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PHOTOSENSITIVITY IN SOUTH AFRICA. III. OVINE HEPATOGENOUS PHOTOSENSITIVITY CAUSED BY THE PLANT *ATHANASIA TRIFURCATA* L. (ASTERACEAE)

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ABSTRACT

KELLERMAN, T. S., COETZER, J. A. W., SCHNEIDER, D. J. & WELMAN, WILHELMINA G., (1983). Photosensitivity in South Africa. III. Ovine hepatogenous photosensitivity caused by the plant *Athanasia trifurcata* L. (Asteraceae). *Onderstepoort Journal of Veterinary Research*, 50, 45–53 (1983)

Hepatogenous photosensitivity was experimentally induced in 1 out of 4 sheep dosed with milled *Athanasia trifurcata*. This is an unpalatable aromatic shrub commonly found along the south-western and south-eastern Cape coast on overgrazed, recently burnt or disturbed veld, up to an altitude of 1 300 m. The liver lesions ranged from a few small multifocal areas of necrosis in 1 animal to various zonal patterns of necrosis (centrizonal, midzonal and peripheral) in each of the other 3. Botanical, toxicological and clinical data are given.

INTRODUCTION

Ovine hepatogenous photosensitivity diseases are of major economic importance in South Africa where a number of plants, a fungus and an alga have been incriminated in their aetiologies (Theiler, 1918; Steyn, 1949; Marasas, Adelaar, Kellerman, Minné, Van Rensburg & Burroughs, 1972; Van Tonder, Basson & Van Rensburg, 1972; Kellerman, Basson, Naudé, Van Rensburg & Welman, 1973; Kellerman, Van der Westhuizen, Coetzer, Roux, Marasas, Minné, Bath & Basson, 1980). Although the aetiologies of the majority of these diseases have been partially or completely elucidated, those of a few remain unresolved. A primary objective of research in this field must therefore be to ascertain the causal agents of the photosensitivities of unknown aetiology so that rational control measures may be evolved.

In this study ovine hepatogenous photosensitivity caused by *Athanasia trifurcata* is described.

FIELD OUTBREAK

The possible toxicity of *A. trifurcata* was brought to our notice when a number of ewes died and a few became photosensitive in a paddock, heavily infested with this plant, near Grabouw. The flock, a large one consisting of 900 adult sheep, had been placed in the paddock with the express purpose of non-selectively grazing down the weeds.

Within 2 days 3 animals were dead and 8 were sick, some showing signs of photosensitivity. The next day the sheep were removed from the pasture but, nevertheless, a further 5 sheep died. Despite advanced autolysis, icterus, scattered haemorrhages and marked hepatosis were evident at necropsy.

DESCRIPTION, DISTRIBUTION AND ECOLOGY OF THE PLANT

Family: Asteraceae (Compositae)

Name: Athanasia trifurcata L.

Common names: Klaaslouwbossie, kouterbossie

Description: (Fig. 1 & 2). Perennial, erect, rigid, aromatic, glandular shrub, much branched from near the base, up to 1,3 m high, whole plant minutely stellate-tomentose, glabrescent or quite glabrous. *Leaves* alternate, dark green, bright green or grey-green, up to 40 mm long but very variable in size, oblong- or obovate-cuneate, much narrowed at the base, rarely entire, commonly 3–5 toothed or lobed in the upper part (very variable in degree of incision), the teeth or lobes minutely mucronate. *Capitula* 5–8 mm in diameter, on long, naked or 1–2-bracteolate pedicels, in dense terminal, racemulose fastigiate corymbs, homogamous, discoid with numerous bright yellow florets. *Involucre* globose; scales light brown, imbricate, scarious, glabrous or nearly so, the outer small, acute, shorter than the inner, the medial obtuse, the innermost somewhat obtuse, lacerate at the membranous margin. *Receptacle* paleate. *Florets* with corolla-tube more or less campanulate above, glabrous or sparsely glandular, 5-toothed; anthers obtuse at the base, with lanceolate apical appendages; style terete, swollen at the base, with linear, truncate branches; ovary 5-ribbed. *Achene* 5-ribbed, oblong; pappus of many short, swollen, brittle, jointed hairs. *Flowering time* from July to April, but mostly in November and December (Harvey, 1865; Adamson & Salter, 1950).

Distribution: (Fig. 3): The plant is common in the south-western and south-eastern Cape Province from Nieuwoudtville to the Gamtoos River mouth. It has been recorded in the following districts: Van Rhynsdorp, Calvinia, Clanwilliam, Piquetberg, Ceres, Hopefield, Tulbagh, Wellington, Bellville, Paarl, Worcester, Cape Town, Wynberg, Somerset West, Stellenbosch, Robertson, Montagu, Caledon, Bredasdorp, Swellendam, Heidelberg (Cape), Riversdale, Oudtshoorn, Calitzdorp, Prince Albert, George, Knysna, Uniondale and Humansdorp.

Ecology: A. trifurcata can be found on all aspects of well-watered or dry rocky hills, mountains or plateaux; on flats and in river beds, on banks of streams and in vleis; in disturbed places such as along railway lines, roadsides, fallow lands or recently burnt veld. The plant prefers to grow on sandy soil, from near sea-level to 1300 m. It is found in grassveld, Macchia, False macchia, Mountain Rhenosterbosveld and Karoo vegetation. Acocks (1975) lists *A. trifurcata* as one of the important species of veld type No. 46, namely, Coastal Rhenosterbosveld. It can become a troublesome weed which spreads on lands and in overgrazed veld.

DOSING TRIALS

MATERIALS AND METHODS

In April 1977, 5 jute bags full of the plants from the toxic camp were dried in the shade and dispatched to the Veterinary Research Institute, Onderstepoort, where it was milled and dosed per stomach tube to sheep (Table 1). The experiment, in which the plant material was dosed daily except at week-ends and on public holidays, was carried out over a period of 5 months. The sheep were examined regularly, kept in the sun and fed on green lucerne. Periodically, the following routine chemical pathological determinations were done on their sera: gamma glutamyl transpeptidase (γ-GT), glutamic oxalacetic transaminase (SGOT), bilirubin (T Br) and urea nitrogen (SUN). At the same time the concentration of phylloerythrin (PHYL) in the sera was measured as described by Perrin (1958). Specimens of various organs

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FIG. 1–2 b *A. trifurcata*

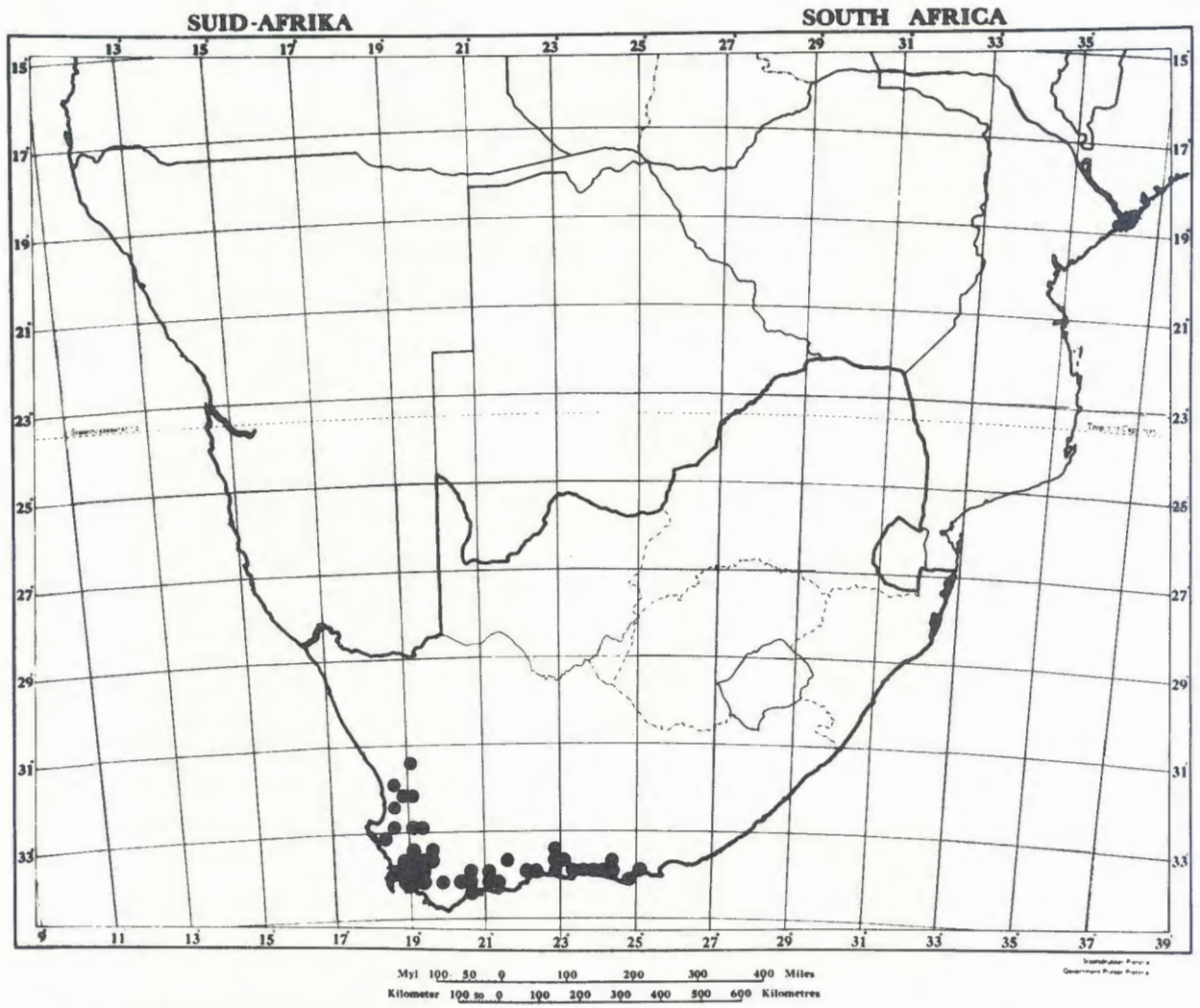


FIG. 3 The distribution of *A. trifurcata*

were collected in 10% buffered formalin at necropsy, embedded in paraffin wax, sectioned 4–6μm and then stained with haemotoxylin and eosin (HE). In addition, special staining techniques such as the Masson's trichrome, Fontana, Wilder's reticulin, Mallory's iron and periodic acid-Schiff stain with and without digestion with diastase were applied to various liver sections (Anon., 1968).

RESULTS

Clinical signs and dosing regimen

The findings are summarized in Table 1.

Sheep 1 became apathetic, suffered from ruminal stasis, refused to eat and displayed forced respiration after receiving 10 g/kg of the plant on 2 consecutive days. During the 2nd night it died.

Sheep 2 died unexpectedly in the night after being given 5 g/kg for 3 days. No clinical signs were observed.

Sheep 3 received 7 doses of 2,5 g/kg in 11 days. On the 11th day it was slightly apathetic, it sought shade, the lips and eyelids were swollen, the sclera were icteric and a coronitis was present. Immediately after becoming photosensitive the sheep was moved to a stable where it was kept for 2 days. Although it was again exposed to

TABLE 1 The toxicity of dried, milled *A. trifurcata* to sheep

Sheep				Dosing regimen				
No.	Mass (kg)	Sex	Age	Dose g/kg × n	Period dosed (days)	Total dose (g)	Duration of experiment (days)	Fate	Result
1	24	F	4t	10 × 2	0–1	480	2	Died	Weak, apathetic, rumen static
2	54	M	4t	5 × 3	0–2	810	3	Died	Died overnight. No clinical signs seen
3	22	F	mt	2,5 × 7	0–10	385	16	Euthanized	Photosensitive on Day 11
4	25	F	mt	2,5 × 10 5 × 10 15 × 2	0–11 14–25 42–43	2545	44	Died	Apathetic, weak, ruminal movements reduced

F = Female
M = Male
mt = Milk tooth
4 t = 4 tooth
g/kg × n = Dose × number of daily administrations

sunlight from Day 13 onwards, no further signs of photosensitivity developed. It was killed for necropsy on Day 16.

Sheep 4 was dosed 10 times with 2,5 g/kg and 10 times with 5 g/kg in 25 days. Dosing was then interrupted for 17 days because the clinical pathological changes seemed to indicate that photosensitivity was imminent (Fig. 7) and because its ruminal motility was temporarily reduced. Upon resumption of dosing (Day 42), when it received 15 g/kg on 2 consecutive days, it suddenly died. Death was preceded by anorexia, apathy and ruminal stasis.

Chemical pathology

The levels of SGOT and γ-GT activity were elevated in Sheep 1 and 2 (Fig. 4 & 5). In Sheep 3 and 4 the maximum activities of these 2 enzymes coincided with peaks in PHYL and T Br retention (Fig. 6 & 7). Sheep 3 became photosensitive when the activities of the enzymes and retention of PHYL and T Br were at their maximum. On the other hand, Sheep 4, which had changes similar to those of Sheep 3, did not become photosensitive.

The chemical pathological changes recorded in these sheep correspond to those expected in ovine hepatogenous photosensitization.

Pathology

Sheep 1: The liver was slightly swollen and friable, with focal, dull greyish-yellow, poorly demarcated patches distributed through its substance. Distinct lobulation coupled with centrilobular congestion gave the organ a mosaic appearance (Fig. 8 & 9). The gall bladder wall was slightly oedematous. Apart from the hepatic lesions, the carcass was mildly icteric and ecchymotic haemorrhages were present, notably on the dorsal side of the neck and perioesophageal connective tissue. Other changes included: hydropericardium and ascites, the fluid having a more yellowish colour than normal and coagulating on exposure; lung congestion and oedema; epi- and endocardial haemorrhages in the ventricles; gastrointestinal stasis and oedema of the abomasal folds.

Despite fairly advanced autolytic changes in the liver, coagulative necrosis and haemorrhages were evident in the midzonal areas (sometimes extending into the centrilobular and peripheral zones) of the lobules, while most hepatocytes in the centrizonal and peripheral areas were degenerated. Some of the hepatocytes in the latter 2 zones were also necrotic (Fig. 10 & 11). Fine basophilic cytoplasmic granules indicative of mineralization were seen in many of the necrotic hepatocytes. In the midzonal area a few neutrophils were distributed among the necrotic hepatocytes and in the sinusoids. There was no indication of bile stasis or pigmentation of hepatocytes and Kupffer cells, while the triads showed only mild ductular proliferation, fibroplasia and oedema. The other organs were too autolyzed for histopathological interpretation.

Sheep 2: In this case also, the liver had a yellowish-brown colour with distinct lobulation, giving it a mosaic appearance. Subcutaneous haemorrhages were again visible on the lateral and dorsal aspects of the neck; a moderate ascites, hydrothorax and hydropericardium were present; the lungs were severely congested and oedematous and epi- and endocardial haemorrhages were evident. Although the autolytic changes in the liver were quite advanced, it was still possible to see a peripheral zone of coagulative necrosis bridging adjacent lobules (Fig. 12 & 13). Faint basophilic stipling was again seen in many of the necrotic hepatocytes, amongst which were scattered a few neutrophils. In the centrizonal and midzonal areas the hepatocytes had noticeably undergone degenerative changes, while a few scattered ones were necrotic. The portal triads were only affected by mild fibroplasia and ductular proliferation.

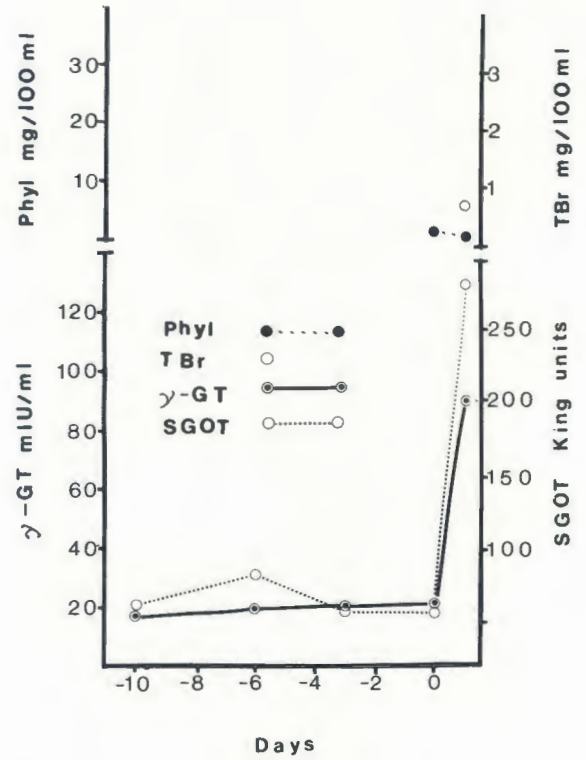
Sheep 3: The skin around the eyes and muzzle had a leathery appearance, but coronitis was not evident. The liver was slightly swollen and discoloured a yellowish-brown. Apart from prominent lobulation, no other lesions were noted in it or the gall bladder. The only other macroscopically affected organs were the kidneys, which were swollen, and the urinary bladder, which had a few petechial haemorrhages in the mucosa.

Unlike that in Sheep 1 and 2, the liver in this animal did not have a zonal pattern of necrosis in the lobules. Instead, diffuse hepatocellular degeneration, including cloudy swelling, hydropic degeneration and mild fatty metamorphosis, interspersed with a few necrotic hepatocytes, were seen in the parenchyma. The necrotic hepatocytes were often accompanied by a neutrophilic and mononuclear cellular response (Fig. 14). Hepatocellular unrest, depicted as hepatocytic anisonucleosis, mitoses and some hepatocytes with 2–3 nuclei occurred throughout the liver. The Kupffer cells were also moderately activated and most of them contained a yellowish-brown pigment. As a result of the above changes the appearance of the parenchyma was more cellular than usual. Apart from a slight ductular proliferation and portal fibroplasia no other lesions were evident.

The kidneys were affected by cloudy swelling and hydropic degeneration as well as yellowish-brown pigmentation of the epithelium of most convoluted tubules. Albuminous casts were common in the lumens of these tubules. No noteworthy lesions were present in any of the other organs.

Sheep 4: The liver was only slightly enlarged and friable, and had a yellowish-brown colour. The right half of the organ was very congested, and as a result there was a conspicuous line demarcating it from the left half (Fig. 15). Although the lobulation was distinct throughout the parenchyma, this was accentuated in the congested part of the liver (Fig. 15 & 16). A few subcapsular and parenchymal ecchymotic haemorrhage were dispersed in the right half of the organ. The gall bladder was slightly oedematous and distended with watery, green bile. Other lesions included severe congestion and oedema of the lungs; slight hydrothorax and hydropericardium; epi- and endocardial haemorrhages in the ventricles; swelling and yellowish-brown discoloration of the kidneys and adrenals; and stasis of the gastrointestinal tract.

Because of the degenerative and necrotic changes in the liver, the lobule could be subdivided into 3 distinct zones (Fig. 17 & 18). Most conspicuous was a centrizonal coagulative necrosis, haemorrhage and congestion, extending partially into the middle of the lobule. This was bordered by a middle zone of extensive lytic necrosis, so severe that almost only the sinusoidal structures lined by swollen endothelial and Kupffer cells remained. The rest of the intact hepatocytes in this area showed a range of degenerative changes and/or eosinophilic necrosis. The third zone comprised a narrow rim of intact but degenerated hepatocytes (cloudy swelling, hydropic degeneration, and mild fatty metamorphosis)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TBr mg/100 ml
γ-GT mIU/ml
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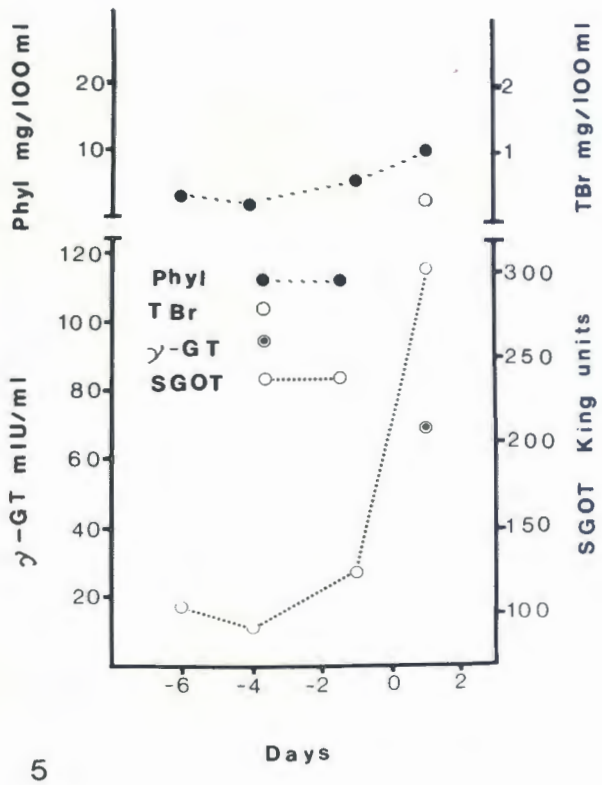
Days

4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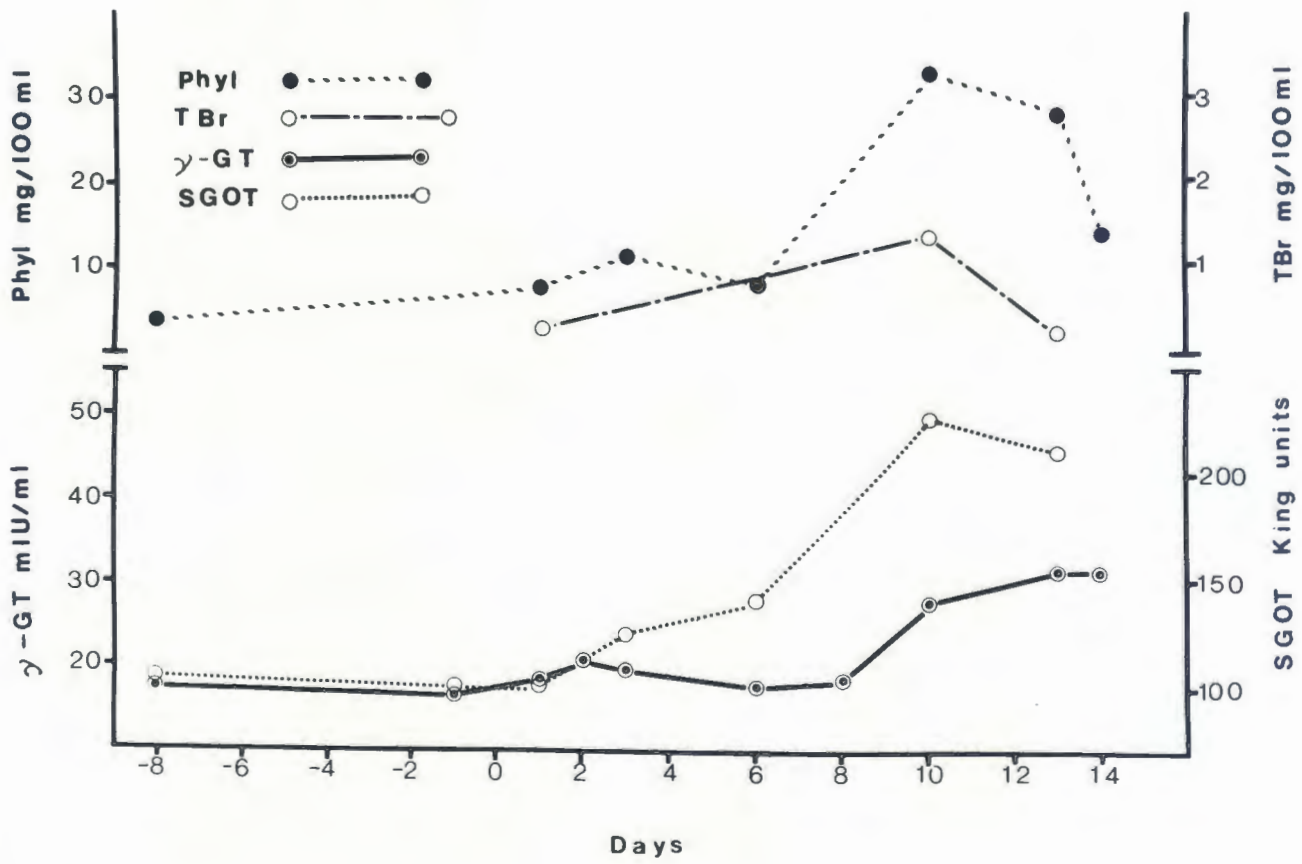
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6

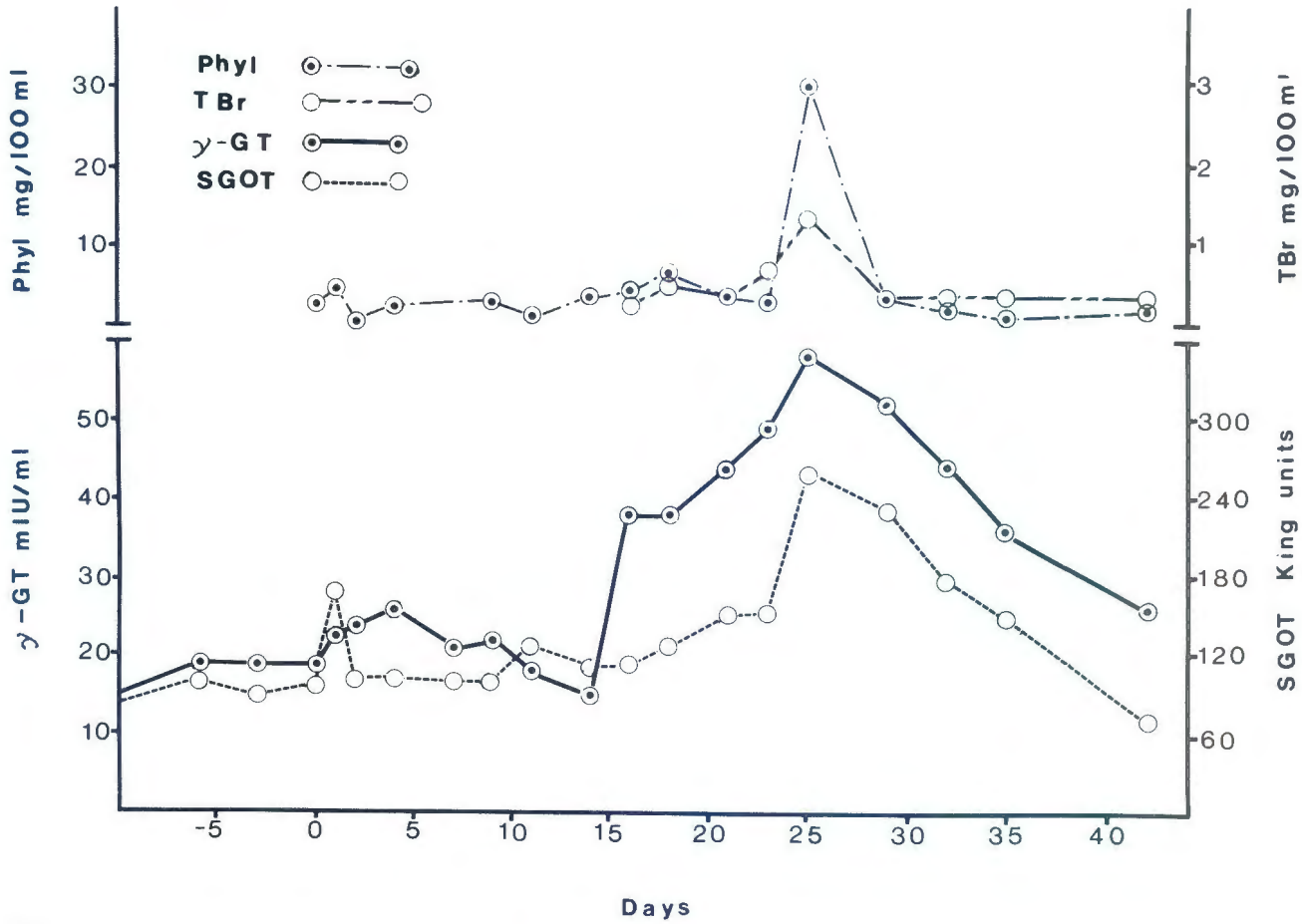


FIG. 4–7 Chemical pathological changes in the blood of sheep poisoned with *A. trifurcata*

surrounding the portal triads. These parenchymal changes were accompanied by portal oedema mild ductular proliferation, fibroplasia and mononuclear cell infiltration.

Apart from the liver, the only other noteworthy lesions were seen in the kidneys, which showed cloudy swelling and hydropic degeneration of the proximal convoluted tubules, with albuminous casts in many of the degenerated tubules.

Discussion

Droughts and overgrazing may result in an acute shortage of forage, forcing animals to graze non-selectively and thus to consume poisonous plants which are usually unpalatable. One such plant is *A. trifurcata*, a hepatotoxic shrub which is responsible for deaths, with or without photosensitization, of sheep in the south-eastern and south-western Cape Province.

Adams (1974) pointed out that plant poisons and mycotoxins could damage the liver at different sites, including the hepatocytes, biliary system, intrahepatic blood vessels and, probably, the stoma. Cytotoxins exert their effect mainly on the hepatocytes, causing various combinations of degeneration and necrosis (Zimmerman, 1978). This investigation showed that in *A. trifurcata* poisoning the insult was directed at the hepatocytes.

In general, hepatic necrosis may be focal, massive or zonally (i.e. centrizonally, midzonally or peripherally) distributed in the lobules. Zimmerman (1978) listed a whole range of toxic drugs, chemicals, plant poisons and mycotoxins that express themselves in different patterns of necrosis in the liver. According to him, although much has been published on the possible pathogenesis, diagnostic significance and sequelae of these lesions, many questions concerning them remain unanswered. It would seem, however, that hepatotoxins that produce zonal necrosis seldom cause the massive type, and *vice versa* (Klatskin, 1975).

Different zonal patterns of necrosis in the livers of sheep and cattle were reported by various workers to be associated with 2 hepatotoxic plants in South Africa, namely, *Asaemia axillaris* and *Lasiospermum bipinnatum* (Adelaar, Terblanche, Smit, Naudé & Codd, 1964; Kellerman *et al.*, 1973; Coetzer & Bergh, 1983). They found the hepatic lesions in ovine *A. axillaris* poisoning could vary from centrizonal, midzonal and peripheral necrosis to diffuse parenchymal degeneration, interspersed with isolated necrosis of hepatocytes and accompanied by hepatocellular unrest and a moderate portal reaction. The necrosis in *L. bipinnatum* poisoning was arranged midzonally and peripherally, while in this study of *A. trifurcata* poisoning the zones of necrosis stretched from the centrilobular to the peripheral areas. One of the animals, Sheep 1, that had received a high dose of plant material, died acutely, with marked midzonal coagulative necrosis that sometimes extended partially into the

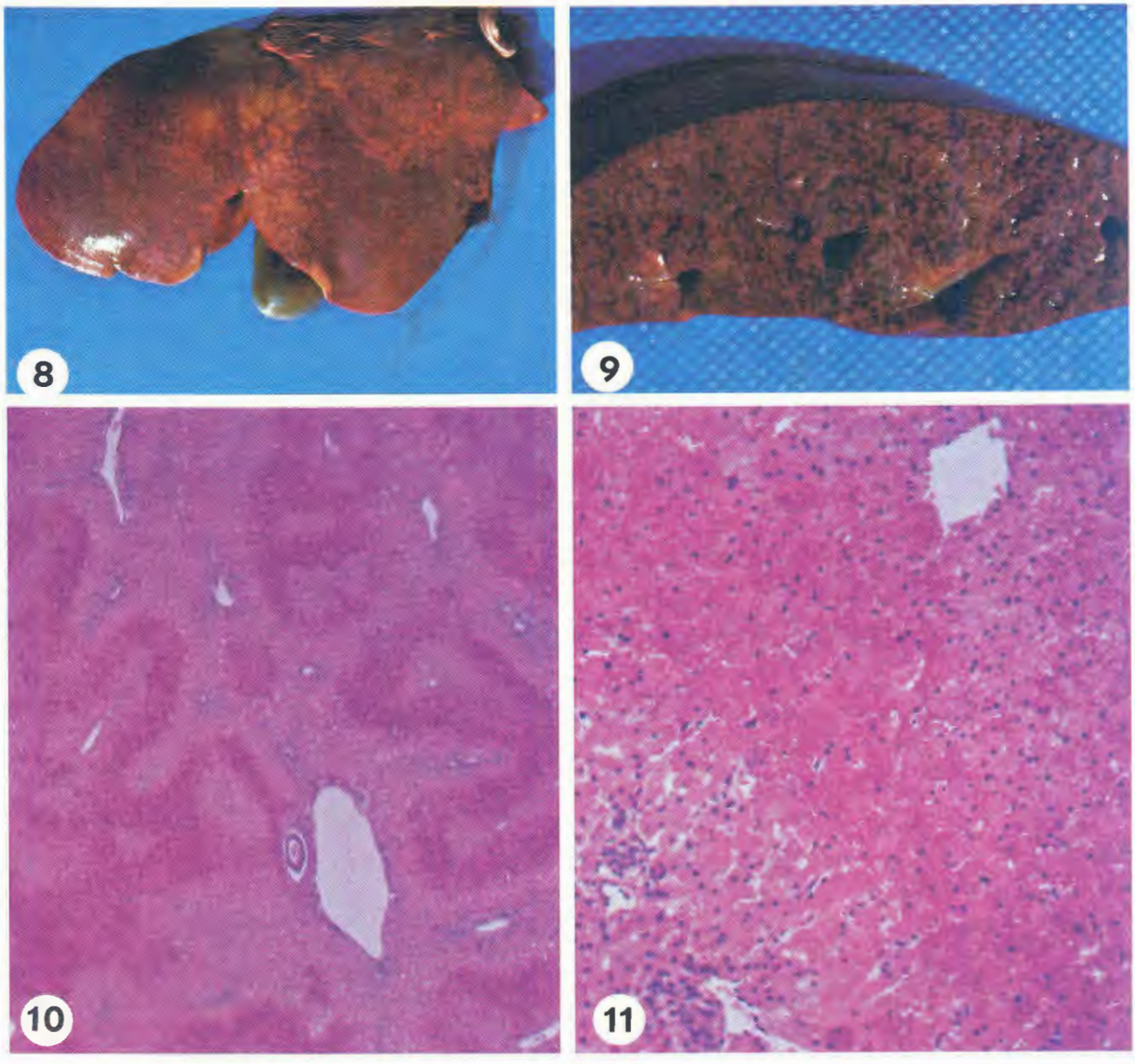
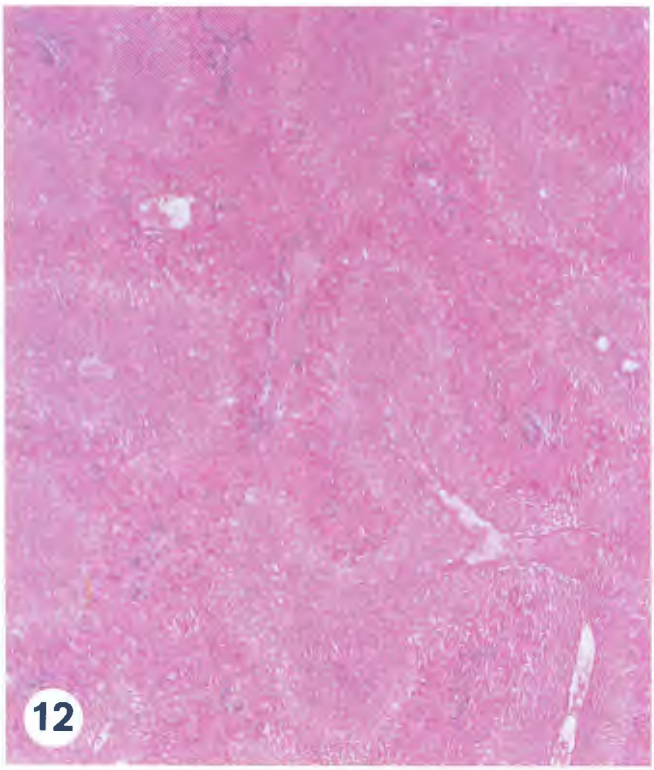


FIG. 8 & 9 Marked discoloration of the liver coupled with accentuation of lobulation

FIG. 10 & 11 Midzonal coagulative necrosis and haemorrhage which sometimes extended into centrilobular and peripheral zones of the lobules in the liver: HE × 40 and 160 respectively

peripheral areas of the lobules. Another, Sheep 2, that received a slightly lower dose, also died acutely, but with peripheral, not midzonal, coagulative necrosis. Dosing of Sheep 4 was stopped when the clinical pathological parameters indicated that it was about to become photosensitive. Later, when the photosensitivity failed to transpire, dosing was resumed, but at a fatally high level (Table 1). It is interesting to note that, while Sheep 3 had become photosensitive on 0,38 kg plant material, Sheep 4 had failed to do so on 2,5 kg. This apparent reduction in toxicity may have been due either to individual variation in susceptibility between sheep or, more probably, to the break-down of toxin in the plant during storage. In contrast to the other sheep the lesions in the liver of Sheep 4 were characterized by centrizonal coagulative necrosis and haemorrhage bordered by a zone of lytic necrosis. A narrow rim of degenerated but intact hepatocytes remained around the portal triads. Only Sheep 3, which received the lowest level of dosing, became photosensitive. When it was killed 5 days later, the hepatic lesions were characterized by a few small multifocal areas of necrosis, hepatocellular degeneration and unrest as well as moderate Kupffer cell proliferation and pigmentation. The results of these trials showed that the zonal pattern of hepatic necrosis could be varied in different animals by manipulating the dosing regimen.

It would seem that, in addition to the toxic effect of a hepatotoxin on certain areas within a lobule, the level and intervals between exposures to the toxin may also be important in determining the final nature, distribution and extent of these lesions in the liver. The findings of this investigation again emphasized the need to study the hepatic lesions in naturally poisoned animals, as those induced under experimental conditions can be aberrant. In the light of these findings as well as those of the workers on *A. axillaris* and *L. bipinnatum* poisoning



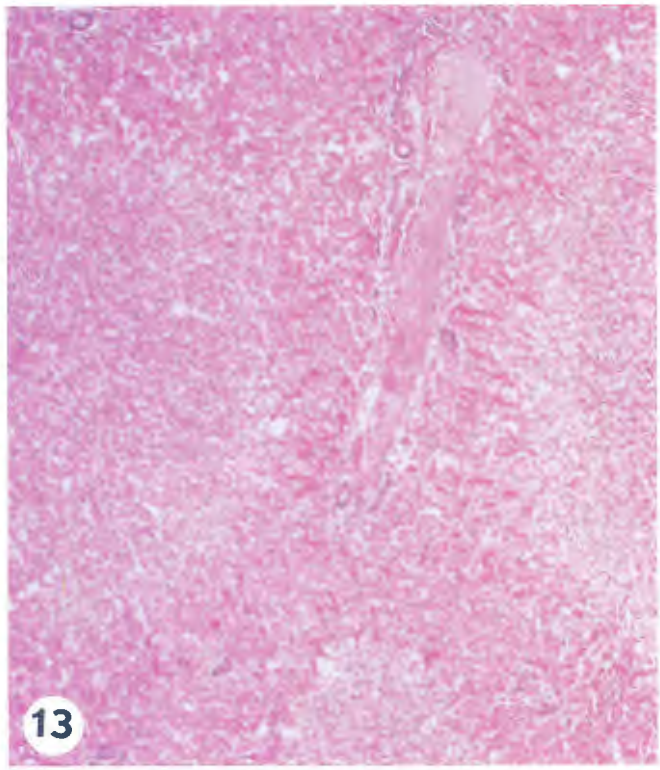


FIG. 12 & 13 Peripheral coagulative necrosis bridging adjacent lobules: HE × 40 and 160 respectively

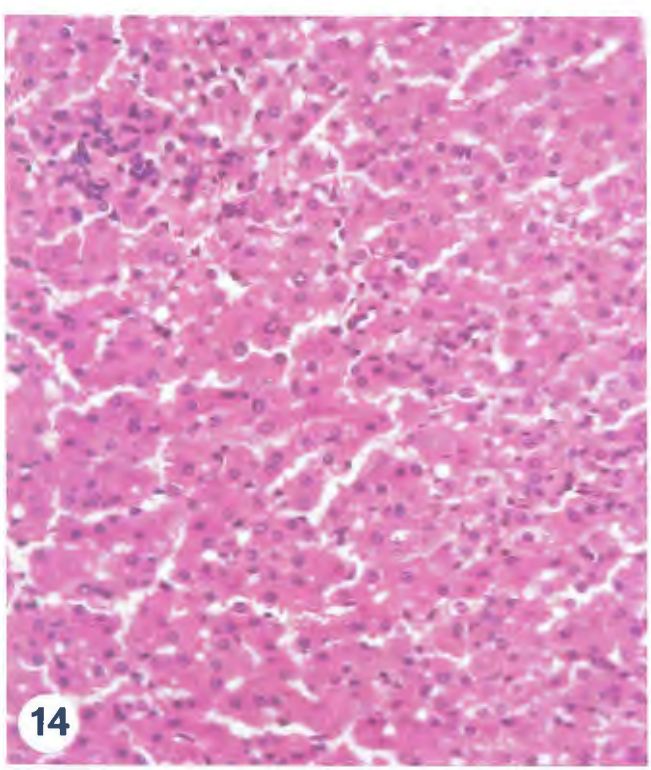


FIG. 14 Small multifocal areas of hepatocellular necrosis accompanied by diffuse parenchymal degeneration: HE × 160

(Adelaar *et al.*, 1964; Kellerman *et al.*, 1973; Coetzer & Bergh, 1983), it might be wise, therefore, not to be dogmatic about the diagnostic value of zonal necrosis and other hepatocellular changes in some plant intoxications.

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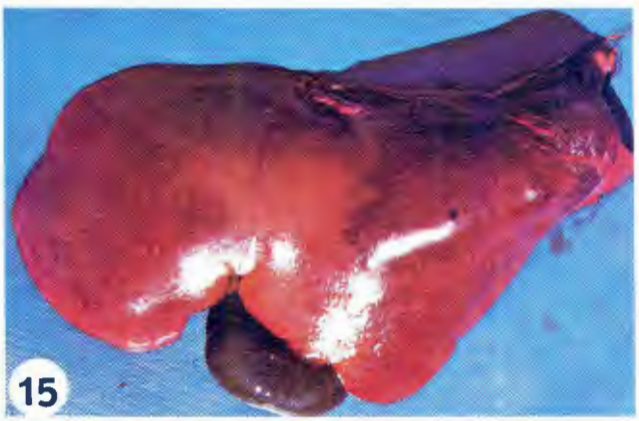

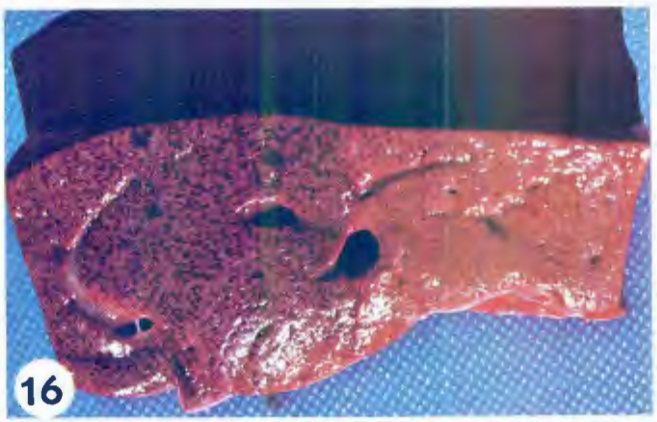

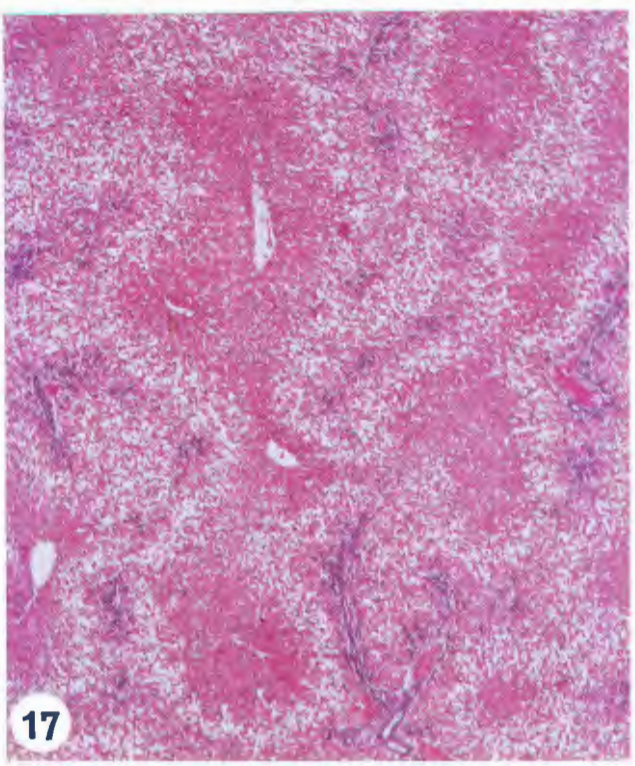

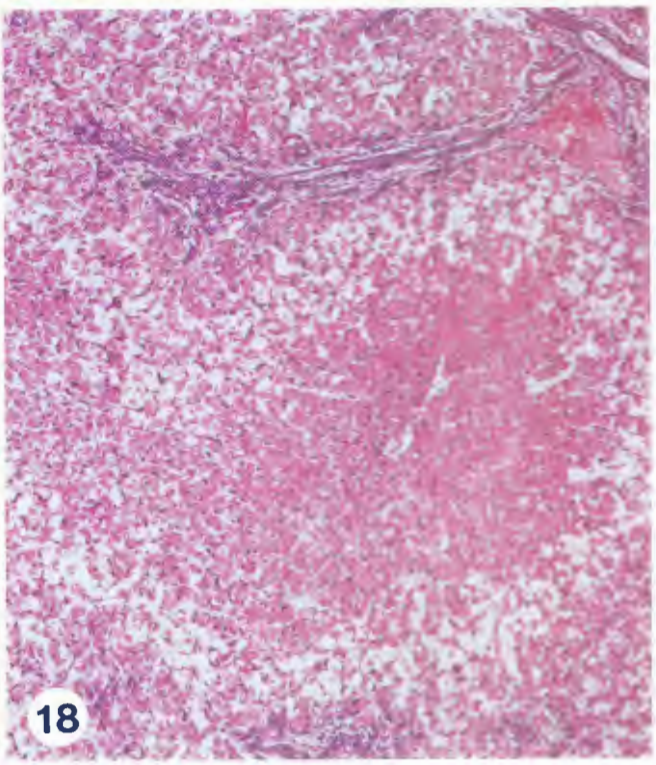

FIG. 15 Note difference in colour between the left and right liver lobes

FIG. 16 Lobulation was particularly accentuated in the congested right lobe

FIG. 17 Massive hepatic necrosis Note the zonal patterns of the necrosis: HE × 40

FIG. 18 Centrizonal coagulative necrosis bordered by a zone of lytic necrosis rimmed by degenerated hepatocytes around portal triads: HE × 250

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