

# INTRODUCTION

Southern Africa is inherently rich in fauna and flora and has many poisonous plants (Kellerman *et al.* 2005), as well as a large number of infectious diseases (Coetzer & Tustin 2004). It is essential, from a diagnostic point of view, to distinguish plant poisonings from other poisonings and from infectious diseases.

A sound knowledge of the economic impact of plant poisonings is important in determining research priorities, evaluating risk and developing or implementing cost-effective control measures (Kellerman, Naudé & Fourie 1995). The losses incurred as a result of plant poisonings can be either direct or indirect. Direct losses entail, amongst others, death, reduced milk yield and reproductive failure (Nielsen & James 1992). Indirect losses include the cost of control measures, for example fencing, strategic grazing practices, supplementary feeding, veterinary expenses, and temporary or permanent non-utilisation of affected pastures, and the diminished value of infested land.

Based on a model developed by Nielsen and James (1992), a study of the economic impact of plant poisonings/mycotoxicoses on the livestock industry of South Africa was conducted by Kellerman, Naudé and Fourie (1995). According to this study the annual countrywide stock losses from all causes, including drought, infectious diseases and internal parasites, were estimated at 3 % for cattle and 5 % for small stock. In the case of cattle, 10 % of the total number of deaths could be attributed to poisonous plants/mycotoxicoses. In the case of small stock this figure was 15 %.

In 1995/96, cattle were valued at R1 531 a head and small stock at R177 a head. Consequently, the estimated cost of plant poisonings/mycotoxicoses in South Africa in 1995/96 was approximately R58 million in the case of cattle and R47 million in the case small stock (Kellerman, Naudé & Fourie 1995). Based on consultation with experienced veterinarians and/or stock owners, the current (2008) mean values for cattle and small stock are taken as R6 000 and R1 000 a head, respectively (L. Prozesky, University of Pretoria, unpublished data 2008). Using the cattle and small stock numbers cited by Kellerman, Naudé and Fourie (1995), the current total annual cost of plant poisonings/mycotoxicoses to the livestock industry in South Africa amounts to approximately R226 million in the case of cattle and R264 million in the case of small stock.

Sixty per cent of stock losses attributed to plant/mycotoxin poisonings were ascribed to six poisonous plants and mycotoxicoses in both cattle and small stock. The diseases in question are cardiac glycoside poisoning, caused by *Moraea* spp. in particular, seneciosis, gifblaar poisoning (*Dichapetalum cymosum)*, gousiekte, *Lantana* poisoning (*Lantana camara)* and diplodiosis (*Diplodia maydis*) in cattle, and geeldikkop (*Tribulus terrestris)* and dikoor, vermeersiekte (*Geigeria* spp.), cardiac glycoside poisoning, seneciosis, gousiekte and diplodiosis in small stock.

Gousiekte (direct translation “quick disease”) is a cardiotoxicosis of ruminants characterised by heart failure four to eight weeks after the ingestion of certain rubiaceous plants (Newsholme & Coetzer 1984; Kellerman *et al.* 2005). Animals may succumb four to eight weeks after a single intake of toxic plant material, even though under natural conditions, animals usually consume toxic material daily over a period of time until they die (Theiler, Du Toit & Mitchell 1923). Animals typically drop dead without premonitory signs and death is usually precipitated by exercise. In a minority of cases symptoms consistent with congestive heart failure can be observed, including weakness, lagging behind the flock, staggering, gasping for breath and dyspnoea (Kellerman *et al.* 2005). *Pachystigma pygmaeum* (North-West Province and Gauteng) is the most important of these plants, followed in descending order of importance by

*Fadogia homblei* (central Limpopo Province, Gauteng, the north-western part of Mpumalanga), *Pavetta harborii* (Limpopo Province), *Pachystigma thamnus* (KwaZulu-Natal), *Pavetta schumanniana* (Mpumalanga and Limpopo Province) and *Pachystigma latifolium* (Mpumalanga and KwaZulu-Natal) (Kellerman, Naudé & Fourie 1995). The wild date, *F. homblei*, apparently causes stock losses mostly in early summer, and *P. pygmaeum* later in the season, while *P. harborii* and *P. schumanniana* are associated with gousiekte throughout the year (Theiler, Du Toit & Mitchell 1923; Kellerman *et al.* 2005; Fourie *et al.* 1994).

In 1995/96, the expected annual impact of mortalities from gousiekte on the livestock industry in South Africa was estimated at approximately R2,3 million in the case of cattle and R1 million in the case of small stock (Kellerman, Naudé & Fourie 1995). Based on the cattle and small stock numbers cited by Kellerman, Naudé and Fourie (1995) and a value of R6 000 a head in the case of cattle and R1 000 a head in the case of small stock, the current (2008) annual impact of mortalities as a result of gousiekte alone is estimated at approximately R9 million (cattle) and R5,2 million (small stock). No values are available for the indirect costs, but these are considerable, particularly as a result of the temporary or permanent non-utilisation of affected pastures and the diminished value of land infested with toxic plants.

## OBJECTIVES OF THIS STUDY

1 To investigate the effect of the duration of latency on the nature of the myocardial lesions in the left free ventricular wall in sheep dosed with *P. pygmaeum.*
2 To characterise microscopical lesion patterns in animals with short and with medium to long latent periods. The latent period is defined as the time that elapses between first exposure of the animal to toxic plant material and death of the animal.
3 To describe the full spectrum of lesions of gousiekte in sheep so that even “atypical” cases can be diagnosed accurately.
4 To study the pathogenesis of the myocardial lesions in sheep exposed to plants associated with gousiekte and rats injected with pavetamine.



# LITERATURE REVIEW

## 2.1 THE DIFFERENT PLANTS THAT CAUSE GOUSIEKTE

### 2.1.1 *Pachystigma pygmaeum* (Schltr.) Robyns (Rubiaceae) (figs 2.1, 2.2)

Also known as the hairy gousiektebossie, *Pachystigma pygmaeum* is a low-growing shrublet with an extensive underground system of stems and roots (fig. 2.1). It occurs mainly in the North-West Province and Gauteng but may also be found in the northern parts of the Free State, Limpopo Province, Mpumalanga and KwaZulu-Natal. The broadly elliptical leaves arise from the stem in opposite pairs and are covered in yellowish hairs. The mature fruit resembles a green tomato (fig. 2.2).

*P. pygmaeum* frequently occurs in open grassland in high-lying areas and remains dormant in the ground during the dry winter months. In early spring, after the first rain, the gousiektebossie sprouts before the grass. The green young shoots are very attractive to animals that have been starved of greenery during the winter and deaths usually occur in the latter half of the summer (Vahrmeijer 1981; Kellerman *et al.* 2005).

Theiler (1906–1907) and Walker (1908–1909) reported the first outbreaks of gousiekte. Sir Arnold Theiler confirmed, by means of a field trial and sub-sequent dosing trials on the farm Witfontein near Kempton Park, that *Vangueria pygmaeum* (now *P. pygmaeum)* was the cause of the disease.

**Figure 2.1** ***Pachystigma pygmaeum*** **is a low-growing shrublet**

**Figure 2.2** **The fruits of** ***P. pygmaeum*** **resemble a green tomato**

### 2.1.2 *Pachystigma thamnus* Robyns (Rubiaceae) (figs 2.3, 2.4)

*Pachystigma thamnus* resembles *P. pygmaeum* except that the former is smooth leaved and occurs mainly in KwaZulu-Natal and Mpumalanga. The suspected toxicity of this plant (Steyn 1949; Codd & Voorendyk 1966) was confirmed by Adelaar and Terblanche (1967).

**Figure 2.3** ***Pachystigma thamnus*** **is smooth leaved**

**Figure 2.4** ***P. thamnus.*** **Note the smooth leaves and mature fruit**

### 2.1.3 *Pachystigma latifolium* Sond (Rubiaceae) (fig. 2.5)

*Pachystigma latifolium* is an underground shrub with massive woody axes. The plant grows approximately 0,5 m tall and the glabrous leaves have short petioles. The large green fruit ripens to dark-brown or black. *P. latifolium* occurs on open and rocky grassland, grassy banks of streams and on coastal sand flats. It is the only plant known to cause gousiekte near the coast (Kellerman *et al.* 2005)

**Figure 2.5 *Pachystigma latifolium* is an underground shrub with massive woody axes**

### 2.1.4 *Fadogia homblei (= F. monticola)* De Wild (Rubiaceae) (figs 2.6, 2.7)

*Fadogia homblei* (wild date) has a perennial taproot with subterranean branches from which aerial stems grow. These are squarish in cross-section and 300–500 mm in height. The leaves have a characteristic dark green, shiny upper surface and a greyish-white, felted lower surface (fig. 2.6). Small, yellowish,

star-shaped flowers form in the axils of the leaves. The round fruits are pea-sized and blacken with age (fig. 2.7). *F. homblei* occurs in central Limpopo Province, Gauteng and the north-western part of Mpumalanga. Hurter *et al.* (1972) investigated outbreaks of gousiekte in the Vaalwater area of Limpopo Province and identified *F. homblei* as a cause of the disease.

**Figure 2.6** ***Fadogia homblei.*** **The leaves have a dark green, shiny upper surface and a greyish-white, felted lower surface**

**Figure 2.7** ***F. homblei.*** **The round fruits are pea-sized and blacken with age**

### 2.1.5 *Pavetta harborii* S. Moore (Rubiaceae) (figs 2.8, 2.9)

*Pavetta harborii* is a perennial, woody shrublet about 50 cm in height, with subterranean branches that give rise to groups of aerial stems (fig. 2.8). The plant occurs in Limpopo Province and Botswana and one plant can cover an area of approximately 2 m in diameter. Opaque bacterial spots may be visible when the leaves are held up against the light (Van Wyk *et al.* 1990). A characteristic feature of the plant is the clusters of white, scented, tubular flowers with star-shaped corolla lobes and protruding styles that appear in early summer on the previous season's growth (fig. 2.9). The fruits are pea sized and become shiny black with age (Kellerman *et al. 2005*).

The discovery of *P. harborii* as a cause of gousiekte resulted from the periodic occurrence of gousiekte in an area where *P. pygmaeum* did not occur. Uys and Adelaar (1957) proved that *P. harborii* caused the disease by feeding the plant to cattle and sheep following heavy stock losses on a farm north-west of Gauteng.

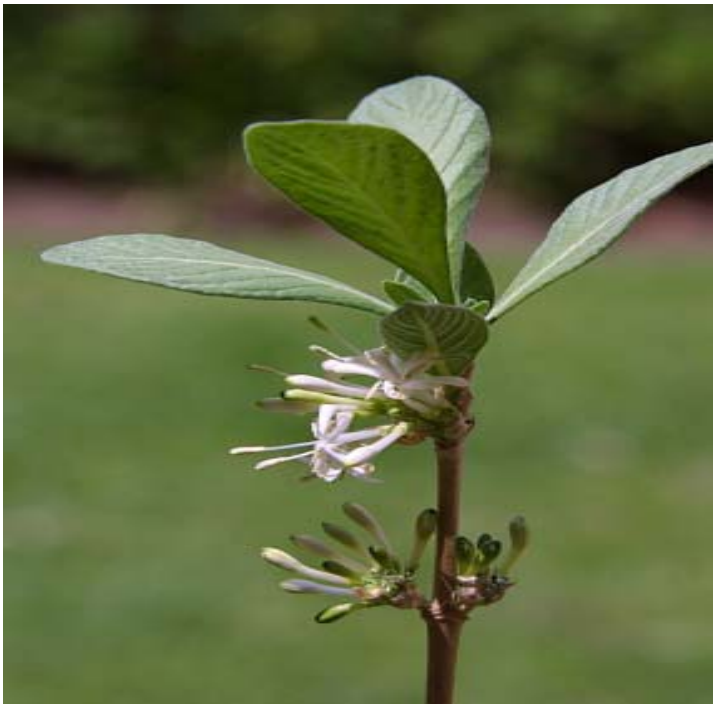

**Figure 2.8 *Pavetta harborii* is a perennial, woody shrublet about 50 cm in height**

**Figure 2.9** ***P. harborii.*** **Note the cluster of white, tubular flowers with star-shaped corolla lobes**

### 2.1.6 *Pavetta schumanniana* F. Hoffm. (Rubiaceae) (figs 2.10, 2.11)

*Pavetta schumanniana* is a deciduous, multi-branched shrub or small tree up to 4 m in height, with dark-brown, furrowed bark (fig. 2.10). The yellowish-green, leathery leaves have a rough upper surface and a hairy lower surface and are conspicuously net veined and covered with dots. The small, white flowers are borne in clusters at the ends of short branchlets, in the axils of fallen leaves on the previous year's growth (fig. 2.11). When mature, the fruits are small and black. *P. schumanniana* occurs mostly in Limpopo Province and favours rocky places (Kellerman *et al.* 2005; Kellerman, Naudé & Fourie 1995). Naudé, Smit and Adelaar (Onderstepoort Veterinary Institute, unpublished data 1962) reproduced the disease experimentally by feeding the plant to sheep.

**Figure 2.10** ***Pavetta schumanniana*** **is a deciduous, multi-branched shrub**

**Figure 2.11** ***P. schumanniana.*** **Small, white flowers are borne in clusters at the ends of short branchlets**

## 2.2 CLINICAL SIGNS

Gousiekte in ruminants is characterised by heart failure four to eight weeks after ingestion of certain rubiaceous plants (Theiler, Du Toit & Mitchell 1923; Newsholme & Coetzer 1984; Kellerman *et al.* 2005). The majority of animals with gousiekte drop dead without showing clinical signs of congestive heart failure. However, a few animals may show lethargy, weakness, lagging behind the flock, staggering, respiratory distress, dyspnoea and tachycardia a few days prior to death (Walker 1908–1909; Theiler, Du Toit & Mitchell 1923; Pretorius & Terblanche 1967; Pretorius *et al.* 1973). In an unusual outbreak of gousiekte in Île-de-France sheep, many animals showed signs of congestive heart failure, such as respiratory distress and oedema, mainly of the head (Prozesky *et al.* 1988).

Death can occur spontaneously or can be precipitated by exercise or other forms of stress, such as handling of the animals (Kellerman *et al.* 2005). During a field outbreak of gousiekte near Potchefstroom in North-West Province, electrocardiograph (ECG) recordings were performed on approximately ten out of a flock of seventy adult sheep. The animals were kraaled and released after the ECG recordings. Six of the animals dropped dead within 200 m of the kraal without showing any premonitory signs of congestive heart failure. Macroscopically, early signs of congestive heart failure, for example accumulation of fluid in body cavities and mild to moderate lung oedema, were present. Microscopical lesions characteristic of gousiekte (*vide infra*) were also noted. The ECG recordings of the affected animals did not reveal any abnormalities prior to death (L. Prozesky, University of Pretoria, unpublished data 1988). According to Pretorius *et al.* (1973), sino-atrial node (SA node) arrhythmias were recorded in 56 % of animals exposed to *P. pygmaeum*. They speculated that cardiac dilatation, which is often associated with gousiekte, causes a gallop rhythm, bundle branch block and an increase in P wave duration.

Pretorius and Terblanche (1967) studied the clinical signs and cardiodynamics in 50 experimentally induced cases of gousiekte (using *P. pygmaeum)* in sheep and goats. They reported that after ingestion of plant material there was a

considerable variation in the time before cardiac abnormalities could be detected by auscultation. Furthermore, not all the abnormalities manifested in all the animals, and the signs occurred in various combinations. Most clinical signs only occurred during the last two weeks before death, and in 10 % of animals no signs could be detected before death (table 2.1).

**Table 2.1 Clinical signs observed in experimentally induced gousiekte (using *P. pygmaeum)* in 50 sheep and goats (Pretorius & Terblanche 1967)**

| Clinical sign | Animals showing clinical signs (%) | Longest period prior to death on which clinical signs were noted (days) |
|---|---|---|
| Dyspnoea | 24 | 1,5 |
| Tachycardia | 86 | 6 |
| Gallop rhythm | 48 | 7 |
| Hyperpnoea | 72 | 10 |
| Split first heart sound | 66 | 10 |
| Systolic murmur | 66 | 11 |
| Arrhythmia | 56 | 11 |
| Dull first heart sound | 50 | 27 |

## 2.3 MACROSCOPICAL LESIONS

Most animals that die of gousiekte show signs of congestive, mild to severe heart failure, including generalised congestion, ascites, hydropericardium, hydrothorax and pulmonary oedema (Theiler, Du Toit & Mitchell 1923; Newsholme & Coetzer 1984; Kellerman *et al.* 2005; Prozesky *et al.* 1988).

According to Theiler, Du Toit and Mitchell (1923) dilatation of both ventricles and thinning of the free ventricular walls were present in the majority of affected animals. Other workers claim that more frequently the hearts of animals that succumb to the disease are normal in size and the ventricular walls are thin and of a tough consistency (Newsholme & Coetzer 1984).

## 2.4 LIGHT-MICROSCOPICAL LESIONS

A diagnosis of gousiekte is usually based on the presence of characteristic microscopical lesions in the myocardium, namely foci of myofibre necrosis that vary in size, with replacement fibrosis and lymphocytic infiltrates of varying intensity, especially in the subendocardial region of the apex and the left free ventricular wall (Theiler, Du Toit & Mitchell 1923; Newsholme & Coetzer 1984; Kellerman *et al.* 2005), and focal or diffuse atrophy of fibres (Prozesky *et al.* 1988).

Various researchers reported marked deviations from the “typical” lesions that characterise a histological diagnosis of gousiekte. Smit (1959) reported degeneration of myofibres as the principal lesion in some naturally poisoned animals. Hurter *et al.* (1972) described multifocal degeneration of myocardial fibres as the most significant lesion in experimental cases. Mortalities were reported in animals without notable lesions during dosing trials by Adelaar, Terblanche and Smit (1966). They attributed these more acute lesions to the high dosage of plant material administered to the animals.

Even though the myocardial lesions associated with gousiekte are well described, little information is available on the chronological development, and consequently on the pathogenesis of the lesions. A study of the development of the lesions is complicated by the fact that acute, subacute and chronic lesions may be present in the same animal.

There appears to be a close similarity in the pattern of the myocardial lesions in the majority of animals that die naturally of gousiekte and that in humans suffering from dilated cardiomyopathy. The latter is regarded as a syndrome in which a variety of aetiological factors, such as viral infections, toxic agents, chronic alcohol abuse and genetic factors, have been implicated (Unverferth 1985; Weekes *et al.* 1999).

## 2.5 TRANSMISSION ELECTRON MICROSCOPICAL LESIONS

Transmission electron microscopical lesions reported in experimentally induced gousiekte in sheep fed *P. pygmaeum* included a lack of register between sarcomeres of adjacent myofibrils and disintegration and necrosis of myofibrils. The disintegration of myofibrils was attributed to a loss of myosin rather than actin (Schutte *et al.* 1984).

## 2.6 PATHOPHYSIOLOGY

Pretorius and Terblanche (1967) suggested that the primary lesion in gousiekte may be inhibition of the contractile mechanisms of the myocardium, induced by the toxic principle in gousiekte plants. Snyman, Van der Walt and Pretorius (1982a) showed that the myocardial lesions in gousiekte are characterised by impaired energy utilisation in the contractile system and a depression of the natural actomyosin (n-actomyosin) ATP-ase activity ratio with reduced sensitivity to activating calcium ions. The same authors also demonstrated a significant reduction in ATP and creatine phosphate levels in the myocardial tissue of sheep with gousiekte. They furthermore postulated that the imbalances in energy production and utilisation along with impaired oxygen uptake by the mitochondria may be primary or secondary in the pathogenesis of heart failure associated with gousiekte.

To study the cardiodynamics of gousiekte, the cardiac pulmonary flow index (CPFI) was used. The CPFI can be defined as the ratio of the cardiopulmonary blood volume to stroke volume, and is equivalent to the number of heartbeats necessary to pump blood from the right side to the left side of the heart through the lungs. The CPFI is obtained by measuring the flow of technetium-labelled erythrocytes through the right and left ventricles using a sodium iodide crystal and collimator system (Van der Walt & Van Rooyen 1977; Van der Walt *et al.* 1981).

An increase in the CPFI is attributed to a decrease in both the stroke volume and the pumping efficiency of the left ventricle relative to the right ventricle,

resulting in an increase in the ventricular filling pressure (volume overload) and pulmonary blood volume (Pretorius *et al.* 1973; Van der Walt & Van Rooyen 1977; Van Rooyen *et al.* 1984). An increase in the CPFI (Van der Walt & Van Rooyen 1977; Fourie *et al.* 1989), serum aspartate transaminase (AST) activity (Fourie *et al.* 1989; Fourie 1994) and tachycardia are reliable clinical and pathophysiological indicators of cardiac damage in sheep with gousiekte (Van der Walt & Van Rooyen 1977; Van der Walt *et al.* 1981; Fourie *et al.* 1989).

## 2.7 TOXIC PRINCIPLE IN GOUSIEKTE PLANTS

Numerous attempts over a period of 30 years failed to isolate the toxic principle of gousiekte plants. The main reasons were the presence of a latent period of approximately six weeks and the variation in toxicity of the plants (Fourie *et al.* 1995). The active principle in plants inducing gousiekte was however eventually isolated (Fourie 1994) and identified as pavetamine (R. Vleggaar, University of Pretoria, unpublished data 1997).

Fractions were tested in sheep and goats and the induction of gousiekte was confirmed on the basis of cardiac failure and microscopically detectable myocardial lesions (Van der Walt & Van Rooyen 1977; Van der Walt *et al.* 1981; Fourie *et al.* 1995). As a result of these studies, rubiaceous plants can now be assayed chemically to determine their toxicity.

The following characteristics of pavetamine were identified:

- It is water soluble.
- It is relatively heat stable.
- It passes through a dialysis membrane.
- It has cationic properties.
- It stains orange when sprayed with ninhydrin on TLC plates.
- It is pH labile.

Pavetamine is a polyamine. Polyamines are a group of biologically highly active substances that affect numerous body functions, including cell growth and the synthesis of new myocardial protein. The inhibition of myocardial protein

synthesis by pavetamine may play a significant role in the chronological development of the myocardial lesions of affected animals (Schultz *et al.* 2001).

## 2.8 *PAVETTA HARBORII* AND PAVETAMINE AS A CARDIOTOXIN IN RATS

An alcohol extract of *P. harborii* was reconstituted and administered subcutaneously to rats to study various cardiodynamic parameters (Pipedi 1999). The results showed a significantly lower myocardial contractile strength and left ventricular systolic pressure in the affected animals, confirming that the *P. harborii* alcohol extract induced left heart failure in rats.

Macroscopical lesions included mild to moderate oedema of the lungs in rats necropsied six days after administration of pavetamine. No macroscopical or light-microscopical lesions were noted in the hearts of the experimental animals, but transmission electron microscopical studies revealed mild lesions, including focal areas of myofibrillar lysis and thickening of the Z bands (Pipedi, 1999). Furthermore, pavetamine inhibited protein synthesis in rat hearts (Schultz *et al.* 2001). Ellis, Schultz and Basson (2007) studied mechanisms of cardiac gene expression in rats following pavetamine intoxication, and according to Hay, Schultz and Schutte (2008), pavetamine significantly reduced systolic function in experimental rats.

Subtractive-suppressive hybridisation (SSH), a technique used to identify differentially expressed genes between two populations (Diatchenko *et al.* 1996), and micro-array analysis, used to study gene expression of the entire genome of an organism, were used to investigate the mechanism of action of pavetamine on the hearts of rats (Ellis, Schultz & Basson 2007). Immuno-labelling of myosin revealed an altered expression of myosin whereas the expression of actin remained unaltered. Heart failure in mammals is characterised by a down-regulation of the alpha isoform and up-regulation of the beta isoform of cardiac protein genes (Sucharov *et al.* 2004). Intoxication with pavetamine gave rise to expression of the beta isoform resulting in a slower contraction and saving of energy. The myosin light chain is the main regulatory protein in muscle contraction and consists of two subfamilies, viz. the

essential light chain and the regulatory light chain (Yamashita *et al.* 2003). In pavetamine intoxication down-regulation of the myosin light chain 2 gene results in impaired contractility of the heart. Furthermore, pavetamine intoxication resulted in increased expression of the four-and-a-half LIM domain proteins (Ellis, Schultz & Basson 2007). The latter proteins are also up-regulated in cases of hypertrophic cardiomyopathy (Lim, Roberts & Marian 2001).

## 2.9 HEART FAILURE

Heart failure is an important aspect of gousiekte and central to the pathophysiology of the disease. The tremendous variation in the extent of the myocardial lesions associated with gousiekte and other cardiotoxic plants underpins one of the major problems in studying cardiac pathology, viz. the assessment of the functional significance of lesions.

On the one hand, lesions that appear severe may be clinically silent, whereas relatively mild lesions may be associated with severe cardiac dysfunction, arrhythmias and death. Acute lesions that may be difficult to detect may also be responsible for severe cardiac dysfunction and death. This is well illustrated in the case of *Dichapetalum cymosum* (gifblaar) and *Moraea* spp. (tulp) poisoning in cattle and sheep (Kellerman *et al.* 2005).

Another problem in investigating cardiac pathology is the evaluation of chronic lesions where scar tissue is all that remains, providing no clue to the aetiology or pathogenesis of the insult. The picture is complicated further by the ongoing, active nature of myocardial reaction patterns in which acute, subacute and chronic processes may overlap, as is the case in most animals that succumb naturally to gousiekte. Even though the initial causes of heart failure in man and in animals with gousiekte differ, most of the anatomical and cardiodynamic changes are similar (Pipedi 1999).

Two types of heart failure are most frequently recognised, namely acute heart failure and congestive heart failure. Both types have been reported in animals

that succumb to gousiekte following an incubation period of four to eight weeks (Theiler, Du Toit & Mitchell 1923).

### 2.9.1 Acute heart failure

Acute heart failure is characterised by a sudden loss of consciousness, falling with or without convulsions, severe pallor of the mucosae and either death or recovery. *Dichapetalum cymosum* (gifblaar) is an example of a plant that causes sudden death in ruminants owing to acute heart failure. The toxic principle, monofluoroacetate (Marais 1944) is absorbed and converted to monofluorocitrate that blocks the tricarboxylic acid cycle by inhibiting aconitase. Affected animals usually drop dead after drinking water or if exerted. Macroscopically and microscopically there is very little or no morphological evidence of damage to the heart (Kellerman *et al.* 2005).

### 2.9.2 Congestive heart failure

The term congestive heart failure denotes a condition in which the heart is unable to meet the haemodynamic demands of the body, all compensatory mechanisms have been exhausted, and the characteristic clinical and pathological signs, particularly expansion of the extracellular fluid volume and oedema, are present. The terms left-sided and right-sided heart failure refer to the failure of the left or the right ventricular capacity to meet the body's needs and involve the pulmonary circulation and the systemic circulation, respectively.

Irrespective of the cause, conditions that result in heart failure can be divided into those that –

- impose a sustained pressure overload on one or both ventricles;
- institute a sustained volume overload on one or both ventricles;
- alter normal contractility of myocardial fibres or result in loss or replacement of cardiac muscle; or
- alter the heart's normal rate and rhythm (Kumar, Cotran & Robbins 2003).

When myocardial contractibility is disturbed, there is a limited set of compensatory responses by the body to increase cardiac output. These are referred to as intrinsic and systemic responses, respectively. Intrinsic responses include the Frank Starling mechanism of increased preload to control ventricular performance (ventricular dilatation), and ventricular hypertrophy. Systemic responses include an increase in heart rate and peripheral resistance, redistribution of blood flow, venular constriction and an increase in blood volume (Jubb, Kennedy & Palmer 1993; Braunwald 1992; Kumar, Cotran & Robbins 2003).

### 2.9.3 Intrinsic cardiac responses to reduced cardiac output

The morphological changes that represent the intrinsic responses to a reduced cardiac output are presented in cases of cardiomyopathy irrespective of the aetiology. Cardiomyopathy is a general diagnostic term designating primary myocardial disease that can be attributed to various causes.

The subdivision of cardiomyopathies is controversial and can be confounding. For example, some authors distinguish between concentric and eccentric hypertrophic cardiomyopathy (Jubb, Kennedy & Palmer 1993) whereas others refer only to hypertrophic cardiomyopathy (Kumar, Cotran & Robbins 2003). This is confusing because the criteria used to distinguish between dilated and eccentric hypertrophic cardiomyopathy are unclear. Restrictive cardiomyopathy is a form of cardiomyopathy seen mainly in humans. It was included in this study owing to the resemblance of the myocardial lesions in advanced cases (subendocardial fibrosis) to those often seen in more chronic cases of gousiekte.

It was therefore decided to resort to the subdivision of cardiomyopathies into three major clinicopathological groups, viz. dilated, hypertrophic and restrictive cardiomyopathy, as outlined by Kumar, Cotran and Robbins (2003).

*2.9.3.1 Dilated cardiomyopathy*

Macroscopically the dilated heart is enlarged and flabby and has a rounded shape with thinning of the free wall of the dilated chamber. Microscopically the myocardial lesions are non-specific and are characterised by varying degrees of myocyte degeneration, necrosis, atrophy and hypertrophy with multifocal interstitial fibrosis and a mononuclear inflammatory infiltrate (Jubb, Kennedy & Palmer 1993; Bastianello *et al.* 1995; Kumar, Cotran & Robbins 2003).

Dilated cardiomyopathy that varies in extent is often seen in natural cases of gousiekte (Theiler, Du Toit & Mitchell 1923). Dilated cardiomyopathy is a syndrome in which a variety of aetiological factors in man and animals, such as viral infections, toxic agents (e.g. cobalt), chemotherapeutic agents (including doxorubicin) (Kumar, Cotran & Robbins 2003), ionophore intoxication (Bastianello *et al.* 1995), chronic alcohol abuse, genetics and tachycardia, give rise to a common cardiac dysfunction (Unverferth 1985; Weekes *et al.* 1999; Byrne *et al.* 2002). Furthermore, a variety of circumstantial evidence suggests that dilated cardiomyopathy can result directly from myocarditis (Pisani, Taylor & Mason 1997; Kumar, Cotran & Robbins 2003).

In bovine hereditary dilated cardiomyopathy a number of myocardial proteins are significantly reduced (Weekes *et al.* 1999; Furuoka *et al.* 2001). Many of these proteins are found exclusively in the mitochondria, suggesting that in this case the myocardium is unable to provide sufficient energy to cope with the increased workload and mechanical stresses associated with the re-arrangement of the muscle fibres.

Dilated cardiomyopathy in humans and animals may be a pathological or a physiological response, for example the requirements of improved performance in racehorses. When it is the result of a pathological condition it is characterised by impaired systolic function with a reduced ejection fraction and increased preload (volume overload) since the heart adapts to maintain a normal stroke volume (Dec & Fuster 1994; Weekes *et al.* 1999). When the dilated cardiomyopathy is a physiological response, an increase in the preload will increase

the contractile force of the heart, which, within certain limits, results in an increase in the stroke volume (Braunwald 1992; Guyton & Hall 2000).

*2.9.3.2 Hypertrophic cardiomyopathy*

Cardiac hypertrophy, also referred to as hypertrophic cardiomyopathy, is characterised by a reversible increase in the mass and wall thickness of the affected chamber and an increase in the size of the papillary muscles and the *trabeculae carneae.* Cardiac hypertrophy is a compensatory response, both physiologically and pathologically, to increased systolic or diastolic workload (pressure overload) and mostly affects the ventricles and the interventricular septum (Jubb, Kennedy & Palmer 1993; Kumar, Cotran & Robbins 2003; Guyton & Hall 2000). It has not been reported in animals that succumbed to gousiekte.

Hypertrophic cardiomyopathy is characterised by powerful contractions that rapidly expel blood from the ventricles. However, the hypertrophic walls impair diastolic filling and consequently cardiac output is reduced. Even though the aetiology is unknown in many cases of hypertrophic cardiomyopathy in humans, abnormalities in the genes that encode sarcomeric contractile proteins appear to play an important role in the development of this syndrome. Other causes in both humans and animals include increased systolic loads as found in aortic stenosis and pulmonic stenosis, and pulmonary hypertension in patent *ductus arteriosus* (Jubb, Kennedy & Palmer 1993; Kumar, Cotran & Robbins 2003; Cunningham & Klein 2007).

The macro-appearance of an affected heart will depend on the chamber affected and the nature of the insult. In general, hypertrophy of the right side of the heart makes the heart broader at its base, hypertrophy of the left side increases the organ's length, and bilateral hypertrophy produces a more rounded shape than normal.

The most characteristic microscopic lesion in hypertrophic cardiomyopathy is a haphazard arrangement of hypertrophic, abnormally branching myocytes. The endocardium may be diffusely opaque as a result of fibrosis. The latter

alteration may be the best indication of hypertrophy in the atria, which may be difficult to assess macroscopically (Jubb, Kennedy & Palmer 1993; Radostits *et al.* 2000; Kumar, Cotran & Robbins 2003).

#### *2.9.3.3 Restrictive cardiomyopathy*

Restrictive cardiomyopathy is characterised by a primary decrease in ventricular function, resulting in reduced ventricular filling during diastole. It is not a common form of cardiomyopathy in humans and animals, and the most common cause in man is a condition (disease) referred to as endomyocardial fibrosis, a disorder of unknown aetiology that accounts for up to 10 % of cases of childhood heart disease in tropical areas. Apparently, genetic factors account for some of the cases. Restrictive cardiomyopathy is sometimes associated with dilated cardiomyopathy.

The atria are usually dilated and the ventricles may be of normal size or dilated, particularly during the later stages of the disease. The endocardium is thickened and opaque, and histological features include endocardial fibrosis that may extend into the underlying myocardium (subendocardial fibrosis), which results in congestive heart failure (Kumar, Cotran & Robbins 2003).

## 2.10 HYPOTHESES

- The myocardial lesions in animals with gousiekte represent a final common pathway of cellular damage rather than a manifestation of a specific type of heart disease.
- Pavetamine affects myocardial protein synthesis but does not selectively affect myocardial fibres in the subendocardial region. The predilection for hypertrophy or degeneration of myofibres in the subendocardial region is related to both the effect of pavetamine and the diminished perfusion that potentiates the primary myocardial dysfunction.
- “Atypical lesions” represent a manifestation of the disease in a progression that terminates with dilated cardiomyopathy.