Recent acute and subacute mycotoxicoses recognized in France

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Review article

Recent acute and subacute mycotoxicoses recognized in France

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Summary — Successful investigation and prevention of mycotoxic problems requires close collaboration between scientists from several disciplines ranging from agronomists and technologists required during production of food and feeds, to toxicologists and pathologists examining the effects of mycotoxins on animals and man. Zootoxic metabolites following fungal infection result from four general mechanisms: (i) secondary fungal metabolism (mycotoxins, eg, aflatoxins); (ii) bioconversion of vegetal compounds (eg, dicoumarol); (iii) plant reactions (phytoalexins, eg, coumestrol); and (iv) plant–fungus associations (endophytes, eg, *Acremonium/Festuca).* In reported pathologic field cases, close cooperation through a selected veterinary network has allowed diagnosis of acute and subacute mycotoxicoses in France. Natural stachybotryotoxicosis may not be limited only to cold climates, but may also occur in mild and warm ones (eg, south west of France, Morocco). A considerable variation was observed in symptoms and lesions depending on toxin levels, ranging from a poor performance in a horse race to a general haemorrhagic syndrome. Several cases of acute equine leucoencephalomalacia, characterized by pathognomonic lesions and recently supported by fumonisin analysis, have been diagnosed in the southern part of France and other countries (eg, New Caledonia and the Ivory Coast). Facial eczema in sheep is endemic in the Basque country, as a result of specific bioclimatic and zootechnic conditions. Reproductive disorders in sheep, cattle, goats and rabbits have been associated with high levels of coumestrol in alfalfa, clover and their derivatives. A few cases of fescue foot disease, associated with the endophyte *Acremonium*, have been diagnosed recently. In addition, several nervous disorders may be due to unknown mycotoxins.These acute or subacute mycotoxicoses suggest a potentially widespread occurrence of low level toxins and insidious asymptomatic mycotoxicoses, and justify interdisciplinary research in order to improve diagnosis and preventative measures.

mycotoxicosis / France / livestock

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Résumé — Mycotoxicoses aiguës et subaiguës diagnostiquées récemment en France. *La recherche et la prévention concernant les problèmes mycotoxiques nécessitent une étroite collaboration entre chercheurs de différentes disciplines, depuis les agronomes et les technologues chargés de la production des denrées alimentaires, jusqu'aux toxicologues et pathologistes étudiant les effets des mycotoxines. Des métabolites zootoxiques consécutifs à un développement fongique résultent de quatre mécanismes généraux : métabolites secondaires fongiques (mycotoxines, ie, aflatoxines), bioconversion de composés végétaux (ie, dicoumarol), réaction de la plante (phytoalexines, ie, coumestrol), et association plante–champignon (endophytes, ie, Acremonium/Festuca). Dans les cas pathologiques rapportés, une coopération étroite grâce à un réseau vétérinaire permit le diagnostic de plusieurs mycotoxicoses aiguës et subaiguës pour la première fois en France et en Europe. La stachybotryotoxicose peut survenir non seulement dans les climats froids, mais aussi dans les régions à climat doux ou chaud (ie sud-ouest de la France, Maroc). Un grand éventail de symptômes et lésions fut observé, depuis une réduction des performances chez le cheval de course jusqu'à un syndrome hémorragique généralisé, selon les concentrations en mycotoxines. Plusieurs cas aigus de leucoencéphalomalacie des équidés, caractérisés par des lésions pathognomoniques et complétés récemment par le dosage de la fumonisine B1, ont été diagnostiqués principalement dans le sud de la France et d'autres pays associés (ie, Nouvelle-Calédonie, Côte d'Ivoire...). L'eczéma facial chez le mouton est endémique dans le pays basque, résultat de conditions climatiques particulières. Des perturbations de la reproduction chez des ovins, caprins, bovins et lapins ont été associées avec des niveaux élevés de coumestrol dans la luzerne, le trèfle et leurs dérivés. Quelques cas de gangrène sèche due à la fétuque («*fescue foot disease*»), associés à l'endophyte Acremonium, ont été récemment identifiés. Enfin, certains désordres nerveux rapportés sont dus à des mycotoxines inconnues. De tels cas de mycotoxicoses aiguës et subaiguës suggèrent une plus grande fréquence des mycotoxicoses chroniques, non détectées du fait de l'absence de symptômes et lésions évocatrices, et apportent une justification à des recherches interdisciplinaires afin d'améliorer le diagnostic et la prévention.*

mycotoxicose / France / bétail

INTRODUCTION

In the field of mycotoxicology, no single research project can be all-encompassing, so there is an overall need to promote cooperation between agricultural scientists, food processing experts, mycologists, organic and analytical chemists, biochemists, toxicologists, veterinary and medical experts. Ways of combatting these worldwide natural toxins rely on an extensive knowledge of the ecological and technical conditions leading to mycotoxic contamination, and on the knowledge of mechanisms of the resulting pathological effects.

Mycotoxins usually come to the attention of the public or governments as a result of acute and subacute outbreaks of animal diseases, which are the most obvious manifestations of the mycotoxin problem.

The occurrence of zootoxic metabolites in foods and feeds resulting from fungal development on plant substrates may result from any of four mechanisms. Firstly, a saprophytic mould growing on a favourable substrate can directly produce secondary toxic metabolites, mycotoxins sensu stricto. Secondly, atoxigenic species may contribute by bioconversion to transform atoxic compounds to toxic ones, eg, dicoumarol in *Melilotus,* responsible for 'sweet clover disease', a lethal haemorrhagic syndrome in cattle. Thirdly, in response to the invasion of phytopathogenic fungi, a living plant can produce many metabolites, some of them at levels that are toxic to animals, eg, coumestrol in lucerne. Fourthly, the association of an endophyte with a living plant can lead to toxicosis in animals, eg, fescue foot disease in cattle.

Having outlined the large number of potential problems, this paper presents an overview of acute and subacute cases of mycotoxicoses which have been recognized,

most of them for the first time in Europe, in France and associated countries. Well-known mycotoxicoses are not reported (eg, toxicoses due to aflatoxins, zearalenone and deoxynivalenol).

Since 1970, the principal research topic of the authors has been the study of biotic and abiotic factors leading to mycotoxic contamination, to determine which toxins occur and under what circumstances, and to study how toxigenic species can develop and produce stable mycotoxins. The approach adopted involves academic work applied to specific practical problems, and collaboration with scientists involved at each stage in the food chain, from the field situation to the consumer. Such successful collaboration has gradually led to a large network for collecting information which contributes to diagnostic and preventative measures.

When a mycotoxicosis is suspected by field veterinarians, or by the staff of veterinary schools, or institutes such as the Centre national d'informations toxicologiques vétérinaires, Institut d'élevage et de médecine vétérinaire des pays tropicaux or Institut Pasteur, the case history is established, and appropriate specimens are collected as soon as possible and analysed without delay. Differential diagnostics are performed by specialists, mainly at the Veterinary School in Toulouse (France). Diagnosis of a mycotoxicosis is based on the current status of knowledge (Ciegler et al, 1971; Kadis et al, 1971, 1972; Purchase, 1974; Moreau, 1974; Uragushi and Yamasaki, 1978; Wyllie and Morehouse, 1977, 1978; Richard and Thurston, 1986; Marasas and Nelson, 1987). The locations of the cases that have been identified as mycotoxicoses are shown in figure 1.

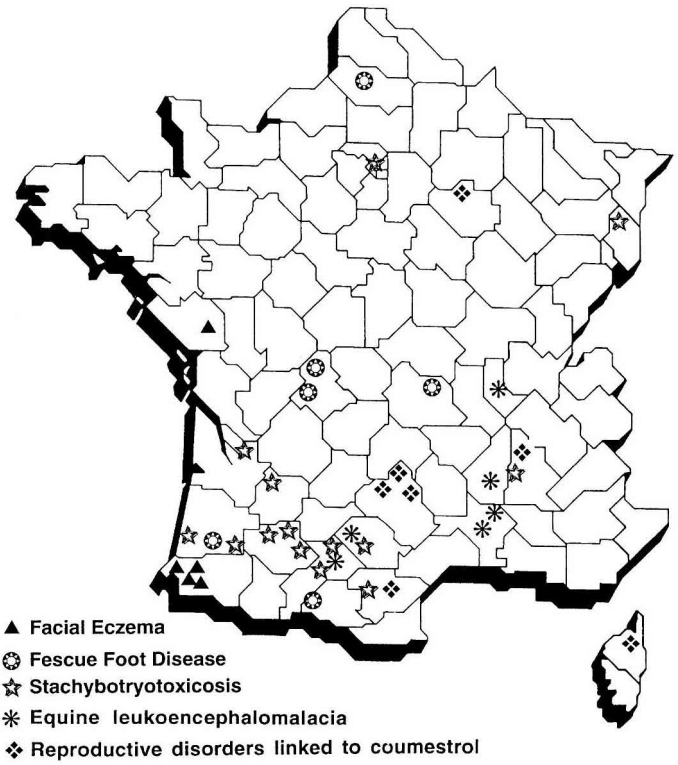


Fig 1. Location of several acute and subacute mycotoxicoses recognized in France.

STACHYBOTRYOTOXICOSIS

An acute case of this mycotoxicosis was reported for the first time in western Europe in 1977, in 28 deer in a zoological park in Paris (Le Bars et al, 1977). This toxicosis, mainly in a chronic form and without pathognomonic disorders, occurs more often than is generally realized. Most of the cases have been identified in horses but it has also been observed twice in deer, once in goats, and has been suspected once in cows (Bordas et al, 1987). *Stachybotrys atra* (fig 2a) is a saprophytic mould which is cellulolytic, hygrophilic and thermo-tolerant (Le Bars and Le Bars, 1991). Observations made during the investigation of stachybotryotoxicosis cases arising from mouldy straw can be divided as follows: (a) spoilage in rectangular bales at the bottom of stacks in areas where the ground is damp or subject to water percolation (eg, in Sologne); (b) verticals streaks of *S atra* developing due to leaks in shed roofing; (c) relatively homogeneous internal contamination of large round bales as a result of harvesting straw in the morning when still wet with dew; (d) superficial development, mainly towards the top of the pile, on large round bales stacked in the field and covered with a plastic sheet, as a result of water condensation; and (e) localized development in a sector of large round bales because of insufficient compression to prevent water penetration during heavy storms. Such *S atra* development has never been observed on hay in France.

Toxigenic strains of *S atra* can develop macrocyclic trichothecenes, such as satratoxin G and H (Harrach et al, 1981). Fifteen per cent of the strains isolated in France were highly toxigenic, the others being very weakly toxigenic (Le Bars and Le Bars, 1991).

In very mild toxicosis, the symptoms are limited to hyperesthesia or decreased performance in race horses, eg, refusal to jump. In this situation, a few horses present rhinitis, conjunctivitis and a mild desquamation on the lips, as a result of contact with the trichothecenes (Servantie et al, 1985) (fig 2b). In more serious cases, necrosis of the oral mucosa appears (fig 2c). The blood coagulation rate increases and sometimes bleeding occurs from small injuries. In more severe cases of toxicosis, there is haemorrhaging in many tissues, particularly the lungs (fig 2d), muscles and the intraperitoneal cavity. More than 800 donkeys, mules and horses died in Morocco in November 1991, most of them exhibiting such gross pathology (collaboration with A Jacquet, Office international des épizooties, Paris, France). In super-acute cases, animals can die in about 15 h after ingestion through heart failure in systole (Le Bars et al, 1977), but without manifesting any other obvious symptoms.

Straw is an often neglected by-product of cereals, although prevention of such problems is achieved by employing the same careful harvesting and storage practices as is necessary for grain. Any lots showing fine black 'soot' should be rejected. In chronic cases which are diagnosed early, horses usually recover within 2–3 weeks following the withdrawal of the contaminated straw.

FACIAL ECZEMA (SPORIDESMIOTOXICOSIS)

Facial eczema is a secondary or hepatogeneous photosensitive disease resulting from the ingestion of sporidesmin (Bonnefoi and Sauvagnac, 1988), produced in pastures by *Pithomyces chartarum* (fig 3a). Outbreaks of this toxicosis in sheep were first noticed in New Zealand at the beginning of this century and this mycotoxicosis was reported for the first time in Europe, in 1984 in the French Basque region (Bezille et al, 1984). The disease is prevalent in ewe-lambs, mainly in this region, and varies in frequency each year, very much depend-

ing on the prevailing climatic conditions. It is particularly frequent in the autumn following a dry summer. Although no incidents of mortality have occurred, a few animals in a flock showed scab formation (fig 3b) and extensive macroscopic cirrhosis as long as 6 months after acute toxicosis.

In 30 breeding units containing 4480 animals, the productivity of both milk and lambs was shown to be 10% lower and the discharge percentage higher, with a few animals clinically photosensitized when compared with 2032 animals on 12 control farms (Bonnefoi et al, 1988a).

Prevention in the French Basque region is based on epidemiological (Bonnefoi et al, 1988b) and ecotoxigenic (Le Bars et al, 1990b) studies. It is achieved by pasture management and by forecasting periods of risk, depending on climatic conditions in summer and early autumn in order to avoid dangerous plots and overgrazing.

EQUINE LEUKOENCEPHALOMALACIA

Field outbreaks of equine leukoencephalomalacia (ELEM), associated with the feeding of mouldy corn, have been known since 1850 in the USA and have since been observed in several other countries. In 1971, this toxicosis was linked to the causative agent *Fusarium moniliforme* (Wilson and Maronpot, 1971) (fig 4a) and the main toxins responsible, the fumonisins (FB1) , were recently identified (Bezuidenhout et al, 1988).

The first case of acute toxicosis in France and Europe was reported in 1983 (Magnol et al, 1983). Only a few cases, involving one or more horses, have been diagnosed in France over the past 15 years. Diagnosis was based on the pathognomonic lesions correlated with a heavy *F moniliforme* contamination of maize or its by-products. The dates and approximate locations were: 1982 and 1983 in the southwest region (Magnol et al, 1983), 1983 near Lyon, two cases in 1991 in the southern part of France, and in 1981, 1983 (Domenech et al, 1985) and 1995 in New Caledonia, and 1990 in Ivory Coast. During the winter of 1992, four acute cases were strongly suspected in the southern region (collaboration with BM Paragon and M Blanchard, Veterinary School, Maisons Alfort, France). Since 1993, FB1 has been analysed in samples of feed (Dupuy et al, 1993a) and the levels of FB1 associated with lethal cases (five to seven per year, always in the same period, from November to January) were 20–90 ppm, mainly in corn screenings.

Two days after the first signs of illness, a horse is apathic, unstable and leans against a wall or other support. It cannot masticate as a result of the paralysis of the tongue and lips, and walks into obstacles. Histopathologically, the white matter of the brain presents irregular empty spaces lacking glial reaction and cellular-infiltrate. The well-known pathognomonic lesions are focal areas of liquefactive necrosis (fig 4b).

Taking into account the worldwide prevalence of toxigenic *F moniliforme* strains, fumonisins production in maize is a permanent threat, chiefly in the days just before and just after harvest (Le Bars et al, 1994). A second step of development and toxigenesis can take place during or after a process requiring hydration. These toxins are stable in grains and their derivatives (Dupuy et al, 1993b).

OESTROGENIC SYNDROME LINKED TO COUMESTROL

Reproductive disorders in bulls (Le Bars and Hurard, 1982), sheep (Brice et al, 1985), goats and rabbits were apparently linked to ingestion of certain batches of lucerne or clover, but without any obvious explanation. The presence of phyto-oestrogens, mainly

coumestrol, was suspected (Le Bars et al, 1990a).

The highest levels of coumestrol occur in late summer and autumn (up to 350 mg/kg dry matter) as a consequence of phytopathogen development, especially leaf pathogenic fungi: *Pseudopeziza medicaginis*, *Leptosphaerulina briosiana* (fig 5a). Coumestrol is stable for several years in hay, silage and dehydrated pellets (Le Bars et al, 1990a).

In sheep, young females appeared more susceptible than adults and the main effects observed were reduction of ovulation rate, fertility level and lambing rate. In several flocks of ewes near Roquefort, 60% of primiparous young females appeared empty by echography 45 days after insemination. After 5 months of pregnancy, the verified abortion rate was more than 10% in primiparous ewes, and only 5% in adult ones. Coumestrol levels ranged from 100–350 mg/kg dry matter, which is 100 times the normal level in healthy lucerne (Le Bars and Le Bars, 1990). Prevention is based on the above considerations and is mainly achieved by avoiding such forages presenting phytopathological lesions in reproductive animals. When alfalfa pellets are used, these can be monitored by carrying out a simple analysis for coumestrol (Le Bars and Le Bars, 1984).

FESCUE FOOT DISEASE

This toxicosis corresponds to the fourth general mechanism discussed in the introduction. Toxin production by *Acremonium coenophialum* in association with *Festuca arundinacea* caused significant losses of productivity in livestock in the USA (Powell and Petroski, 1992), because of the widespread occurrence of infected tall fescue. In France, this forage plant is used much less than in the USA.The first case of fescue foot disease, however, was identified by F Iceaga in 1990 near Poitiers, France (Raynal, 1991) when 10 out of 120 Charolais cattle, grazing a 15-year-old pasture of tall fescue, presented characteristic necrosis of their tails and feet, and a significant reduction in milk production. Mycelium of *Acremonium* was detected in the leaf sheaths (fig 5b) and seeds. A few cases have also been suspected in other regions. Because the fungus is transmitted only by seeds, obtaining endophyte-free seeds would theoretically be the best means of prevention. The ideal solution would be obtaining atoxigenic strains of this endophyte keeping the agronomic advantage of the fungus–plant association.

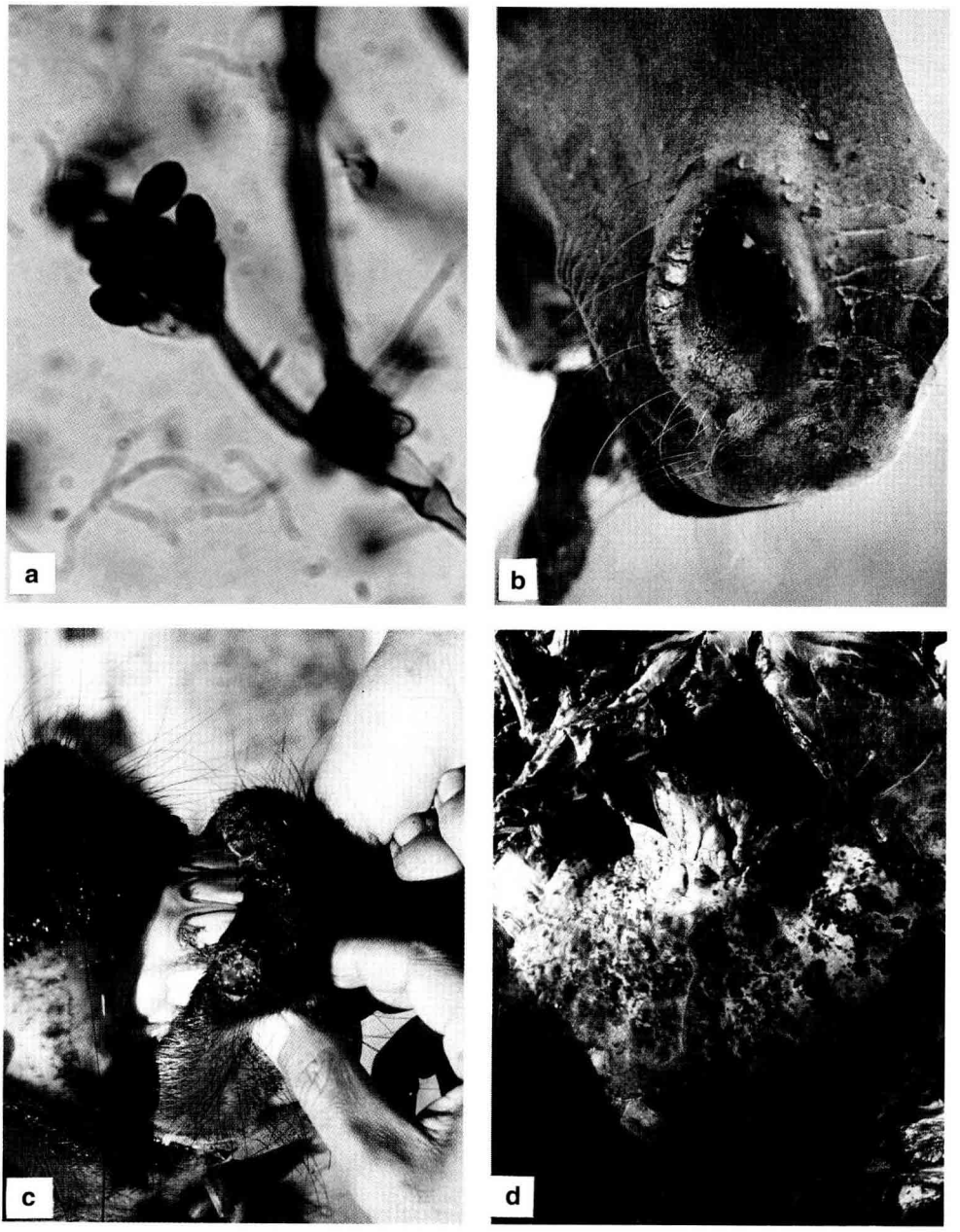
Symptoms and lesions of this mycotoxicosis are the same as the gangrenous form of ergotism, which is seldom reported to us. It is chiefly found in extensive grazing on mountainous pastures, during the August–September period after a cold spring (fig 5c). To stop the similar deleterious effects of these toxins, it is very important to distinguish between fungal origins.

MYCOTOXIC NERVOUS SYNDROMES

The convulsive form of ergotism seems rare. The last identified case, in September 1994, concerned young roe deer (E Le Gall) in the Chizé forest (Deux-Sèvres, France), associated with ingestion of rye-grass with sclerotia of *Claviceps purpurea* (fig 5c). More

Fig 2. Stachybotryotoxicosis: **(a)** *Stachybotrys atra* (photo P Le Bars, conidia size: ca 10 x 6 µm); **(b)** desquamation of the nose of a horse (photo J Servantie); **(c)** necrosis of the lip; **(d)** haemorrhages in lungs (photo A Jacquet).

Fig 3. Facial eczema: **(a)** *Pithomyces chartarum* (photo P Le Bars, conidia size: ca 23 x 13 µm); **(b)** scab formation on the ear of a sheep (photo P Bézille).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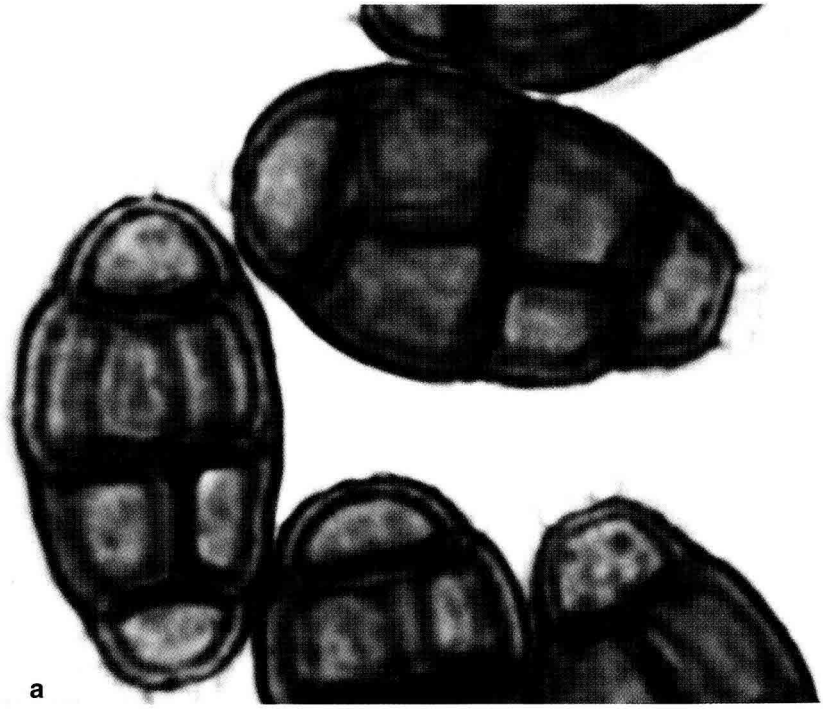
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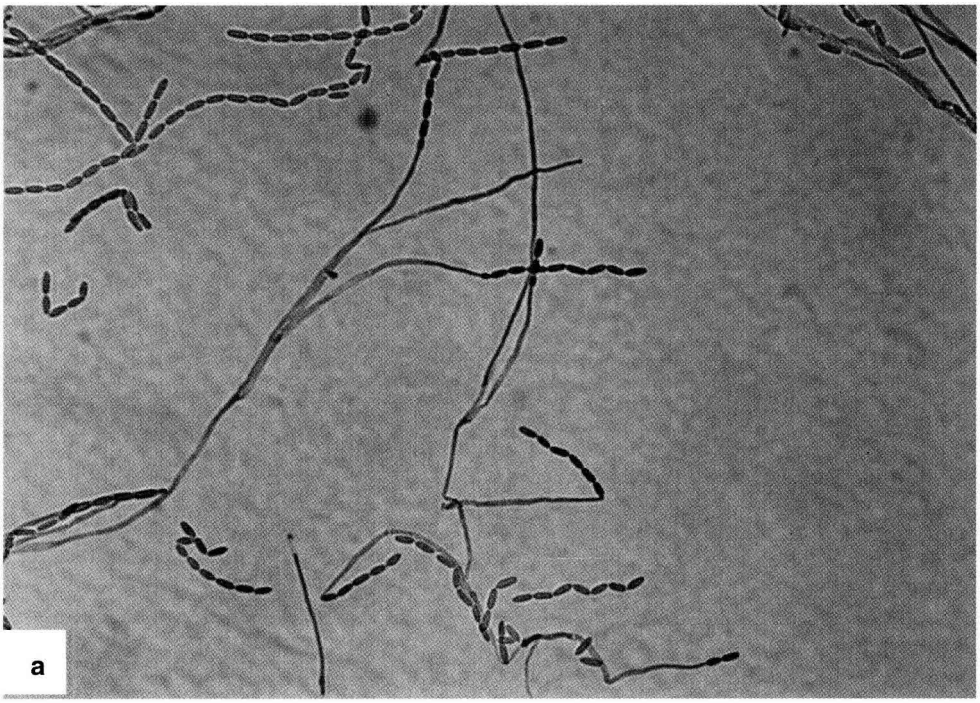

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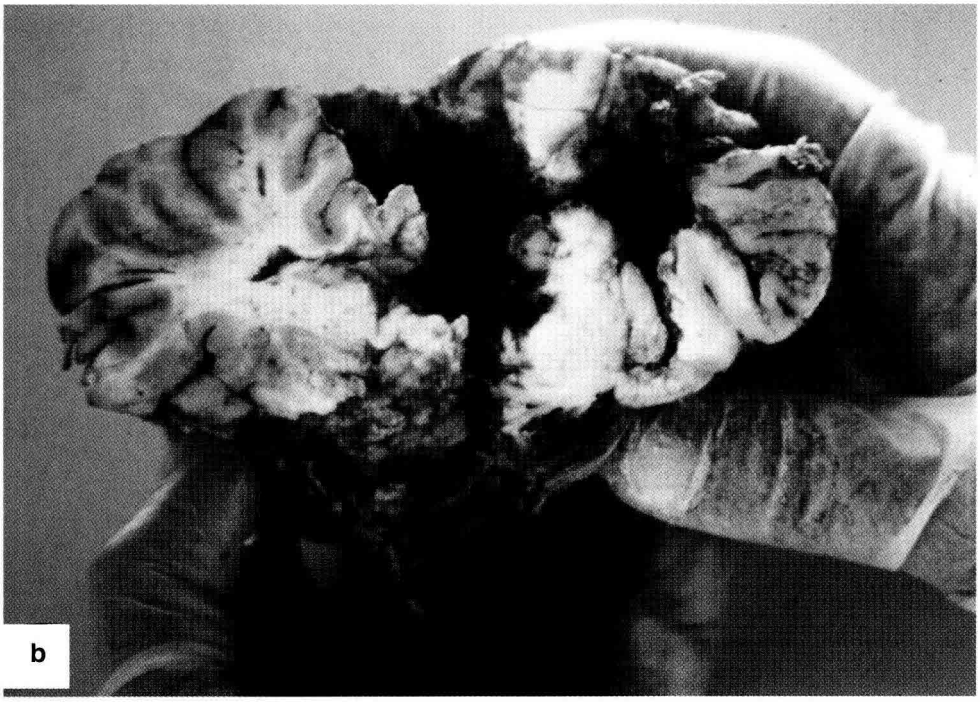

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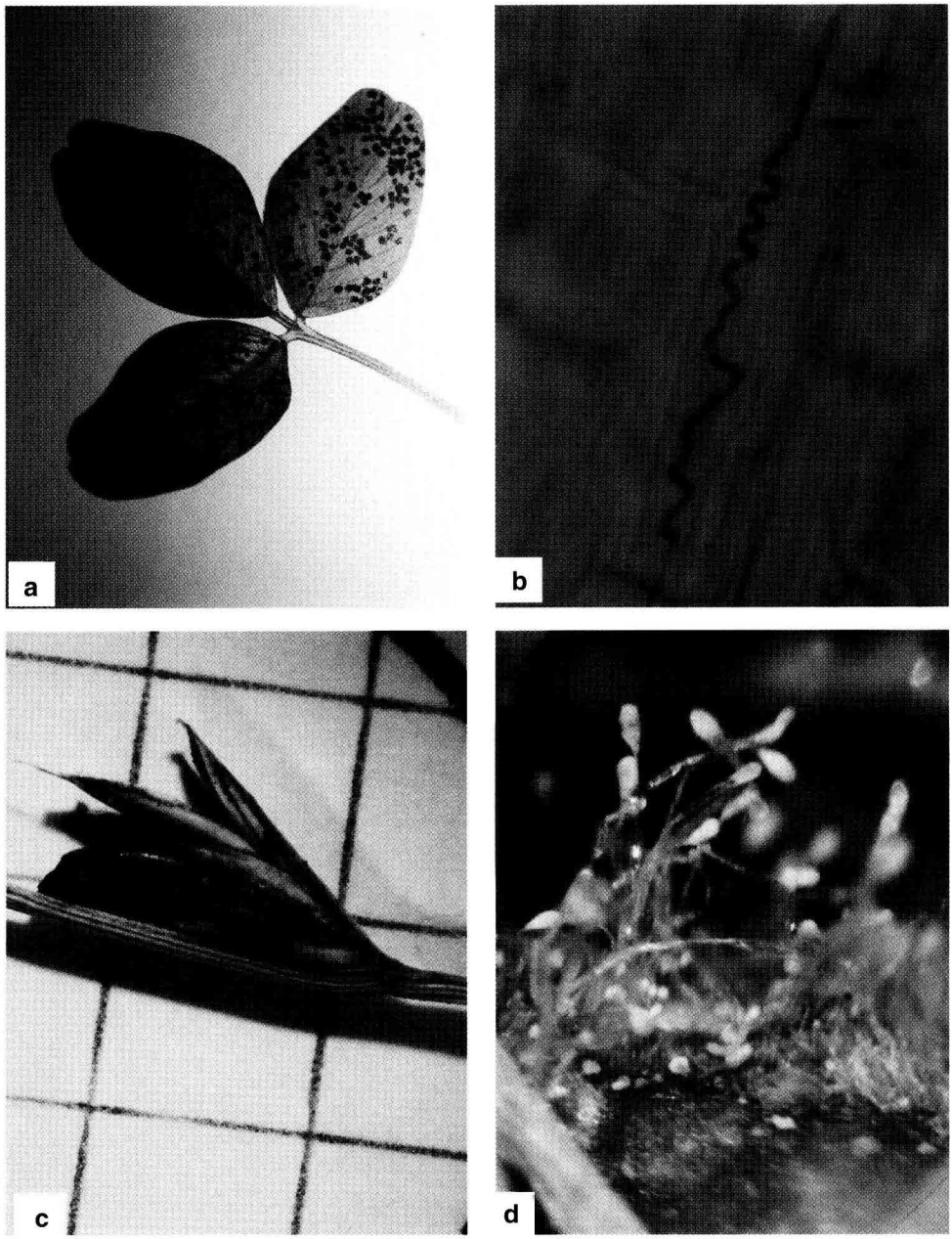
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frequent is toxicosis due to *C paspali* in cattle in the southern part of Landes (southwest of France; Raynal, 1992). A few cases of 'rye-grass stagger disease', due to *Lolium perenne* contaminated with the endophyte *Acremonium lolii,* have been observed by G Raynal (personal communication).

Among the other various pathological disorders associated with fungi and partly reproduced in laboratory animals using extracts of the isolated fungi cultured on the same healthy substrates, several nervous disorders have been linked to: (i) heavy development of *Penicillium roqueforti* in pressed sugar beet pulp; (ii) *Aspergillus fumigatus* in hay in large round bales; and (iii) *A clavatus* in hydroponic cultures (fig 5d), associated with death of 8 out of 18 heifers in an inter-institute zootechnical experiment. This toxicosis was not due to patulin because no isolated strains produced this mycotoxin, and patulin was not detected in the toxic samples (Le Bars, 1985).

CONCLUSION

These acute and subacute mycotoxicoses, caused by zootoxic compounds following fungal development, result mainly from foods and feeds which are not subject to dilution effects, as is the case for grains mixed in large silos or processed through the food industry. Like the classic example of an iceberg of which only a small part is visible, these mycotoxicoses indicate that potentially more insidious pathological effects, and perhaps more significant economic effects, may be occurring but are not obvious. They are an indication of potentially widespread low toxin levels and asymptomatic mycotoxicoses, and interdisciplinary research should be coordinated in order to improve diagnosis and preventative measures.

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Fig 4. Equine leukoencephalomalacia: **(a)** *Fusarium moniliforme* (photo P Le Bars, conidia size: ca 5 x 2 µm); **(b)** cavities caused by liquefaction necrosis of the white matter of the brain (photo P Magnol).
Fig 5. (a) *Pseudopeziza trifolii* on clover; **(b)** *Acremonium coenophialum* in leaf sheaths of *Festuca* (photo G Raynal, mycelium diameter: ca 2 µm); **(c)** sclerotium of *Claviceps purpurea* on rye grass; **(d)** *Aspergillus clavatus* on hydroponic cereals (photos P Le Bars, conidial heads: ca 300 x 150 µm).

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