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STUDIES ON ASPERGILLUS FUMIGATUS, EXPERIMENTAL MYCOTOXICOSIS IN MICE, CHICKS AND PIGS WITH THE APPEARANCE, IN PIGS, OF PERIRENAL EDEMA

By

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A toxin derived from Aspergillus fumigatus (AF) mycelia was claimed by *Henrici* (1939) and by *Tilden et al.* (1961) to be lethal to experimental animals (rabbits, guinea pigs, mice, chicks, and dogs). These authors observed extensive lung hemorrhages in rabbits, guinea pigs, and dogs following the parenteral administration of large amounts of toxin. When smaller amounts of toxin were administered the patho-anatomical picture was dominated by kidney lesions with necroses of the tubules. In some instances, in rabbits and guinea pigs, fatty infiltration of the liver parenchyma was demonstrated, and according to *Henrici* peripheral necroses of liver lobules were seen in single instances. The kidney lesion was said to be the only patho-anatomical change observed in mice and chicks.

In a previous paper *Rutqvist* (1965) described the production of toxin and the study of the serologic relationship between toxins derived from mycelial material of different AF strains. The present paper deals with the lesions observed in mice, chicks, and pigs following parenteral administration of the toxin.

MATERIAL AND METHODS

Preparation of the toxin

Preparation of toxin from AF mycelial material has been as described earlier (*Rutqvist* 1965). The mycelial mats grown for 6 days at 20 °C on the surface of yeast extract broth in Roux' flasks

were washed, when harvested, with 0.9 % NaCl solution, dried between filter papers, and stored at —40°C for 2—4 days.

To every 100 g frozen mycelial material 75 ml of a 0.9 % NaCl solution were added and the material was homogenized in a mixer. The homogenate was stored at 4°C for 5 days and centrifuged and the supernatant passed through Seitz EK-filters. The filtrates (the toxins) were stored at 4°C.

Determination of LD_{50} for mice

The number of LD_{50} for mice per ml toxin was calculated according to Kärber. White mice, strain NMRI from the Naval Medical Research Institute, Bethesda, Ma, USA and weighing 16—18 g each, in groups of 6—10 were injected i.p. with each of serial ten fold dilutions of toxin. The volume of the inoculum was adjusted to 0.5 ml per mouse with 0.9 % NaCl solution. The mice were observed for ten days.

Post-mortem material

Mice: 188 mice were autopsied. They died following i.p. injection of 0.5—60 LD_{50} of toxin from AF strains 3, 938, 1854, 2144, 2833, 6868, 6869, and 6870 (*Rutqvist*). The injected volume was 0.5 ml per mouse and 0.9 % NaCl solution was used as diluent. Survival times, dosage of the toxins, and the distribution over different strain toxins are seen from Table 1.

In order to study the development of the histopathologic changes produced by the AF toxin 38 mice were injected i.p. with 0.25 LD_{50} of strain 938 toxin. The mice were sacrificed at intervals from 7 hours to 13 days p.i.

Chicks: I.v. injection in the wing vein with 10—100 LD_{50} per kg body weight of strain 938 toxin was made on 8 Light Sussex chicks weighing about 250 g each. Number of chicks per injected dose, doses, and survival times of the chicks are seen from Table 2.

Pigs: Pigs of the Swedish land-race belonging to two litters of 4 piglets each and weighing 11—14 kg and 15—18.5 kg, respectively, were injected i.v. in the auricular vein with 15—90 LD_{50} per kg body weight of strain 938 toxin. The dosage of the toxin and the survival times of the pigs are seen from Table 2.

The effect of orally administered toxin from strain 938 given by oesophageal tube, was tested on 6 mice, 5 chicks, and 2 pigs as seen from Table 3.

Histopathological examinations

Animals sacrificed during the experiments were autopsied immediately after killing. Animals that died were autopsied as soon after death as possible. In no case more than 16 hours elapsed between death and autopsy.

Tissue material for histopathological examination was fixed in a 10 per cent aqueous formaldehyde solution and in Carnoy's fluid, and, for chick kidneys, also in absolute alcohol. All specimens were sectioned after embedding in paraffin and stained with hematoxylin-eosin, PAS with and without diastase treatment, combined staining of acid and periodate polysacharides according to Ritter and Olesen, fat staining with Sudan Black B, silver methenamine according to Jones, and lipofuchsin staining according to Long-Ziehl-Neelsen.

RESULTS

Mice

Toxicology. Mice injected intra-peritoneally with toxin from 8 different AF strains in doses of 0.5—60 LD_{50} per mouse showed anorexia and increasing listlessness and usually died within four days p.i. (Table 1). In no instance any nervous symptoms were observed. The mice given a toxin dose of 0.25 LD_{50} per mouse of strain 938 toxin and being sacrificed at different intervals p.i. showed normal appetite and no signs of disease.

Gross pathology. The lesions shown by mice, dead following i.p. inoculation with toxin from 8 different AF strains (Table 1), were uniform. The kidneys were swollen and pale and the cortex was mottled by pin point hemorrhages. The kidney lesions were more conspicuous in mice which survived for a longer period. A constant observation was that the upper part or often even the total length of the small intestine and in many instances also the large intestine were lax and dilated with watery, mucous contents, which, in 67 mice surviving for 1—5 days, also contained a varying amount of blood. In 6 mice surviving for 2—4 days the presence of bleeding erosions in the gastric mucous membrane could be observed. Toxin from 7 different AF strains caused slight — moderate hydrothorax in 15 mice which survived for 1—5 days.

The mice given 0.25 LD_{50} per mouse of strain 938 toxin and sacrificed at different intervals p.i. showed no conclusive gross lesions. The impression that, in mice killed 2—3 days p.i., the

Table 1. Deaths in mice after i.p. administration of toxins from different A. fumigatus strains.

Survival time Days	Dose as number LD_{50} per mouse (mice)															
	0.5—5								6—10							
	Strain, number								Strain, number							
	3	938	1854	2144	2833	6868	6869	6870	3	938	1854	2144	2833	6868	6869	6870
1	2	6								6					5	4
2	7	4	3	8	2		4	4					4	2	1	1
3	6	1	14	7	3	4	3	3						3		
4	2		2	4	4	2	6	5					2	1		1
5					3			1								
	17	11	19	19	12	6	13	13	0	6	0	0	6	6	6	6

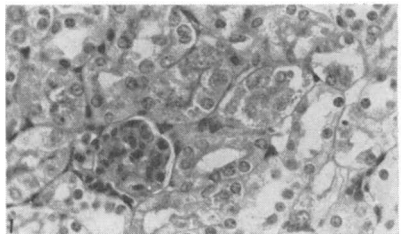
Survival time Days	Dose as number LD_{50} per mouse (mice)																Total number of dead mice
	11—20								21—60								
	Strain, number								Strain, number								
	3	938	1854	2144	2833	6868	6369	6870	3	938	1854	2144	2833	6868	6869	6870	
1		6			2	3	6	5						3	6	6	60
2					4	2		1						3			50
3																	44
4						1											30
5																	4
	0	6	0	0	6	6	6	6	0	0	0	0	0	6	6	6	188

kidneys appeared slightly more lightly coloured than normally was uncertain.

Histopathology. The severity of kidney lesions varied according to the amount of toxin. In mice, which had received large amounts of toxin the proximal convoluted tubules were entirely necrotic and numerous hyaline cylinders giving positive PAS reaction could be observed in the distal convoluted tubules, the loop of Henle, and the collective tubules. In mice given a smaller amount of toxin degeneration of epithelial cells appeared in the intermediate parts of the proximal convoluted tubules with opulent occurrence of PAS-positive droplets in the epithelial cell cytoplasm and the tubular lumen. The distal convoluted tubules seemed to be somewhat dilated and generously filled with PAS-

positive material. A certain swelling of the epitehlial cells of the glomeruli could also be observed (Fig. 1).

Even in the liver lesions could be observed, including enlargement, and degenerative changes of the liver cell nuclei, fatty infiltration of the parenchymal cells, and edema of the space of Disse (Fig. 2).



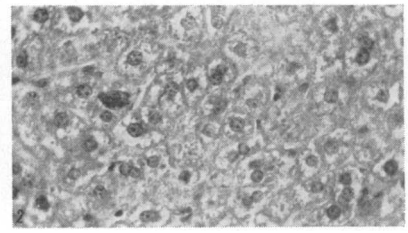


Figure 1. Kidney. Mouse (P 278/64), killed 31 hours following i.p. injection of 0.25 LD_{50} of Aspergillus fumigatus (AF) strain 938 toxin. Several PAS-positive protein absorption droplets in the proximal tubules. Glomeruli small, with contracted, empty capillaries. PAS.

Figure 2. Liver. Mouse (P 284/64), killed 48 hours following i.p. injection of 0.25 LD_{50} of AF strain 938 toxin. The liver cells are swollen and show fatty infiltration. The glycogen content is decreased. PAS.

At examination of the mice which were given 0.25 LD_{50} of strain 938 toxin and killed at different intervals p.i. it was revealed that PAS-positive granules in the proximal convoluted tubules appeared within 24 hours p.i. At the same time degenerative changes including fatty infiltration and a decrease in glycogen content were observed in the liver cells. In visibly undamaged liver cells the glycogen was baked together into clots.

Chicks

Toxicology. Two chicks given 100 LD_{50} toxin per kg bodyweight i.v., both showed dyspnoea immediately p.i. They were unable to stand on their feet and died within 10 minutes p.i. Following injection of 20 and 60 LD_{50} toxin per kg body weight, respectively, four chicks died within 24—48 hours, whereas two chicks given 10 LD_{50} toxin per kg body weight were killed 8 days p.i. The chicks which died, showed anorexia, increasing listlessness and were unwilling to move around, whereas those killed

showed only a slight lack of appetite but no other visible signs of illness.

Gross pathology. The two chicks (O 1954 and O 1955, of Table 2) which died immediately p.i. showed acute circulatory disturbances such as congestion and edema of the lungs. The trachea and larynx were filled with a foaming fluid. Even the liver and the kidneys were congested.

Table 2. Intravenous administration of toxin from A. fumigatus, strain 938.

Animal	Weight per animal	LD_{50} per kg body weight (mice)	Number dead / Number inoculated
Chicks			
O 1954, O 1955	250 g	100	2/2 (0,0) [a]
O 1959, O 2003	250 „	60	2/2 (1,2)
O 2004, O 2005	250 „	20	2/2 (2,2)
O 2156, O 2157	250 „	10	Killed after 8 days
Pigs			
O 3984	18 kg	90 [b]	1/1 (7)
O 3969	17 „	55 [b]	Killed after 4 days
O 3877	19 „	45	Killed after 1 day
O 3985	15 „	35 [b]	1/1 (6)
O 4894	14 „	30	1/1 (4)
O 4906	11 „	30	1/1 (5)
O 4941	14 „	15	Killed after 5 days
O 5011	13 „	15	1/1 (8)

Figures within ( ): Survival time in days.
[a] Both chicks died within 10 minutes p.i.
[b] Inoculation dose divided in two, given with a one-day interval.

All of the six remaining chicks showed the same gross appearance which was predominantly that of renal and visceral gout.

Histopathology. In chicks dead within 1—2 days following the injection of toxin (O 1959, O 2003, O 2004, and O 2005), and in the chicks killed 8 days p.i. (O 2156 and O 2157) the proximal convoluted tubules showed complete necrosis. The epithelial cell cytoplasm was disintegrated and contained a large number of PAS-positive droplets. The convoluted tubules and the interstitial tissues contained a few uric acid crystals. Some glomeruli showed

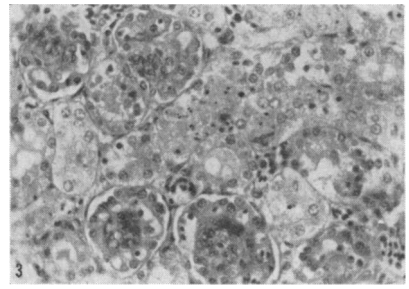


Figure 3. Kidney. Chick (O 2005/64), dead 2 days following i.v. injection of 20 LD_{50} per kg body weight of AF strain 938 toxin. Necrosis of proximal tubules with pyknotic and lytic nuclear changes. Distal tubules (arrow) are dilated with PAS-positive contents in their lumina. Glomeruli are enlarged owing to increase of the number of cells, thickening of the capillary walls and swelling of the epithelial cells. Hematoxylin-eosin.

enlargement and increase in cell number, thickening of the mesangium, and swelling of the epithelial cells (Fig. 3).

The livers of all the six chicks examined showed dissociation of the liver cells and edema of Disse's space (Fig. 4). In one of the chicks (O 2004), which received 20 LD_{50} toxin per kg body weight, the liver was observed to contain centrolobular necrotic foci diffusely bordering upon the surrounding parenchyma and showing little or no cellular reaction (Fig. 5).

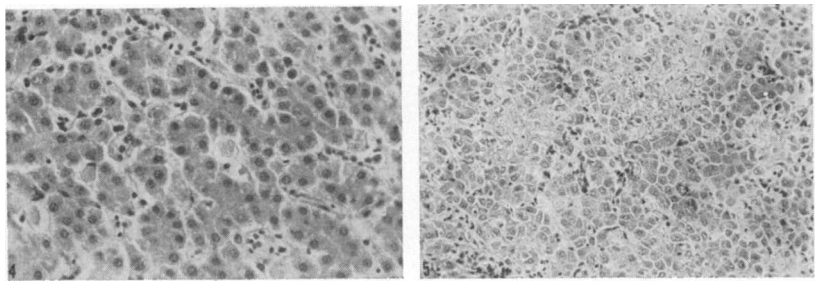


Figure 4. Liver. Chick (O 2005/64), dead 2 days following i.v. injection of 20 LD_{50} per kg body weight of AF strain 938 toxin. Edema of the space of Disse.
Hematoxylin-eosin.

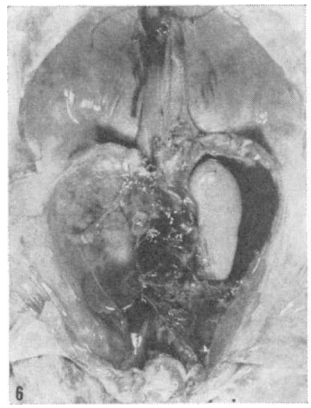
Figure 5. Liver. Chick (O 2004/64), dead 2 days following i.v. injection of 20 LD_{50} per kg body weight of AF strain 938 toxin. Centrolobular liver cell necroses and liver cell dissociation.
Hematoxylin-eosin.

Pigs

Toxicology. Pigs, receiving 15—90 LD_{50} toxin per kg body weight i.v. showed increasing anorexia and unwillingness to move. A few days p.i. they showed a tendency to bend their backs and fits of muscular trembling, especially in the muscles of the hind quarters. Concomitantly they seemed to have increasing difficulties in rising and walking. One pig, given 30 LD_{50} toxin per kg body weight vomited vigorously some 90 minutes p.i.

Five pigs died within 4—7 days p.i., and 3 pigs were killed within 1—5 days p.i. The pig, killed one day p.i. showed no visible signs of illness (Table 2).

Gross pathology. Pig O 3877, given 45 LD_{50} toxin per kg body weight i.v., and killed one day p.i. showed no gross lesions on post-mortem examination. The remaining pigs, no matter if dead or killed, were anemic and showed marked kidney lesions. The kidneys were anemic and embedded in an extensive edema in and beneath the perirenal capsule as well as retroperitoneally. The edema extended from the diaphragm backwards to the entrance of the pelvic cavity (Fig. 6). In 3 of the pigs (O 4894, O 4906, and O 4941) the edema had a strong hemorrhagic com-



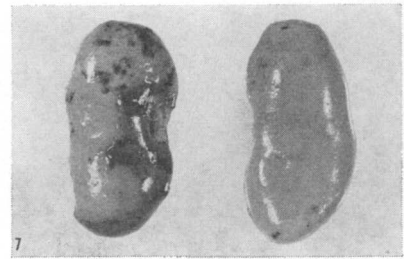


Figure 6. Kidneys. Pig (O 3985/64), dead 6 days following i.v. injection of 35 LD_{50} per kg body weight of AF strain 938 toxin. Strong perirenal edema. The left hand side renal capsule has been cut open. The kidney is pale and compressed and surrounded by a large amount of red stained edema fluid.

Figure 7. Kidneys. Pig (O 3985/64), dead 6 days following i.v. injection of 35 LD_{50} per kg body weight of AF strain 938 toxin. The kidneys are pale. In the superficial layers of the cortex there are several pin point, sometimes confluent hemorrhages.

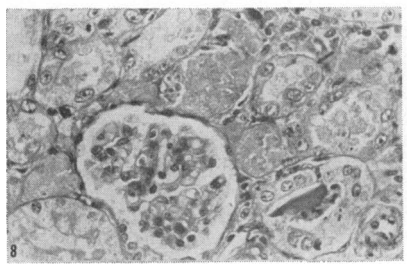
ponent. In the renal cortex pin point, sometimes confluent, hemorrhages could be observed (Fig. 7). Extensive edema could be observed also subperitoneally in the abdominal wall and the large intestine.

Two of the pigs (O 3984 and O 3985) showed congestion and edema of the lungs and hydrothorax and ascites. Bleeding erosions in the border area between the cutaneous and the glandular gastric mucous membrane were seen in two pigs, O 4894 and O 4906.

Histopathology. All pigs, even pig no. O 3877, which showed no gross lesions, showed similar histopathological changes. The proximal convoluted tubules were necrotic. The distal convoluted tubules, the loop of Henle, and the collective tubules were dilated and filled with PAS-positive cylinders. The glomeruli showed no consistent lesions (Fig. 8).

Parenchymatous degeneration with swelling and vacuolisation of the parenchyma cells and edema of Disse's space was observed in the liver (Fig. 9).

In the experimental animals (6 mice, 5 chicks, and 2 pigs, Table 3) which were given toxin orally no signs of illness and no gross or histopathological lesions whatsoever could be observed.



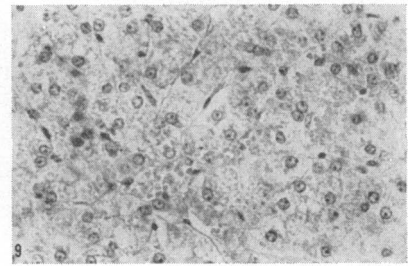


Figure 8. Kidney. Pig (O 4894/64), dead 4 days following i.v. injection of 30 LD_{50} per kg body weight of AF strain 938 toxin. Complete necroses of the proximal tubules. The distal tubules show dilation of the lumina and degenerative nuclear changes (arrows). No changes of the glomeruli.
PAS.

Figure 9. Liver. Pig (O 4894/64), dead 4 days following i.v. injection of 30 LD_{50} per kg body weight of AF strain 938 toxin. Swelling and vacuolization of the liver cells and edema of the space of Disse. Some liver cells exhibit caryolysis.
Hematoxylin-eosin.

Table 3. Peroral administration of toxin from A. fumigatus, strain 938.

Animal species	Weight per animal	Number of animals	LD_{50} per kg body weight (mice)	Observed time for
Mice	16—18 g	6	3000	10 days
Chicks	250 „	4	2000	8 „
Chick	250 „	1	12000 a)	90 „
Pig	12 kg	1	400	8 „
Pig	20 „	1	1800 b)	10 „

a) Toxin dose divided: 2000 LD_{50} toxin per kg body weight, given daily for 6 consecutive days.

b) Toxin dose is the total amount of toxin, given at 7 different occasions during the lapse of 14 days. Autopsy was made 10 days following the last administration.

DISCUSSION

Toxin from 8 different AF strains all produced similar pathological lesions in mice. The predominating lesion in mice, chicks, and pigs was a kidney damage, which seemed to initiate by degeneration of the intermediate parts of the proximal convoluted tubules when provoked by small amounts of toxin and manifested itself as a complete cortical necrosis when larger doses of toxin were given. On i.v. administration of large toxin doses to two chicks, death from shock resulted in a few minutes.

The kidney lesion following administration of the AF toxin closely resembles a kidney lesion described in mice, guinea pigs, rabbits, ducks, and dogs by *Henrici* (1939) and by *Tilden et al.* (1961) as the result of parenteral administration of AF toxin. These workers stated that the kidney lesion seemed to be the only one that could be proven in mice and chicks, whereas in guinea pigs and rabbits degenerative changes such as fatty infiltration, and according to *Henrici* even necrosis, could be observed also in the liver. In rabbits (*Henrici*) and dogs (*Tilden et al.*) massive lung hemorrhages were observed in a few instances.

In our material a liver lesion could invariably be observed in mice and chicks as well as in pigs. This lesion consisted of liver cell degeneration and fatty infiltration. In mice, chicks, and pigs swelling of the liver cells following increased absorption of fluid, and edema of the space of Disse was observed and in one chick

also disseminated miliary necroses. In the chicks the kidney lesion was also followed by visceral gout.

In 15 mice and 2 pigs, slight to moderate hydrothorax was present and in 6 mice and 2 pigs gastric erosions were observed.

No lesions suggesting "hemorrhagic disease", which was thought by *Forgacs & Carll* (1962) to be caused by *inter alia* AF, were observed in the chicks of our material.

The ability of the toxin to cause edema, especially of the perirenal tissues of the pig is of utmost interest. In the pig there exist two disease syndroms mainly characterized by edema formation, namely edema disease and intracapsular renal hygroma.

Edema disease, since first described by *Shanks* (1938) has been reported to occur all over the world. *Willinger* (1964) recently reviewed the literature on this disease, and none of the authors referred to by him has reported on the finding of kidney lesions.

Christensen (1951, 1955) described a disease syndrom in newly weaned piglets, which was clinically characterized by sudden deaths or an acute disease with *inter alia,* ataxia, loss of weight, polydipsia, polyuria, and albuminuria. The predominating gross lesions were large perirenal edema, mostly in combination with extensive perirenal hemorrhages and varying size hemorrhages in the renal capsule and in the cortex (intracapsular renal hygroma). Edema in the subcutaneous tissues and sometimes in the mesentery, and transudation to the thoracic and abdominal cavities were also observed. Histopathology revealed degenerative changes of the renal tubules and intertubular hemorrhages, but no damage to the glomeruli. In some pigs dystrophic changes of the liver were observed. *Christensen* assumed that nutritional factors might be involved in the aetiology of the disease.

The lesions found by us after i.v. administration of AF toxin closely coincide with the disease syndrom described by *Christensen.* It is distinguished from edema disease by, above all, the damage to the renal parenchyma.

Zietzschmann (1902) and *Schmey* (1915) describe the presence of perirenal cyst formations in pigs, bearing some resemblance to the syndrom of *Christensen.* Chronic nephritis is an ingredient in both authors' materials and they claim that the perirenal edema is the result of lymph stasis causing the edematous

mesh work of the perirenal tissues to join into cyst-like perirenal accumulations of fluid.

Reporting on a disease spontaneously occurring in several pig herds and assumed to be perirenal edema *Larsen et al.* (1962) describe the gross lesions in the kidneys of 8 pigs, slaughtered some 4 months after the occurrence of the disease in the herd. In one instance there were obvious traces of a healed peri-renal edema, which had caused a deep impression upon the renal cortex. Other changes of the kidneys were enlargement, light colour and fibrosis. In some instances several cysts could be observed in the cortex. It was not possible to verify the cause of the disease, but the authors point out that the gross lesions do not differ from the kidney disorder observed in pigs by *Larsen* (1928) following the feeding of mouldy grain.

An interesting point in this connection is whether the AF toxin studied by us is able to be of practical consequence for the occurrence of acute and/or chronic kidney disorders in pigs and for the appearance of perirenal edema and disease pictures referrable to the healing out of that syndrom. The toxin, though, as is apparent from the experiments described in the present paper, has not caused any disease symtoms whatsoever following oral administration. The question as to its importance as a disease agent under field conditions, therefore, so far has to be left without answer. The nephrotoxic effect of the toxin following parenteral administration and the fact that it produces, in pigs, a renal histopathological picture, which is identical with that in a naturally occurring renal disorder, seem to make further studies worth while.

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SUMMARY

The post-mortem picture following parenteral administration of toxin from Aspergillus fumigatus in mice, chicks, and pigs was dominated by a kidney lesion. It seemed to initiate as a degeneration of the intermediate parts of the proximal convoluted tubules, aggravated, on the administration of larger amounts of toxin, into a complete cortical necrosis.

The pig carcases were richly edematous, especially in the perirenal region, where the edema was localized inter- and subcapsularly. Edema was also present subperitoneally in the abdominal wall and the large intestine. In some of the pigs the edema fluid was generously mixed with blood.

In some pigs and mice there was a hydrothorax, the pigs thereby also presenting ascites.

All the animal species examined presented a liver lesion consisting of fatty infiltration, swelling, and vacuolization of the liver cells, and edema of the space of Disse. In one chick centrolobular liver necroses were observed.

The similarity of the lesions observed in the pigs to those in other diseases characterized by edema in this species, and especially perirenal edema, is discussed.

No clinical symptoms and no post-mortal lesions were observed in the experimental animals following per oral administration of the toxin.

ZUSAMMENFASSUNG

Studien über Aspergillus fumigatus; experimentelle Mycotoxikose bei Mäusen, Hühnern und Schweinen unter Auftreten eines perirenalen Oedemes bei den Schweinen.

Nach parenteraler Applikation von Aspergillus fumigatus-Toxin ist bei Mäusen, Hühnern und Schweinen eine Schädigung der Nieren

die dominierende pathologisch-anatomische Veränderung. Der Nierenschaden scheint mit einer Degeneration der intermediären Teile der proximalen Tubuli contorti zu beginnen. Nach grösseren Toxingaben kommt es zu einer Cortexnekrose.

In den Schweinekadavern wurde — vor allem in dem perirenalen Bereich — reichlich mit Oedemflüssigkeit sowie ein inter- und subkapsuläres Oedem festgestellt. Auch subperitoneal in der Bauchwand und in der Colonspirale kam reichlich Oedemflüssigkeit vor. Bei einigen Schweinen war die Oedemflüssigkeit stark blutbemengt.

Bei einigen Schweinen und Mäusen kam Hydrothorax vor. Die Schweine hatten gleichzeitig Ascites.

Sämtliche untersuchten Tiere wiesen Leberschäden in Form von Verfettung, Anschwellung und Vakuolisierung von Leberzellen sowie Oedem im Disse'schen Raum auf. Bei einem Huhn wurden zentrolobuläre Leberzellnekrosen festgestellt.

Die Ähnlichkeit der beim Schwein auftretenden Veränderungen — insbesondere des perirenalen Oedems — mit anderen bei dieser Tierart auftretenden Oedemkrankheiten wird besprochen.

Nach peroraler Applikation des Toxines konnten weder klinische Symptome noch pathologisch-anatomische Veränderungen bei den Versuchstieren beobachtet werden.

SAMMANFATTNING

Studier av Aspergillus fumigatus; experimentell mycotoxikos hos möss, kycklingar och svin med uppträdande av perirenalt ödem hos svin.

Vid parenteral administration av toxin från Aspergillus fumigatus till möss, kycklingar och svin utgjorde en njurskada den dominerande förändringen vid patologisk-anatomisk undersökning. Njurskadan synes debutera med degeneration av de intermediära delarna av proximala tubuli contorti och vid tillförsel av större mängder toxin uppträde en fullständig cortical nekros.

I griskadavren iakttogs en riklig mängd ödemvätska framförallt i den perirenala regionen med ödemet beläget inter- och subkapsulärt. Även subperitonealt i bukväggen och i kolonspiralen förekom riklig mängd ödemvätska. Hos några av grisarna var ödemvätskan rikligt blodtillblandad.

Hos en del grisar och möss förekom hydrothorax och hos samma grisar förelåg även ascites.

Samtliga undersökta djurslag uppvisade en leverskada i form av förfettning, ansvällning och vakuolisering av levercellerna samt ödem i Disse'ska rummet. Hos en kyckling påvisades centrolobulära levercellsnekroser.

De hos svin uppträdande förändringarnas likhet med andra ödemsjukdomar hos detta djurslag speciellt perirenalt ödem diskuteras.

Vid peroral administration av toxinet iakttogs inga kliniska symtom eller patologisk-anatomiska förändringar hos försöksdjuren.

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