, New Mexico, altitude 6,720 ft, in the mid 1980s. RHG was again the treating veterinarian and the horse in question was not treated with furosemide. In this particular incident, once the acute/sudden death horse went down, two following horses "went over" the "down' horse/jockey. The horse died on the racetrack, and the jockey sustained career ending injuries [RGH].

These photographic presentations emphasize that EIPH related acute/sudden deaths of horses on the racetrack are not infrequent occurrences, and when they do occur, they have immediate highly significant implications for the health and welfare of the horses and jockeys involved. Additionally, we must also keep in mind that when a horse goes down in a racing situation, there is always a statistical probability of following horses and jockeys becoming involved in the event, and this sequence of secondary events is more likely to occur in Thoroughbred than in Quarter Horse racing.

Figure 3: *EIPH related sudden death, Thoroughbred racehorse, Ruidoso Downs,NM, mid 1980s. Photograph courtesy of Dr. Richard H. Galley, Willow Park, Texas.*

These findings are in good agreement with the clinical experiences of two of us, Dr. A. Morales Briceño and Dr. Diana Villoria Leon, presented in detail elsewhere in their recently published work [2011].[7] Reporting on the incidence of EIPH related acute/sudden death in racing at "Hippodromo La Rinconada," the National Racecourse in Caracas, Venezuela, they recorded 23 cases of acute/sudden death due to/caused by EIPH. These diagnoses were confirmed by full diagnostic necropsies and toxicological examination for medications related to EIPH, which evaluations were performed on each individual animal over the 3- year period from 2008 to 2011, inclusive.

Over these 3 years at "Hippodromo La

Rinconada," there were a total of 44,928 starts, and this population of starters yielded 23 acute /sudden deaths that were on necropsy confirmed as being due to or caused by EIPH. This amounts to one EIPH related acute/sudden death per 1,953 starts. Additionally, we [AMB, DVL] noted the incidence of jockey injuries associated with these EIPH events, which involved 85% of the jockeys riding these horses. Based on this percentage jockey injury rate, there was one jockey injury from EIPH related acute/sudden death per 2,298 starts over this 3-year period of racing at La Rinconada. At this time, however, we have no data on the nature and severity of the injuries sustained by the jockeys involved in these EIPH related acute/sudden death incidents in Caracas.

This rate of acute/sudden deaths caused by EIPH in racing in Caracas is significantly higher than the rate reported by Gunson and co-workers, who estimated one EIPH related sudden death per 1,500 races, with 9 horse fields. On this basis, the Pennsylvania rate works out at about one EIPH driven acute/sudden death event per 13,500 starts. This approximately seven fold higher EIPH acute /sudden death rate in Caracas compared with the estimated rate in Pennsylvania is unexpectedly large, and the reasons for this difference are not immediately apparent.

One major difference between the Pennsylvania and Caracas racetracks is the higher altitude of the Caracas racetrack. This racetrack, La Rinconada, at about 2,950 feet above sea level, is elevated compared with Penn National racecourse, at an elevation of 459 feet, and Pennsylvania Park, at an elevation 36 ft. Similarly, Centennial Racetrack, Littleton, Colorado, is at an altitude 5,389 feet and Ruidoso Downs, New Mexico, is at an altitude of 6,720 feet, as noted in figs 2a and 2b and 3.

With respect to the effect of altitude, we note that the principal scientific report to date on the relationship between altitude and EIPH is that of Weideman et al [2003][18] who reported that in South Africa EIPH appeared to be more frequent at sea level than at higher altitudes. If this interpretation is correct it suggests that the altitude of the Vaal Racecourse, Johannesburg, South Africa, at 4,671 ft., made the Hinchcliff et al [12] demonstration of the preventative effect of lasix on EIPH more challenging than such a demonstration would have been at sea level. This interpretation is also consistent with the unusually small number of class 4 EIPH scores in the Hinchcliff data, as pointed out by a colleague in discussions on this matter. Additionally, as a further confounding factor in these EIPH acute/sudden death studies, we note the significant variability in pathological diagnoses on entire equines[16, 17] presumably due at least in part to the extremely large volume of equine tissue to be subjected to histopathological analysis during equine necropsies.

In summary, for reasons that are unclear, and apparently unrelated to altitude, thoroughbred horses racing in Caracas, Venezuela, show an unusually high incidence of EIPH associated acute/sudden deaths, about one EIPH associated acute/sudden deaths per 1,953 starts. This acute/sudden death rate is about six-fold the rate reported in the earlier Pennsylvania study, and the reason or reasons for these differences are not clear. The fact that racing at La Rinconada is at about 2,950 feet above sea level is considered by Weideman et al. to work against the apparent discrepancy, since he and his colleagues consider that altitude above sea level is associated with a reduced incidence of EIPH. We also note, however, that the concept of increased altitude reducing the rate of EIPH is not consistent with the clinical experience of veterinarians, including one of us [RGH], working in the Western United States, where racing takes place at attitudes of up to 6,720 feet at Ruidoso Downs, New Mexico. Unrelated to the role of altitude, however, is the hard reality that 85% of the jockeys involved in EIPH related acute/sudden death events in horses racing at La Rinconada suffered injury, and that although the extent and severity of these injuries are not available to us, at least one jockey in the

experience of one of us [RHG] suffered a career ending injury associated with acute/sudden death from EIPH [fig 3].

From the data of Gunson and her colleagues we can conservatively estimate the number of EIPH related acute/sudden death related events likely to occur in one year in American Thoroughbred racing. Based on their data, Gunson and their colleagues estimated about one EIPH related acute sudden death per 1,500 starts. Gunson reports nine horse fields, which works out at one EIPH related acute sudden death per 13,500 starts. There are about 417,492 plus thoroughbred racing starts per year in the United States, so this works out at about 31 acute/sudden-death EIPH related events /year in thoroughbred racing in the United States, on the assumption that furosemide is permitted. In the absence of furosemide, however, based on the data in figure 1, we may expect a four to five fold increase in the number of acute sudden-death EIPH related events, to around 155 events/year, or more than three per week.

Gunson also noted that 2 of her 9 reported EIPH cases were acute sudden death in not racing horses, so the final figure is about 120 acute sudden death cases in U S racing per year based on Gunson's data. However, what it is not possible to estimate at this time is the number and intensity of the jockey injuries likely to be associated with these 120 more or less EIPH related acute/sudden-death events in American racing per year in the absence of furosemide, although most of these injuries are likely to be highly significant for the actual individuals involved. [fig 3].

CONCLUSION

These scientific findings, therefore, have implications far beyond equine health and welfare. This is because while pretreatment of racing horses with furosemide serves to reduce the incidence of epistaxis and the various equine pulmonary syndromes associated with intense exercise and EIPH by about 80%, there is every reason to believe that furosemide also serves to reduce, again by about 80%, the incidence of EIPH driven acute/sudden death syndrome in horses in training and racing. By definition, such EIPH related acute/sudden death incidents have the potential to cause severe, including career ending [fig 3] and potentially fatal injuries to jockeys and others riding these horses. As such, the currently in place regulatory approval for use of furosemide in the prevention of EIPH related syndromes in racing horses has a very direct positive and ongoing protective effect on the health and safety of jockeys racing in the United States and elsewhere in the Americas.

Given these scientific realities, we respectfully suggest that it would be unethical and inappropriate, on humane grounds with respect to equine health and welfare, and also on humane and workplace safety grounds with respect to jockeys, for any entity to ban the use of furosemide in racing horses. This is because to do so would be to knowingly significantly increase the risk of serious injury or death for jockeys or others riding racing/performance horses. In sum, any move to disapprove or to withdraw approval for furosemide as an EIPH preventive in racing horses is, from review of the available scientific literature, a move that will immediately and directly increase the risk to life and limb for both the horses and jockeys involved in racing or any other equine event involving exercise sufficiently intense to induce pulmonary hemorrhage.

LIST OF ABBREVIATIONS

[EIPH] Exercise-Induced Pulmonary Hemorrhage

COMPETING INTERESTS

The authors declare no competing interests

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NOTE ADDED IN PROOF

With respect to the data of figure #1 re-plotted from Heller 2002, our attention has recently been drawn to an undated memorandum on the New York Racing Association (NYRA) letterhead of Dr. Anthony Verderosa, DVM, Chief Examining Veterinarian. In this memorandum Dr. Verderosa notes that his analysis of the data on the rates of epistaxis in New York racing for the years 1990 to 2000, that is before and after the introduction of furosemide, showed that the introduction of furosemide in 1995 produced a ">400% decrease" in post race Epistaxis ("Bleeders") EIPH. This is essentially the same conclusion that we drew from what are presumably the same data presented in the Heller book, and appear to fully and independently support our analysis and conclusions presented herein concerning the clinical efficacy of furosemide in preventing epistaxis in New York Racing.

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