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THE PATHOLOGY OF CHRONIC *DRECHSLERA CAMPANULATA* TOXICOSIS IN INBRED RATS

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ABSTRACT

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Cultures on autoclaved maize of the phytopathogenic fungus, *Drechslera campanulata*, were incorporated into diets and fed to male inbred BDIX rats.

In a pilot trial, a diet containing 30 % *D. campanulata* culture material killed 5 out of 5 rats in 15–25 days. Lesions included gastric corpus erosions, gastrorrhagia and ulcerative typhlitis.

Diets containing 5 % or 10 % culture material induced erosive to ulcerative typhlitis and oedema and hyperplasia of the ileocaecal lymph nodes in 40 out of 40 rats. Other changes included: mass loss; normocytic, hyperchromic anaemia; leukocytosis with neutrophilia; reductions in plasma proteins, creatinine, calcium and cholesterol; elevated serum enzymes; hepatosis, nephrosis and mycoplasma-like interstitial pneumonia. No lesions were present in control rats, and their profiles were normal.

Ulcerative typhlitis induced by *D. campanulata* in rats resembles that seen in chronic piperonyl butoxide intoxication as well as that due to single treatments of indomethacid, although small intestinal ulcers are more frequent in the latter. Overgrowth of intestinal flora may be involved in ulcer pathogenesis. The pathology of drechsleratoxicosis in rats is compared to that in sheep and goats where necrotic lesions in the forestomach and, to a lesser extent, in the caecum are characteristic findings.

INTRODUCTION

Drechslera campanulata (Lèv.) Sutton, a phytopathogenic fungus, has been isolated from leaf spots on oat plants associated with outbreaks of disease in goats and cattle in the western Cape Province (Van der Westhuizen, Marasas & Schneider, 1985). Pure cultures of the fungus grown on autoclaved maize proved to be highly toxic to ducklings, sheep and goats. Drechsleratoxicosis in sheep and goats causes anorexia, apathy, rumen stasis, diarrhoea and death. Necrosis of forestomach mucosa is the most characteristic gross lesion produced in these animals (Schneider, Marasas, Collett & Van der Westhuizen, 1985).

In a continuation of toxicological studies on this highly toxic fungus, chronic toxicity tests were conducted in inbred rats with culture material of *D. campanulata*. This paper describes the results of these experiments in which the principal lesions included ulcerative typhlitis (with associated complications), chronic interstitial pneumonia, hepatosis and nephrosis.

MATERIALS AND METHODS

Fungal cultures

The MRC 2855 and MRC 3199 single-conidial cultures of *D. campanulata* were obtained from the collection of the South African Medical Research Council (MRC), Tygerberg. Both cultures were isolated from leaf spots on oats associated with outbreaks of a syndrome of unknown aetiology in goats and cattle in the western Cape Province (Schneider *et al.*, 1985). Conidial suspensions of each isolate were used to inoculate autoclaved maize kernels and the 2 maize cultures were then incubated for 21 days at 25 °C, dried overnight at 45 °C, and ground to a fine meal (Schneider *et al.*, 1985).

Pilot trial

A diet containing 30 % (by mass) *D. campanulata* MRC 2855 maize culture material and 70 % commercial duckling mash was fed *ad libitum* to a group of 5 rats. Control rats were fed a diet containing 30 % autoclaved, uninoculated maize meal and 70 % (m/m) commercial duckling mash. The duckling mash contained no antibiotics, coccidiostats or growth stimulants.

Chronic toxicity test

Diets containing maize culture material of *D. campanulata* MRC 2855, MRC 3199 or uninoculated, autoclaved maize meal were fed *ad libitum* to 55 male, inbred, BDIX rats as summarized in Table 1. Rats were mass-measured weekly during the course of the experiment; thus, statistical comparisons could be made between treatment groups and the single age-matched control group.

Termination: Under phenobarbitone sodium anaesthesia (50 mg/kg i.p.), the surviving rats were exsanguinated from the aortas to obtain the blood samples for haematology and clinical chemistry evaluations. They were then perfused with a mixture (by volume) of 1 % glutaraldehyde and 4 % formaldehyde (310 mosmol/ℓ buffered to pH 7,2) (McDowell & Trump, 1976) via the caudal vena cava with simultaneous drainage of remaining blood from a severed peripheral vein.

Haematology: Full and differential blood counts were performed with a Coulter Counter (model S880) on aortic blood collected into vacuum tubes containing ethylenediamine tetra-acetic acid[1]. The variables measured were white blood cells (WBC), red blood cells (RBC), haemoglobin (Hb), haematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelets (P), lymphocytes (L) and neutrophils (N).

Clinical chemistry: Serum was separated from aortic blood collected into vacuum tubes without anticoagulant[2]. The following variables were determined by a Technikon Auto-analyser: urea, creatinine, total protein, albumin, globulin, calcium, inorganic phosphate, cholesterol, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH) and total alkaline phosphatase (ALP). The enzymes were measured, because changes in their serum levels may indicate degeneration and necrosis of hepatocytes, myocytes and enterocytes or accelerated metabolism in bone.

Statistical analysis: The differences in duration of exposure between treatment Groups 1, 3 & 4 (Table 1) arose for practical reasons related to necropsy schedules

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TABLE 1 Dietary composition (by mass), duration of experiment and terminal results of the chronic *Drechslera* groups and controls

Groups	n*	Ration			Duration of experiment
		Drechslera culture %	Maize meal %	Duckling mash %	
1	10	MRC** 2855 5	45	50	Terminated after 142 days
2	10	MRC 2855 10	40	50	1 died, 9 terminated after 48 days
3	10	MRC 3199 5	45	50	Terminated after 121 days
4	10	MRC 3199 10	40	50	Terminated after 144 days
Control	15	— —	50	50	Terminated after 144 days

*n = number of inbred rats/treatment
**MRC = Medical Research Council fungus culture number

and should not have affected results for haematology, clinical chemistry or pathology. Treatment effects on growth were analysed by the 2-tailed t test (Table 2). Haematology and clinical chemistry results for treatment Groups 1, 3 & 4 were analysed by non-parametric Mann-Whitney and median tests because of the data distributions in the small samples (Tables 3 & 4). Results for Group 2 are presented in these tables and are generally concordant, but they were not analysed statistically because they were terminated 96 days before the control group. The comparisons between treatment Groups 1, 3 & 4 and controls created 3 simultaneous pairwise comparisons in which the probability required for significance was 0,05/3 = 0,0167, or less, which imposed a more stringent test (Tables 3 & 4). The haematology and clinical chemistry data are presented in the conventional way as means and standard deviations in Table 5.

Pathology: Necropsies were performed on all of the treated rats as well as 5 out of 15 of the control rats. Fixation of tissues was accomplished in those rats that died or was completed after perfusion by immersion in 10 % neutral buffered formalin, which was also infused into the lungs via the trachea and unopened lumen of the entire gastro-intestinal tract. Tissue blocks and sections for light microscopy were cut in the usual way from the liver, spleen, kidney, lung, brain, spinal cord, bone, oesophagus, stomach (forestomach and corpus), duodenum, jejunum, ileum, caecum, colon, rectum, heart, muscle, lymph nodes, thymus, salivary glands, testis and accessory glands, urinary bladder, skin, nasal and oral mucosa, trachea, pancreas, thyroid and adrenal. In addition to routine haematoxylin and eosin (HE) staining, special stains were performed on selected sections. These stains included toluidine blue for mast cells, Gram, Masson's trichrome, Sudan black, Hall's for bilirubin, Turnbull's for iron, Schmorl's for lipofuscin and periodic acid-Schiff with and without diastase.

TABLE 2 Body masses of treated rats compared to age-matched controls

Drechslera groups	Average masses (g) at termination*	Average masses (g) of age-matched controls*	P**
1. MRC 2855 (5 %)	272,5(15,9)	373,1(24,8)	<0,01
2. MRC 2855 (10 %)	99,8(15,9)	285,5(25,3)	<0,01
3. MRC 3199 (5 %)	253,8(19,0)	364,3(24,5)	<0,01
4. MRC 3199 (10 %)	180,1(22,3)	373,1(24,8)	<0,01

* Standard deviations in brackets
** Probability of the difference in mass, 2 tailed t test

RESULTS

Pilot trial

All 5 rats that received the diet containing the fungal material died within 15–25 days. Two rats had erosions in the corpus of the stomach adjacent to the limiting ridge. Gastrorrhagia was also present. Four of the 5 rats had erosions and ulcers in the caecum. Other lesions included hepatosis, nephrosis and purulent interstitial pneumonia. No mortalities or clinical signs occurred in the control rats.

Chronic toxicity test

Mortality: There were no deaths in the controls or in the treated Groups 1, 3 and 4. One rat died in Group 2 and the remaining 9 rats in the group were killed on the same day (Table 1).

All the rats in the *D. campanulata*-treated groups showed significant ($P \leq 0,01$) reductions in mass gain compared with that of the controls (Table 2).

Clinical signs: Mass losses relative to controls and soft stools were present in all the rats in the treated groups (Table 2).

TABLE 3 Haematology: Median values for controls and *Drechslera* groups

Variable	Controls (brackets: interquartile range*)		Group 1 MRC 2855 (5 %)		Group 2** MRC 2855 (10 %)	Group 3 MRC 3199 (5 %)		Group 4 MRC 3199 (10 %)	
WBC ($\times 10^9/\ell$)	4,8	(1,5)	17,8	***	17,8	12,9	***	22,4	***
RBC ($\times 10^{12}/\ell$)	7,57	(0,42)	6,33	***	4,91	5,73		5,32	***
Hb (g/dℓ)	15,1	(0,93)	12,3	***	11,7	12,9	***	11,2	***
Ht (% v/v)	41,1	(2,6)	34,1	***	29,4	30,7	***	28,0	***
MCV (fℓ)	54,4	(0,8)	53,8	***	58,8	48,7	***	52,3	***
MCH (pg)	19,9	(0,6)	19,2	***	23,9	17,0		21,3	***
MCHC (g/dℓ)	36,6	(1,0)	35,7	***	39,5	34,8		40,7	***
Platelets ($\times 10^9/\ell$)	1 028	(37)	1 174	***	1 570	1 171	***	1 781	***
Lymphocytes (%)	61	(9)	30	***	17	28	***	28	***
Neutrophils (%)	34	(8)	69	***	80	69	***	71	***

* The interquartile range is between the 25th and 75th percentiles
** Group 2 was not tested for differences from controls (see statistical analysis in text)
*** The difference from the control median has a probability of 0,0167 or less by the Mann-Whitney test
WBC = white blood cells; RBC = red blood cells; Hb = haemoglobin; Ht = haematocrit; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration

TABLE 4 Clinical chemistry: Median values for controls and *Drechslera* groups

Variable	Controls (brackets: interquartile range*)		Group 1 MRC 2855 (5 %)		Group 2** MRC 2855 (10 %)	Group 3 MRC 3199 (5 %)		Group 4 MRC 3199 (10 %)	
Urea (mmol/ℓ)	5,6	(1,9)	5	*** mt	5	3,6	*** mt	5,1	
Creatinine (mmol/ℓ)	71	(9)	27	*** mt	35	52	*** mt	52	*** mt
Total protein (g/ℓ)	58	(5)	47	*** mt	39	45	*** mt	44	*** mt
Albumin (g/ℓ)	33	(1)	26	*** mt	22	24	*** mt	23	*** mt
Globulin (g/ℓ)	25	(2)	22	*** mt	17	21	*** mt	21	*** mt
Calcium (mmol/ℓ)	2,48	(0,1)	2,08	*** mt	2,13	2,12	*** mt	2,10	***
Phosphate (inorganic) (mmol/ℓ)	1,78	(0,26)	1,87		2,07	2,18	***	1,86	
Cholesterol (mmol/ℓ)	1,61	(0,21)	1,38	***	1,27	1,30	***	1,46	
AST (u/ℓ)	102	(27)	237	*** mt	169	158	*** mt	161	***
ALT (u/ℓ)	32	(24)	43	mt	30	28		31	
LDH (u/ℓ)	631	(343)	1 367	*** mt	324	426	***	427	
ALP (u/ℓ)	223	(40)	293	*** mt	577	235		389	***

* The interquartile range is between the 25th and 75th percentiles

** Group 2 was not tested for differences from controls (see statistical analysis in text)

*** The difference from the control median has a probability of 0,0167 or less (mt = median test, otherwise Mann-Whitney test)

AST = Aspartate transaminase
ALT = Alanine transaminase
LDH = Lactate dehydrogenase
ALP = Alkaline phosphatase (total)

TABLE 5 Means and standard deviations (bracketed) for haematology and clinical chemistry variables for the controls and *Drechslera* groups

	Control		*Drechslera* groups							
			1 MRC 2855 (5 %)		2 MRC 2855 (10 %)		3 MRC 3199 (5 %)		4 MRC 3199 (10 %)	
WBC*	5,1	(1,4)	17,3	(3,5)	18,7	(7,5)	13,8	(4,8)	21,2	(6,3)
RBC	7,6	(0,4)	6,3	(0,5)	4,9	(0,2)	5,9	(1,8)	5,3	(0,7)
Hb	15,0	(0,6)	12,1	(1,1)	11,6	(0,7)	10,6	(3,3)	11,3	(1,0)
Ht	41,2	(1,8)	33,9	(2,3)	29,4	(1,8)	29,1	(8,8)	27,8	(3,7)
MCV	54,3	(0,4)	54,1	(1,4)	60,3	(3,4)	49,4	(2,4)	52,4	(0,5)
MCH	19,8	(0,4)	19,2	(0,2)	23,7	(1,7)	18,0	(2,6)	21,5	(1,0)
MCHC	36,6	(0,6)	35,5	(1,2)	39,4	(1,9)	36,3	(3,4)	41,2	(2,4)
Platelets	1 024	(358)	1151	(105)	1 502	(194)	1 206	(248)	1 745	(208)
Lymphocytes	60,6	(8,6)	29,4	(11,2)	16,6	(4,5)	29,6	(10)	27,5	(5)
Neutrophils	34,1	(8,7)	68,7	(11,8)	79,4	(4,4)	67,8	(10)	69,7	(5,8)
Urea	5,5	(1,0)	4,8	(0,3)	5,1	(0,6)	3,6	(0,1)	5,1	(0,3)
Creatinine	66,5	(8,7)	28,4	(6,7)	41,0	(7,8)	51,2	(7,2)	51,2	(7,2)
Total protein	58,3	(3,7)	47,2	(1,8)	38,6	(1,7)	45,2	(1,6)	43,2	(2,7)
Albumin	32,5	(1,2)	25,4	(1,3)	21,9	(1,6)	24,2	(1,3)	22,6	(2,1)
Globulin	25,9	(2,9)	21,8	(0,8)	16,7	(0,7)	21	(1,2)	20,8	(1,5)
Calcium	2,45	(0,1)	2,04	(0,1)	2,18	(0,1)	2,14	(0,1)	2,10	(0,2)
Phosphate	1,78	(0,3)	1,90	(0,2)	2,24	(0,5)	2,21	(0,2)	1,81	(0,1)
Cholesterol	1,6	(0,2)	1,4	(0,1)	1,3	(0,1)	1,3	(0,1)	1,4	(0,3)
AST	105	(23)	240	(21)	205	(109)	153	(9)	180	(35)
ALT	38	(14)	52	(17)	70	(86)	28	(5)	41	(19)
LDH	621	(187)	1 330	(152)	474	(384)	418	(69)	410	(136)
ALP	218	(31)	287	(14)	570	(91)	254	(46)	370	(55)

* For units and abbreviations, see Tables 3 & 4

TABLE 6 Pathological changes in chronic *Drechslera campanulata* toxicity tests in rats

Groups	No. of rats/group	Erosions/ulcers caecum	Caecal lymph nodes*	MRM**
1. MRC 2855 (5 %)	10	10/10	10/10	4/10
2. MRC 2855 (10 %)	10	10/10	10/10	9/10
3. MRC 3199 (5 %)	10	10/10	10/10	9/10
4. MRC 3199 (10 %)	10	10/10***	10/10	10/10
Control	5****	0/5	0/5	0/5

* Oedema and lymphoid hyperplasia
** MRM = suspected murine respiratory mycoplasmosis (lung lesions)
*** One rat also ulcerative ileitis
**** Selected at random from 15 rats, all of which were healthy and grew normally throughout

Haematology: There were significant changes relative to controls throughout the profile (Table 3). Peripheral leukocytosis with neutrophilia and inversion of L:N ratios were consistently present. There was mild anaemia which tended to be normocytic and hyperchromic. Platelet counts were elevated in a dose dependent response. The results for RBC, MCH and MCHC in treatment Group 3 seem paradoxical in that the medians of these variables for this group (which statistically show no significant difference) are further away from the medians of the control group than the medians for the same variables for Group 1 (where the differences are significant).

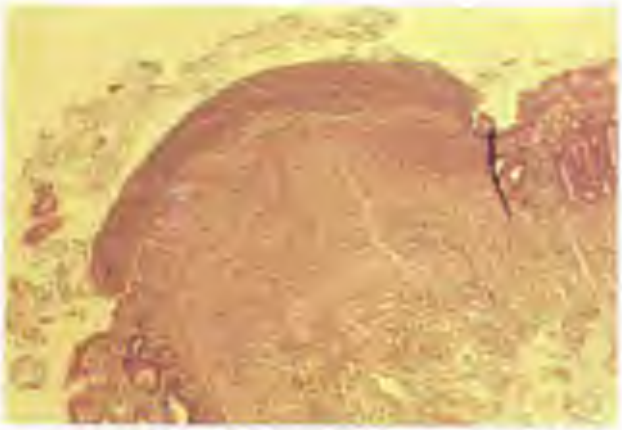

FIG. 1 Caecal ulcer covered with necrotic debris. HE × 20

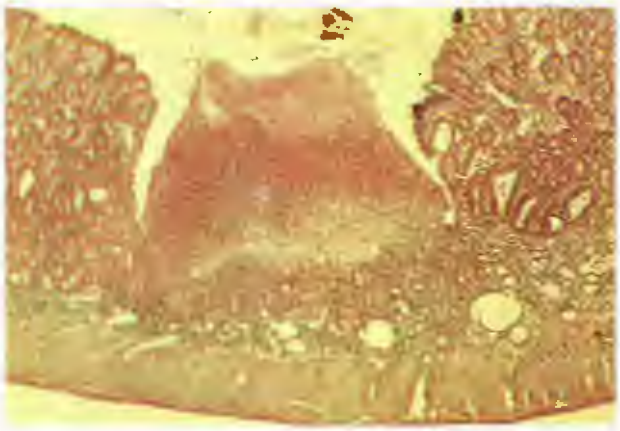

FIG. 2 Caecal ulcer with submucosal oedema. Masson's trichrome × 20

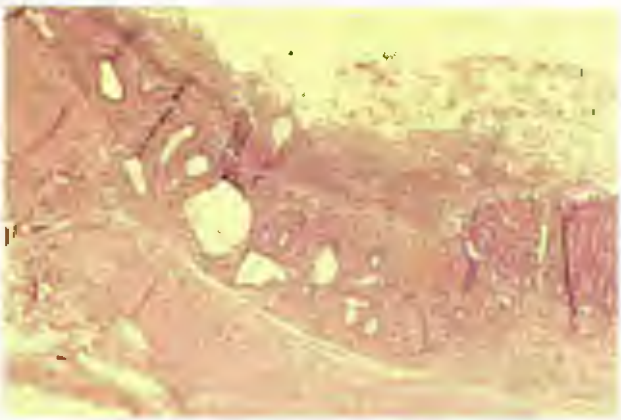

FIG. 3 Ulcer and dilated crypts with evidence of regeneration. HE × 20

FIG. 4 Ulcer overlying hyperplastic Peyer's patch with focal haemorrhage into lumen. HE × 20

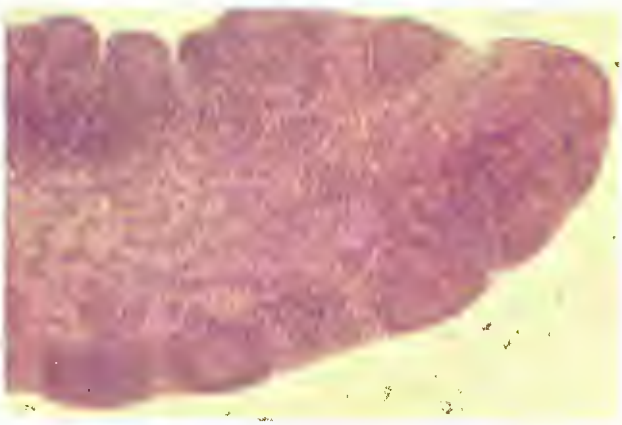

FIG. 5 Normal ileocaecal lymph node (control rat). HE × 20

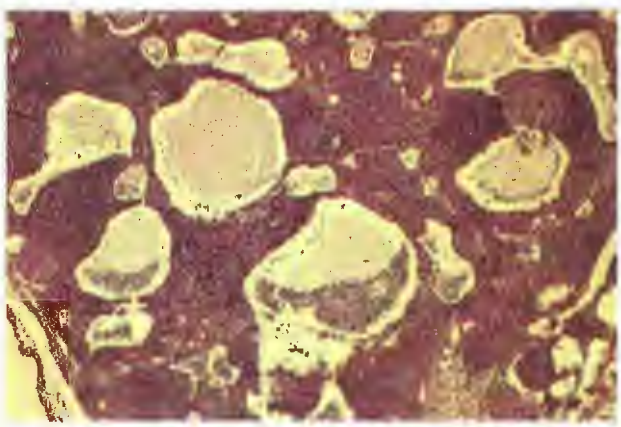

FIG. 6 Portion of ileocaecal lymph node showing gross enlargement due to oedema and lymphoid hyperplasia. HE × 20

Clinical chemistry: Treated groups showed significant reductions in serum creatinine, proteins, calcium and cholesterol relative to those of the controls (Table 4). Conversely, there were increases in inorganic phosphate, AST, LDH and ALP. The average serum albumin/globulin ratio for the animals in the control group was 1,25, while that in each of the treatment Groups 1, 2, 3 & 4 was 1,17; 1,32; 1,15 and 1,10, respectively.

Gross pathology: The treated rat that died early (Group 2) had a large oval ulcer (15 mm in length) in the caecum, the lumen of which was completely obstructed by a hard tangled mass of fibrin and necrotic debris. Apart from generally poor condition, the most striking finding in all of the remaining rats in the treated groups was severe enlargement of all the mesenteric lymph nodes, especially the ileocaecal nodes. The cause of this enlargement appeared to be due to oedema and lymphoid hyperplasia. The mucosa of the intestinal tract was also diffusely but moderately oedematous, and the mesenteric vasculature was slightly congested. Many of these rats had round to oval, well demarcated, single, mucosal erosions or ulcers in the caecum. The ulcers were covered by necrotic debris and ranged from 1–6 mm in diameter. All the erosions and ulcers were situated on the lesser curvature of the caecal mucosa between the ileal and colonic orifices. In one rat in Group 4, several ulcers were also present in the terminal ileum. No other significant changes were noted in the treated rats and no lesions were detected in the 5 control rats that were necropsied.

Histopathology: Significant light microscopy findings are summarized in Table 6. Lesions were present in the caeca of all 40 treated rats, and these ranged from shallow mucosal erosions associated with a diffuse, mixed inflammatory cell reaction in the lamina propria as well as submucosal oedema, to ulcers of varying size and depth. The latter were associated with a massive infiltration of neutrophils, smaller numbers of eosinophils, macrophages and lymphocytes, and proliferation of fibroblasts (Fig. 1). The cell infiltration extended into the surrounding submucosa and muscle layers, disrupting the latter, and was associated with oedema in which there were few or no inflammatory cells (Fig. 2). In a few cases where ulceration was especially deep many mast cells were also present in the granulation tissue and muscle layers in the vicinity. The mucosa near the ulcers was hyperplastic and glandular dilatation was prominent in areas bordering the ulcers (Fig. 3). Where ulcers overlaid Peyer's patches, lymphoid hyperplasia was detected in the latter (Fig. 4). Vascular leukostasis was prominent in the vicinity of the ulcers which occasionally showed focal haemorrhage into the lumen of the gut and/or surrounding tissues. Abundant bacteria consisting of gram negative filaments and colonies of gram positive cocci occurred in the necrotic tissue in the ulcers in most instances.

FIG. 7 Caecal ulcer with adjacent portion of lymph node (bottom left) with severe oedema of medullary sinus. Masson's trichrome × 20

FIG. 8 Villus atrophy and oedema of the lamina propria (ileum). HE × 50

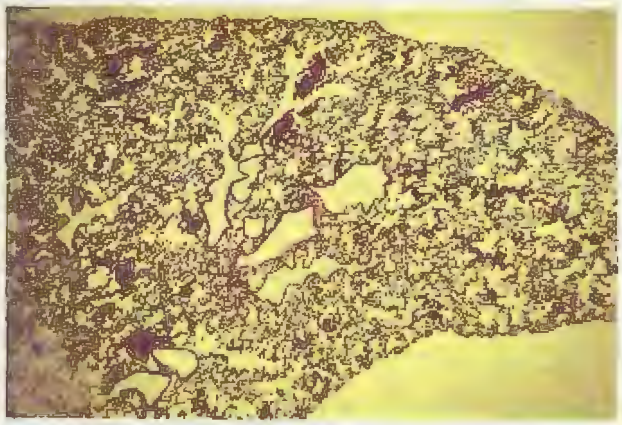

FIG. 9 Normal lung from control rat. HE × 10

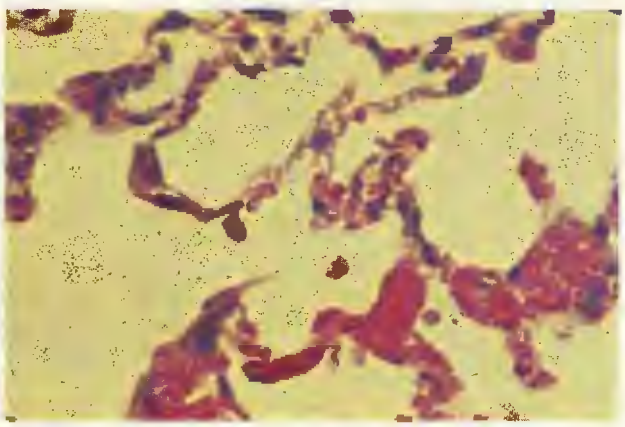

FIG. 10 High power of normal lung. HE × 200

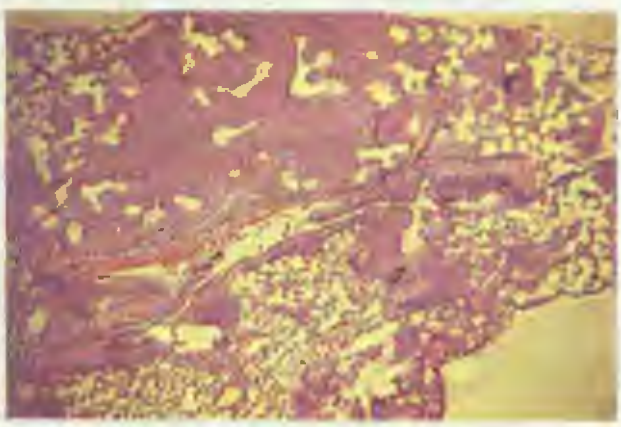

FIG. 11 Lung from treated rat with MRM-like lesions. HE × 10.

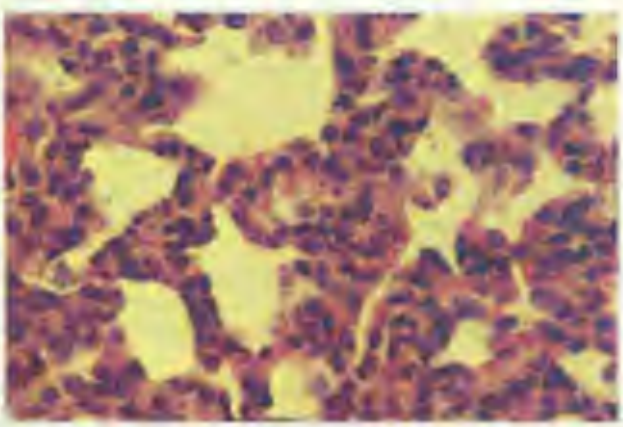

FIG. 12 High power of treated rat lung showing interstitial pneumonia. HE × 200.

In many of the treated rats, dematiaceous (=cell walls pigmented brown or black) fungal "hyphae" were seen in the lumen of the gastrointestinal tract from the stomach to the colon. Those in the large intestine appeared well-preserved despite digestive processes.

Associated ileocaecal lymph nodes were hyperplastic and severely oedematous and revealed many cystic fluid-filled spaces (Fig. 5–7).

Mild to severe villus atrophy of the small intestine was encountered in all the treated rats (Fig. 8). In Peyer's patches, small numbers of lymphocytes were karyorrhectic. The only change in the colon of treated rats was a mild to severe non-inflammatory submucosal oedema.

Diffuse hydropic degeneration of hepatocytes characterized the livers of treated rats. In the kidneys, hydropic degeneration of the proximal convoluted tubular epithelium was fairly constant, and brownish pigment globules (identified as lipofuscin/ceroid by special stains) were conspicuous in the cytoplasm of these cells. This nephrosis with pigmentation contrasted markedly with kidneys from control animals that were considered to be normal.

The spleens of all the treated rats had neutrophil infiltration in the marginal sinuses and the bone-marrow appeared hypercellular with abundant megakaryocytes.

The lungs of most rats in the treated groups contained lesions. These were characterized by proliferation of pericytes and peribronchial lymphoid tissue, together with infiltration of macrophages, causing focal consolidation. Other lesions included a mild interstitial pneumonia as well as bronchiectasis and bronchiolectasis. Lungs of control rats were normal (Fig. 9–12).

No pathological changes were observed in other organs of treated rats or in the controls.

Discussion

Drechslera spp. are dematiaceous fungi and evidence of their consumption was presented by their detection in stomach, intestinal, caecal and colonic contents of the treated rats on histopathological examination. Attempts were made to culture *Drechslera* from the intestinal tract of treated, intoxicated rats but this was unsuccessful (W. F. O. Marasas, laboratory data, 1986).

As rats receiving a toxic ration often prefer to starve than eat it, reduced feed intake, therefore, could have contributed to the mass loss in the treated rats. A chronic malabsorption syndrome with blood and protein loss would also explain the mass loss as well as the haematology and clinical chemistry findings. The leukocytosis, neutrophilia, inverted L:N ratio and oedema and hyperplasia of the ileocaecal lymph nodes were regarded as responses to infection complicating caecal ulceration.

Stewart & Jones (1941) described a spontaneous disease in rats which they called "chronic ulcerative cecitis". They stated that "because of the relatively frequent occurrence of spontaneous cecitis in laboratory rats, particular care should be exercised to avoid confusion of the lesions of this disease with experimentally produced changes". Their rats included a number of strains, the majority of which were Wistar and Wistar-crosses. Various diets were fed, but no attempt was made to correlate diet with the caecal lesion. The pathological changes that they described are very similar to those seen in the present experiment except that the arteritis resembling polyarteritis nodosa which they found in the caecum was absent.

The fact that none of the control rats in this experiment showed evidence of caecal pathology supports the contention that drechsleratoxicosis in the treated rats was responsible for the caecal lesions. The cause of the erosive to ulcerative typhlitis seen in the treated groups could involve a direct effect of the *Drechslera* mycotoxin(s), an infection by an opportunistic pathogen or a combined synergistic effect.

Ileocaecal ulceration in rats is also an outspoken lesion in chronic, oral piperonyl butoxide intoxication in Fischer 344 rats (Maekawa, Onodera, Furuta, Tanigawa, Ogiu & Hayashi, 1985), while single, oral doses of indomethacin cause ulceration in the jejunum and ileum (occasionally caecum and colon) of Simonsen rats (Kent, Cardelli & Stamler, 1969).

Experimental drechsleratoxicosis in sheep, goats and calves causes consistent necrotic lesions in the mucosa of the forestomach as well as erosions and ulcers in the caecum (Schneider *et al.*, 1985; M. G. Collett, unpublished observations, 1985). Although no forestomach lesions were present in the treated rats in this experiment, in the pilot trial of drechsleratoxicosis (high dose), 2 out of the 5 rats did develop erosions of the gastric corpus with gastrorrhagia, in addition to caecal erosions and ulcers.

Caecal ulceration may be a feature in the pathology of some infectious diseases in rats. These include paratyphoid (*Salmonella enteriditis* or *S. typhimureum*), plague (*Yersinia pestis*) and pseudotuberculosis (*Y. pseudotuberculosis, Y. enterocolitica*). Kent *et al.* (1969) showed that the intestinal flora played a significant role in the exacerbation of ulcers. Oral antibiotics were found to prevent bacterial overgrowth and thereby greatly to reduce the severity of ulcers. The microbial status of the *Drechslera*-treated rats and those in the piperonyl butoxide study (Maekawa *et al.*, 1969) was not defined. In future work, blood, lymph nodes and intestines of intoxicated animals will have to be examined for pathogens, and the role of the intestinal flora in the development of caecal ulcers must be determined.

Factors common to the sites of ulcer formation in the forestomachs of ruminants and in the caecum of rats are fermentation of ingesta and prolonged contact time. It is probable that either or both could be contributory to ulcer pathogenesis. By comparative pathology, this suggests that drechsleratoxicosis may cause ulcerative typhlitis in horses.

The only other lesions possibly of infectious origin were in the lungs. The lung lesions resembled those of murine respiratory mycoplasmosis (MRM) (Benirschke, Garner & Jones, 1978). In subsequent investigations, mycoplasmas could not be cultured or visualized under the transmission electron microscope (J. E. Fincham, laboratory data, 1986). Since lungs from necropsied control rats were normal, drechsleratoxicosis may be directly responsible for the MRM-like lesion in treated rats. Another possibility is that a secondary infection (e.g. mycoplasmosis) may have complicated a state of immunosuppression, induced either by stress (resulting from the ulcerative typhlitis) or a direct effect of the mycotoxicosis.

Raised enzyme levels in treated rats were probably the result of the hepatosis and caecal ulceration. Despite the nephrosis seen histologically, clinical chemistry tests did not confirm renal malfunction. Low-grade toxaemia or physiological renal compensation in response to fluid and electrolyte loss in the intestinal tract may have contributed to the nephrosis. This could have caused swelling of the proximal tubules and the "wear and tear" pigmentation. Enhanced renal clearance of creatinine may explain the low serum creatinine values.

In conclusion, chronic *D. campanulata* toxicosis in male, inbred BDIX rats consistently causes ulcerative typhlitis with associated changes in the regional lymph

nodes. Mycoplasma-like lung lesions may also be a direct or indirect effect of this poisoning. Degenerative changes were found in the liver and kidneys. In contrast to the findings of Schneider *et al.*, (1985) in small ruminants, no lesions were found in the forestomach. It is hypothesized that drechsleratoxicosis may cause ulcerative typhlitis in horses.

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