

**A STUDY OF THE PATHOLOGY AND PATHOGENESIS OF MYOCARDIAL  
LESIONS IN GOUSIEKTE, A CARDIOTOXICOSIS OF RUMINANTS**

**by**

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**Submitted in fulfilment of the requirements for the degree  
of  
DOCTOR OF PHILOSOPHY  
in the Department of Paraclinical Sciences, Faculty of Veterinary  
Science, University of Pretoria**

**Date submitted: 2008**



## DEDICATION

*This work is dedicated to my wife Lindie,  
and my two children Ruardt and Natasha.*

*Your encouragement and love never waver.*

*Thank you for your support and for giving meaning to my life.*

**I would like to express my sincere gratitude and appreciation to the following people:**

- Dr S. S. Bastianello (Gribbles Vet Lab, 33 Flemington Street, Glenside, SA 5065, Australia), Dr N. Fourie (Intervet, Private Bag X2026, Isando, 1600 South Africa), Mrs R.A. Schultz, Mrs L. Labuschagne, Mr B.P. Martens of the Division of Toxicology, Onderstepoort Veterinary Institute (OVI) and Prof. F.T. Kellerman, for their unconditional support throughout the project and the positive spirit in which we collaborated over many years. It was indeed a privilege to work with all of you as a team.
- Mrs E. van Wilpe of the Electron Microscopical Unit of the Faculty of Veterinary Science, for her support.
- Prof. P.N. Thompson of Production Animal Studies of the Faculty of Veterinary Science, for his support regarding the interpretation of the statistical analysis results.
- Prof. J. A. Lawrence and Prof. C. J. Botha, for their valuable inputs, ongoing support and for the proofreading of and advice on the manuscript.
- Mrs E. Vorster, for typing the thesis in its final form.



## DECLARATION

I was assisted with the dosing trials by Prof. N. Fourie (Intervet, Private Bag X2026, Isando, 1600 South Africa), Mrs L. Labuschagne and Mrs R.A. Schultz (Division of Toxicology, (OVI).

With the exception of the abovementioned assistance this thesis is the candidate's own original work. It is not submitted concurrently in candidature for any other degree.

**Candidate: L. Prozesky**

## TABLE OF CONTENTS

	PAGE
Dedication .....	ii
Acknowledgements .....	iii
Declaration .....	iv
Summary .....	vii
Opsomming .....	xi
List of tables.....	xv
List of figures .....	xvi
<b>CHAPTER ONE: Introduction .....</b>	<b>1</b>
Objectives of this study .....	3
<b>CHAPTER TWO: Literature review .....</b>	<b>4</b>
2.1 The different plants that cause gousiekte.....	4
2.1.1 <i>Pachystigma pygmaeum</i> (Schltr.) Robyns (Rubiaceae) .....	4
2.1.2 <i>Pachystigma thamnus</i> Robyns (Rubiaceae) .....	6
2.1.3 <i>Pachystigma latifolium</i> Sond (Rubiaceae).....	7
2.1.4 <i>Fadogia homblei</i> (= <i>F. monticola</i> ) De Wild (Rubiaceae) .....	7
2.1.5 <i>Pavetta harborii</i> S. Moore (Rubiaceae) .....	9
2.1.6 <i>Pavetta schumanniana</i> F. Hoffm. (Rubiaceae) .....	10
2.2 Clinical signs .....	12
2.3 Macroscopical lesions .....	13
2.4 Light-microscopical lesions .....	14
2.5 Transmission electron microscopical lesions .....	15
2.6 Pathophysiology .....	15
2.7 Toxic principle in gousiekte plants .....	16
2.8 <i>Pavetta harborii</i> and pavetamine as a cardiotoxin.....	17
2.9 Heart failure .....	18
2.9.1 Acute heart failure .....	19
2.9.2 Congestive heart failure .....	19
2.9.3 Intrinsic cardiac responses to reduced cardiac output .....	20
2.9.3.1 Dilated cardiomyopathy .....	21
2.9.3.2 Hypertrophic cardiomyopathy .....	22
2.9.3.3 Restrictive cardiomyopathy .....	23
2.10 Hypotheses .....	23
<b>CHAPTER THREE: A macro- and light-microscopical study of the pathology of gousiekte in sheep .....</b>	<b>24</b>
3.1 Introduction.....	24
3.2 Materials and methods.....	25
3.2.1 Dosing trial .....	25
3.2.2 Pathology .....	26
3.2.3 Imaging analysis.....	26
3.3 Results .....	28
3.3.1 Macropathology.....	29
3.3.2 Histopathology .....	32
3.3.3 Imaging analysis.....	42
3.3.3.1 Descriptive statics .....	42
3.4 Discussion .....	45
3.5 Conclusions .....	51
<b>CHAPTER FOUR: A transmission electron microscopical study of the myocardial lesions in sheep with gousiekte.....</b>	<b>53</b>
4.1 Introduction .....	53



	<b>PAGE</b>
4.2	Materials and methods ..... 54
4.2.1	Dosing trial ..... 54
4.2.2	Pathology ..... 55
4.2.2.1	Light-microscopy ..... 55
4.2.2.2	Transmission electron microscopy ..... 55
4.3	Results ..... 56
4.3.1	Light-microscopy ..... 56
4.3.2	Transmission electron microscopy ..... 57
4.4	Discussion ..... 69
<b>CHAPTER FIVE: A study of the pathological lesions in rats exposed to pavetamine ..</b>	<b>73</b>
5.1	Introduction ..... 73
5.2	Materials and methods ..... 74
5.2.1	Pavetamine extraction ..... 74
5.2.2	Experimental animals and dosing regimen ..... 74
5.2.3	Pathology ..... 76
5.2.3.1	Transmission electron microscopy (TEM) ..... 76
5.2.3.2	Light-microscopy ..... 76
5.2.3.3	Imaging analysis ..... 76
5.2.3.4	Statistical analysis ..... 77
5.3	Results ..... 77
5.3.1	Clinical signs ..... 77
5.3.2	Macroscopical examination ..... 79
5.3.3	Light-microscopical examination ..... 79
5.3.4	Transmission electron microscopical examination ..... 82
5.3.5	Statistical analysis ..... 84
5.4	Discussion ..... 87
<b>CHAPTER SIX: General discussion and conclusions on the pathogenesis of gousiekte ..</b>	<b>92</b>
6.1	Introduction ..... 92
6.2	Effect of pavetamine on heart muscle ..... 95
6.3	Myocardial lesions ..... 100
6.4	Evidence of ventricular failure ..... 106
6.5	Compensatory mechanisms ..... 109
6.6	Conclusions ..... 110
6.7	Proposed future research areas ..... 112
<b>BIBLIOGRAPHY ..</b>	<b>113</b>
<b>APPENDIX Gousiekte research publications of which the candidate was either the main author or a co-author ..</b>	<b>126</b>

## SUMMARY

### A STUDY OF THE PATHOLOGY AND PATHOGENESIS OF MYOCARDIAL LESIONS IN GOUSIEKTE, A CARDIOTOXICOSIS OF RUMINANTS

by

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Trials were performed in sheep and rats to elucidate the pathogenesis of the myocardial lesions in gousiekte. In the first trial the macro- and light-microscopical lesions and myofibre morphometrical changes were studied in ten sheep exposed daily to *Pachystigma pygmaeum* at 10 g/kg live body weight for 23 to 31 days. All the treated animals either died or were euthanased *in extremis* between 31 and 51 days after the commencement of dosing. In the second trial the myocardial ultrastructural lesions were studied in six sheep dosed with *Fadogia homblei* at a dosage rate of 10 g/kg per day live body weight for 22 to 23 days. All the treated animals either died or were euthanased *in extremis* between 34 and 57 days after the commencement of dosing. The main objective of the third trial was to compare the myocardial lesions in rats exposed to pavetamine with lesions recorded in sheep exposed to *P. pygmaeum* and *F. homblei* plant material. Seven rats were injected intraperitoneally with pavetamine at a dosage rate of 5 mg/kg on day 0 and three were killed on day 6. The remaining four were injected with a second dose of pavetamine at a dosage rate of 3 mg/kg on day 27 and euthanased on day 42.

In the sheep exposed to *P. pygmaeum* pulmonary oedema and hydropericardium were present in eight, hydrothorax in four and ascites in two

cases. In two sheep cardiac dilatation was associated with subendocardial pallor (fibrosis) and transmural myocardial mottling. Myofibre hypertrophy was recorded in all the sheep, myofibre necrosis and replacement fibrosis occurred in seven animals the latter being particularly evident in animals with medium to long latent periods. A mononuclear cellular infiltration that varied from mild to severe was evident in all the cases and endocardial thickening, which is an indication of cardiac dilatation, was present in seven animals. Myofibre atrophy occurred in eight animals and was the most striking lesion in a sheep with a short latent period. “Typical” gousiekte lesions, characterised by myofibre necrosis and atrophy, replacement fibrosis and an associated round cell infiltration in the subendocardial region, were present in eight of the sheep. “Atypical” lesions, characterised by hypertrophy of myofibres with multifocal coagulative necrosis or myofibre atrophy, were recorded in two sheep, both of which had short latent periods. The myofibre diameter and nuclear area in the affected animals differed statistically from those of the controls (larger) and anisocytosis and anisonucleosis were particularly striking in sheep with intermediate to long latent periods.

The most striking ultrastructural lesions included breakdown of myofibrils, involving in particular what appeared to be thick (myosin) filaments; selective proliferation of organelles such as mitochondria and sarcoplasmic reticulum in areas previously occupied by myofibrils; excessive folding of the myofibre sarcolemma; and advanced myocardial injury characterised by complete loss of myofibrils with loss of intercellular connections and necrosis of myocardial cells.

No lesions were present in the rats exposed to a single dose of pavetamine, although they became anorexic and lost weight. Rats exposed to pavetamine twice became anorexic within two to three days after the first exposure and regained weight within a few days (on about day 7). However, they kept on losing weight after the second exposure and continued to do so until termination of the experiment. As a general rule the myocardial lesions were mild in the rats dosed twice with pavetamine. Transmural multifocal myocardial necrosis, with an associated round cell infiltration and replacement fibrosis, was the most striking light- microscopical lesion. The lesions were comparable with “atypical”



lesions in ruminants. Ultrastructural lesions in degenerative/necrotic fibres included karyolysis, swelling of the mitochondria and focal lysis of myofilaments. In rats exposed to pavetamine twice there was statistical evidence of myofibre atrophy.

Based on the information emanating from this study and previous research the following deductions are made to explain the pathogenesis of the myocardial lesions:

1. Pavetamine has a prolonged effect on the myocardium owing to inhibition of protein synthesis, and also influences the energy production system, which affects the function of myocytes. The structure of the myocytes is not affected during the early stages of the latent period but eventually myofibre hypertrophy, atrophy, degeneration and necrosis are seen.
2. Replacement fibrosis in the subendocardial region is a sequel to the effect of pavetamine on myofibres and the consequence of ischaemia owing to impaired myocardial perfusion of, particularly, the subendocardial region, as a result of decreased myocardial contraction, increased diastolic pressure, tachycardia and myofibre hypertrophy.
3. Cardiac dilatation is a compensatory mechanism, a result of the myofibre damage inflicted by pavetamine and ischaemia (pathological dilatation).
4. Lesions in animals with gousiekte represent a final common pathway of cellular damage rather than a manifestation of a specific type of heart disease. Animals may die during any stage in the development of the lesions. "Atypical" lesions represent a manifestation of the disease in a progression that terminates with dilated cardiomyopathy if the animal does not die during the early stages.

These deductions provide an explanation, for the first time, for the latent period between ingestion of the plant and the onset of illness in gousiekte. They also explain the wide range of lesions seen in experimental cases. It



furthermore demonstrate that the “typical” lesions of gousiekte are not pathognomonic, and that the absence of “typical” lesions does not rule out a diagnosis of gousiekte in situations where exposure to the causative plants and the clinical history support such a diagnosis.



## OPSOMMING

### A STUDY OF THE PATHOLOGY AND PATHOGENESIS OF MYOCARDIAL LESIONS IN GOUSIEKTE, A CARDIOTOXICOSIS OF RUMINANTS

deur

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Proewe is gedoen in skape en rotte om die patogeenese van die miokardiale letsels in gousiekte te ontrafel. In die eerste proef is die makro- en ligmikroskopiese letsels en morfometriese veranderinge in miokardiale vesels bestudeer in tien skape blootgestel aan *Pachystigma pygmaeum* teen 'n dosis van 10 g/kg per dag lewende gewig vir 23 tot 31 dae. Al die behandelde diere is óf dood, óf in ekstremis genadedood toegedien tussen 31 en 51 dae na aanvang van die dosering. In die tweede proef is die miokardiale ultrastrukturele letsels bestudeer in ses skape wat gedoseer is met *Fadogia homblei* teen 'n dosis van 10 g/kg per dag lewende gewig vir 22 tot 23 dae. Al die behandelde diere is óf dood, óf genadedood toegedien in ekstremis tussen 34 en 57 dae na aanvang van die dosering. Die hoofdoel van die derde proef was om die miokardiale letsels in rotte blootgestel aan pavetamien te vergelyk met letsels waargeneem in skape blootgestel aan plantmateriaal van *P. pygmaeum* en *F. homblei*. Sewe rotte is intraperitoniaal ingespuut met pavetamien teen 'n dosis van 5 mg/kg op dag 0 en drie is doodgemaak op dag 6. Die oorblywende vier is ingespuut met 'n opvolgdosis pavetamien teen 3 mg/kg op dag 27 en is genadedood toegedien op dag 42.

In die skape blootgestel aan *P. pygmaeum* is longedeem en hidroperikardium waargeneem in agt skape, hidrotoraks in vier en askites in twee gevalle. In twee skape is kardiëse vergroting geassosieer met subendokardiale bleekheid (fibrose) en transmurale miokardiale spikkeling waargeneem. Miovesel-

hipertrofie is waargeneem in al die skape, miovesel-nekrose en verplasingsfibrose is waargeneem in sewe diere en laasgenoemde was veral prominent in diere met medium tot lang latente periodes. 'n Mononukluêre sellulêre infiltrasie wat varieer van matig tot erg is waargeneem in al die gevalle en endokardiale verdikking, 'n aanduiding van hartvergroting, was teenwoordig in sewe diere. Mioveselatrofie het in agt diere voorgekom en was die mees opvallende letsel in 'n skaap met 'n kort latente periode. "Tipiese" gousiekteletsels, gekarakteriseer deur miovesel-nekrose en atrofie, verplasingsfibrose en 'n geassosieerde rondeselinfiltrasie in die subendokardiale area is waargeneem in agt van die skape en "atipiese" letsels, gekarakteriseer deur hipertrofie van miovesels met multifokale koagulatiewe nekrose of mioveselatrofie, is in twee gevalle waargeneem, albei met kort latente periodes. Die mioveseldeursnee en die kernoppervlakte in die aangetaste diere het statisties verskil van die kontroles (groter) en anisositose en anisonukliose was veral opvallend in skape met intermediêre tot lang latente periodes.

Die opvallendste ultrastrukturele letsels het die volgende ingesluit: afbreek van miofibrille, met aantasting van veral dik (miosienfilamente) selektiewe proliferasie van organelle soos mitochondria en sarkoplasmiese retikulum in areas wat vroeër deur miofibrille in beslag geneem is; oormatige vouing van miovesel-sarkolemma; en gevorderde miokardiale beskadiging gekenmerk deur 'n algehele afwesigheid van miofibrille met verlies van intersellulêre verbindings en nekrose van miokardiale selle.

Geen letsels is waargeneem nie in rotte blootgestel aan 'n enkele dosis pavetamien, hoewel hulle anoreksies was en gewig verloor het. Rotte tweemalig blootgestel aan pavetamien was anoreksies binne twee tot drie dae na die eerste blootstelling en het toe weer gewig opgetel binne 'n paar dae (teen ongeveer dag 7). Hulle het egter aangehou om gewig te verloor na die tweede blootstelling en dit het voortgeduur totdat die eksperiment beëindig is. As 'n algemene reël was die miokardiale letsels in rotte wat twee keer met pavetamien gedoseer is baie matig. Transmurale multifokale miokardiale nekrose, met 'n geassosieerde rondeselinfiltrasie en verplasingsfibrose was die algemeenste ligmikroskopiese letsels. Die letsels kan vergelyk word met "atipiese" letsels in herkouers. Ultrastrukturele letsels in degeneratiewe of



nekrotiese vesels het die volgende ingesluit: kariolise, swelling van die mitochondria en fokale lise van miofilamente. In rotte tweemalig blootgestel aan pavetamien was daar statistiese bewys van mioveselatrofie.

Op grond van die inligting voortspruitend uit hierdie studie en vorige navorsing is die volgende hipoteses ontwikkel om die patogenese van die miokardiale letsels te verklaar:

1. Pavetamien het 'n verlengde effek op die miokardium weens inhibisie van proteïensintese, en het ook 'n invloed op die energieproduksiesisteen wat die funksie van miovesels beïnvloed. Die struktuur van miosiete word nie geaffekteer gedurende die aanvangstadiums van die latente periode nie maar uiteindelik word miovesel- hipertrofie, atrofie, degenerasie en nekrose waargeneem.
2. Verplasingsfibrose in die subendokardiale gebied is die gevolg van die uitwerking van pavetamien op miovesels en die gevolg van isgemie weens verminderde miokardiale perfusie van veral die subendokardiale area, as gevolg van 'n verswakte miokardiale sametrekking, verhoogde diastoliese druk, tagikardie en miovesel-hipertrofie.
3. Kardiese vergroting is 'n kompensatoriese meganisme, as gevolg van miovesel-skade teweeggebring deur pavetamien en isgemie (patologiese vergroting).
4. Letsels in diere met gousiekte verteenwoordig 'n finale algemene beginsel van sellulêre beskadiging eerder as 'n manifestasie van 'n spesieke hartsiekte. Diere kan tydens enige stadium in die ontwikkeling van die letsels doodgaan. "Atipiese" letsels verteenwoordig 'n manifestasie van die siekte in 'n progressie wat termineer in gedilateerde kardiomiopatie as die dier nie reeds in die vroeër stadiums doodgaan nie.



Die hipoteses maak voorsiening vir 'n verklaring, vir die eerste keer, vir die latente periode tussen inname van die plant en die begin van die siekte. Dit verklaar ook die wye spektrum van letsels waargeneem in eksperimentele gevalle. Dit demonstreer dat “tipiese” letsels van gousiekte nie patognomonies is nie, en dat die afwesigheid van “tipiese” letsels nie 'n diagnose van gousiekte uitskakel nie in situasies waar die blootstelling en teenwoordigheid van veroorsakende plante en die kliniese geskiedenis 'n diagnose van gousiekte ondersteun.



## LIST OF TABLES

Table 2.1	Clinical signs observed in experimentally induced gousiekte (using <i>P. pygmaeum</i> in 50 sheep and goats (Pretorius & Terblanche 1967)	13
Table 3.1	Sheep examined after dosing with <i>Pachystigma pygmaeum</i>	28
Table 3.2	Macroscopical pathological features in ten sheep dosed with <i>Pachystigma pygmaeum</i>	29
Table 3.3	Histopathological lesions in the subendocardial region of the left ventricle of ten sheep dosed with <i>Pachystigma pygmaeum</i>	33
Table 3.4	Affected group	43
Table 3.5	Control group	43
Table 4.1	Sheep dosed with <i>Fadogia homblei</i>	56
Table 5.1	Rats exposed to pavetamine. Dosing regimen, fate and light microscopical myocardial lesions	75
Table 5.2	Effect of pavetamine on body weight (g) of rats	78
Table 5.3	Measurements in the endocardial region of the control group	85
Table 5.4	Measurements in the epicardial region of the control group	86
Table 5.5	Measurements in the endocardial region of the affected group	86
Table 5.6	Measurements in the epicardial region of the affected group	86



## LIST OF FIGURES

Figure 2.1	<i>Pachystigma pygmaeum</i> is a low-growing shrublet	5
Figure 2.2	The fruits of <i>P. pygmaeum</i> resemble a green tomato	5
Figure 2.3	<i>P. thamnus</i> is smooth leaved	6
Figure 2.4	<i>P. thamnus</i> . Note the smooth leaves and mature fruit	6
Figure 2.5	<i>Pachystigma latifolium</i> is an underground shrub with massive woody axes	7
Figure 2.6	<i>Fadogia homblei</i> . The leaves have a dark green, shiny upper surface and a greyish-white, felted lower surface	8
Figure 2.7	<i>F. homblei</i> . The round fruits are pea-sized and blacken with age	8
Figure 2.8	<i>Pavetta harborii</i> is a perennial, woody shrublet about 50 cm in height	9
Figure 2.9	<i>P. harborii</i> . Note the cluster of white, tubular flowers with star-shaped corolla lobes	10
Figure 2.10	<i>Pavetta schumanniana</i> is a deciduous, multi-branched shrub	11
Figure 2.11	<i>P. schumanniana</i> . Small, white flowers are borne in clusters at the ends of short branchlets	11
Figure 3.1	Transmission electron microscopical picture of a cross-section of a myofibre of illustrate the measurement of the myofibre diameter at the level of the centre of the nucleus (arrows). (Bar = 5µm)	27
Figure 3.2	Normal heart	30
Figure 3.3	Dilated heart in sheep 10 with a long latent period. Note round shape and flabby appearance with collapse of right ventricle because of loss of tone (arrow)	30
Figure 3.4	Pulmonary oedema depicted as dilatation of the interlobular septae (arrow) and hydrothorax (star) in sheep 10 that died of gousiekte after a long latent period of 51 days	31
Figure 3.5	Hydropericardium (arrow) in sheep 9 that died after a long latent period of 51 days	32
Figure 3.6	Normal myofibres in subendocardial region of the left free ventricular wall of a control animal. (HE)	33
Figure 3.7	Fibre hypertrophy (top solid arrow) and atrophy (bottom solid arrow) in the subendocardial region of an animal with a long latent period (sheep 10). Note the thickened endocardium (dotted arrow). HE	34
Figure 3.8	Atrophic fibres (top arrow) intermingled with hypertrophic fibres (bottom arrow) in the subendocardial region of a sheep with a long latent period (sheep 9). HE	35
Figure 3.9	Moderate multifocal to diffuse round cell infiltration (arrow) in sheep 7. HE	36
Figure 3.10	Cross-section of myocardial fibres with multifocal to diffuse severe replacement fibrosis (arrow) in the inner third of the myocardium of sheep 8. Masson's	36





	trichrome	
Figure 3.11	Longitudinal section of myofibres with multifocal replacement fibrosis (arrow) in sheep 8. Masson's trichrome	37
Figure 3.12	Multifocal necrosis (bottom arrow). Also note the interstitial fibrosis (top arrow) in sheep 6. Masson's trichrome x 100	38
Figure 3.13	Normal endocardium (arrow) in control animal. HE	39
Figure 3.14	Note the thickened endocardium (arrow) in sheep 10. HE	39
Figure 3.15	Severe medial oedema in two arteries in sheep 10 (arrows). HE x 400	40
Figure 3.16	Diffuse atrophy of fibres throughout the myocardial wall in sheep 1. HE	41
Figure 3.17	Severe lung oedema (top arrow) with emphysema (bottom arrow) in sheep 10. HE	41
Figure 3.18	Centrilobular hepatic necrosis (arrow) with dilatation of sinusoids in sheep 10. HE	42
Figure 3.19	Comparison of myofibre diameter distribution between control and affected animals	44
Figure 3.20	Comparison of myofibre nucleus perimeter distribution between control and affected animals	44
Figure 3.21	Comparison of myofibre nucleus area distribution between control and affected animals	45
Figure 4.1	Myofibre from a control animal with intact sarcomeres (dashed arrow) with clear Z bands (solid arrow) and evenly spaced mitochondria between myofibrils (dotted arrow)	57
Figure 4.2	Myofibre of an animal with a short latent period. Note nuclear hypertrophy (solid black arrow) and large numbers of mitochondria between fibrils (dotted arrow)	58
Figure 4.3	Sheep with short latent period. Note large variation in myofibril diameter (dashed arrows) and large spaces between myofibrils with mitochondria proliferation (star). Also present is lysis of myofibrils (solid arrow)	59
Figure 4.4.	Sheep with intermediate latent period. Note myofibre with severe myofibrillar loss (star) in the vicinity of the nucleus (dashed arrow) with a few intact myofibrils below the sarcolemma (solid arrow)	60
Figure 4.5	Myofibrils have a reduced diameter (dashed arrow) with thickening of Z band material (solid arrow). Some of the myofibrils have disintegrated almost totally (dotted arrow)	61
Figure 4.6	Myofibrils in a sheep with a long latent period have a frayed appearance (solid arrow) and thickening of Z band material (dotted arrow). Note the large numbers of mitochondria (bottom star) and endoplasmic reticulum (top star) intermingled with disintegrating myofilaments (dashed arrow)	62
Figure 4.7	Myofibre with disintegration of myofibrils (solid arrow) and streaming of Z bands (dotted arrow)	63
Figure 4.8	Sheep with long latent period. Cytoplasmic	64

	components, including mitochondria (dotted arrow) and sarcoplasmic reticulum (bottom solid black arrow), replace disintegrating myofilaments (dashed arrow). Note the dilated sarcoplasmic reticulum (top solid arrow)	
Figure 4.9	Mitochondria varied considerably in size and shape (dotted arrow) and showed various alterations, including the formation of concentric cristae (solid arrow)	65
Figure 4.10	Control sheep. Note the normal, step-like intercalated disc (solid arrow) with abundance of dense material (dotted arrow) surrounding the opposing membranes (gap junction) (dashed arrow) at the insertion of the myofilaments into the end of the cell	66
Figure 4.11	Cross-section of the myocardium. Note folding of intercalated disc with slight separation of opposing membranes (solid arrow) and disintegration of myofilaments (dotted arrows). Also present is large, electron-dense granule in mitochondria (dashed arrow)	67
Figure 4.12	Disintegration of myofilaments (star) at the level of the intercalated disc (solid black arrow). Note thickening of Z band material of the affected myofibrils (dotted arrow)	67
Figure 4.13	Necrotic fibre with chromatin margination (arrow). Note perinuclear disintegrating myofilaments and intracellular organelles (dotted arrow)	68
Figure 5.1	Body weight (g) gain of control rats and rats exposed to pavetamine on day 0 and day 27	78
Figure 5.2	Normal myocardium of a control rat. HE	79
Figure 5.3	Multifocal round cell infiltration in the myocardium (arrow) of rat P4 exposed to pavetamine and euthanased on day 42. HE	80
Figure 5.4	Focal myocardial necrosis with an associated round cell infiltration (arrow) in rat P5 exposed to pavetamine. HE	81
Figure 5.5	Replacement fibrosis associated with myofibre necrosis (arrows) in rat P5 injected with pavetamine and euthanased on day 42	81
Figure 5.6	Myofibre of a control rat with a nucleus (dotted arrow) in the centre. Note the distribution of the mitochondria (solid arrows) and myofibril diameter	82
Figure 5.7	Myofibre with necrotic nucleus evidenced by karyolysis. The nuclear envelope is still intact (arrow)	83
Figure 5.8	Swelling of mitochondria (white arrow) with the presence of dense matrical deposits (dashed arrow)	83
Figure 5.9	Myofibre of rat P5 euthanased on day 42. Note the variation in myofibril diameters with loss of contact between myofibrils (arrow)	84
Figure 5.10	Myofibre of a rat (P5) exposed to pavetamine and euthanased on day 42. Note the segmental myofibrillar lysis (arrow)	85