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«TRAINING ACTIVITIES ON FOOD CONTAMINATION CONTROL
AND MONITORING WITH SPECIAL REFERENCE TO MYCOTOXINS»

A. Kh. SARKISOV

MICOTOXICOSES IN MAN AND ANIMALS

(EPIDEMIOLOGY, ETIOLOGY,
PATHOGENESIS)



Centre of International Projects, GKNT

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Sarkisov A.Kh.

Introduction

Microfungi (micromycetes) play a very important role in our lives. This large group of microorganisms is actively involved in improving soil structure, thereby increasing grass growth and crop yield and raising the productivity of agricultural animals. Man has learned to grow fungi for food purposes. Suffice it to say that the world yield of agaric mushrooms grown in various countries has reached tens of thousand of tonnes-135 thousand tonnes in France, 55 thousand tonnes in England, 130 thousand tonnes in the USA.

The useful properties of micromycetes enable them to be used for the industrial production of antibiotics, vitamins, sterols, enzymes as well as such indispensable amino acids as lysin and methionine.

Nevertheless, among the fungi described above there are some which cause great damage to the national economy and industry by their destructive activity. It is well known that there are micromycetes which negatively affect the human and animal organism, inducing serious and even fatal diseases.

The toxicity of some fungi (for example, Amanita phalloides, etc.) was described by Hippocrates and Gallen as early as the last centuries B.C. Nevertheless, the etiology of most of the diseases in men and animals caused by toxic fungi was discovered only in the thirties and forties of this century.

It should be noted that complex studies performed in the Soviet Union which led to the identification of the causes of previously unexplained diseases (stachybotryotoxicosis and dendrochoiotoxicosis in 1937-1939; alimentary toxic aleukia (ATA) in man, and fusariotoxicosis in animals in 1942-1944) prompted intensive investigation into the role of toxic fungi in the pathology of man and animals in many countries of the world. Unfortunately, some of those, who have recently embarked on a study of this problem, assume that the formation of mycotoxicology is connected with the work done on aflatoxicoses as they do not have at their disposal all the data on the history of mycotoxicoses studies.

As far back as 1947 we (Sarkisov A.Kh.) suggested that the whole group of diseases caused by pathogenic, toxic fungi be sub-divided into mycoses and mycotoxicoses. The etiology of the majority of mycoses was established in the last century. The principle difference between mycoses and mycotoxicoses is that a mycosis involves infection, contagion, with the pathogenic organism residing as a parasite in the living tissues and organs of humans and animals.

Mycotoxicoses are alimentary diseases of a non-infectious character, and no reproduction of micromycetes in the organism has been established. The etiopathogenesis of mycotoxicoses is caused by the toxic products of the fungal cell itself (whether dead or alive) or by secondary fungal metabolites formed on the dead substrate, which is infected by the fungi.

The taxonomy suggested above establishes the basic features of the etiology and pathogenesis of the diseases in question

and is in general use at the present time. Assignment of names to different mycotoxicoses is not as yet based on a common principle, i.e. the name "stachybotryotoxicosis" corresponds to the generic name of the causal fungus Stachybotrys, while alimentary toxic aleukia (ATA) is so named according to the pathogenesis of the disease, etc.

EPIDEMIOLOGY, EPIZOOTOLOGY

The danger in various parts of the world of the formation of mycotoxins in food and animal feed depends upon many factors, of which the main ones are as follows:

1. Occurrence of toxigenic strains of micromycetes on areas under crop and pastures, and the degree of contamination of the vegetable substrate (food, fodder) by these toxigenic strains.
2. The level of aeration and ambient temperature, as well as the moisture content of the plants infected with toxic micromycetes, in storage after harvesting.

It is essential to avoid errors in sampling when checking collected and stationary stored crops for infection with toxic microfungi and contamination with mycotoxins.

The difficulty in sampling for mycotoxins arises because of the inequality of mycotoxin distribution in vegetable and other products, and it is important to ensure that the sample drawn is representative.

Errors are most frequently made in sampling hard unprocessed commodities. Fluids and well-mixed processed products such as flour, milk, beer, juices, and oils do not present such a

sampling problem as the distribution of mycotoxins is uniform and errors are encountered by way of exception (WHO/FAO, 1979).

The season of the year affects the formation of mycotoxins in the substrate. A number of micromycetes, particularly phytopathogenic parasites, become dangerous for the animal organism in the period when cereal plants are ripening at the end of summer and the beginning of the fall, e.g. ergot- Claviceps purpurea - or C. paspali. Other fungi produce toxins after harvesting, most frequently in the fall and during the winter months (Stachybotrys alternans). Finally, the active production of toxins causing ATA may take place in snow-covered overwintered cereal crops in the winter and spring periods. This explains why outbreaks of some mycotoxicoses are seasonal and are limited to the final period of toxin formation, and the pattern described above should be always taken into consideration when forecasting possible outbreaks of mycotoxicoses.

Mycotoxicoses may be divided into 2 major groups with regard to zones and magnitude of occurrence:

Group A. Mycotoxicoses recorded in the majority of countries of the world and not limited to specific natural and climatic conditions, - fusariotoxicoses, stachybotryotoxicosis, aspergillotoxicoses (with the exception of aflatoxicoses), ergotism.

Group B. Mycotoxicoses whose occurrence is strictly limited to certain geographical zones primarily defined by natural, climatic, and ecological conditions favouring the infection of some species of plants by toxic fungi widespread in this region. For example, sporodesmiotoxicosis (facial eczema) in Australia and New Zealand; clavicepstoxicosis in Africa and South America; aflatoxicoses in tropical countries.

Most of mycotoxins preserve their toxic properties for a long time. Thus, grain, overwintered in the field and containing fusariotoxin (F_2), and roughage containing stachybotryotoxin, were stored by us, after harvesting, under conditions similar to those in granaries and storehouses and preserved their toxicity over a period of 11-12 years (the period of personal observations). Mycotoxins isolated from these vegetable substrates (as was shown by a regular rabbit dermal toxicity test) had retained their toxicity after being kept in storage for 30-32 years. Therefore vegetable products containing mycotoxins present a potential menace to the health of men and animals for a long time. (Sarkisov, 1971).

When vegetable products contaminated with mycotoxins are simultaneously consumed by a large number of people or animals, a sudden and massive outbreak of the disease is observed, thus simplifying diagnosis. The diagnosis of a mycotoxicosis is extremely difficult with just a few cases of poisoning.

Vegetable substrates- cereals, groats, oilseeds, industrial crops, and forage crops- infected with toxic fungi and containing mycotoxins still appear to be the only primary sources of mycotoxicoses. Mycotoxins may also enter human food via meat and milk products from animals fed on vegetable products containing mycotoxins. Ingestion of such products over a long period of time may induce illness in man, but such cases are rare. Mycotoxins may be inhaled or penetrate mechanically while processing any vegetable raw materials infected with toxic fungi and containing mycotoxins (cereals, roughage, oilseeds, cotton seeds, jute, copra, etc.). They are introduced into the respiratory tract together with dust particles and

affect the nasal mucosa, nasopharynx and lung tissues.

Previously it was thought that some animals were resistant to certain mycotoxins and this phenomenon was unexpectedly explained recently. In the 40s, in zones where equine stachybotryotoxicosis was widespread, roughage infected with a strongly toxic strain of Stachybotrys alternans and ingestion of which inevitably proved fatal for horses, was fed to cattle, since they were considered resistant to the toxin. None of the cattle died. It turned out that this was due to the highly alkaline saliva of the ruminant, which detoxified the infected feed at the primary stage of digestion, the process being completed during digestion in the farding bag. Unfortunately, the introduction over the last 20 years of large quantities of acidic products into the diet of ruminants (silage, by-products from the alcohol, fermentation, food and processing industries) creates conditions which encourage the preservation of stachybotryotoxin in animal feeds, thus decreasing cattle resistance to stachybotryotoxicosis. Recent outbreaks of stachybotryotoxicosis in cattle, sheep and other animals may be attributable to this fact (Povazhenko, 1964).

The mechanism of the action of mycotoxins on the organism of animals has not yet been fully investigated and elucidated. The conducted research by Pokrovsky A.A., Tuteljan V.A., Kravchenko L.V. is of particular interest. They consider the mycotoxin Fusarium sporotrichiella to be a representative of the membranotoxins, which are characterised by somal tropeness, and they have denoted it by the term "lysosomemembranotoxin".

Virtually all animals are susceptible to mycotoxins, but the degree of susceptibility varies for different species as well as for different individuals within the same species.

Susceptibility may vary even with sex. Thus, the LD₅₀ value for aflatoxin was 7.2 mg/kg body weight for male rats and 17.9 mg/kg body weight for female rats.

A number of mycotoxicoses are observed both in man and animals (ergotism, ATA), whereas some of them are not observed in man since many vegetable substrates are not typical of the human diet.

ECONOMIC DAMAGE

Losses due to mycotoxicoses are considerable and include:

- high mortality and the forced slaughter of animals, particularly when a rapid and correct diagnosis is difficult;
- a marked decrease in the productivity of animals (milk, gain in weight, egg-laying rate);
- disturbances in reproduction;
- expenditure on controls (medication, prevention and the employment of specialists);
- rejection of large quantities of grain, feed concentrates, coarse fodder, and livestock products contaminated with mycotoxins.

Economic damage develops into an important social problem if we assume that a number of mycotoxins play a part in human carcinogenesis. (Mycotoxins, WHO, 1979).

According to the data reported at the FAO/WHO/UNEP conference in Nairobi (1977) world losses of peanuts due to infection with moulds constitute 4.2%, those of corn-3%, oilseeds (with the exception of peanuts)- 12%, rice-5%, soybeans-3%, amounting to a total value of 16 billion US dollars.

MYCOTOXICOSES COMMON TO MAN AND ANIMALS
EXPERIMENTALLY DEMONSTRATED AND RECORDED UNDER
PRACTICAL CONDITIONS

Nos	Disease, pathogenic organism	Susceptibility	Authors, year
1.	<u>Ergotism</u> <i>Claviceps purpurea</i> Tul.	Humans (highly susceptible) All species of farm animals Poultry	Tulaane (1853)
2.	<u>Fusariotoxycosis</u> <i>Fusarium graminearum</i> Schw.	Humans Pigs, horses, ruminants, poultry, laboratory animals	Voronin, Palchevsky (1890)
3.	<u>Stachybotryotoxycosis</u> <i>Stachybotrys alternans</i> Bonord. var. <i>Jateli</i> Pidopl.	Humans Horses, cattle, sheep, poultry, lab. animals	Jatel, Drobotko et al. (1938)
4.	<u>Fusariotoxycosis - ATA</u> <i>Fusarium</i> section <i>Sporotrichiella</i> , <i>F. sporotrichioides</i>	Humans (highly susceptible) All species of farm animals, particularly pigs, poultry, laboratory animals	Sarkisov et al. (1944)
5.	<u>Aflatoxycosis</u> <i>Aspergillus flavus</i> and other <i>Aspergillus</i> spp. and <i>Penicillium</i> spp.	Poultry, particularly waterfowl pigs, ruminants. Rainbow trout. Humans ? Laboratory animals	Sargeant, O'Kelly I., Carnaghan R.E.A., Allcroft (1961).
6.	<u>Ochratoxycosis</u> <i>Aspergillus ochraceus</i> and other <i>Aspergillus</i> spp.	Pigs and other animals Humans ? Laboratory animals	W. Turner (1971) P. Krogh (1974)

Intensive research is being carried out to find a method of detoxifying mycotoxin in plant raw materials (food, animal feed) but as yet this problem has not been solved.

In the process of seed infection with micromycetes, mycotoxins penetrate deep into the kernels and link up with the mitochondrions and, possibly, with the lysosomes of the cells. Toxins may be destroyed by high temperatures, acids, alkalis and other active chemical and physico-chemical agents but in this case the nutritive value of the food and forage is either decreased or completely lost. The majority of the most dangerous mycotoxins are not destroyed by making silage from coarse forage. Detoxification may be achieved by treating straw contaminated with stachybotryotoxin with weak alkaline solutions (0.5% OH, weak ammonia solution (1%), ozone gas) but as the object of detoxification has a large volume (straw) it requires considerable water resources and involves a significant expenditure of labour, making this measure impractical from the economic point of view.

CLINICAL MANIFESTATIONS, DIAGNOSIS

As a rule, the period between the ingestion of pathogenic toxic food and feed-stuffs and appearance of the primary symptoms of the disease varies from several hours to 2-3 days. Rapid diagnosis of the disease makes it possible to detect toxic food and feed-stuffs and to prevent its further consumption by susceptible organism.

The clinical picture of mycotoxicoses varies and may be divided into the acute form and the chronic form.

With the acute form of mycotoxicoses, the clinical picture reveals the symptoms of lesion of the central nervous system. The disease lasts for a maximum of 2-3 days, there is leukocytosis and the outcome is always fatal. Postmortems show hemorrhagic lesions along the entire digestive tract. Hypersensitivity of some specimens within the same species has been noted. In such cases the course of the disease is rapid and is accompanied by the development of the nervous syndrome, shock. For example in the case of a horse, weighing 450-500 kg, infected with stachybotryotoxicosis, the clinical picture may emerge and result in a fatal outcome during the first day after the ingestion of about 200g. of heavily contaminated fodder (the fungus culture on straw). The major clinical manifestations are shock, leukocytosis, loss of vision, paralysis of the hind legs, persistent hemorrhages. In the typical prolonged form of the disease these symptoms are not observed.

In the chronic form of the disease, when feed-stuffs containing small quantities of mycotoxin are ingested over a long period of time, hemorrhages and necrotic lesions of the digestive tract are observed starting from the oral mucosa, but most noticeable in the large intestine, together with lesions of the kidneys and liver. The processes of hemopoiesis are sharply disturbed: agranulocytosis (leukopenia, thrombopenia); there is marked hemorrhagic diathesis, the blood fails to coagulate, clot retraction time increases. Pregnant animals have miscarriages or bear non-viable offspring.

The nephrotoxic, teratogenic, and estrogenic effect of mycotoxins has been recorded under farm conditions from the *Fusarium* and *Penicillium* species, and has also been reproduced experi-

mentally.

Mycotoxins are nonantigenic fungal metabolites. Repeated ingestion of feeds contaminated with mycotoxins increases the susceptibility of the animal rather than producing immunity. There are data on the immuno-inhibiting effect of mycotoxins and the inhibition of hemagglutinin formation in animals (Pier, 1973). There are no antitoxic sera for mycotoxicoses. A number of active mycotoxins have a cytopathogenic effect on the cultures of primitive replanted cells (Hela, Reiss, 1968).

The simultaneous ingestion of a large dose of mycotoxin enables it to be detected in the kidneys, liver and the contents of the digestive tract. With chronic mycotoxicosis (which is more difficult to diagnose) fungal toxins may accumulate in the organs of animals and may be carried over to meat products and milk.

The diagnosis of mycotoxicoses is a complicated matter and should be carried out comprehensively, with account taken of epidemiological and epizootological factors, peculiarities of the source of food (feed-stuffs)- the source of mycotoxin, dietary conditions, feeding conditions (pasture or stall feeding), clinical and pathoanatomical pictures, blood indices, mycological examinations, analysis of isolated cultures for toxigenicity, indications of mycotoxins, elimination of infections (viral and bacterial), pesticides, poisonous plants.

There are various methods for detecting mycotoxins in food and feed-stuffs. Forty years have passed since it was established that Stachybotrys alternans produced a necrotic dermal effect when applied to the skin of a rabbit, and the rabbit dermal toxicity test was developed for distinguishing toxic from nontoxic

strains of S.alternans in animal feeds infected with this fungus (Sarkisov, 1944). The principles of this method were used by us during the years which followed, and helped us to establish the toxicity of overwintered cereals inducing alimentary toxic aleukia (ATA), and to reveal toxic strains of Fusarium. After years of verification the rabbit dermal toxicity test has been recognised as the most reliable method for the primary detection of toxic fungi (Bamburg, 1976; Palyusik, 1981).

Nevertheless, not all the toxic properties of fungi (substrate) are revealed by the dermal toxicity test, as is the case with ergotism. Other available methods should be applied for detecting mycotoxin in such cases. Several methods have been proposed: determination of the toxicity of fungi on micro-organism (yeast, infusoria), on animals (pigeons, hen embryos, guinea pigs, white mice, cats, aquarium fish- guppi), physical and chemical methods (thin-layer chromatography, gas-liquid chromatography, mass spectroscopy), and many others. No doubt it is necessary to find fine methods of quantitative analysis for mycotoxins for research purposes, but in practical diagnosis laboratories it is advisable to use simple techniques and universally available laboratory animals.

For many mycotoxicoses there are no clearly established data on the maximum permissible quantities of mycotoxin in animal feed-stuffs. Detection of extremely small quantities of mycotoxins in food and feed-stuffs may lead to erroneous conclusions that they may be associated with mycotoxicoses, and hence to unjustified actions, including the rejection of food and feed-stuffs which are not the cause of illness.

Mycological analysis is yet another method of detecting toxigenic fungi which is extremely useful, but it is a lengthy process and it is impossible to rely completely on the results. The detection of a toxigenic fungi in the examined product is not in itself the evidence of the toxicity of the product, and is not sufficient proof that the disease induced by it is a mycotoxicosis, but merely indicates the need for further investigations aimed at establishing the etiology of the given mycotoxicosis.

Over the past 40 years, in the course of identifying the causes of previously unexplained diseases, we have noted erroneous conclusions regarding the role of toxic fungi in the appearance of these diseases. Such efforts have rendered the efforts of practical specialists to control these diseases and have complicated the use of control measures against non-mycotoxic diseases.

When establishing the etiology of ATA (septic angina) in man, we examined a large number of samples of snow-covered overwintered grain. We isolated about 1200 strains of micromycetes from them which were referred to various classes (Phycomycetes, Ascomycetes, Basidiomycetes, Deuteromycetes, and Actinomycetes). A part of the fungi isolated in 1942-1944 proved to be toxic according to the dermal toxicity test, and when fed to the animals caused their death. Nevertheless, clinical manifestations and the pathoanatomical picture did not coincide with the known course of ATA in man. We tested a large variety of animals: horses, cattle, sheep, pigs, dogs, rabbits, guinea-pigs, white mice and poultry. The animals were susceptible to the pathogenic feed-stuffs, some of them died, but even this was not a

sufficient reason for us to assert that the fungi being tested played a part in ATA. We decided that we would accept as proof of the participation of a species of toxic micromycetes in the etiology of ATA only the complete reproduction in an animal of all the clinical symptoms which occur in ATA in man (including changes in blood and the picture of postmortem dissection). This animal turned out to be a cat, which developed all the clinical symptoms of ATA in man (1943-1948).

In 1975 Sato et al. and in 1978 Lutsky et al. completely confirmed our data on the possibility of using cats as a model for the reproduction of ATA with toxigenic cultures of Fusarium sporotrichiella.

This positive experience of solving a complicated problem should be taken into account by research workers involved in research to elucidate the causes of little known diseases in men and animals, such diseases, unfortunately, are still fairly numerous. We would like in particular to draw attention to the work of Akhmetely M.A. et al. on establishing the weak carcinogenic effect of F. sporotrichioides on mice.

Mycotoxicoses may be referred according to their nature to those diseases, the prevention and control of which depend on exact and rapid diagnosis and knowledge of the specific control measures.

The World Health Organisation (WHO) and the Food and Agriculture Organisation (FAO) of the United Nations Organisation, having reviewed the data collected in many countries on environmental hazards associated with the contamination of plant products with mycotoxins, gave serious consideration to this problem.

In its report (No 543, 1975) "Diseases Induced Through Food" the WHO Task Group assumes that it has been firmly established that mycotoxins contained in food products may represent, under certain conditions, a serious menace to the health of consumers.

In November 1972 we (Sarkisov A.Kh.) made a report on mycotoxicoses in man and animals to the WHO in Geneva. The problem of mycotoxins and mycotoxicoses was discussed twice in Geneva by the members of the Task Group on Environmental Health Criteria for Mycotoxins, first in March, 1977, and then in June, 1978. In 1979 a detailed report on this important problem was published based on the results of the work of this Task Group. The progress attained in this field represents a good beginning, but further systematic investigations are needed on this problem, in which many factors are still unclear.

A four-decades of experience in elucidating the etiology of mycotoxicoses and studying many of them enables us to formulate a number of recommendations for further studies in this field.

These recommendations may be briefly summarized as follows.

IN THE FIELD OF MEDICINE AND AGRICULTURE

- to carry out extensive epidemiological studies into the link between the exposure of food-stuffs to various levels of mycotoxin contamination and the incidence of diseases of unknown etiology, particularly malignant tumors (hepatomas).

- To develop simple methods for the rapid detection and measurement of mycotoxins level in various food and feed-stuffs to be used by practical sanitary-hygenic and veterinary laboratories.

- To establish the degree of occurrence of mycotoxin-producing fungi on areas under crops.
- To develop a complex of agrotechnical practices preventing the occurrence of toxic fungi in the environment.
- To improve diagnostic methods for mycotoxicoses and to elucidate the effect of mycotoxins on the productivity and reproduction of farm animals.
- To develop methods for the decontamination of plant products which do not cause a deterioration of their hygienic and nutritive values.

GENERAL PROBLEMS

The syllabi of medical, veterinary and agricultural educational institutions should be expanded and should reflect the latest data on mycopathology.

The problem of mycotoxicoses is now discussed at international congresses and symposia and at meetings of special bodies of the United Nations. It has been included among the subjects dealt with in international and national encyclopaedias. The number of publications on this topic is steadily growing. Such attention is justified. Our efforts should be directed at finding ways to prevent the formation of mycotoxins in food and feed-stuffs at developing reliable methods for controlling toxin fungi in the environment and protecting man and animals from the serious diseases known as mycotoxicoses.

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