A GENETIC ANALYSIS OF THE OCCURRENCE OF PULMONARY HAEMORRHAGE IN RACING THOROUGHBREDS IN SOUTHERN AFRICA

By

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"Declaration

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously in its entirety or in part submitted it at university for a degree.

ABSTRACT

TITLE   A GENETIC ANALYSIS OF THE OCCURRENCE
OF PULMONARY HAEMORRHAGE IN RACING
THOROUGHBREDS IN SOUTHERN AFRICA.

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This study was carried out to investigate whether environmental and/or genetic factors had an effect on the incidence of epistaxis related to exercise-induced pulmonary haemorrhage among racehorses in Southern Africa. A further aim was to estimate the heritability of liability to epistaxis in the Southern African Thoroughbred population. For the purpose of the environmental study, the data covering the period 1986-2001 and involving a total of 778 532-race runs, were analysed. This included the following race start information: date of race (day/month/year), age, sex, breeder, trainer, distance, jockey, state of going, weight carried, centre of racing and altitude. The genetic part of the data was two-fold in nature and included firstly the analysis of all horses that suffered epistaxis whilst racing in Southern Africa from 1986 to 2001 and involving 1118 individual bleeders. The second genetic analysis included the same Southern African population plus those Southern African horses exported to Mauritius and then being recorded as bleeders in that country (1252 bleeders in total). Pedigree data covering the period 1960-1986 was used as required to calculate the incidence of bleeding amongst ancestors of the post 1986 era. Only pedigrees of horses that raced

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were included in this study as it was not possible to predict whether non-runners would have bled had they raced. Consequently all non-runners and also those that raced overseas in countries where bleeding occurrence was not recorded were excluded.

Veterinarians employed by the Jockey Club suspended officially recorded horses that showed epistaxis as demonstrated by frank bleeding from the nostrils after racing. On-course endoscopy is not employed as a routine on any of the Southern African racetracks.

In the environmental study epistaxis was identified in 1 287 race starts (0.165%). Epistaxis related to exercise-induced pulmonary haemorrhage was significantly (p < 0.001) associated with altitude, age, race year, month and the day of racing. More horses demonstrated epistaxis at sea level than at altitude, between the months of May – October than the rest of the year, in older horses than in horses less than three-years old, after 1995 than between the years 1986 and 1995, and on Fridays and Sundays than on any other week day. No association could be established between epistaxis and breeder, trainer, distance, jockey, state of going, sex and weight carried.

The heritability of liability method as described by Falconer (1989) was used to estimate the relative importance of heredity and environment. For the period investigated, the population incidence for epistaxis in Southern African horses was 2.1%. The estimation of heritability of liability showed that first-degree relatives had a figure of 55.4%. The heritability of second- and third degree relatives were 41.3% and 30.4% respectively. The data investigated depicts horses that bled almost exclusively on race days as only a small percentage (~ 5%) was reported as having bled during exercise. Accordingly, the full extent of epistaxis amongst racing Thoroughbreds in Southern Africa is difficult to gauge.

Pedigree and race run data from Thoroughbreds racing in Southern Africa, covering the period 1986-2002 (63 146) horses in pedigree data-set and 778 532 race runs, were further analysed in order to study genetic and environmental factors affecting the incidence of epistaxis as associated with EIPH (exercise-induced pulmonary haemorrhage). As fixed effects for the model, variables that were tested significantly in a preliminary data analyses, were included. Various combinations of such

variables namely age, weight, altitude, sex, month and going were tested. Fixed effects that were included in the final model were gender, going and altitude. The heritability estimates from a logit transformed analysis for epistaxis fitting both the animal and sire generalized mixed models were 0.23 and 0.40 respectively, which indicated that epistaxis as associated with EIPH in the Southern African Thoroughbred sires has a strong genetic basis. Genetic trends indicating an increase in epistaxis were also found.

It is concluded that the frequency of epistaxis related to pulmonary haemorrhage is associated with altitude, winter and spring months and the horse's age. It is suggested that racing at a lower altitude may increase the probability of exercise-induced pulmonary haemorrhage.

It is clear that epistaxis in the racing Thoroughbred has a strong genetic basis. It is further suggested that horses showing frank bleeding from the nostrils after racing or exercise, be suspended and not used for breeding purposes. This would result in relatively fast progress being made towards eradicating this costly scourge of the modern Thoroughbred racehorse. Affected stallions and those racing whilst being treated with furosemide, should be barred from breeding and not be considered as future sires. Estimated breeding values for epistaxis should be used as a tool for selecting against it and be considered in breeding programmes to decrease the incidence thereof.

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OPSOMMING

TITEL   'n GENETIESE ANALISE VAN DIE VOORKOMS VAN
                  LONGBLOEDING IN DIE SUID-AFRIKAANSE RENPERD.

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Die doel met hierdie studie was om vas te stel of omgewings- of genetiese faktore enige invloed op die voorkoms van longbloeding in die Suid-Afrikaanse renperd het. 'n Verdere doelstelling was om die oorerflikheid op die onderliggende verspreiding van longbloeding in die Suid-Afrikaanse Volbloedpopulasie te bepaal. Vir die omgewingstudie is data wat oor die periode 1986-2001 strek en wat 'n totaal van 778 532 wedren-deelnames ingesluit het, statisties ondersoek. Die data het die volgende inligting ingesluit: datum van deelname, ouderdom, geslag, teler, afrigter, afstand van wedren, jokkie, toestand van baanoppervlakte, gewig gedra, sentrum waar deelname plaasgevind het en die hoogte bo seespieël van die sentrum. Die studie van die genetiese aspekte het eerstens 'n analise van al die perde wat longbloeding tydens 'n wedren in Suider-Afrika gedurende die jare 1986-2002 ondervind het (1118 perde), en tweedens dieselfde populasie perde, plus die Suiderlike-Afrikaanse perde wat uitgevoer is na Mauritius en bloeding daar ondervind het, (1252 perde), ingesluit. Ter aanvulling is uitgebreide stamboomdata van voorouers gedurende 1960-1986 gebruik om die voorkoms van longbloeding tydens die post 1986 tydvak te bepaal. Slegs stambome van renperde wat aktief aan renne deelgeneem het, is in die data ingesluit aangesien dit nie moontlik was om te voorspel of 'n perd wat nooit aan wedrenne deelgeneem het nie, longbloeding sou ondervind indien dit wel deelgeneem het. Dus is alle renperde wat nooit aan wedrenne deelgeneem het, asook daardie perde wat in die buiteland deelgeneem en waar longbloeding nie aangeteken word nie, uitgesluit.

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Alle perde wat bloeding van die neus na wedrenne getoon het, is deur veeartse in diens van die Jokkie Klub van Suid-Afrika ondersoek, as 'n bloeier aangeteken en van verdere deelname aan wedrenne geskors. Endoskopie word op geen van die Suid-Afrikaanse renbane as 'n standaard praktyk na wedrenne uitgevoer nie.

Longbloeding het in 1 287 perde of gedurende 0.165% van alle wedrenne plaasgevind. Longbloeding soos geassossieer met EIPH, (exercise-induced pulmonary haemorrhage), is betekenisvol (p < 0.001) met hoogte bo seespieël, ouderdom, dag van deelname, maand, en jaar verbind. Meer perde het longbloeding by seevlak in vergelyking met hoër vlakke bo seespieël ondervind, tussen die maande Mei-Oktober as die res van die jaar, in perde ouer as drie-jaar, na 1995 as tussen die jare 1986-1995, op Vrydae en Sondae as enige ander dag van die week. en meer by reuns as by merries of hingste. Geen verwantskap kon tussen bloeding en teler, afrigter, afstand, jokkie, toestand van baan, geslag en gewig gedra, gevind word nie.

Die oorerflikheid op die onderliggende verspreiding vir longbloeding soos omskryf deur Falconer (1989), is gebruik om die relatiewe belangrikheid van oorerflikheid en omgewing te bepaal. Vir die periode bestudeer, was die voorkoms van longbloeding in die Suid-Afrikaanse renperd 2.1%. Die oorerflikheid van longbloeding was 55.4% vir eerste-graadse verwantes. By tweede-graadse verwantes was die ooreflikheid 41.3% en by derde-graadse verwantes 30.4%. Die data wat ondersoek is, was bykans uitsluitlik die van perde wat tydens wedrenne gebloei het en slegs 'n baie klein persentasie (~ 5%) was aangeteken as perde wat tydens oefening gebloei het. Dus is die volle omvang van longbloeding in Suider-Afrikaanse Volbloedperde moeilik om akkuraat te bepaal.

Die stamboom- en wedrendata van Suid-Afrikaanse Volbloedperde is verder ontleed in 'n poging om die genetiese en omgewingsfaktore se invloed op die voorkoms van longbloeding, soos geassosieer met EIPH te bepaal. As vaste effekte vir die model is veranderlikes wat betekenisvol gevind was, ingesluit. Verskeie kombinasies van hierdie veranderlikes soos ouderdom, gewig, hoogte bo seespieël, geslag, maand en toestand van die baan is ingesluit. Die vaste effekte wat in die finale model ingesluit is, was geslag, toestand van die baan en hoogte bo seespieël. Die beraamde oorerflikheid verkry vanaf 'n "logit" getransformeerde analise vir longbloeding wat

beide die diere- en vader- gemengde model gepas het, was onderskeidelik 0.23 en 0.40, wat 'n aanduidending is dat longbloeding, soos geassosieer met EIPH, 'n sterk genetiese grondslag het. Genetiese tendense het ook gedui op 'n toename in die voorkoms van longbloeding, veral oor die laaste vyf jaar van die studie.

Samevattend is die bevinding dat die frekwensie van longbloeding 'n betekenisvolle verwantskap toon met hoogte bo seespieël, winter en lente maande en die perd se ouderdom. Dit word voorgestel dat renperde wat deelneem aan wedrenne by laer vlakke van hoogte bo seespieël, meer onderhewig aan longbloeding sal wees.

Uit die resultate verkry is dit duidelik dat longbloeding 'n genetiese grondslag het. Dit word voorgestel dat perde wat fisiese simptome van neusbloeding na of gedurende wedrenne toon, geskors word van verdere deelname en ook nie toegelaat word om mee te teel nie. Hierdie maatreëls behoort aanleiding te gee dat relatief vinnige vordering gemaak sal word in die strewe om hierdie ongewenste sindroom in die moderne Volbloed te verminder. Aangetaste hingste, asook dié wat aan wedrenne deelgeneem het terwyl hul behandeling ontvang met furosemide, moet nie toegelaat word om te teel en nie as toekomstige teelhingste oorweeg word nie. Die waarde van voorspelde teelwaardes vir longbloeding moet nie onderskat word in seleksie daarteen nie en moet in teelprogamme om die voorkoms daarvan te verminder, oorweeg word.

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CHAPTER 1

General introduction

" Hermit, with his grandson Gallinule, despite their undoubted claims to rank as pillars of the Stud Book, are very largely responsible for the incidence of bloodvessel breaking" as quoted by Robertson (1913), and suggests that heredity might be an important factor in epistaxis. Epistaxis is a common disorder that affects many horses all over the world. It is almost always exercised-induced and was once thought to be of a nasal origin caused by increased airflow that irritated and ruptured swollen nasal turbinates. Although it is widely accepted that epistaxis adversely affects racing performance, especially when profuse bleeding is present, such an effect is difficult to prove as most riders, when seeing the blood, ease their mounts out of the race. The loss of blood itself is rarely the problem. However, blood in the airways induces inflammation. With repeated haemorrhage, the problems increase with interstitial fibrosis and chronic changes occur within the small airways. This could lead to a horse losing its racing potential through lungs that are no longer functioning optimally. Epistaxis should be suspected in horses that display sudden, unexpected fatigue during a race. Such animals suddenly quit running during a race and tire markedly toward the end of a race. Frequent coughing post race is usually a good sign that a horse might be bleeding whilst an increased tendency to swallow seems to be the most reliable indicator. Epistaxis is of great concern because of large financial losses in the multimillion rand racing industry, resulting from decreased performance, suspension of horses from racing, lost training days and the cost of pre-race medication.

Robertson (1913) published the first and only article referring to the heredity of epistaxis and erroneously believed that a vessel ruptured because of the strain that sudden engorgement imposes upon the vessel's abnormally thin or weakened walls. It was only during 1974 that Cook showed that the lung and not nasal cavity was the primary site of bleeding and this condition became known as pulmonary haemorrhage. This may vary from a slight trickle of blood from one nostril (unilateral

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epistaxis) or from both nostrils (bi-lateral epistaxis) or profuse haemorrhage, usually from both nostrils, where death may occur in exceptional cases within a matter of minutes. Mahaffey (1962) found that the haemorrhage occurred from the rupture of alveolar capillaries, but could find no histological evidence to indicate the reason for this, while Johnson *et al.* (1973) and Cook (1974), noted that the specific region of haemorrhage was the dorsal caudal lung lobe.

A great deal of controversy surrounds the use of Lasix (furosemide) as a pre-race medication for the supposed suppression of epistaxis. Some breeders and owners are of the opinion that considerable prices paid for horses at sales, increase the frustration should it be found that their purchase was a bleeder and could not be given pre-race medication even though such medication existed. On the other hand, the majority of owners, trainers and veterinary surgeons are of the opinion that there is only one route and that is "medication free" racing. A further group of breeders hold the opinion that if medication is administered pre-race for any problem, the breed will be seriously downgraded. It must be emphasized, however, that research recently undertaken as to the efficacy of Lasix, produced conflicting results varying from the prevention or reduction of bleeding in horses as indicated by Manohar *et al.* (1994) and Geor *et al.* (2001), limited success only, notably Kindig *et al.* (2001), or even no success as shown by Sweeney *et al.* (1990).

The earliest bleeder to be found in the literature of the racehorse is Bartlett's Childers (1716), who, according to Robertson (1913), enters into the pedigree of every thoroughbred horse in the world at that time. The mode of genetic transmission of epistaxis is not clear although Robertson stated that as a general rule, blood vessel breaking would seem to be expressed as a recessive character inherited according to simple Mendelian genetics. He continues by saying that "in certain characters which depend on structural or physiological peculiarities and which are marked departures from normality, one intense dose of the usually latent or abnormal character may be sufficient to overcome the normal condition, which has been inherited from the sound parent. However, that tracing the character, other than through known bleeders, in the later and more lengthy pedigrees is not quite such a simple manner. It may be likened to tracking to its source a subterranean stream which throughout its

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meanderings only appears on the surface at rare intervals and not infrequently there is more than one path which the latent character could have followed".

Thoroughbred horses have been bred exclusively for racing in England since Tudor times and spread quickly to most countries resulting in Thoroughbred racing presently being practiced in over 40 countries and involving more than half-a-million horses worldwide. The genetic origins of the Thoroughbred go back largely to horses imported from the Middle East and North Africa to England in the late seventeenth and early eighteenth centuries. Since the establishment of the English Stud Book in 1791, the population has been effectively closed to outside sources, and over 80% of the Thoroughbred population's gene pool is derived from 31 known ancestors from this early period.

The first consignment of English Thoroughbreds reached Cape Town in 1792 and consisted of three stallions and two mares (Wyndham, 1924). The earliest Thoroughbred studs were situated in the vicinity of Cape Town, but new studs were soon established in the North Eastern Cape (Karoo) in the Colesberg area, where the best horses of that era were produced. According to Nelson (1952) there were only about a dozen studs of any consequence in existence in South Africa during the early 1900's with four studs dominating the breeding scene up to the Anglo-Boer War. The small number of studs at that time could have contributed to the statement by Cook (1974) hinting at the possibility that breeding may be a factor influencing the occurrence of epistaxis and Pfaff (1976) mentioning that increased susceptibility, resulting from inbreeding, may well explain the widespread nature of epistaxis in South Africa. After the Anglo-Boer War, there was a considerable increase in the number of breeders and although on a small scale, Thoroughbred breeding appears to have shown good progress during this period. Despite various setbacks such as the First World War and the subsequent economic depression, the production of Thoroughbreds continued to develop. During the period after the First World War, no importation of horses was possible ensuring that the local horses were in good demand but once again highlighting the problem of inbreeding due to a generally small local gene pool with very little outcrossing possibility.

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Because of the great distances between studs and inadequate means of transporting stock between studs, breeders tended to limit their mares to their own farm's stallions, which in part accounts for the large blocks of years dominated by single stallions in the leading sires list, and which had the undesirable subsidiary effect of ultimately limiting outcrossing. The demand for breeding stock during these years was largely met by the dispersal of the studs of the late Dudley Nourse who, at that time, had huge interests in the breeding industry. There was, however, a great shortage of horses with first-class sire credentials and this shortage led to the use of sires that would not otherwise been used. Although a number of these sires made the grade, the majority of them turned out to be of poor class that might have had a detrimental effect on the South African breeding industry.

During the period leading up to the Second World War, there was a spate of importations into South Africa, mainly for racing purposes and only a few sires imported for stud purposes. With the outbreak of war, there followed a total cessation of importations, and South Africa was thrown back on its own resources. When the war ended, both racing and breeding flourished and, for the first time in the history of breeding in South Africa, the majority of breeders looked overseas for their sires. This resulted in a record number of breeders establishing stud farms all over South Africa. Owing to the post-war affluence, breeders could import into the country a number of sires whose credentials as racehorses were vastly superior to those previously used. In addition to horses imported by breeders, there was also a large influx of horses for racing purposes, although this type of horse found little favour with the leading South African breeders, who continued to import their sires rather than draw from local bloodstock, whether imported or indigenous. However, this period was to be short-lived as a total ban on the importation of horses for racing purposes was imposed by the South African Government from 1948 to 1963. This ban was, according to Faull (1982), imposed for economic reasons and not for the protection of local breeders from competition from abroad. Since the lifting of the ban in 1963, there have been restrictions on the annual number of yearlings or unraced two-year-olds imported, but no restrictions on the number of raced colts or fillies allowed to be imported for racing and breeding purposes. All these importations, however, have to comply with strict criteria of form and/or pedigree as

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laid down by the Thoroughbred Breeders Association in conjunction with the Jockey Club of Southern Africa in order to ensure that better quality bloodstock is imported.

In the period shortly after the Second World War, the Karoo housed the majority of the leading studs in South Africa. Both the Natal Midlands and the Ashton/Robertson areas were in their infancy with only a few studs established in those districts. A quarter of a century later (1970's), the studs in the Karoo consolidated their position not only numerically but also qualitatively by producing the best horses year after year, which could be ascribed to the top quality sires being based in this area. The Natal Midlands and in particular the Bonnievale/Ashton/Robertson (Bar Valley) areas were then starting to attract more breeders and become increasingly popular. However, a number of factors caused changes to occur, shifting the once predominantly inland breeding operations to the coastal and adjoining areas. With the passing away of a number of top breeders in the Karoo area, and the pressure of an ever-worsening rand to dollar/pound exchange rate, a number of others were forced to stop breeding and this area seemed to lose popularity. Most breeders moved away from farming extensively on huge farms where mares and foals were allowed to run out all year and not stabled for the majority of the year regardless of the extreme temperature variation and climate experienced in those areas. Horses were rather kept intensively on smaller farms using irrigated pastures to maintain and produce their bloodstock under temperate climatic conditions. Importing good breeding stock became prohibitively expensive and according to Faull (1986) the class of horse imported was not of the same quality of those imported during the 1960's and 1970's. Although some very good sires were imported after this, they were few when compared to the total number of imported stallions and most were extremely expensive to acquire. Faull (1982) is of the opinion that the revolutionisation of the marketing of horseracing by the Americans and its far-reaching effects on bloodstock price levels has placed potential sires of high caliber beyond the reach of the South African breeding industry. With so few top quality stallions available, it did make sense standing these sires in areas like the Bar Valley and the Natal Midlands with their very dense mare populations. Traveling mares a few thousand kilometers in order to breed them, like it was done 20 to 30 years ago, became very expensive and good quality stallions standing in remote areas were no longer as well supported. The Bar Valley now became by far the most important breeding area (most of the top

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sires being based in this area) with the Ceres area making its mark as the cradle of a number of studs producing excellent quality bloodstock. The Natal Midlands had for the last 25+ years held its own by producing very competitive and good quality stock. The Karoo no longer features as one of the prime breeding areas mainly because of the distances and costs involved in traveling mares to stallions and of the changing (intensive versus extensive) nature of stud farming. The rest of South Africa produces horses on a small scale while Zimbabwe (falling under the jurisdiction of the Jockey Club and Stud Book of Southern Africa), continued its breeding industry through very trying times but were finally rewarded for their efforts by producing a number of top class horses including the worlds top female during the beginning of this century.

During the whole period reviewed, amongst the many problems that befell the breeder/owner/trainer/punter, was the continued and increasing prevalence of epistaxis amongst racing Thoroughbreds in Southern Africa. This is a major problem for a number of reasons. Not least is the mandatory three-month recuperation period away from the racecourse for horses identified as having bled. This leads to a loss of potential income from an affected horse during the period of suspension, as well as additional costs for treatment over and above regular training fees. It is not difficult to see this makes it a very costly experience and one can sympathize with the connections, but any type of pre-race medication would surely be to the detriment of the breed.

The present study was initiated to examine whether identifiable environmental factors had any effect on epistaxis associated with exercise induced pulmonary haemorrhage in Southern Africa. Although an appreciable number of studies have been undertaken in the past, variable results were reported and only a few studies have been published concerning the effects of atmospheric conditions on epistaxis.

Only one reference relating to the inheritance of epistaxis in the horse could be found in the available literature. Although a number of researchers mentioned that breeding might be a factor influencing the occurrence of epistaxis in the Thoroughbred, no recent research into the mode of inheritance has been carried out.

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The objectives of the present study were to examine environmental and genetic factors that might have an influence on epistaxis and to determine the prevalence of epistaxis in a population of Southern African Thoroughbreds racing in Southern Africa and Mauritius.

CHAPTER 2

The influence of environmental factors impacting on epistaxis related to exercise-induced pulmonary haemorrhage in South African Thoroughbreds

2.1 Introduction

Epistaxis is defined as bleeding from the nostril(s) and this condition has been known for at least 300 years. During this time, Robertson (1913) thought it to be of a nasal origin, due to unusually weak vessel walls within the nose. In 1974, the lung was identified as the primary site of bleeding by Cook and after examining racehorses with the flexible fibreoptic endoscope, the lung was confirmed as the site of haemorrhage by Pascoe *et al.* (1981). They coined the term 'exercise-induced pulmonary haemorrhage' (EIPH), linking the readily identifiable features, exercise and lung haemorrhage, for an apparently common clinical problem. This term was felt to provide a more accurate description of the problem than earlier descriptive terms such as "blood vessel breaking", "bleeder" and "epistaxis". Although some horses manifest epistaxis after exercise, a much larger percentage had endoscopic evidence of pulmonary haemorrhage without showing epistaxis. Whereas epistaxis shows a relatively low incidence ranging between 0.8% (Raphel & Soma, 1982) and 13.5% (Kim *et al.*, 1998), EIPH has an incidence of 26.5% – 74.5% in Thoroughbreds as shown by Pascoe *et al.* (1981). Most horses afflicted with EIPH do not show frank bleeding from the nostrils.

According to Jones (1998) it was clear that more research was needed into a number of aspects of the EIPH problem, such as the reason why some horses are affected to a greater extent or bleed more severely than others and the relationship between the amount of blood seen and the real volume of haemorrhage. Based on the severity of the haemorrhage, at least five separate levels of pulmonary haemorrhage were identified by Harkins *et al.* (1997). This ranged from the simple rupture of capillary endothelium allowing red blood cells to escape into the interstitial tissue (level 1), to

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level 3 where the amount of blood flowing into the alveoli is sufficient to ascend into the trachea and be visualized. Level 4 demonstrates evidence of blood at the nostril (epistaxis) and level 5, resulting in death during or post-race from severe pulmonary failure. Following Takahashi *et al*. (2001), this condition is refered to as epistaxis related to EIPH, a term used throughout the present study.

A number of hypotheses have been put forward regarding the pathophysiology of epistaxis associated with EIPH, for instance that upper airway obstruction or lower airway disease are necessary to induce abnormalities in ventilation and increases in alveolar pressure that would eventually lead to tearing of lung tissue. West *et al*. (1994) suggested that bleeding from the lungs is caused by stress failure and rupture of the capillary bed of the pulmonary circulation, a finding substantiated by Birks *et al*. (1997) who showed that Thoroughbred horses develop extremely high pulmonary vascular pressures during racing. A pressure of between 75 and 100 mmHg was required to cause stress failure of the pulmonary capillaries in horses. In a later study Schroter *et al*. (1998) suggest that the lung is subjected to high levels of locomotor derived impulsive force during high-speed exercise. They proposed that during locomotion, the force following ground-strike of the front legs is transmitted through the forelimbs to the scapulae, which in turn produces an impulsive force on the rib cage. As a result pressure waves are transmitted through the lungs causing a complex pattern of wave interaction within the lung leading ultimately to haemorrhage.

According to the Jockey Club's Racing Calendar of Southern Africa (volumes 95-98), approximately 110 Southern African horses are annually stricken with epistaxis as associated with EIPH. Worldwide, EIPH is of great concern because of the financial implications resulting from decreased performance, suspension of horses from racing, lost training days, and the necessity for pre-race medication. An appreciable number of horses have died as a result of EIPH during racing as shown by Gelberg *et al*. (1985) and Gunson *et al*. (1988). There appears to be a consistent pattern of incidence of EIPH around the world despite many differences in environmental factors, including climate, training and management practices, racing surfaces and types of competition. Clarke (1985) reported that *post mortem* examinations and epidemiological studies had failed to demonstrate any clear relationship between variable factors and the cause of EIPH.

The present study was initiated to examine whether identifiable environmental factors had any effect on epistaxis associated with exercise induced pulmonary haemorrhage in Southern Africa.

2.2 Materials and Methods

The data of racehorses that experienced epistaxis as associated with EIPH whilst racing in Southern Africa, was examined. Racing in South Africa and Zimbabwe falls under the control of the Jockey Club of Southern Africa. Veterinarians employed by the Jockey Club, examine all runners before and after racing. Any horse showing epistaxis is reported as a bleeder and is subsequently suspended from racing. Horses demonstrating an initial bout of epistaxis are automatically suspended from racing for a period of three months. A repeated bleeder receives a six-month suspension and any further incident of bleeding results in permanent suspension. Due to time and cost constraints, on-course endoscopy is not employed as a routine on any of the South African tracks. The use of furosemide is not allowed in South African Thoroughbred racing. Data of Jockey Club reported cases has been recorded for all the racing centres in South Africa and Zimbabwe. The passport number (identification), name of horse, age, sex, breeding, stud where born and raised, trainer, distance raced, date and race when pulmonary haemorrhage occurred, centre of racing, date of last run before EIPH occurrence, state of going, jockey, weight carried, altitude and the date of return to racing of suspended horses were recorded and is available from the Jockey Club of Southern Africa's database. Racing in Southern Africa is conducted at sea level (Durban, Cape Town and Port Elizabeth), approximately 1 000 meters above sea level (Pietermaritzburg) and 2 000 meters plus a.s.l. (Johannesburg, Bloemfontein, Kimberley and Zimbabwe).

The data covering the period 1986 – 2001 and involving 51 465 individual runners that raced a total of 778 532 runs was analysed. Classification trees methodology was used according to Breiman *et al.* (1993) in order to determine the influence of various predictor variables on epistaxis as demonstrated in Thoroughbreds. This methodology splits up the data into various subgroups based on the predictors. If the predictors have an influence on the occurrence of epistaxis, then certain subgroups

will have proportionately more epistaxis than other subgroups. The subgroups were determined by rules that are constructed based on the predictors. χ^2 tests (Statistica 6) for contingency tables were used to determine the significance of differences between subgroups.

The association of pulmonary haemorrhage with a number of variables was tested statistically using classification trees (Cart version 5). Due to the very small proportion of epistaxis that occurred (0.002, or 1287 occurrences from 778 532 race starts), it was decided to draw samples from the original data with more manageable proportions of epistaxis. The samples were drawn as follows: All the horses that demonstrated epistaxis were included (1118 horses). This did not include any data for starts following the first episode of epistaxis. From the remaining horses, 1118 were selected randomly. This was referred to as a 50% sample and was duplicated using a further 1118 randomly selected horses. In the same manner a sample containing the 1118 bleeders and 4472 randomly selected horses (a 20% sample) was acquired and duplicated. Finally, a single 9.1% sample was drawn using all the bleeders and 12298 randomly selected horses. Comparing the five sample sizes showed identical or very highly comparable values and for the purpose of illustration, the 50% sample was used in this study. All the race starts for each selected horse were included. The 50% sample included a total of 43 863 races with a proportion of 0.026 episodes of epistaxis. Thirty-eight cases where epistaxis was observed after training were excluded from analyses when relevant data was not available.

Weighbridges were installed at both Kenilworth- and Durbanville racecourses during 1998 and all horses are weighed prior to racing. These courses are situated in the Western Cape and are the only courses in Southern Africa where runners are weighed and the weights recorded and made available to the general public. The data investigated included the weight of the horse on the day that epistaxis occurred as well as the penultimate and anti-penultimate weights for all bleeders. As a control the same data was collected for 300 normal horses (individuals that did not exhibit epistaxis). These samples were taken at random in order to eliminate possible year- and seasonal effects. Data were analysed by using SAS (1990) in order to establish whether the "bleeder" was in a (negative) weight loss or (positive) weight gain on the

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whether the "bleeder" was in a (negative) weight loss or (positive) weight gain on the day of bleeding compared to the weights of the previous two runs. The assessment of a fit racehorse's weight when racing at the top of its form is regarded by horsemen to be a very important factor and, once established, is a good indicator of the degree of its fitness. Most racehorses return to racing after being rested for periods of time that could vary from weeks to a few months. Other horses have an enforced rest due to injury and could be incapacitated for longer periods of time. Horses returning from these lay-offs usually return to racing burlier in condition due to a lack off sufficient exercise and usually require a few runs to race at true potential. The mass of these horses shows a decline as the training programme advances until an optimum mass is reached and top performance can be expected.

The frequency at which Southern African racehorses compete annually was also investigated and analysed using version 6.12 of the statistical package SAS (1990). The total race runs per individual horse per year was calculated for the years 1986-2002 with a year stretching from the first of January to the end of December and not as the South African racing year from the beginning of August to the end of July.

2.3 Results

Positive relationships were established between pulmonary haemorrhage and race year, altitude, age, the day of racing and month. An exponential increase in the incidence of epistaxis related to exercise-induced pulmonary haemorrhage is shown for the period 1986-2001 in Fig.2.1.
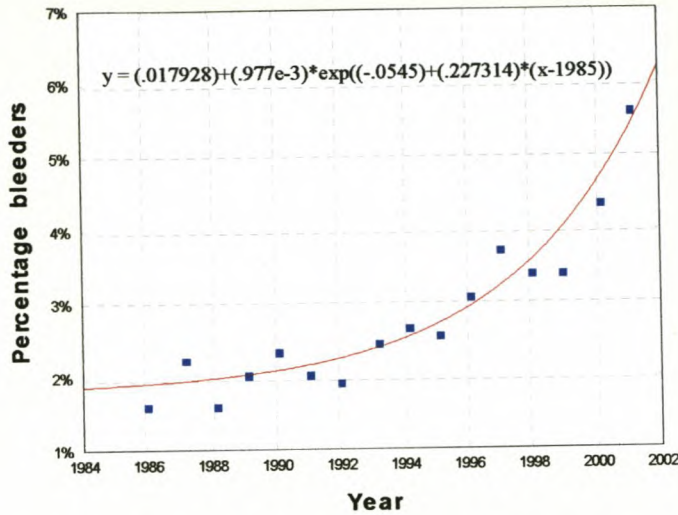
$$y = (.017928)+(.977e\text{-}3)*\exp((-.0545)+(.227314)*(x\text{-}1985))$$

Fig. 2.1 The percentage of epistaxis of randomly selected sample by individual year

A significantly higher incidence of epistaxis related to exercise-induced pulmonary haemorrhage was experienced in Southern Africa after 1995 ($p < 0.001$), as shown in Fig.2.2.
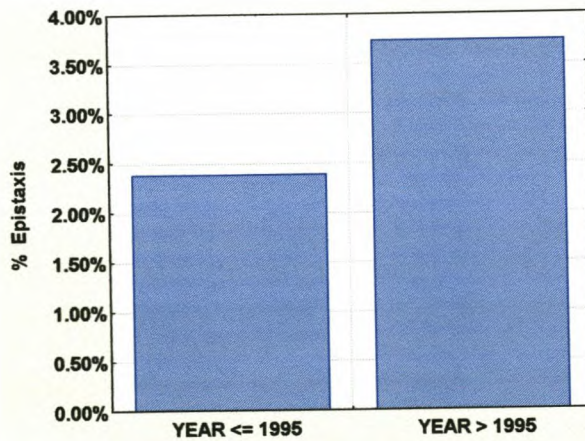
Fig. 2.2 Percentage epistaxis per year

The histogram in Fig. 2.3 shows that a significantly larger percentage ($p < 0.001$) of pulmonary haemorrhage occurred in horses racing at sea level compared to those racing at altitude.
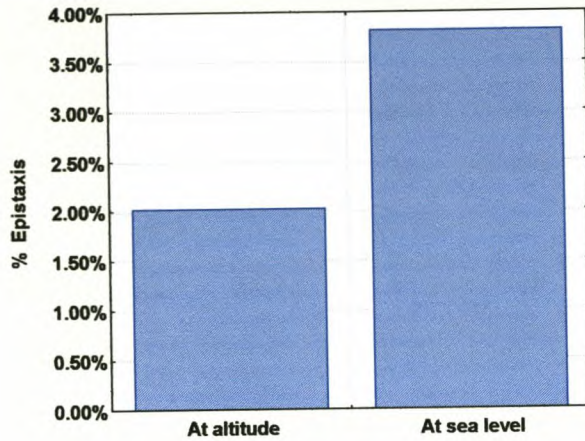
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Fig. 2.3 The percentage epistaxis at different altitudes

The randomly selected sample established an association between pulmonary haemorrhage and age and is shown in Fig. 2.4.

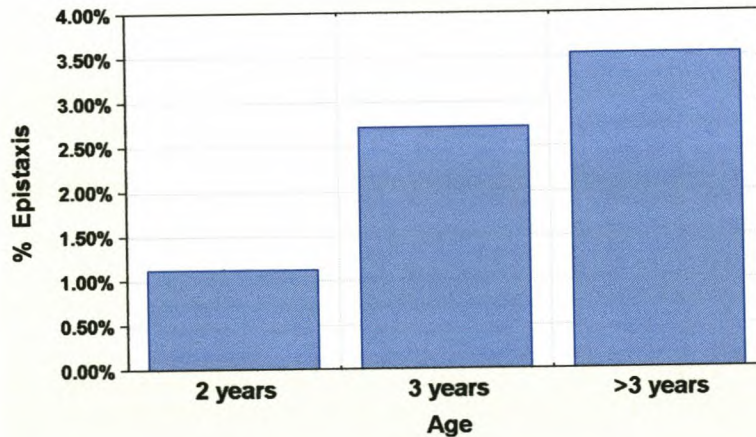**Fig. 2.4 The percentage epistaxis per age group**

Only 1.1% of two-year olds are stricken with epistaxis during their first year of racing. The 3-year olds showed a significant increase in the incidence of pulmonary haemorrhage to 2.7% ($p < 0.001$). The ages 4-years and older showed a further significant increase when compared with both the two-year olds ($p < 0.001$) and the 3-year old group ($p = 0.0186$).

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Racehorses in Southern Africa experience pulmonary haemorrhage significantly more on Sundays and Fridays than at any other day of the week as demonstrated by Fig. 2.5.
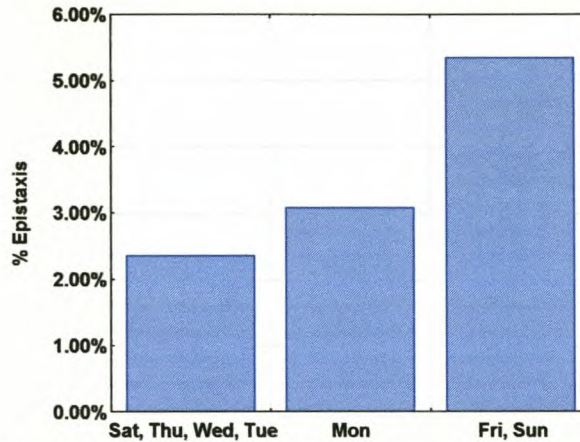
Fig. 2.5 Percentage epistaxis occurrence on Sundays and Fridays compared to other days of the week

A significant difference ($p < 0.001$) in the incidence of epistaxis was observed during the winter and spring months (months 5-10 or May-October) as compared to summer and autumn (months 11-4 or November- April) and is shown in Fig.2.6.

Fig. 2.6 Percentage epistaxis according to the months of the year

No association was found between going, trainer and location of track, which was in agreement with an earlier study by Mason *et al.* (1983). The present study could not establish any relationship between distance raced and EIPH. This is also in agreement with other studies by Speirs *et al.* (1982) and Mason *et al.* (1983). However, in studies

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by Raphel & Soma (1982) and Roberts *et al.* (1993), a positive association was shown between distance raced or breezed and epistaxis as associated with EIPH.
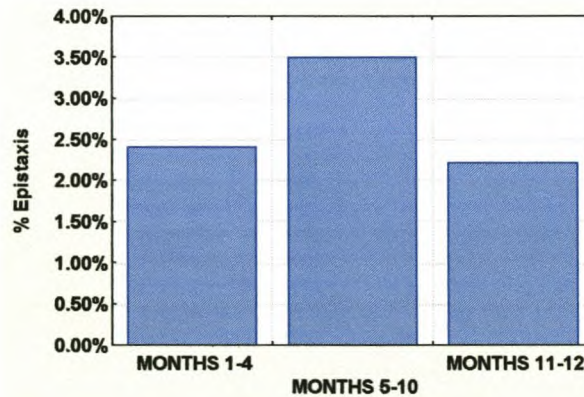
2.4 Discussion

In the present study, epistaxis was observed following 0.16% of all race starts, which was appreciably lower than the (0.84%) showed by Kim *et al.* (1998) in an earlier study but compares favourably with the (0.15%) found by Takahashi *et al.* (2001) in a comparable study in Japan. In the Japanese study, the authors suggested that the low incidence could have been the result of lower mean age of horses racing there than in other countries. Sixty-four percent of horses racing in Japan are ≤ 3 year olds, which is equal to or higher than the percentage in other countries. In the present study, which confirmed that the frequency of epistaxis increased with age, it was found that approximately 40.4% of horses in racing were 2- and 3-year olds as compared to 40.3% 4- and 5-year olds.

A total of 1118 (2.1%) individual racehorses suffered from epistaxis related to EIPH during or after racing, with 150 (13.4%) showing a repeated bout of epistaxis and a further 12 horses (1.0%) experiencing a third bout and permanent suspension from racing.

2.4.1 Altitude

Only one reference to the relationship between altitude and pulmonary haemorrhage could be found in the available literature, and according to Raphel & Soma (1982), it was based on racing records that were not statistically analysed. The reference refers to a study undertaken by Pfaff (1976) who found that epistaxis was more likely to occur at sea level than at an altitude of approximately 2000 meters, a finding substantiated by the present study. The paucity of research regarding any relationship between altitude and epistaxis related to EIPH, may be ascribed to the fact that most European and Eastern countries race at sea level or slightly above.

Takahashi *et al.* (2001) reported that geographic and environmental factors might influence the frequency of EIPH related epistaxis. In the present study significantly more racehorses manifested epistaxis related to EIPH at sea level when compared to horses racing at altitude. It could be rewarding to investigate this further, especially in the United States of America (USA) where a good deal of racing is done at altitude and particularly as a popular belief exists, according to Raphel & Soma (1982), that epistaxis occurs with greater frequency in the mid-Atlantic states (mostly at sea level) compared with the remainder of the USA. The use of furosemide is allowed in horses racing in a number of states in America and as such, this supposed suppressor of pulmonary haemorrhage in horses, may hamper research in the USA. An increase in both the resting packed cell volume and red cell numbers was demonstrated with increased exposure to altitude by Wickler & Anderson (2000). The authors further found that the ascent to altitude was accompanied by an increase in total blood volume, which was, according to them, due to the expansion of the red cell volume. Further research on the pulmonary mechanism in horses with EIPH at different altitudes, is clearly indicated.

2.4.2 Age

Several researchers showed a positive association between age and EIPH during the seventies and eighties, including Bourke (1978), Cook (1974), Raphel & Soma (1982), Mason *et al.* (1983), Sweeney & Soma (1983) and Kim *et al.* (1998) and that the severity of EIPH increased with age (Roberts *et al.*, 1993). A possible link between age and epistaxis was indicated by Pfaff (1950) and a later study (1976) by the same author showed that the tendency to bleed in racehorses increases up to the age of five years, but that four and five year olds probably do more racing than horses of other ages. The low incidence of epistaxis among two-year olds can be attributed mainly to horses being introduced to racing late in their two-year old careers. Sweeney & Soma (1983) are of the opinion that the higher frequency of haemorrhage in the older horse could also indicate that there may be cumulative effects of pulmonary damage. No association between a horse's age and EIPH was demonstrated in two other studies by Pascoe *et al.* (1981) and Speirs *et al.* (1982).

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2.4.3 Day of week

In order to obtain a representative picture of days of the week when raced, a close scrutiny of Saturdays and Wednesdays must be made to establish whether there is any significance to this finding. This shows that these were the traditional racing days in Southern Africa. In 1986, 14% of all meetings took place on Wednesdays. Saturdays have always occupied the "elite" position on the racing calendar and between 2, 3 and even 4 meetings were held on this day whereas no racing took place on Sundays. Presently, with new strategies to combat the threat of other gambling alternatives, it has become necessary to increase horse racing's exposure by racing most days of the week. Racing consequently takes place every day of the week, which was unheard of during the 1980's. Most of the racing done since the middle nineties on Fridays and Sundays took place at Port Elizabeth (at sea level) with an additional meeting every Sunday at either Cape Town, Durban or Johannesburg. Days of week were thus partly confounded with altitude. It is improbable that the increase in bleeding on Fridays and Sundays could be ascribed to racing on those two days alone. It could be speculated that as more racing at sea level took place on these days, a greater frequency of epistaxis was to be expected.

When compared to horses racing at the major Southern African centres, the average performance of horses participating at Port Elizabeth is slightly below the average. The benchmark merit rating handicap system presently employed by the Jockey Club rates the average Port Elizabeth horse 4 pounds (2 kg) lower than the average horse in the major centres. Horses unable to earn their keep in the main centers, gravitate to Port Elizabeth, and horses that bleed at work in other centres might, according to Pfaff (1950), be quietly sent there. The theory that horses bleed more on Fridays and Sundays due to most racing on those two days taking place at Port Elizabeth, is challenged by the fact that the same class of horse participates at Bloemfontein (same merit rating as Port Elizabeth) and Kimberley (2 pounds or 1 kg lower than Port Elizabeth) race tracks with comparable racing frequency but a smaller incidence of pulmonary haemorrhage. If this is so, then altitude (racing at sea level), as an environmental factor, indeed has an effect as demonstrated above. This warrants further investigation.

2.4.4 Month/season of racing

Investigations on the New York racing tracks have shown that most horses bleed during the seasons of fall and spring (Johnson *et al.,* 1973; Kim *et al.,* 1998), while the worst months for bleeding were found by Pfaff (1976) to be the cooler months of April to July (winter), a finding substantiated by this study where most horses were found to bleed during the cooler months of the year (May-October). This could possibly be ascribed to a negative relationship between air temperature and EIPH. A significant negative correlation ($p = 0.0007$, $r^2 = 0.39$) was found by Lapointe *et al.* (1994) between air temperature and the proportion of EIPH, i.e. more horses were EIPH-positive as temperature decreased. Temperatures were categorically classified as warm ($T > 10°C$), tempered ($0°C < T \leq 10°C$) or cold ($T < 0°C$) by these authors. According to them, since there is no physiological reason for this, one can only speculate as to the nature of the relationship between air temperature and EIPH. A possible hypothesis could be that any factor, such as cold air, would render the capillary walls more fragile, therefore increasing their tendency to rupture during exercise.

2.4.5 Year of racing

Reasons for the sharp increase in epistaxis in Southern African Thoroughbreds since 1995 is not clear. Although no scientifically based evidence of an increase in epistaxis associated with EIPH has been demonstrated (because of not reporting or suspending bleeders), it is clear that worldwide this syndrome has become a major problem and steps need to be taken to contain its spread.

2.4.6 Weight of horses when competing

Kim *et al.* (1998) showed that heavier horses were more prone to bleed and suggested that body weight regulations with conditioning is recommended and that this should

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be controlled in order to reduce the incidence of EIPH. Data analysed in the present study of the body weight of bleeders on the day of bleeding showed no significant difference when compared to the weight of horses that did not bleed.

2.4.7 Frequency of competing

Kim *et al*. (1998) found that the average racing frequency of bleeders (1.05 times/month) was more than that of all the racehorses (0.8 times /month) racing in Korea. With regard to the frequency of entering races, the authors recommend that horses should be monitored and restricted as to the number of races individual horses may partake in during a specific period of time. In the present study, χ^2 tests could not establish any significant difference in the racing frequency of bleeders compared to that of all the racehorses racing in Southern Africa. It was found that bleeders raced on average 6.2 times per year compared to the average of 5.6 times for non-bleeders.

2.5 Conclusions

A number of environmental factors were identified as having a positive association with epistaxis as associated with EIPH. A few of these factors were also found as having a positive relationship with epistaxis in previous studies as discussed. One of the factors not covered in the literature, or receiving little coverage, was altitude, that appears to be an important factor as significantly more racehorses manifested epistaxis related to EIPH at sea level in South Africa when compared to horses racing at altitude. This is an area that requires further research as very little is known about the possible influence that altitude may have on epistaxis. A significantly higher incidence of epistaxis was also recorded with a decrease in temperature but this was physiologically difficult to account for. A further worrying aspect was the exponential increase in the incidence of epistaxis of Thoroughbreds racing in Southern Africa since 1995. Although no possible explanation could be tendered for this trend, further research into whether genetic factors had an influence, should shed more light on this phenomenon.

The use of furosemide is allowed in a number of states in the USA, purportedly to decrease the incidence of EIPH. This medication could mask the symptoms of EIPH

and result in bleeders not being identified. The indiscriminate use of such horses for stud purposes when their epistaxis status is not known, could have a possible negative influence on the breed regarding EIPH as associated with epistaxis. This will be investigated in a further study.

CHAPTER 3

The inheritance of liability to epistaxis in the Southern African Thoroughbred

3.1 Introduction

Epistaxis is a common disorder that affects many horses all over the world. Authors have discussed this clinical syndrome since the days of Markham, a Turf historian writing in the late 1500's. It was noted that many horses, especially young horses, were often seen bleeding at the nose, which was at times profuse and difficult to stop. Epistaxis is almost always exercised-induced and was according to Robertson (1913) once thought to be of a nasal origin caused by increased airflow that irritated and ruptured swollen nasal turbinates.

Worldwide, EIPH is of great concern because of the financial implications resulting from decreased performance, suspension of horses from racing, lost training days and the necessity for pre-race medication. This could run into the millions in most major racing countries of the world. There appears to be a consistent pattern of incidence of EIPH around the world despite many differences in environmental factors, including climate, training and management practices, racing surfaces and types of competition.

A number of hypotheses have been proposed to explain the pathophysiology. Several earlier theories proposed that either upper airway obstruction or lower airway disease were necessary to induce abnormalities in ventilation and increases in alveolar pressure that would eventually lead to tearing of lung tissue. A recent theory by West *et al.* (1994) supposes that bleeding from the lungs is caused by stress failure and rupture of the capillary bed of the pulmonary circulation due to an increase in blood pressure caused by strenuous exercise. This was later confirmed by Birks *et al.* (1997) who showed that a pressure of between 75 and 100 mgHg was required to

cause stress failure of the pulmonary capillaries in horses. Schroter *et al.* (1998) proposes that during locomotion as the horses' hooves hit the ground; a force (shock) is transmitted through the legs to the chest and then to the rib cage. As a result pressure waves are transmitted through the lungs causing a complex pattern of wave interaction within the lung leading ultimately to haemorrhage. A third theory that when the horse is involved in strenuous exercise, the stomach and intestines could swing into the sides (ribs) and back to the lungs – thus rupturing capillaries within the dorso-caudal part of the lungs.

Several investigations into the non-genetic factors as the cause of epistaxis have been undertaken over the past 25 years, but according to Takahashi *et al.* (2001) the primary factors responsible for EIPH have not been identified. A variety of findings have been reported. These include a positive relationship between EIPH and age (Takahashi *et al.,* 2001), EIPH and the cooler months of the year (Johnson *et al.,* 1973), EIPH and sex (Pfaff 1976), and EIPH as associated with pulmonary haemorrhage and altitude (see Chapter 2). On the other hand, similar studies could not establish any relationship between EIPH and sex (Lapointe *et al.,* 1994), EIPH and the distance raced (Speirs *et al.,* 1994), while no association was found between EIPH and trainer or going (Mason *et al.,* 1983).

No scientifically based and only a few speculative references relating to the inheritance of epistaxis in the horse could be found in the available literature. Robertson (1913), an expert on racehorse pedigrees, went to considerable effort to prove that the stallion was the prime, if not sole source of epistaxis in the English Thoroughbred. He showed the tendency to break blood vessels (bleeding from the nose) is inherited as a simple recessive character. According to him a horse, however, is not likely to break a blood vessel unless he carries the homozygous recessive genes. Pfaff (1950) published the first report regarding the incidence of epistaxis in a group of racing Thoroughbreds in South Africa. This study found that at least 1.2% of horses bled from the nose after racing. According to this author, it is said that all bleeders trace back to the stallion Herod (foaled in 1758), and that the names of the stallion Hermit (foaled in 1864) and of his grandson Gallinule (foaled in 1884), appear in the pedigrees of many bleeders in South Africa. In the same paper the possibility of a genetic link between epistaxis and heredity is discussed, highlighting

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Robertson's (1913) findings. In a later publication by Pfaff (1976), it is suggested that heredity might be an important factor in the expression of epistaxis, corroborating a statement made by Cook (1974) that infers that breeding might be a factor influencing the occurrence of epistaxis in racing Thoroughbreds.

No research into the mode of inheritance of epistaxis could be found in the available literature. After an initial analysis of the data it seemed that simple Mendelian inheritance as mode of inheritance could be ruled out (Weideman, unpublished). It is thus assumed that it is inherited in a polygenic manner expressing itself as a threshold trait in a categorical way. Epistaxis would appear not to be inherited in a simple manner by a single gene but may have some degree of hereditary basis, demonstrated by a higher incidence among relatives of affected individuals than among the general population.

The estimation of the heritability of liability has been widely applied in the study of the inheritance of human diseases. Estimates obtained for the heritability of liability range from 85% for schizophrenia to 35% for congenital heart disease. Knowledge of the heritability is useful in genetic counseling for calculating recurrence risks in families because it allows all the information about a family to be combined correctly. The increasing prevalence of epistaxis in Southern African Thoroughbreds, as shown in Chapter 2, might be an indication that breeders have, through selective breeding, developed horses whose lungs can no longer sustain the stress of strenuous exercise. The objective of this study was to estimate the heritability of liability to epistaxis in the South African Thoroughbred population.

3.2 Materials and Methods

In this study a group of bleeders with a suspected heritable anomaly was selected and their families investigated. The data of all horses that suffered epistaxis whilst racing in Southern Africa and Mauritius from 1986 to 2002, and involving a total of 1252 bleeders were analysed. Due to costs and time constraints, on-course endoscopy is not employed as a routine on any of the Southern African tracks. Only horses that

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showed frank bleeding from the nose (epistaxis) were recorded as a bleeder and included in this study. About 13% of bleeders showed a repeated bout of epistaxis and a further 1% of all recorded bleeders experienced a third bout and permanent suspension. The Jockey Club of Southern Africa started electronic data capture during the 1986 racing season and pedigree information was available as from that time. Earlier information required to calculate the incidence of bleeding amongst ancestors of the post 1986 era was researched retrospectively to 1960 in order that a complete pedigree data file was available for the period 1960 – 2002. Only records of animals with full pedigree information were considered. Pedigree depth was, on average, three to four, but not more than six generations.

About 1 400 Southern African Thoroughbreds that raced with varying degrees of success in Southern Africa were exported to Mauritius during the period 1985-2002. These horses all raced in Southern Africa before exportation and were selected by bloodstock agents and had to pass a veterinary examination as part of the buying process. Because of the screening of horses before acquisition and checking the bleeding status, no horse that was officially recorded as a bleeder in South Africa was exported. Data acquired from the Mauritian Jockey Club showed that appreciable numbers of these imports were recorded as having bled since 1990 and these horses were included in the final data set. In total 148 horses that raced in Southern Africa before exportation suffered epistaxis whilst racing in Mauritius and were suspended. Bleeders in Mauritius are, similar to South African practice, recorded and suspended for periods varying from 3 months for first time bleeders to 6 months for repeat bleeders and permanent suspension for third time bleeders. Only the pedigrees of horses that raced were included in this study as it was not possible to predict whether non-runners would have bled, had they raced. This necessitated the exclusion of non-runners as well as all those horses that raced overseas in countries where bleeding occurrence was not known, recorded or substantiated. Accordingly, the data of sires, grandsires and uncles (being almost exclusively imported or having raced overseas) and those imported females that were unraced or raced abroad, were excluded for the purpose of this study. As to be expected, checking whether horses qualified as runners took painstaking time to research, as there was no easily accessible reference that could be used giving all the required information. Every horse was thus scrutinized individually for racing performance, making use of the Jockey Club of

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Southern Africa's Racing Calendar (South African runners) and website and the Action Racing Online's (ARO) website.

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In an effort to illustrate the transmission of epistaxis from generation to generation, postproband segregation analysis was done of a foundation mare after researching all her direct offspring. The mare used in the example was chosen because she is from a very prominent South African family with good numerical representation over the six generations researched.

In order to estimate the relative importance of heredity and environment, the heritability of liability method developed by Falconer (1965) and further described by Falconer (1989), was utilized. This method is described by Wynne-Davies (1970) as a device for converting the information contained in the incidence of bleeding in the general population of racehorses that ran and in the relatives of those bleeders, into an estimate of the correlation between relatives. The term "liability" includes all the causes that make an individual more or less likely to bleed. The genetic analysis in terms of liability are valid only if liability is multifactorial with many causes of variation, all with relatively small effects, and the genetic control is by genes at more than one or a few loci. According to Curnow & Smith (1975), should a character have an underlying continuity with a threshold, which imposes a discontinuity on the visible expression, and the underlying variable is below this threshold level, the individual has one form of the phenotypic expression, being normal. When it is above the threshold, the individual has the other phenotypic expression, namely affected (bleeder). On a phenotypic level, individuals can thus have only one of two possible values, which might be designated 0 for normal and 1 for affected. In other words, an individual either bleeds or not. Falconer (1965) states that mean/average values between groups of animals/families might differ and would thus vary between 0 and 1, while groups of individuals, however, such as families, or the population as a whole, can have any value, in the form of the proportion or percentage of individuals that are affected. This is referred to as the incidence. With liability being normally distributed, then, the unit of liability is its standard deviation σ. For genetic analyses, incidences must be converted to mean liabilities. The mean liability is then related to the incidence by the (single tailed) normal deviate x, which is the deviation of the

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threshold from the mean in standard-deviation units of liability. Values of x for different incidences are then taken from Falconer (1989) giving the truncated normal distribution for large samples with the proportion of the population with values exceeding the truncation point. Thus, from data consisting of the incidences of bleeding in relatives and the general population, the correlation between relatives in respect of liability can be calculated, and from this the heritability can be estimated.

There were altogether 1252 bleeders whose relatives were analysed. The relatives and degree of relationship between them are described in Table 3.1. Of these, sire-son, sire-daughter, grandfather and uncle were not used as the bleeder status for imported and unraced horses were not known. Since the liability of individuals cannot be measured, it has to be derived from the mean liabilities of groups of individuals.

Table 3.1   Relatives showing the coefficients for different levels of relationship

First-degree 0.50	Second-degree 0.25	Third-degree 0.125
*Sire – son	*Grandfather	
*Sire – daughter	Grandmother	
Dam – son	*Uncles	
Dam – daughter	Aunts	
Full-brothers	Nephews	First cousins
Full-sisters	Nieces	
Full-brother/sister	Grand sons	
Half brother/sister	Grand daughters	

*Data excluded as bleeder status for imported and unraced horses were not known.

3.3 Results

The numbers of relatives examined and the numbers affected with epistaxis are shown in Table 3.2.

Table 3.2 The number of relatives affected with epistaxis according to degree of relationship

DEGREE OF RELATIONSHIP	r	AFFECTED	TOTAL	p%
1st degree	0.50	202	2406	8.4
2nd degree	0.25	251	6845	3.7
3rd degree	0.125	106	4031	2.6

r = coefficient of relationship between relatives

p% = proportion of population affected

The population incidence of epistaxis in Southern African horses was 2.1%. The corresponding values of x and i were taken from Appendix Table A (Falconer, 1989). The correlations, t, were calculated from the approximate formula $t = \frac{M_p - M_r}{i} = \frac{X_p - X_r}{i}$ also from Falconer (1989) where the subscripts p and r refer to the population and the relatives, respectively, m is the mean as a deviation from the threshold, x is the normal deviate of the threshold from the mean and i is the mean deviation of affected individuals from the population mean.

For first-degree relatives

$t = (2.034 - 1.37)/ 2.40 = 0.277$ and

$h^2 = 2t = 0.554$

Results for 1st, 2nd, and 3rd degree relatives are shown in Table 3.3.

Table 3.3   The heritability of liability in the Southern African Thoroughbred population

	p%	x	i	t	r	h²%
Population Relatives	2.1	2.034	2.40			
1ˢᵗ degree	8.4	1.412		0.277	0.50	55.4
2ⁿᵈ degree	3.7	1.786		0.103	0.25	41.3
3ʳᵈ degree	2.6	1.911		0.038	0.125	30.4

where p = proportion of population with values exceeding the truncation point T. x = deviation of T from the mean, in standard-deviation units. r = the coefficient of relationship between relatives. i = mean deviation of individuals with values exceeding T, in standard-deviation units from the population mean.

In order to get a clearer picture as to the transmission of epistaxis from generation to generation, the pedigree of bleeders produce from a South African broodmare, extending back over six generations, were examined and this example is shown in Figure 3.1.
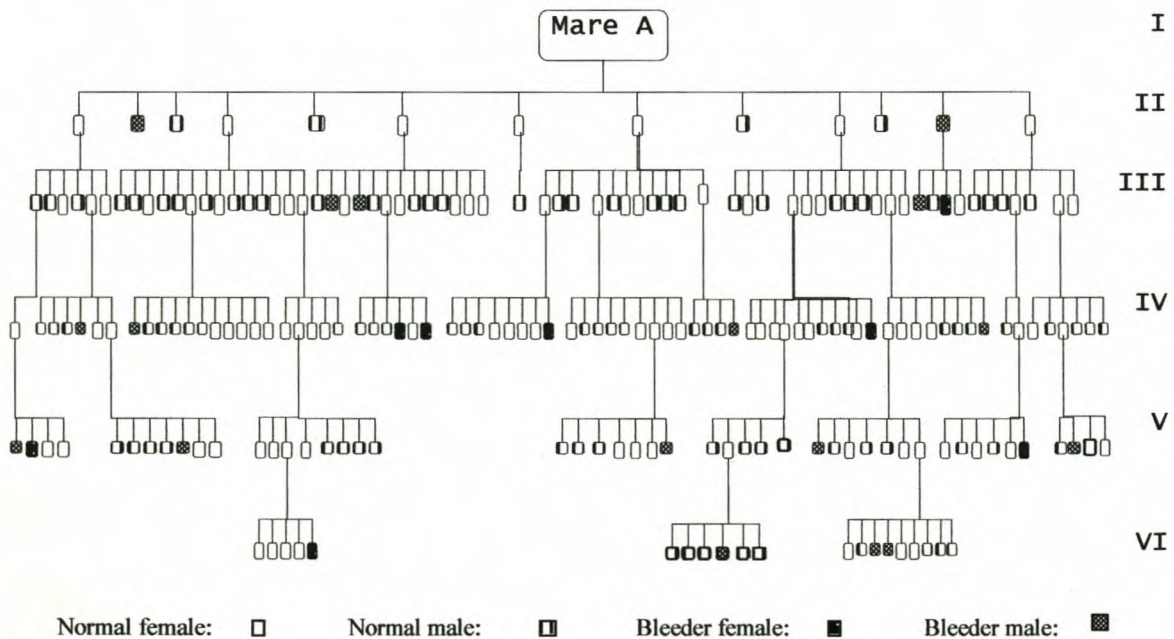

Fig. 3.1   Genealogy of offspring included in a postproband study of a foundation mare (A), used as an example to illustrate the transmission of epistaxis.

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3.4 Discussion

Figure 3.1 shows that the foundation mare "A" produced 13 foals in all, namely six males and seven females. Two of the affected males raced in South Africa, one of which produced bleeders while the other did not go to stud. Although none of the second-generation females demonstrated epistaxis, all but one of these transmitted this trait to future generations. It would appear that this trait might skip generations and appear even after an absence of four generations. Mostly, however, it appears in successive generations or after missing one generation. In total 25 descendants of mare "A" were affected and this syndrome appears to be genetic.

As the bleeding status of most of those sires whose progeny appear in Figure 3.1 (except for those that raced in South Africa) and of most sires used in Southern Africa are unknown (being imported), the affected-to-affected mating (mating bleeder to bleeder), which would be the most efficient way to demonstrate the mode of inheritance, is extremely limited. Presently a small number of stallions that raced in South Africa and were recorded as bleeders, are used at stud. Breeding trails involving these sires could be valuable in reproducing this disorder in an experimental setting and the mode of inheritance proven through a series of designed matings.

The heritability estimates varied from 55.4% to 30.4%, which indicated that the trait has a strong genetic basis. The estimation of heritability of liability shows that the first-degree relatives had a figure of 55.4%, a figure likely to be the most accurate of the three levels of relationship, as it most likely has the smallest standard error because the number of affected relatives is greatest and the standard error of t is multiplied by 2 rather than 4 or 8. The second-degree relatives had a heritability of 41.3% and the third-degree relatives a figure of 30.4%. From Table 3.2, the third-degree relatives had, contrary to expectation, a smaller proportion of total number of relatives (4031) compared to first- degree (2406) and second-degree (6845) relatives. This, however, is explained by the fact that most male pedigrees, being imported, had to be excluded from analysis because of insufficient or unrecorded bleeder data and that a large proportion of imported fillies never raced or were from unraced dams or had raced overseas where bleeder data was not available. The most reliable estimate

is, according to Falconer (1965), probably that from second-degree relatives because first-degree relatives may have some environmental correlation through maternal effects. Curnow & Smith (1975) are of the opinion that second- and third-degree relatives could be very useful in discriminating between different models of inheritance. However, because of the lower degrees of relationship, larger numbers of such relatives will be required for example to get heritability estimates with low standard errors, and the information on these relatives is often less reliable than on first-degree relatives.

The heritability of liability shown in this study could be masked and the full extent not known. This is ascribed to the fact that all officially recorded bleeders are suspended from racing for periods varying from 3 months to permanent suspension. This figure depicts horses that almost exclusively bled on race days, were recorded and suspended after racing by veterinarians licensed by the Jockey Club. Only a small percentage (about 5% of all recorded bleeders) were reported as having bled during exercise and officially recorded as such. However, it is no secret that a good number of horses bleed during or after exercise while preparing for future engagements and are not reported. The reason for this is obvious, as fearing suspension, only a very small number of horses showing epistaxis during training are actually reported and accordingly the full extent of epistaxis amongst racing Thoroughbreds in Southern Africa is extremely difficult to gauge. On average about 25% - 30% of all registered foals never saw the racecourse or had less than five starts (Weideman, unpublished). A good percentage of horses raced very sparingly (one to three runs only, and others less than would be expected). This was most probably due to anatomical defects leading to injuries that made it impossible to race or the individual showing poor potential as a racehorse and having its career consequently curtailed. A proportion of the racehorse population was thus probably not taxed adequately to establish whether they would have suffered epistaxis had they stayed in training for a longer period of time or had been more intensively trained.

Worldwide, varying results were found for the incidence of epistaxis in the Thoroughbred as shown in Table 3.4.

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Table 3.4   Reported worldwide incidence for epistaxis since first report (1950)

Country	Epistaxis (%)	Source of report
Australia	1.21	Hutchins (1998)
Hong Kong	0.66	Mason *et al.* (1983)
Singapore and Malaysia	2.50	Choy (1973), as cited by Cook (1974)
South Africa	1.20	Pfaff (1950)
South Africa	2.10	Present study
Great Britain	0.25	Robertson (1913)
United States of America	0.80	Pascoe *et al.* (1981)
United States of America	7.00	Raphel & Soma (1982)
United States of America	6.80	Sweeney & Soma (1983)
United States of America	5.20	Hillidge & Whitlock (1986)
Korea	13.50	Kim *et al.* (1998)
Mauritius	10.80	Present study

Kim *et al.* (1998) established an incidence of epistaxis for a Korean population of racehorses at 13.5%, which compares favourably with that of the present study of Southern African horses racing in Mauritius (10.8%). There are two similarities between Korea and Mauritius that require mentioning. Neither has breeding industries as such and have to import racehorses from a number of countries, and racing in both countries takes place at sea level or slightly above. Imported racehorses are usually horses that have raced before importation, and of average or slightly above average ability. Although none of the horses exported to Mauritius were officially recorded as having bled, it is possible that some of these horses suffered epistaxis during training and was subsequently disposed of to these countries. This and the fact that racing takes place at sea level, showed that epistaxis was more likely to occur at sea level than at an altitude of approximately 2000 m, could explain the increased incidence (see Chapter 2).

Until such time as owners, trainers, jockeys and breeders own up and divulge all horses stricken with this unfortunate affliction, very slow progress will be made in reducing the incidence of epistaxis in South Africa.

3.5 Conclusion

It is clear that epistaxis in the racing Thoroughbred has a strong genetic basis. The increase in the incidence could be curtailed and reduced through genetic selection where relatively fast progress could be made if bleeders were not used for breeding.

In order to eradicate epistaxis, horses showing frank bleeding from the nostrils after racing or exercise should be suspended and not used for breeding purposes. Stricter measures should be enforced to identify bleeders at exercise and training and after racing. Horses should be monitored for at least half an hour or longer after racing to observe whether any signs of external bleeding are obvious. Horses at training or exercise should also be checked for signs of epistaxis in the pull-up area after exercising and possibly shortly thereafter. Trainers, jockeys and grooms should be advised as to the need to report such horses to the betterment of racing and breeding. If bleeders are not reported, strict measures (fines, suspensions) should be enforced as a preventative measure.

CHAPTER 4

A genetic analysis of epistaxis as associated with EIPH in the Southern African Thoroughbred

4.1 Introduction

Pfaff (1950) published the first report on the incidence of epistaxis in a group of racing Thoroughbreds in South Africa where it was found that at least 1.2% of horses bled from the nose after racing. In the present study, an incidence of 2.1% was recorded for the period 1986-2001 and a sharp increase, especially during the last five years, was noted (see Chapter 2). These figures are in line with most research done world-wide, although an incidence as high as 13.5% was recorded by Kim *et al.* (1998) for Thoroughbreds racing in Korea. Although the incidence is low, it has serious financial implications and of more concern, is the already mentioned increasing trend in the incidence of epistaxis.

Very few references relating to the inheritance of epistaxis in the horse could be found in the available literature. Although a number of researchers mentioned that breeding might be a factor influencing the occurrence of epistaxis in the Thoroughbred, no recent research into the mode of inheritance of epistaxis has been carried out. Robertson (1913), an expert on racehorse pedigrees at that time, went to considerable effort to prove that the stallion was the prime source of epistaxis, suggesting a possible, sex-linked gene inheritance, with most cases in entire males or geldings, although this finding was not statistically tested. It was concluded that bleeding from the nose is inherited as a simple recessive character in the English Thoroughbred, and horses are not likely to break blood vessels unless they carry the homozygous recessive genes, but failed to give more clarification. In a preliminary study (Weideman, unpublished), breeding data of dams and sires that suffered epistaxis

whilst racing, were subjected to a series of test crosses in order to establish whether they were possible carriers of a recessive gene for "bleeding". In the case of mares that "bled", and could thus be regarded as homozygous recessive, these produced only 8.1% "bleeders" against an expected 50% when bred to heterozygous stallions and 0% to homozygous dominant stallions.

Unfortunately, the bleeding status of most stallions is unknown due to the majority of sires being imported and the data of only four sires that raced locally and bled, could be used. Bleeder stallions (assumed to be homozygous recessive) bred to assumed heterozygous or homozygous dominant mares produced 9.7% bleeders against the 50% or 0% expected, respectively. Only one example of an assumed homozygous recessive x homozygous recessive mating was found in the data and this resulted in a bleeder as would be expected (100%). Most of the test crosses thus showed that Robertson (1913) was incorrect in his assumption that epistaxis is inherited as a simple recessive gene and this finding led to the present study being undertaken. Consequently, it is assumed that it is inherited in a polygenic manner expressing itself as a threshold trait.

The use of furosemide (a supposed suppressor of bleeding in racehorses) is prohibited from any racing that falls under the jurisdiction of the National Horseracing Authority of Southern Africa (formerly the Jockey Club of Southern Africa). The increasing prevalence of epistaxis in Southern African Thoroughbreds, as shown in Chapter 2, might be an indication that breeders have, through selective breeding, developed horses whose lungs can no longer sustain the stress of strenuous exercise.

The aim of the present study thus was to obtain more information on the genetic aspects of epistaxis through the use of REML procedures in all the relations of bleeders for Thoroughbreds racing in Southern Africa.

4.2 Materials and Methods

A horse demonstrating epistaxis (frank bleeding from the nose) after racing is reported as a "bleeder" by veterinarians employed by the National Horseracing Authority and was included in the dataset as such. For the purpose of this study the

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dataset did not include any data for starts following the first episode of epistaxis. Bleeders are subsequently suspended. Data of the reported cases has been recorded for all the racing centres in South Africa and Zimbabwe and is available from the National Horseracing Authority of Southern Africa's database. Racing in Southern Africa is conducted at sea level (Durban, Cape Town and Port Elizabeth), approximately 1 000 meters above sea level (Pietermaritzburg) and 2 000 meters a.s.l. (Johannesburg, Bloemfontein, Kimberley and Zimbabwe).

The data covering the period 1986 – 2001 and involving 51 465 individual runners that raced a total of 778 532 runs was analysed. Pedigree information was made available by the National Horseracing Authority of Southern Africa. This included the initial runners from the data as well as the sire, dam and paternal- and maternal grandparents and is shown in Table 4.1. The pedigree-file used in this data set was extended by 11681 animals in order to create more genetic ties. The total number of animals was thus 63 146. The pedigree depth was, on average, three to four, but not more than six generations.

Table 4.1   Description of the data set for epistaxis as associated with EIPH

Total number of race runs	778 532
Total number of animals	63 146
Animals in extended pedigree file	11681
Number of sires	1471
Number of sires producing bleeders	354
Number of dams	16 277
Number of grand sires	2 368
Number of grand dams	10 796
Average incidence for the period	2.1%

The bleeder status of most sires (being imported) and a good deal of imported fillies and mares that raced overseas, was unknown. The data also included a large percentage of unraced dams of runners and grand dams of runners, including those in the extended part of the pedigree file.

In order to estimate heritabilities (h²), including a full pedigree relationship matrix, variance components were obtained by Restricted Maximum Likelihood (REML) procedures after a logit transformation of the data with a linear mixed model using ASREML was fitted (Gilmour *et al.*, 1998). The transformation used in logistic regression is a transformation of the predicted scores of Y (Y') and instead of using Y', the log of probabilities is used as shown in the model

$$\ln\left(\frac{P}{1-P}\right) = a + bX.$$

The ASREML programme estimates variance components for mixed models by restricted maximum likelihood, employing an average information algorithm (Bunter, 2002). As fixed effects for the model, variables that were tested significantly ($p < 0.0001$) in a preliminary data analysis were fitted. In this preliminary analysis of (SAS, 2000), various combinations of variables, age, weight, altitude, sex, month and going were tested. Fixed effects chosen included in the model were gender (females, gelded males, entire males), going (heavy, soft, good, firm), and altitude (at altitude or ± 2000 meters, mid- altitude or ± 1000 meters, sea-level or ± 0 meters). Although all the fixed effects except month, tested significant, only the above-mentioned three, which described the largest part of the overall total variance, were selected, as including all fixed effects caused convergence problems. P-values for these fixed effects are presented in Table 4.2, indicating that age, altitude and going are the most important fixed effects influencing the occurrence of epistaxis as associated with EIPH.

Table 4.2   P-values of fixed effects

FIXED EFFECT	GENMOD P-value
Age	0.0001
Weight	0.0073
Altitude	0.0001
Sex	0.0076
Going	0.0001
Month	0.5464

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In order to investigate the sensitivity of parameter estimates for epistaxis, a series of alternative random effect models were employed. These included animal, maternal and sire models. Analyses were done using linear, logit and probit procedures. Data was subsequently analysed allowing for a binomial distribution of the observed variables (generalised linear mixed models, GLMM). Engel *et al.* (1995) developed the theory behind, and methodology for, the analysis of binary data for estimating fixed and random effects in the context of the GLMM and noted that the iterative restricted maximum likelihood (IRREML) was a simple modification of the usual generalised linear model (GLM). The IRREML approach is very accessible and variants of this procedure have been implemented in publicly available estimation software packages such as ASREML (Gilmour *et al.*,1998). However, Engel *et al.* (1995) found that this approach could result in biased estimates of heritability in the context of animal models or extreme incidences, or where a sizeable number of fixed effects are present in the data. Mixed model methodology has been developed to estimate variance components for categorical traits assuming an underlying scale (Lopez-Villalbos & Garrick, 1999). According to Gilmour *et al.* (1985), an appropriate analytical procedure, based on the binomial distribution, could be accommodated in the class of generalised linear mixed models (GLMM). Animal model methodology has become the standard method for genetic evaluation in horse breeding overseas and the increased application of mixed model methodology to assess genetic values has been an extremely important contribution to breeding in horses as stated by Koenen & Aldridge (2002). The advantages of using the animal model are, amongst others, that it maximises the accuracy of breeding values and the expected genetic gain from selection; that it yields unbiased estimators of genetic and environmental trends in the population and corrects for non-random mating. It also has the ability to improve the estimation of fixed effects and genetic parameters and has the ability to use all available information in the prediction of breeding values. For the majority of fixed effects, convergence was achieved without needing to fix or constrain variance components in any way.

4.3 Results and Discussion

Heritability estimates and standard errors for epistaxis are presented in Table 4.3.

Table 4.3 Heritability estimates and standard errors (S.E.) for epistaxis using logit transformation for different models

Model	Heritability	S.E.
Animal	0.230	0.0225
Maternal	0.001	0.0026
Sire	0.400	0.0555

The estimated breeding values (on the transformed scale) from the sire model of Southern African sires were predicted and are shown in Table 4.4 (sires displaying the highest estimated breeding value for epistaxis), and Table 4.5 (sires showing the lowest estimated breeding value), respectively.

The highest negative values indicated those sires breeding the most bleeders and high positive values those not inclined to breed bleeders.

Table 4.4 **The highest estimated breeding values (sire model and animal model) for epistaxis of Southern African based sires that produced runners during the period 1986-2001 according to their country of origin, year of birth, number of runners (progeny that raced) and number of bleeder progeny produced by individual sires**

Sire	Year of birth	Estimated sire breeding value	Estimated animal breeding value	*Country of origin	Number of progeny that raced	Number of bleeder progeny
Print	1982	-1.38	-2.35	GB	101	11
Lost Chord	1973	-1.26	-2.39	GB	275	17
Al Mufti	1985	-1.24	-2.08	USA	284	21
Folmar	1973	-1.16	-1.98	USA	380	21
Man Of Property	1980	-1.15	-1.91	SAF	139	12
Mansky	1977	-1.12	-1.62	USA	58	6
Barbarolli	1985	-1.12	-1.94	USA	125	10
Nissr	1977	-1.11	-2.01	USA	285	14
Lucy's Axe	1976	-1.10	-1.86	USA	167	13
Unicorn	1980	-1.08	-1.40	SAF	14	4
Flaming Rock	1987	-1.07	-1.72	IRE	119	11
Northern Guest	1977	-1.07	-2.15	USA	817	46
Pochard	1980	-1.05	-1.60	ARG	97	6
Sportsworld	1988	-1.04	-1.66	USA	164	12
Allied Flag	1986	-1.04	-1.66	USA	162	9
Arbat	1987	-0.95	-1.55	USA	121	9
Dominion Royale	1984	-0.94	-1.60	GB	147	10
Broad Reach	1983	-0.93	-1.42	NZ	108	7
Our Casey's Boy	1981	-0.92	-1.75	USA	417	21
Buffo	1969	-0.92	-1.33	GB	160	6
Best By Test	1982	-0.91	-1.67	USA	266	16
Raise a Tradition	1986	-0.91	-1.40	USA	82	7
Comic Blush	1983	-0.88	-1.36	USA	136	9
Sunny North	1979	-0.79	-1.30	USA	178	10
Welsh Harmony	1971	-0.77	-1.23	IRE	190	5

*GB = Great Britain, IRE = Ireland, CAN = Canada, USA = United States of America, NZ = New Zealand, FR = France, ARG = Argentina and SAF = South Africa

Table 4.5   The lowest estimated breeding values (sire model and animal model) for epistaxis of Southern African based sires that produced runners during the period 1986-2001 according to their country of origin, year of birth, number of runners and number of bleeders produced

Sire	Year of birth	Estimated sire breeding value	Estimated animal breeding value	*Country of origin	Number of progeny that raced	Number of bleeder progeny
Peaceable Kingdom	1966	+ 0.72	+ 0.80	USA	370	0
Gallic League	1985	+ 0.66	+ 1.03	IRE	181	0
Song of Songs	1974	+ 0.65	+ 1.00	GB	277	0
Jamaico	1964	+ 0.63	+ 1.41	FR	392	0
Hobnob	1972	+ 0.63	+ 0.95	FR	384	1
All Fired Up	1981	+ 0.60	+ 1.16	USA	461	3
Piaffer	1975	+ 0.60	+ 0.83	USA	250	1
Gallantry	1977	+ 0.59	+ 1.01	SAF	242	0
Really and Truly	1975	+ 0.59	+ 0.46	USA	250	0
Qui Danzig	1987	+ 0.58	+ 0.93	USA	268	1
Sledgehammer	1970	+ 0.53	+ 0.78	NZ	215	0
Over The Air	1974	+ 0.52	+ 0.72	SAF	178	1
Mexico II	1962	+ 0.50	+ 0.79	GB	460	2
Wardlaw	1973	+ 0.50	+ 0.77	USA	101	0
Lustra	1985	+ 0.49	+ 0.75	USA	197	1
Dolpour	1986	+ 0.49	+ 0.78	IRE	200	1
Imperial March	1972	+ 0.49	+ 0.52	CAN	118	0
Speedwona	1981	+ 0.48	+ 0.77	SAF	48	0
On Stage	1980	+ 0.46	+ 0.72	GB	264	2
Bashkirov	1986	+ 0.46	+ 0.69	USA	102	1
Melun	1981	+ 0.45	+ 0.70	USA	122	0
Main Man	1983	+ 0.45	+ 0.75	SAF	200	1
Quick Turnover	1975	+ 0.45	+ 0.62	USA	110	0
Caerdeon	1968	+ 0.44	+ 0.94	GB	269	1
Instrument Landing	1976	+ 0.42	+ 0.49	USA	107	0

* See Table 4.4

The estimated breeding value for epistaxis for all Southern African sires active during the 1986-2001 period, varied from a high of −1.38 to a low of +0.72 while the

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animal breeding values ranged from a high of -2.39 to a low of 0.46. A frequency distribution of the breeding values fitting an animal model and breeding values fitting a sire model are presented in Figures 4.1 and 4.2, respectively, indicating a skewed distribution and a high peak for both sires and animals at approximately zero breeding values. The highest negative values indicated those sires breeding the most bleeders and high positive values those not inclined to breed bleeders.
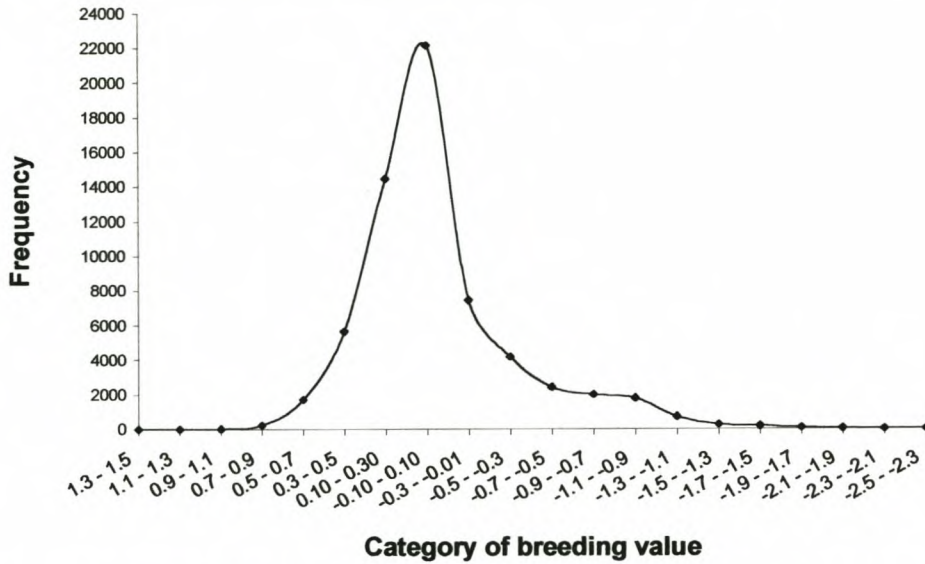

Figure 4.1 Frequency distribution of BLUP of breeding values fitting an animal model (n = 63 142)
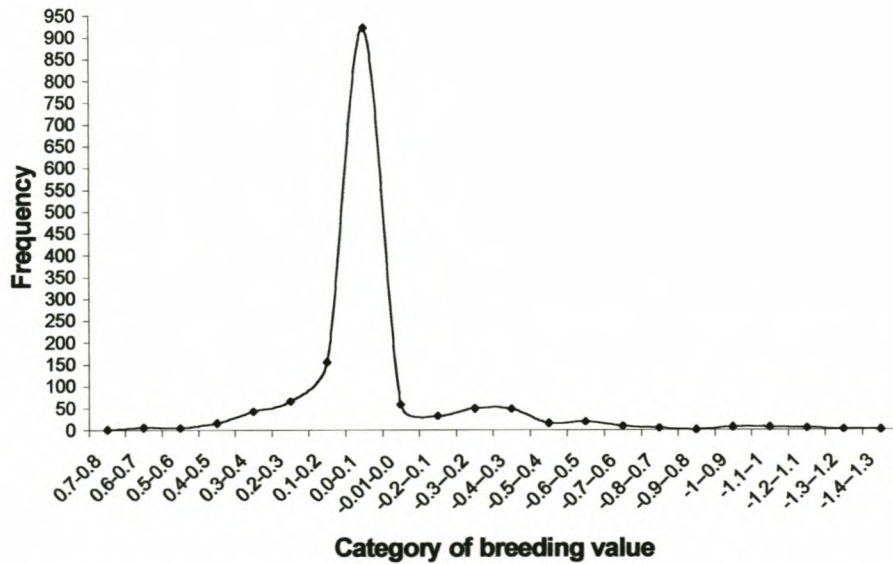

Figure 4.2 Frequency distribution of BLUP of breeding values fitting a sire model (n = 1 471)

Unfortunately, for the purpose of this study, probit analyses did not converge, and only results from the logit transformation are presented. No heritability for maternal effects was evident as shown in Table 3.4. However, the animal and sire models yielded heritability estimates of 0.23 and 0.40, respectively. Gilmour *et al.* (1985) demonstrated a downwards bias of heritability estimates under a sire model if the number of progeny per sire was low, or the incidence was extreme, as was the case in this study (2.1%). Conversely, Engel *et al.* (1995) showed an upwards bias in heritability estimates for simulated data, attributing the positive direction of bias to the increased number of fixed effects included in the simulation data generated and subsequently the analytical model applied. According to Bunter (2002), the above mentioned factors make the prediction of probable direction of bias in heritability estimates for generalised linear mixed model methodology applied to real data sets, extremely complicated. It is thus not possible to speculate about the possibility of bias in these estimates. In several other studies on threshold traits, the sire model yielded higher estimates than the animal model (Snyman *et al.*, 1998; Rust & Groeneveld, 2002). The regression of breeding values of sires fitting a sire model on the corresponding breeding values fitting an animal model are illustrated in Figure 4.3 with a R^2 = 0.93, indicating little change in rank between corresponding BLUP estimates.
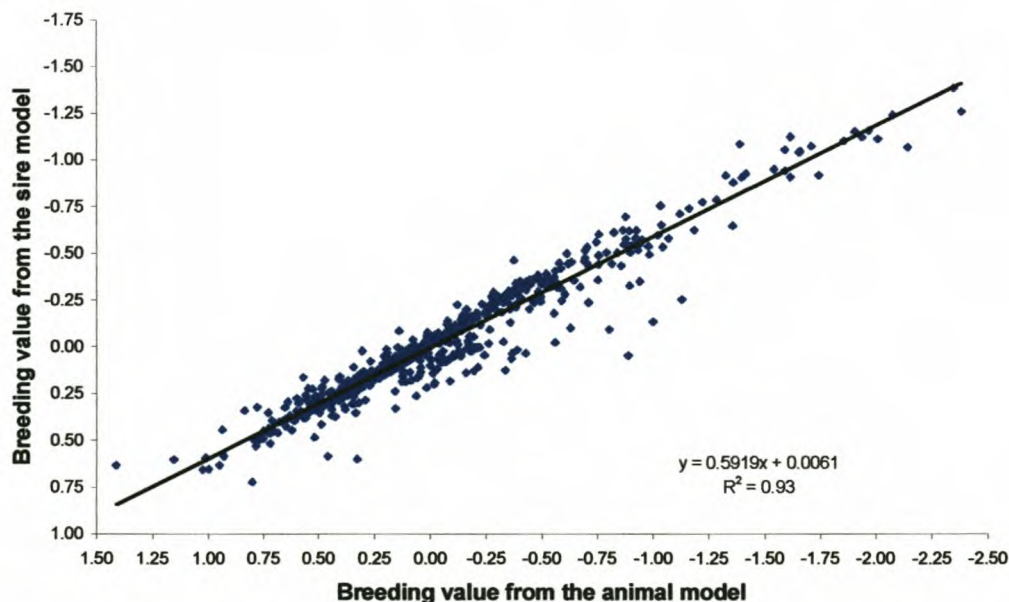

Figure 4.3 Regression of BLUP of breeding values of the sires (n=1471) fitting a sire model on the corresponding breeding values fitting an animal model

No references relating to the heritability of epistaxis in the horse could be found in the available literature. In the previous Chapter (Chapter 3) the heritability of liability to epistaxis according to the procedure of Falconer (1989) was 0.54 for first-degree relatives, 0.41 for second-degree relatives and 0.30 for third-degree relatives. This study estimated the heritability of epistaxis related to EIPH of sires in Southern Africa at 0.40 and considered this to be of a high heritability. Selection against this trait should be effective and relatively fast progress be made at reducing the incidence of this disorder.

The modern international racing and breeding industries allow for a great deal of movement of horses between countries. Only a few of these countries have measures in place where horses demonstrating epistaxis are officially recorded and suspended from racing. Presently, there is no regulation regarding the use of horses for stud purposes in any of the major racing countries. Stallions and mares may be used regardless of performance or physical soundness. Due to insufficient relevant bleeder information of sires and dams being available, a number of problem areas were identified. The main problem hinges around the fact that most sires used at stud in Southern Africa and a small proportion of fillies and mares, are imported. Although it is clear that the introduction of new blood is essential for the future of the horse breeding and racing industry, it unfortunately also has a negative connotation in that imported horses are of unknown bleeder status. Most countries where horses are imported from, either do not officially record epistaxis episodes, or race on furosemide, a supposed suppressor of epistaxis related to EIPH. Some of those imported horses could have bled in their country of origin, where it was knowingly or unknowingly not divulged as it could have a negative effect on their future stud career. However, a number of countries, notably Australia, Hong Kong, New Zealand, South Africa, Dubai, Mauritius, Singapore, Malaysia and some states of the USA, have rules in position regarding the recording and suspension of bleeders while England, Ireland, France, South America and the majority of states in the USA, take no or very limited action. In order to establish an international protocol for bleeders, it is imperative that all racing countries comply with the minimum requirement of recording bleeders. Lists containing the names and breeding of all recorded bleeders should be made available and such afflicted horses should be suspended and not

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registered for breeding purposes. Breeders looking overseas for sires to replenish the local gene pool will now be aware, through screening, as to the bleeding status of such horses and should not consider these as possible acquisitions. Although some high quality and very well bred sires may now no longer be considered, the long-term benefits of not using affected sires far outweigh the possible advantages of using sires predisposed to breeding bleeders.

Over the past four to five decades a marked shift has occurred regarding the country of origin of imported sires into Southern Africa. Whereas most sires were imported from England/Ireland and France during the 1960's and 1970's, towards the end of the 20th century the greater majority of sires were being imported from the USA as shown in Table 4.6.

Table 4.6   The distribution of sires based in Southern Africa according to their country of origin (General Stud Book of South Africa 1960-2000)

Period	*Country of origin (%)							
	GB/IRE	USA	SAF	FR	NZ	ARG	AUS	OTHER
1960-1964	31.1	0.6	57.5	6.0	0.0	0.0	0.0	4.8
1968-1971	37.0	3.2	52.9	4.4	0.0	0.0	0.0	2.5
1980-1983	25.3	10.3	58.0	2.0	1.1	0.7	0.6	2.0
1988-1992	21.6	31.1	37.3	3.3	1.5	3.9	0.4	0.9
1996-2000	17.6	38.8	34.0	3.2	1.9	2.9	0.9	0.7

*GB/IRE = Great Britain/Ireland, USA = America/Canada, SAF = South Africa, FR = France, AUS = Australia, ARG = Argentina, NZ = New Zealand and Other = Chile, Denmark, Germany, Italy, Kenya, Pakistan, Spain, Sweden, Uruguay and sires sired north of line (equator) and south of the line.

This shift could most likely be attributed to the very unfavourable English pound/South African rand exchange rate during the 1980's and 1990's, making it nearly impossible to import superior male breeding stock. South African breeders, with limited resources in hand, alternatively entered the American sire market looking for sires to replace a dwindling band of top quality sires in South Africa. However, they encountered a serious breeding stumbling block, which has stood in the way of meaningful progress if accorded with the upswing in bleeding in South Africa since the 1990's (see Chapter 2).

Unfortunately, very few references could be found relating to the incidence of epistaxis in the United States of America, making comparisons impossible. However, in a number of states of America the use of Lasix (furosemide) in horses during racing was legalized for the prophylaxis of epistaxis associated with EIPH in those racehorses. According to Barnes (2000), data obtained from the New York Racing Association showed that since furosemide was allowed in racing, 76% of all horses that ran and 80% of winners had received this supposed suppressor of bleeding prior to participating in the race. To the lay person, this wide-spread use could indicate that furosemide does indeed prevent or reduce bleeding in horses as indicated by Manohar *et al*. (1994) and Geor *et al*. (2001), but a number of other studies proved limited success notably (Kindig *et al*., 2001), or even no success as shown by Sweeney *et al*. (1990). If it is accepted that furosemide has a prophylactic effect, even a slight effect at reducing the incidence of bleeding, would mean that a good deal of potential sires that raced on furosemide in the USA and did not demonstrate epistaxis, would probably have bled had they raced without it. Furosemide could then be described as having a masking effect, masking epistaxis or reducing the severity thereof so that it is no longer externally visible. These are the sires that could hold danger to the unsuspecting breeder, as the transmission of the epistaxis genes will only become obvious about three-four years later when the offspring of affected horses compete in races. By this time, however, three further crops consisting of unraced two-year olds, yearlings and a crop of unborn foals could be ready to perpetuate the bleeding genes everybody would like to eliminate. Offspring performing above average could, regardless of its bleeding status, be used as the parents of the next generation and the transmission of unwanted genes spread very quickly, sometimes skipping a generation. In order to overcome the problem, breeding values for epistaxis could be estimated which take into account information on the individual as well as related animals (sire, dam, sons, daughters, etc.).

Figures 4.4 and 4.5 show the genetic trend for epistaxis breeding values for all the animals (animal model) and only sires (sire model), respectively. The breeding values from the animal model in Figure 4.4 illustrate that epistaxis has increased from about 0.04 in 1982 to –0.12 in 1998. A similar tendency in the incidence of epistaxis was found in the sire model (Figure 4.5) where an approximate increase from 0.02

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(1970) to -0.08 (1987) was shown. These would indicate that over an 18- year period, a consistent increasing genetic trend was demonstrated.
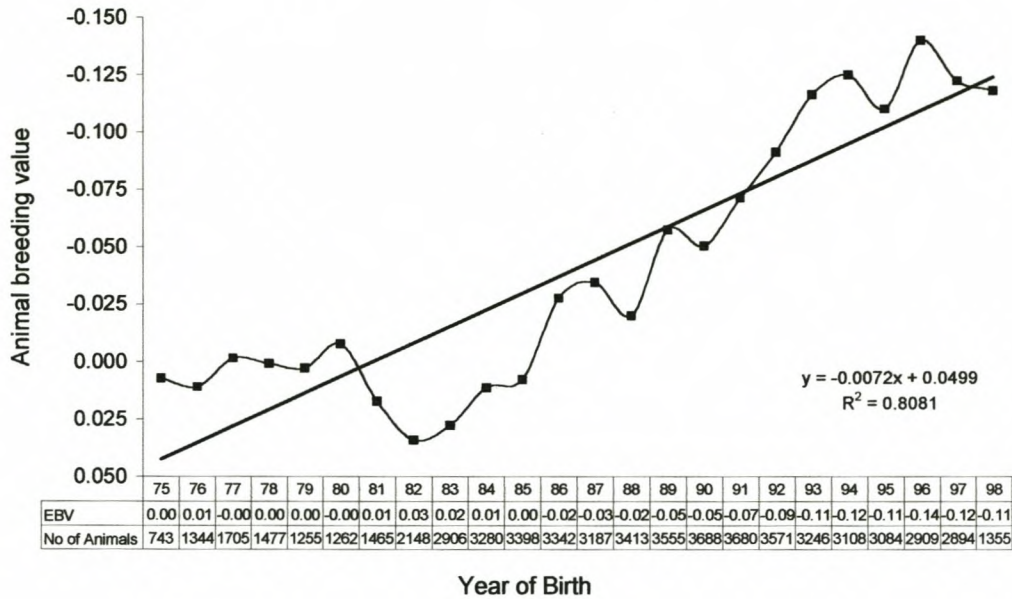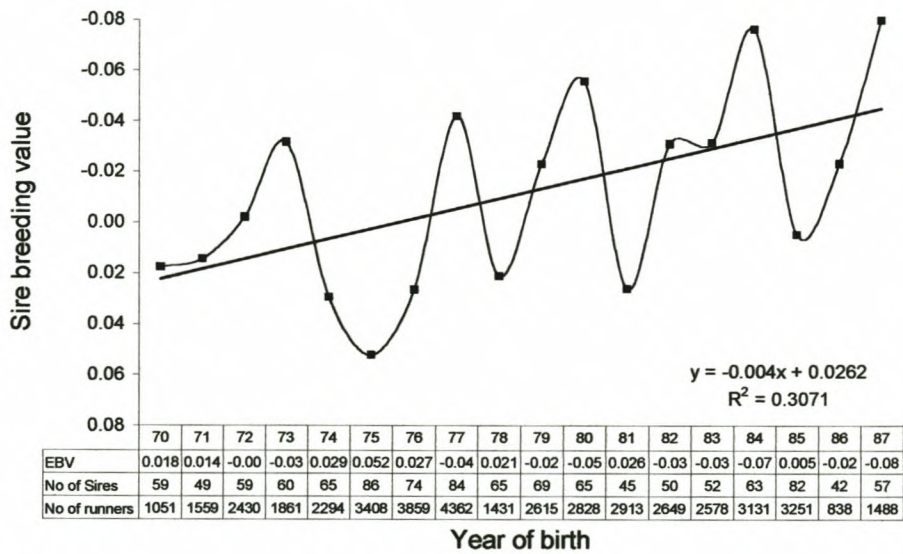

Figure 4.4 **Genetic trend for epistaxis (animal model)**

Figure 4.5 **Genetic trend for epistaxis (sires model), with number of sires per year and number of runners sired.**

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Predicted breeding values also account for the effect of management on an animal suffering epistaxis or not. This is achieved through the use of genetic links between studs. Genetic links are created through the use of mares visiting "outside" stallions and the sale of breeding stock from one stud to another. Through these methods, animals of a related genetic background are raised in different studs, thus studs become linked. Because BLUP or mixed model methodology account separately for the effects of environment and genetics, the management effect can be removed, allowing valid comparisons of breeding stock in different studs. One of the benefits of this methodology is that all animals are evaluated simultaneously, thus breeding values are obtained for animals, ancestors and progeny. The breeding value of individuals could be an invaluable tool when selecting mares to be mated with sires that will minimize the incidence of bleeding in the offspring. Sires having high breeding values, should be mated to mares with low breeding values and *vice versa*, in order to reduce the probability of the occurrence of bleeding in the offspring. From Tables 4.4 and 4.5 it can be seen that both sires having high negative and positive breeding values for epistaxis, have large numbers of progeny and consequently a high level of accuracy. From these tables it is also clear that in order to get a clear picture regarding the breeding values for epistaxis of sires, only those sires that have completed a good number of years at stud and produced a large number of offspring, were selected. All potential sires have to prove their ability on the racetrack before being selected and commencing stud duties, which could mean racing to the age of 5-years and being retired to stud at the age of six. Another 4 to 5-years could be added on to that in order that some (1 to 2 crops) progeny are tested on the racetrack. This indicates that relatively accurate breeding values can only be estimated at 10+ years of age. The reliability of breeding values of sires with a few progeny will not be as high as values for sires with many progeny. As the number of progeny records increase, so will the accuracy of the breeding value.

From Table 4.4, amongst the sires displaying the highest (negative) breeding value for epistaxis, Sportsworld 1988, was the youngest sire, while from Table 4.5, Qui Danzig 1987, was the youngest sire appearing in the table displaying the lowest (positive) breeding value. This implies that reliable breeding values obtained by fitting a sire model can only be estimated at a relatively advanced age which is unfortunate, as sires of this age are mostly regarded as past their best and breeders would rather

support younger, more fashionable and promising sires. Selection bias could also be a problem easily overlooked as this occurs when a sire is represented by only selected daughters at stud (only those females that were good performers on the racetrack or the very well related ones, - the poor performing females being culled). Very few South African bred males (less than 2%) enter the stallion ranks, and the effect of selection bias on the sires can thus largely be ignored. If a good deal of a sire's poorly performing daughters and sons are culled before being adequately exposed and tested on the racetrack, its evaluation would be appreciably higher than its true genetic value. In contrast to the sire model, the animal model uses information from the maternal side of the pedigree and the genetic merit of all relatives plus the animal's own performance are used to estimate the animal's genetic merit. Sires can thus be evaluated appreciably earlier using the animal model. Breeding values obtained by fitting an animal model are thus of great value giving an immediate value, provided that sufficient links are created between studs.

Another alternative could be to "challenge" sires as described by De Greef *et al.* (2001) in broilers. In order to exactly establish the epistaxis position of sires of unknown status, young outstanding sires may be "challenged" for bleeding by testing these stallions' offspring in an epistaxis-challenging environment. As a clear positive relationship between racing at sea level and epistaxis was established (see Chapter 2), it might be fruitful to challenge the Southern African sires, comparing all offspring produced that raced at sea level and at an older age, clearly unfavourable conditions. According to Falconer (1989) it is possible to control the incidence by external means and to make it more nearly optimal and if the character being selected is a reaction to some environmental factor(s), then the effect of those factor(s) can be intensified or reduced so that the incidence is altered. The incidence of the character selected for (epistaxis) can thus be increased through racing horses at sea level (an unfavourable environmental factor). This changed incidence is best regarded as a shift in the threshold relative to the mean liability of the population and, by shifting the threshold, selection could be more effectively applied.

4.4 Conclusions

This study has shown that epistaxis as related to EIPH in the Southern African Thoroughbred sires, has a strong genetic basis. The results obtained suggest that genetic determination of epistaxis is of enough importance to warrant inclusion in a global breeding strategy. This should include the establishment of an international database for epistaxis and that estimated breeding values be used in the selection of parents. Further steps should include the disqualification of "bleeders" from being registered in the Stud Book and that furosemide be banned internationally from racing, or failing that, breeders should refrain from buying potential sires that have raced on this drug. In an effort to get a clearer picture of stallions transmitting epistaxis, sires used in Southern Africa could be tested and exposed by having their offspring compete in a challenging environment (racing at sea level versus at altitude). This may shed more light on the predisposition of imported sires with unknown bleeder status and those who raced after treatment with furosemide, to produce a sizeable number of bleeders.

CHAPTER 5

General conclusions

A sound breeding objective is a prerequisite for any breeding programme. The identification of selection objectives is the first step in developing such breeding plans. The main object is to ingrain the best qualities of the breed, while upgrading the weaknesses. Only by getting rid of the least desirable genes and concentrating the best can the gene pool be changed. Modern Thoroughbred breeders are becoming less inclined in culling weaknesses, as the number of unsound females and females that bled whilst racing and were then retired to stud, will testify. Well related fillies that demonstrated epistaxis are indiscriminately mated with sires (mostly of unknown bleeder status) giving rise to offspring of very doubtful predisposition to epistaxis. A closer study of the pedigree of such affected females to establish the prevalence of epistaxis in her immediate family may be of great value especially if estimated breeding values of sires and dams can be used in conjunction with a pedigree scrutiny. Although it may not be possible to predict with certainty whether offspring would bleed or not (due to a number of factors including: sire or dam bleeding status unknown, sire or dam unraced, whether sire or dam raced on Lasix, altitude, age etc.), a good indication of the possibility of bleeding may be achieved if some or all of those factors are known. Inbreeding, according to Pfaff (1976), has for many years been regarded as one of the main factors to be blamed for producing "softer" horses and increased susceptibility to epistaxis.

Breeding based on drug free performance is the ideal and should surely be the ultimate objective of any racing and breeding enterprise. In a number of states of America the use of Lasix (furosemide) in horses during racing was legalized for the prophylaxis of epistaxis associated with EIPH in those racehorses. According to Barnes (2000), data obtained from the New York Racing Association showed that since furosemide was allowed in their racing, 76% of all horses that ran and 80% of winners had received this supposed suppressor of bleeding prior to participating in the race. With some of the recently retired racehorses and the present population of racehorses receiving treatment (furosemide), breeding to eradicate the problem is not

possible if the efficacy of this drug is related to the number of horses competing on it. All of the world's leading racing jurisdictions with the exception of some states in America believe, and recently confirmed, that the presence of medication in racehorses during races, is undesirable and must be prohibited. Hancock, a well known American breeder is quoted by Barnes (2000) stating that since America abandoned the traditional standard of " hay, oats and water," by allowing certain drugs during racing, the quality of this country's Thoroughbreds has steadily declined. Although there is no scientific evidence that the use of medication in American racing has caused or contributed to the decline in the average annual number of starts per horse, the data produced by the Jockey Club in the United States reveals a significant and ongoing trend. According to Hancock as cited by Barnes (2000), the breed gets weaker and weaker as it gets more and more medication and he further states that in 1970, regarded as the dawn of the medication era, the average American horse made 10.2 starts per year. After producing generation after generation of drug-dependent horses, the figure declined to 9.2 starts per horse in 1980, 7.9 starts in 1990, 7.2 per year in 1999 and 6.8 starts per year in 2002. The widespread use of race day medication (Lasix) and or used in conjunction with phenylbutazone in the United States, could be creating a gene pool requiring drugs to perform.

A huge stumbling block to overcome in efficiently analysing the bleeder position in Southern Africa (and the rest of the world) is that the bleeding status of imported dams and granddams that raced overseas, is not known. A good deal of bleeders recorded in Southern Africa are from imported mares (15 % of the total number of bleeders) and/or are out of dams from imported mares (28% of total number of bleeders). This, in effect, means that approximately one third of the female Thoroughbred population at stud in Southern Africa is a closed book regarding the inheritance and possible transmission of the bleeder genes. This, coupled with the fact that most sires at stud in Southern Africa are imported (and is thus also of unknown bleeder status), further emphasizes the problem of an incomplete bleeder database. It is clear that in order to establish a total picture as to the extent of bleeding internationally, it is imperative that all racing countries record and suspend bleeders and that an easily accessible international database for such bleeders be introduced.

A number of factors unfortunately prevent this apparently easily attainable goal - the fact that pre-race treatment with Lasix (furosemide) is allowed in a number of states in America coupled with a lax or non existent bleeder protocol evident in a number of countries. Until all countries adhere to the basic prerequisites of a drug free race day environment and the recording and suspension of bleeders are met, little progress in eliminating this affliction will be made.

Taking into account the high heritability estimates obtained, the possibility of the inheritance of a major gene(s) or a trait loci or (QTL) cannot be ruled out. This should be investigated further. Most of the major genes thus far identified were initially detected through strong familial trends in recorded data for the trait of interest. The greatest application of major genes is likely to be for traits that are difficult or expensive to measure such as epistaxis, meaning that only a few populations are likely to record data for these traits. Use of these populations and the analysis of phenotypic data to detect segregation of major genes, should provide for further studies aimed at exploiting genetic markers. The identification of genetic markers for epistaxis is an area that could help to disclose horses genetically predisposed to this condition. The availability of a genome map for horses is fundamental in finding markers showing the chromosomal location of genes. The identification of such markers for epistaxis could facilitate the breeding of animals not susceptible to this disease. Through the identification of genetically predisposed horses early in life, selecting against these genes by excluding these horses from being registered for breeding, should result in making good progress towards eliminating this affliction.

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