OBSERVATIONS ON THE CLINICAL, CARDIAC AND HISTOPATHOLOGICAL EFFECTS OF FLUOROACETATE IN SHEEP

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ABSTRACT

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Fluoroacetate was dosed per stomach tube to 17 Merino sheep at the rate of 0,05–1,0 mg/kg/day. The clinical signs, haemodynamic changes, chemical pathology and pathology of acute, subacute and chronically intoxicated cases are described.

Tetanic convulsions were seen in acutely intoxicated animals and in them respiratory failure, occurring concomitantly with cardiac failure, may have been the cause of death. Subacute intoxication resulted in less conspicuous clinical signs when the sheep were at rest, but they developed apparent nervous signs on being handled, and later tended to lie down. Chronically intoxicated animals were only mildly affected.

At all levels of intoxication changes in the chemical pathological parameters were either absent or were mild and transient.

The microscopic lesions in the hearts of acutely intoxicated sheep included degeneration as well as necrosis of individual or small groups of myocardial fibres. In the subacutely and chronically intoxicated animals the multifocal myocardial lesions were more widespread and in various stages of development or resolution.

INTRODUCTION

Large stock losses in the Republic of South Africa (RSA) caused by *Dichapetalum cymosum* (gifblaar) intoxication were first described by Stent (1916) and Steyn (1928). More recently, Tannock (1975) investigated the seasonal variation in toxicity of the plant in Zimbabwe. Monofluoroacetic acid, the toxic principle, was isolated from *D. cymosum* (Marais, 1944) in the RSA, from *Palicourea marcgravii* St Hil (De Oliviera, 1963) in South America, and from *Acacia georginae* (Oelrichs & McEwan, 1962), *Gastrolobium* spp. and *Oxylobium* spp. (Aplin, 1967, 1968) in Australia. The distribution of known toxic *Dichapetalum* spp. in Africa has been described by Vickery & Vickery (1973).

A characteristic feature of fluoroacetate poisoning is the latent period which usually lasts for at least 2 h before the onset of symptoms (Pattison & Peters, 1959). Barnes (1958) found that *A. georginae* in cattle caused polypnoea and respiratory arrhythmia during convulsive attacks. He also described terminal acute cardiac failure with tachycardia, ending in ventricular fibrillation, dyspnoea, cyanosis, anoxic convulsions, collapse and sudden death. In field cases, death very often occurred after intoxicated animals had drunk water. Subacutely affected animals were dull and lethargic, their noses ran, they salivated, dragged their hindlegs, developed polyuria, had increased respiratory rates, drooping ears, arched backs, muscular tremors, and knuckled over. They were often hypersensitive, exercise intensifying the clinical signs. Sheep ran around blindly after being intoxicated with *A. georginae* (Bell, Newton, Everist & Legg, 1955), and goats too after receiving highly toxic gifblaar (Basson, Norval, Hofmeyer, Ebedes & Schultz, 1982).

Electrocardiographic changes associated with fluoroacetic acid intoxication included: arrhythmia, decreased T wave amplitude, prolonged PR time intervals and pulsus alternans ending in ventricular fibrillation (Chenoweth, 1949). Increased heart frequency and indications of increased contractility, with sporadic bradycardia and terminal heart block, occurred in sheep intoxicated with 9,6 mg/kg potassium monofluoroacetic acid (Quinn & Clark, 1947).

Chemical pathological estimations in blood indicated an increased citrate level after fluoroacetate had been dosed to a sheep (McEwan, 1964). He also noted increased citrate levels in the tissue of 1 sheep, particularly in the diaphragm, heart and kidneys. Estimates by Annison, Hill, Lindsay and Peters (1960) in acutely intoxicated sheep (LD_{100}) indicated increased levels of blood glucose, lactate and ketones 1,5 h after dosing. These returned to normal after 12 h. Conspicuously increased levels of citrate in heart muscle and kidney specimens occurred in 1 sheep intoxicated with sublethal doses (0,1 mg/kg) at 3-day intervals till death.

Bell *et al.* (1955) found no pathonomonic macroscopic lesions, and Jensen, Tobiska & Ward (1948) observed no consistent histologic changes. Whittem & Murray (1963), however, described acute multifocal injury to the myocardium with a cellular response composed mostly of lymphocytes with some histiocytes, followed, in some cases, by proliferation of sarcolemmal nuclei in natural and experimental *A. georginae* intoxication as well as fluoroacetate poisoning. In non-fatal cases the damaged myocardium was repaired by the formation of scar tissue. Microscopic lesions occurred after intoxication with fluoroacetate at doses as low as 0,11 mg/kg/day, 3–7 doses being fatal.

Deaths of ruminants with multifocal fibrotic myocardial changes are reported from time to time on veld containing *D. cymosum* where gousiekte-causing plants are absent. This raised the question whether gifblaar, taken in sublethal doses over a long period, could cause lesions similar to those of gousiekte. Accordingly, in this study, sheep were chronically intoxicated with fluoroacetate in an attempt to reproduce gousiekte-like lesions.

Owing to the economic importance of gousiekte it was felt that reproduction of such lesions would be of considerable diagnostic significance.

MATERIALS AND METHODS

Seventeen Merino wethers (milk tooth-full mouth) with live masses varying between 22 and 38 kg were used. The experiment reported here was conducted on lines similar to those described by Naudé & Schultz (1982) as set out in Tables 1 and 2.

The carotid arteries were exteriorized in 2 of the sheep. All the animals were stabled and fed *ad libitum* on lucerne hay, plus *c.* 500 g of a standard concentrate ration per day. Observations included daily clinical examination and registering of respiratory movements, electrocardiograms (ECG), phonocardiograms, carotid blood pressures, and the first derivatives of the blood pressure (dp/dt). The following standard chemical pathological determinations were periodically done on the blood: erythrocyte sedimentation rate, haematocrit, haemoglobin, serum glucose, lactate, glutamic oxalacetic

transaminase (GOT), glutamic pyruvic transaminase (GPT), bilirubin, urea nitrogen (SUN), ketones, calcium, sodium, potassium, magnesium and phosphorus.

The acid-base balance of the blood, using standard techniques, was calculated in some cases. The citrate levels were determined according to the method of Taylor (1953) on blood and organ specimens of selected sheep.

Fluoroacetate* was dosed in aqueous solution per stomach tube after the animals had been deprived of food and water for 24 h.

Autopsies were performed as soon as possible after death of the animals.

A wide range of tissues was collected in 10% buffered formalin and were routinely processed and embedded in paraffin wax. Sections were cut at 4–6 μm and stained with haematoxylin and eosin (HE). Frozen sections of the heart muscle were stained with oil red O (Pearse, 1961).

RESULTS

Clinical signs and haemodynamic changes

Acute intoxication. As indicated in Table 1, the clinical signs included depression of ruminal movements/ atony, polypnoea, dyspnoea and tachycardia, followed more or less in sequence by frequent urination, weakness, muscular spasms and tetanic convulsions. One sheep (Sheep 8) became transiently frenzied and ran blindly into objects.

During a typical tetanic convulsion, which usually lasted for only about 1 min or so, breathing ceased entirely, but no marked ECG changes occurred (Sheep 6). Electrocardiographic changes, however, were apparent in the periods of calmness between convulsions. These included: tachycardia, AV dissociation, ectopic foci, prolonged QRS intervals and ST segment changes (Sheep 6 and 7). In the 2 sheep in which blood pressure was recorded, one (Sheep 3) developed transient hypertension and an increased dp/dt followed by progressive hypotension and decreasing dp/dt, while the other (Sheep 5) showed only hypotension (Fig. 1).

A latent period was always present before the onset of the clinical signs (Table 1).

Subacute and chronic intoxication. Apart from tachycardia and/or polypnoea in some sheep when they were excited, there were no conspicuous clinical signs in those repeatedly dosed with sublethal amounts (0,05–0,1 mg/kg, i.e. a total of 0,6–2,1 mg/kg) (Table 2). The haemodynamic changes were limited to configurational changes and increased amplitudes of the ECG waves. Only in Sheep 12 was AV dissociation recorded.

At higher individual doses (0,05–0,19 mg/kg) the sheep, all of which appeared clinically normal at rest, developed apparent nervous signs when handled; for example, their muscles trembled, they fell down and struggled ineffectually to rise (Sheep 15–17). After lying exhausted for a while, they stood up and staggered about, often with an aberrant gait, lifting their legs abnormally high and knuckling over. Recovery followed, but as the experiment progressed, they became increasingly reluctant to stand, preferring to lie down instead. No pronounced ECG changes were noticed, even in Sheep 17, on which a recording was made immediately after a convulsive attack.
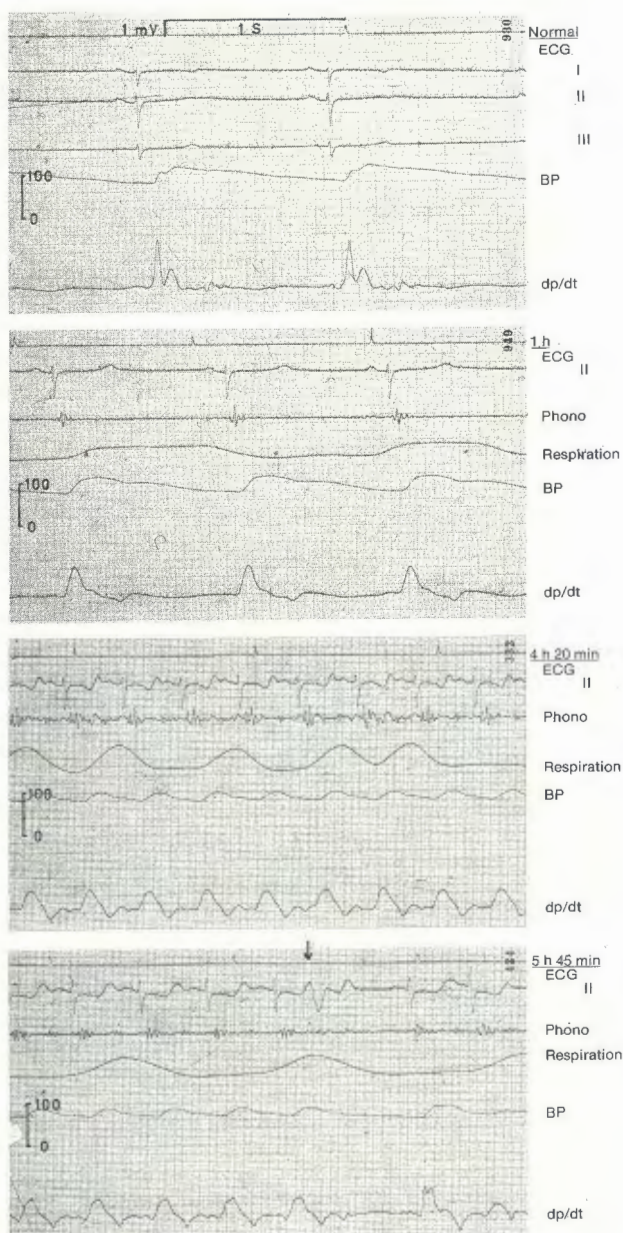
* Fluka AG, 98% pure

FIG. 1 Registered parameters of Sheep 3 before and after dosing fluoroacetate (1 mg/kg)

Normal: Blood pressure $^{120}/_{80}$ mm Hg

1 h: Decreased systolic blood pressure ($^{116}/_{76}$ mm Hg) and dp/dt (60% of normal)

4 h 20 min: Decreased systolic blood pressure ($^{100}/_{80}$ mm Hg) and dp/dt (32% of normal). Increased heart rate (120/min) and T wave configuration changes. Respiratory movements arrhythmic and the rate increased (80/min)

5 h 45 min: Extra systolic beat with compensatory pause, ST depression, decreased blood pressure (86/66 mm Hg)

Chemical pathology

Acute intoxication. The levels of citrate, lactate and glucose were slightly and transiently elevated in the blood of Sheep 8 and 10 within c. 24 h of dosing. In addition, mild increases of GOT activity were recorded in the serum of Sheep 2 and 8 on Day 7. No conspicuous changes were noticed in the other chemical pathological parameters (Table 3).

Subacute and chronic intoxication. No conspicuous chemical pathological changes were recorded (Sheep 11–17).

TABLE 1 Observations on sheep acutely intoxicated with a single or two high doses of fluoroacetate

Sheep			Dose mg/kg	Clinical signs			Haemodynamic changes	Necropsy
No.	Mass (kg)	Age		Nature	Duration Onset	Duration Death		
1	34	fm	0,5	Decreased ruminal movements	5 h 30 min	24 h	T wave: decreased amplitude (1 h) and sporadic configuration changes, tachycardia (120/min), polypnoea (44/min)	Venous congestion, hydrothorax, hydropericardium, pulmonary oedema, small intestine content haemorrhagic
2	36,5	fm	0,5 on Day 0 0,75 on Day 7	Decreased ruminal movements, restlessness, frequent urination	17 h	7 × 24 h	T wave: transient configuration changes (Day 0–3), ST segment elevation (Day 1–2), tachycardia (Day 1–4)	Venous congestion, hydropericardium, pulmonary oedema
3	38	fm	1	Double respiratory effort (3 h), restlessness, ruminal atony, frequent urination, polypnoea (4 h), convulsive spasms (7 h 23 min–7 h 35 min)	3 h	7 h 35 min	T wave: configuration changes and progressive increased amplitude (3 h), hypertension (144/80) followed by progressive hypotension ($^{42}/_{22}$ at 7 h 15 min), ST depression, ectopic foci (5 h 30 min), AV dissociation with ventricular tachycardia (7 h 20 min)	Venous congestion, mild pulmonary oedema, nephrosis
4	35	6t	1	Dyspnoea, sporadic deep jerky movements (1 h 20 min), arrhythmic breathing, polypnoea (60/min at 2 h)	1 h 30 min	7 h 45 min	Arrhythmia (3 h 20 min), T wave configuration changes, ST depression, progressive tachycardia (150–260/min from 4 h 40 min—death)	Venous congestion, pulmonary oedema
5	27	fm	1	Frequent urination (4 h), rumen stasis, polypnoea, progressive anxiety (6 h), died in tetanic convulsions (8 h)	4 h	8 h	Tachycardia progressive hypotension ($^{121}/_{96}$–$^{78}/_{60}$ from 2 h 40 min onwards)	Venous congestion, mild pulmonary oedema
6	32	fm	1	Polypnoea, anxiety and grinding of teeth (4 h 20 min), ruminal atony (7 h 45 min), terminal respiratory crisis (8 h 20 min)	4 h 20 min	8 h 20 min	Tachycardia, T wave configuration changes (4 h 20 min), ST depression, sporadic ectopic foci (8 h) followed by AV dissociation	Venous congestion, ascites, mild pulmonary oedema
7	33	fm	1	Polypnoea (1 h 30 min—death), tetanic convulsions (7 h and 10 h 30 min)	1 h 30 min	10 h 30 min	Changes started during first tetanic convulsions: prolonged QRS interval, elevation of ST segment, tachycardia (7 h), ST depression (7 h 40 min–9 h 15 min) followed by sporadic AV dissociation and ectopic foci. Terminally P and T waves superimposed but remained rhythmic	Venous congestion (especially of lungs, abomasum and colon), pulmonary oedema, mild nephrosis
8	33	4t	0,5 on Day 0 0,5 on Day 7	Tachycardia (24 h), sudden attack of frenzy (24 h 35 min), the sheep running blindly into objects, recovered slowly over 1 h: muscular tremor, tachycardia, polypnoea. Died suddenly after 2nd dose	24 h	7 × 24 h	No changes observed on Day 1–3 and Day 7	Mild hydropericardium, severe pulmonary congestion
9	27	5t	0,75	Polypnoea, decreased ruminal movements (7 h 30 min), terminally hypersensitive (24 h)	7 h 30 min	30 h 30 min	Tachycardia (7 h and 24 h)	Acute and subacute pneumonia, mild oedema of tricuspidal valves, few epicardial petechiae
10	26	6t	1	Tachycardia (120–220/min), polypnoea (48–100/min at 2 h–7 h), weakness, hindquarter muscle tremors, frequent urination (7 h)	2 h	7 h	T waves terminally conspicuously enlarged, QRS configuration changes but no AV conduction abnormalities	Venous congestion, hydropericardium, endocardial petechiae, pulmonary oedema and mediastinal oedema

mt = milk tooth
S = Sacrificed
fm = full mouth
t = teeth

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TABLE 2 Observations on sheep chronically intoxicated with repeated low doses of fluoroacetate

Sheep			Dose mg/kg	Clinical signs				Haemodynamic changes	Necropsy
No.	Mass (kg)	Age		Nature	Duration				
					Onset	Death			
11	30	4t	0,1 × 8 in 41 days Total: 0,8	No changes seen	21 × 24 h	41 × 24 h S		Prolongation of QT time (10,7%) on Day 8, inversion of T wave (Day 21—death), deviation of QRS electrical axis with subsequent QRS configuration changes (Day 25–41)	Hydropericardium, fibrin clot in pericardial sac, mottled and parboiled discoloration of myocardium, Cysticercus cyst in myocardium and diaphragm, lung oedema, focal subacute pneumonia
12	30	4t	0,1 × 10 in 66 days Total: 1,0	Transient polypnoea (after 2nd, 5th, 6th and 10th dose)	5 × 24 h	71 × 24 h S		Transient tachycardia (after 5th dose), inverted T wave (after 3rd, 8th and 10th dose and terminally), AV dissociation with ventricular tachycardia or coincidental AV synchronization (Day 27)	Hydropericardium, endocardial haemorrhages, mottled and parboiled discoloration of myocardium, oedema at implantation of chordae tendinae, emphysema
13	37	6t	0,1 × 6 over 33 days Total: 0,6	Tachycardia and polypnoea after handling (Day 6, 13 and 20)	6 × 24 h	40 × 24 h S		Inverted T wave (Day 5), electrical alternans (Day 13 and 20)	Hydropericardium
14	22	mt	0,05 × 42 over 100 days Total: 2,1	No changes seen	24 h	100 × 24 h S		T wave amplitude increased (1,0 mV from Day 15 onwards), T wave configuration changes (Day 60 onwards)	Mottled and parboiled discoloration of myocardium, endocardial petechiae
15	22	mt	0,05–0,1 × 72 over 167 days 0,11–0,19 × 5 over 12 days Total: 4,11	Polypnoea (Day 154 onwards). When disturbed, it fell down and remained temporarily unstable (Days 163 and 164), it became progressively reluctant to stand	154 × 24 h	179 × 24 h S		Tachycardia (Day 158–161), T wave: configuration changes (Day 58 onwards) and increased amplitudes (as high as 1,2 mV, Day 43 onwards)	Mild ascites, hydropericardium and epicardial petechiae
16	28	2t	0,1 × 6 over 18 days 0,13 × 23 over 30 days Total: 3,59	Polypnoea (Day 20 onwards), prefer to lie down (Days 44–48), when disturbed reacted the same as sheep 15. Decreased ruminal movements/atony (Days 46–48)	20 × 24 h	48 × 24 h S		Tachycardia (Day 20 onwards), T wave: transient increased amplitude (1,6 mV)	Congestion and cyanosis, mild ascites, hydrothorax, hydropericardium, severe lung oedema
17	28	2t	0,1 × 14 over 24 days 0,12–0,16 × 10 over 11 days Total: 2,72	From Day 21 onwards polypnoea, decreased ruminal movements/atony and preference to lie down. When disturbed, reacted the same as Sheep 15	21 × 24 h	35 × 24 h		T wave: increased amplitude (Day 22 onwards), after spasms (Day 22) tachycardia (200/min) and increased T wave amplitude (1,7 mV)	Congestion and cyanosis, mild hydrothorax, hydropericardium, severe lung oedema, mottled and parboiled discoloration of myocardium

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TABLE 3 Some chemical pathological changes in 5 sheep dosed with fluoroacetate

Sheep No.	Dose mg/kg	Time elapse after dosing	Blood citrate µg/ml	Blood lactate mg%	Blood glucose mg%	SGOT K U	Time of death
2	0,5 on Day 0 0,75 on Day 7	Day 0 Day 1 Day 7			40,5 64,0 34,25	112 119 (200)	Day 7
3	1	0 h 1 h 2 h 3 h 4 h 5 h 6 h 7 h			37,9 36,25 38,5 39,5 52,75 (87,5) (80,5) (70,5)	118,5 152 139 125 132	7 h 35 min
8	0,5 on Day 0 0,5 on Day 7	Day 0: 0 h 3 h 6 h Day 1: 0 h 6 h Day 2 Day 3 Day 7: 0 h 3 h	24 26 23 19 (36) 13 (36,5) 17,5 13,5	10,6 15,7 11,2 (140) (85,5) 40,2 34,6 13,8 20,7	49,12 41,25 50,5 (101,5) 40,5 (78,25) 53,75 47,5 51,25	77 86 132 (180)	Day 7
9	0,75	Day 0: 0 h 2 h 4 h 6 h Day 1: 24 h	18,5 11 12,5 18 23	16,6 9,5 10,7 20,8 27	46 45,5 40,25 (64) 57,75	65 86	Day 1
10	1	Day 0: 0 h 2 h 4 h 6 h	27 (36) 29 8	22,8 12,3 18,4 (53,3)	41 36,25 38,5 (70,25)	80	7 h

Values in brackets not within normal limits

Macroscopic pathology

The animals generally showed venous congestion, cyanosis, lung oedema and hydropericardium, these changes being sometimes accompanied by a slight hydrothorax and ascites as well as epi- and endocardial haemorrhages (Table 1 & 2). The myocardium of the subacute and chronic cases (Table 2) had a parboiled and mottled appearance (Sheep 11, 12, 14 & 17).

Microscopic pathology

Myocardium. Microscopic lesions were seen in the heart muscle in all the animals that died acutely after a single high dose (0,5–1,0 mg/kg body mass) of fluoroacetate or after prolonged exposure to a lower dosage level (0,05–0,1 mg/kg). The lesions were distributed throughout the atrial and ventricular walls, but would appear to be more common in the endocardium.

Acute intoxication. In animals that died within 15 h of dosing, the lesions ranged from inconspicuous, cloudy swelling, hydropic degeneration, mild fatty changes, to Zenker's degeneration and necrosis of individual or small groups of myocardial fibres. Circumscribed, small, multifocal areas of discrete Zenker's degeneration were observed in sheep that survived for 40 h. Although no cellular reaction accompanied the myocardial lesions in those cases that succumbed within 15 h, a mild inflammatory response (neutrophils, lymphocytes and macrophages) and sarcolemma nuclei proliferation were associated with the degenerated and necrotic muscle fibres in animals that died between 15–40 h (Fig. 2 & 3).

Subacute and chronic intoxication. Lesions in different stages of development, ranging from early degeneration and necrosis accompanied by no cellular response to areas where resolution was in progress, were seen in all the animals. Generally, the lesions in the myocardium were more widespread than in the acute cases.

A prominent change, mainly in the endocardium, was the presence of numerous fibres which were swollen and ballooned, stained less intensely with HE, showed some loss of cross striation, and had a rarified appearance, particularly in the perinuclear region. These fibres were sometimes interspersed with a few macrophages and lymphocytes and accompanied by mild sarcolemma nuclei proliferation, giving the myocardium a more cellular appearance (Fig. 4–7).

The acute multifocal degenerative and necrotic lesions were similar to those described earlier *(vide supra)* (Fig. 8 & 9). However, many of the areas of necrosis were infiltrated mostly by lymphocytes and macrophages and a few neutrophils. Fibroplasia and/or proliferation of sarcolemma nuclei, sometimes accompanied by hypertrophy of myocardial fibres, were in evidence in some of the foci which were in the stage of resolution (Fig. 10 & 11). A slight lymphocytic infiltration occurred in the interstitial connective tissue and around some of the blood vessels in the myocardium (Fig. 12). Although the Purkinje fibres were not primarily involved, a few fibres were surrounded by fibroplasia and lymphocytes when bounded by a focal myocardial lesion (Fig. 13).

Other organs. Apart from congestion of most tissues, lung oedema and a mild nephrosis in some animals, no noteworthy lesions were seen in the brain, liver, spleen, lymph nodes, adrenals or skeletal muscles.
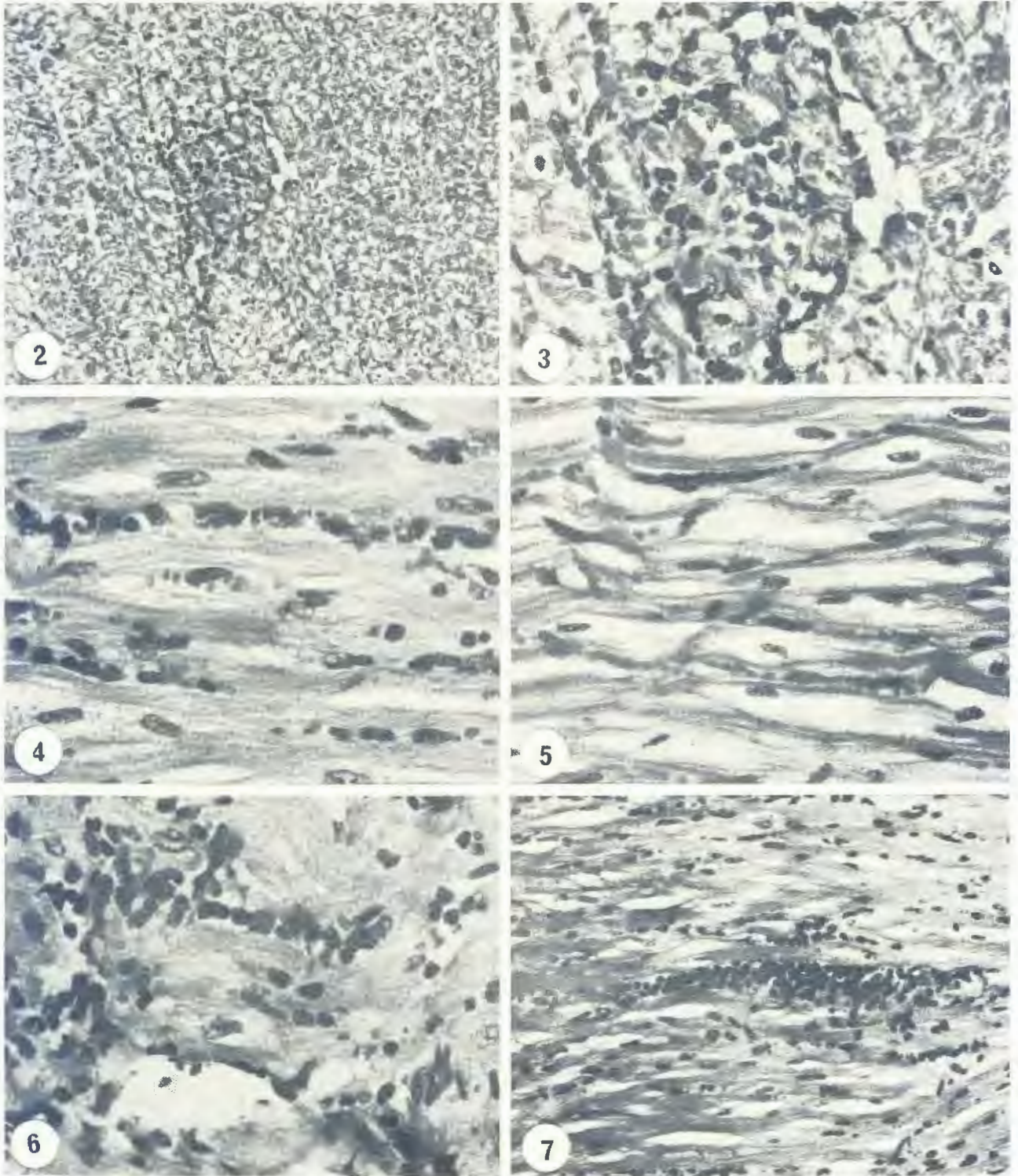
FIG. 2 Focal necrosis in myocardium infilrated by inflammatory cells: HE × 160

FIG. 3 Lymphocytes and macrophages interspersed between degenerated and necrotic myocardial fibres: HE × 400

FIG. 4 Perinuclear rarification of myocardial fibres: HE × 400

FIG. 5 and 6 Rarified myocardial fibres interspersed with lymphocytes, macrophages and proliferating sarcolemma nuclei: HE × 400

FIG. 7 Sarcolemma nuclei proliferation as well as numerous lymphocytes among rarified heart muscle fibres. Note increased cellularity of myocardium: HE × 160
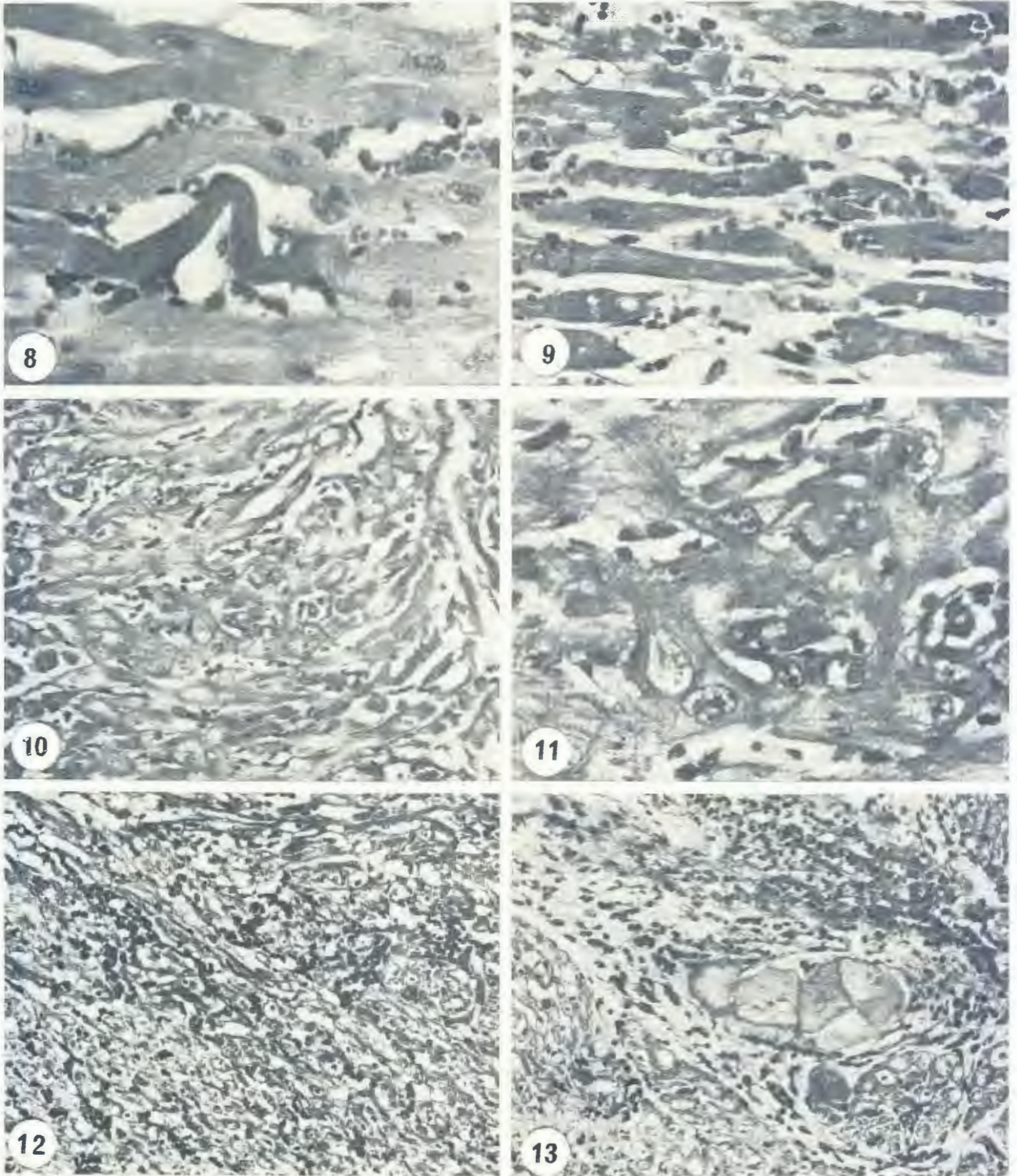
FIG 8 & 9 Zenker's necrosis of individual or groups of myocardial fibres: HE × 400

FIG. 10 Fibroplasia and regenerative changes in a focal area of necrosis in heart muscle: HE × 400

FIG. 11 Higher magnification of regenerating myocardial fibres. Note bizarre sarcolemma nuclei and hypertrophic and interwoven myocardial fibres: HE × 1000

FIG. 12 Lymphocytic infiltration between affected myocardial fibres and in interstitial connective tissue: HE × 160

FIG. 13 Fibroplasia and infiltration of lymphocytes and some macrophages around Purkunje fibres: HE × 160

DISCUSSION

A latent period of variable duration (Table 1) similar to that described by many other authors was evidend in this investigation.

Although the respiratory movements were often still rhythmic just before death, some respiratory involvement was always evident during the course of intoxication. Transient or persistent polypnoea occurred (Basson et al., 1982) as well as arrhythmia and apnoea (Barnes, 1958). These respiratory signs were often preceded or followed by restlessness, uneasiness, frequent urination, hypersensitivity or convulsions and paralysis. One sheep ran around blindly, displaying the muscular tremors described by Basson et al. (1982) in goats poisoned with highly toxic D. cymosum and by Bell et al. (1955) in sheep poisoned with A. georginae.

The clinical signs and haemodynamic changes indicate that respiratory failure, occurring concomitantly with cardiac failure, may have been responsible for the deaths. Tachycardia (Quinn & Clark, 1947; Basson et al., 1982), often accompanied by ST segment and T wave changes, for example, increased or decreased amplitudes (Chenoweth, 1949) and/or configuration changes, was always present. These changes were often followed by AV dissociation with ectopic foci and a bizarre ECG, bearing out the suggestion of Jarrett & Packham (1956) that death could result from heart block. The blood pressure recordings made in 2 sheep reflected a progressive decline, accompanied by decreasing dp/dt values, although an initial elevation occurred in 1 of them. The signs could be precipitated by stimuli (Barnes, 1958), as was the case in this investigation during which subacutely intoxicated sheep developed apparent nervous signs when handled. Some of the signs were comparable with those in cattle intoxicated with fluoroacetate (Robison, 1970) and A. georginae (Barnes, 1958), as well as those of captured antelopes receiving D. cymosum (Basson et al., 1982). The nervous signs reported by Barnes (1958) in cattle grazing on A. georginae on the range are seldom if ever seen in natural D. cymosum poisoning in the RSA.

Citrate values in blood from normal sheep (mean value for 4 sheep was 19 μg/mℓ) were comparable with those obtained by McEwan (1964) (mean value for 4 sheep was 17,5 μg/mℓ). Transient elevated blood citrate levels, as high as 36 μg/mℓ, occurred after intoxication. Elevated blood citrate levels, however, seemed to be too inconsistent to be of diagnostic value, and our finding concurs with those of Jarrett & Packham (1956), who found that the symptoms were not closely correlated with citrate in the blood after intoxication with fluoroacetate.

Elevated citrate values in heart muscle (50 and 80 μg/g) and diaphragm specimens (83 and 52 μg/g), however, were conspicuous enough to be of possible diagnostic value, but other factors such as instability of citrate in specimens kept at various temperatures may render such analyses valueless. Moreover, the number of replicates used both by us in this trial and by other workers (McEwan, 1964; Annison et al., 1960) were too small for valid conclusions to be drawn. The stability of citrate in tissues requires further investigation.

Fluoroacetate did not act as a cumulative poison in this investigation. Jarrett & Packham (1956) obtained the same results when it was administered orally or subcutaneously to sheep on rations that contained proteins (e.g. lucerne hay), as in this investigation, but their animals died when fed on wheaten chaff alone. In the latter case, heart block and periodic tetanic convulsions occurred at a dose of c. 0,05 mg/kg/day.

The macroscopic findings, such as venous congestion, lung oedema, hydrothorax, hydropericardium and endocardial haemorrhages in the acutely intoxicated sheep, resembled those found in cardiac and respiratory failure, and were comparable with those described by Bell et al. (1955) with A. georginae poisoning. Jensen et al. (1948) observed the same clinical and necropsy findings in sheep with fluoroacetate poisoning. According to them, cardiac failure occurred before respiratory failure. The microscopic lesions in the myocardium generally corresponded with those decribed for A. georginae and fluoroacetate poisoning in sheep and cattle (Whittem & Murray, 1963) and experimental D. cymosum poisoning in goats and different antelopes (Basson et al., 1982). In sheep dying acutely after a single high dose (0,5–1,0 mg/kg) of fluoroacetate, the myocardial lesions were sometimes inconspicuous while, in those animals which were subacutely and chronically intoxicated, the multifocal areas of necrosis were in various stages of development or resolution. These focal lesions were accompanied by rarified and ballooned myocardial fibres, mainly in the endocardium.

Gifblaar (D. cymosum) is most toxic in spring when the plant is in the early growth stage, and is responsible for sudden death in cattle in the RSA (Steyn, 1928; Tannock, 1975). According to Whittem & Murray (1963), gifblaar is 50 times more toxic than A. georginae in Australia. In gifblaar poisoning, most animals die soon after the intake of the highly toxic leaves. The acute myocardial damage is thus not accompanied by a cellular response.

The heart lesions in the few animals that may recover are characterized by multifocal Zenker's degeneration and necrosis which are infiltrated by inflammatory cells or may show evidence of fibroplasia (J. A. W. Coetzer, unpublished observations, 1976). Whittem & Murray (1963) described macroscopic scars up to 1 centimetre in diameter in the myocardium of animals which had presumably suffered previous, non-fatal attacks of A. georginae poisoning.

The myocardial lesions of subacute and chronic fluoroacetate poisoning should be differentiated from those reported for gousiekte ("quick disease"), a disease caused by the Rubiaceous plants Pavetta harborii, P. schumanniana, Pachystigma pygmaeum, P. thamnus and Fadogia monticola (Theiler, Du Toit & Mitchell, 1923; Uys & Adelaar, 1957; Adelaar & Terblanche, 1967; Hurter, Naudé, Adelaar, Smit & Codd, 1972). Apparently unaffected sheep and cattle with marked gousiekte lesions in their hearts die acutely when exited (e.g. when handled, dosed or chased). These animals often show macroscopic signs of acute heart failure, such as venous congestion and cyanosis, hydrothorax, ascites, hydropericardium and lung oedema. The endocardium may have a greyish-brown colour as a result of replacement fibrosis that has taken place. This is sometimes accompanied by thinning of ventricular walls and dilatation of the heart.

Most of the sheep, subacutely and chronically intoxicated with fluoroacetate, did not die of acute heart failure but had to be euthanized. Apart from a mottled and parboiled discoloration of the myocardium, no other noteworthy macroscopic lesions were seen in the heart. Although the myocardial fibrosis in gousiekte can be focal, it tends to be more diffuse and extensive and is mostly confined to the endocardium of the apex, interventricular septum and left ventricle. The lesions in fluoroacetate poisoning tend to be multifocal in nature, are less widespread and more or less evenly distributed throughout the myocardium. The replacement fibrosis was never as prominent as in gousiekte.

In both gousiekte (Pretorius & Terblanche, 1967; R. Anitra Schultz & T. W. Naudé, unpublished data, 1974) and chronic fluoroacetate poisoning, ECG wave configurational changes are evident, but, as these configurations also vary in normal sheep, undue importance should not be attached to them. Ectopic foci do occur in both gousiekte and acute fluoroacetate poisoning, but in the former they are not coupled with AV dissociation.

Generally speaking, in neither gousiekte nor acute fluoroacetate poisoning are the ECG changes sufficiently specific to be of much diagnostic importance. Electrocardiograms may, however, be useful in a research situation where successive recordings from a particular sheep can be evaluated for signs of cardiac disturbance. Comparisons between sheep, however, are less valid because of individual variation.

In the light of the above discussion there sems to be little likelihood of reproducing typical lesions of gousiekte by the administration of fluoroacetate alone. Future attempts at reproducing these lesions should, therefore, involve the dosing of the plant itself.

ACKNOWLEDGEMENTS

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