

THE IMPACT OF MYCOTOXICOSES ON HUMAN HISTORY*

Maja PERAICA and Dubravka RAŠIĆ

Institute for Medical Research and Occupational Health, Zagreb

Received in May 2012
CrossChecked in August 2012
Accepted in September 2012

Mycotoxicoses are acute or chronic diseases of humans and animals caused by mycotoxins, toxic compounds produced by moulds. Of about 400 known mycotoxins only a small number are known to cause mycotoxicoses in humans. Organs that are most targeted are those in which mycotoxins are metabolised, that is, the liver and kidneys, but the lesions may affect the neurological, respiratory, digestive, haematological, endocrine, and immune systems as well.

The epidemics of mycotoxicoses are often connected with times of famine, when population consumes food that would not be consumed in normal circumstances. Mycotoxicoses have influenced human history, causing demographic changes, migrations, or even influencing the outcomes of wars. Fortunately, epidemics affecting so many persons and with so many fatalities belong to the past. Today they only appear in small communities such as schools and factory canteens. This paper presents epidemics and pandemics of mycotoxicoses that influenced human history.

KEY WORDS: *alimentary toxic aleukia, ergotism, putrid malignant fever, slow fever disease, tenth plague*

In ancient times, it was believed that humans could not escape their destiny and that diseases were the punishment from gods for their own sins or sins committed by their ancestors. Therefore, they did not look for the cause of the disease. Some hygienic rules prescribed in the Bible indicate that Jews were aware of moulds in their environment, and it seems that this is the first mention of them (1).

Ancient Romans were aware of the untoward effects of moulds and in the seventh century BC they honoured the god Robigus, protector of grains and trees (2). They also established the festival called the "Robigalia" which was celebrated on 25th April

because that was the most likely time for crops to be attacked by rust or mildew (3). The Robigalia started with a procession from Rome to a point outside the city where a sheep and a dog were sacrificed to propitiate the god Robigus to protect crop. Christianity accepted this festival like many other pagan traditions and it became St Marcus' celebration. Until 598 AD, the Christian procession in Rome followed the way of the pagan procession, and blessing of the fields with prayers to protect crops were in use until recently.

The first mentioned mycotoxin is probably ergot, the product of fungal genus *Claviceps*. It was described on an Assyrian cuneiform tablet about 600 BC as a "noxious pustule in the ear of grain" (4). The name of the mycotoxicosis caused by ergot, *ignis sacer* (holy fire), was coined by Lucretius, although he used it for

* The subject of this article has partly been presented at the International Symposium "Power of Fungi and Mycotoxins in Health and Disease" held in Primošten, Croatia, from 19 to 22 October 2011.

another disease, erysipelas. *Ignis sacer* was used for ergotism during the Middle Ages.

Although the most threatening features of mycotoxins are their carcinogenicity and mutagenicity, they may also cause acute or chronic diseases, called mycotoxicoses. Mycotoxicoses, which may even have a fatal outcome, occur mostly as the consequence of ingestion of contaminated food, but other ways of exposure, such as dermal and respiratory, are also possible. The history of mankind was sometimes severely affected by the epidemics of mycotoxicoses spreading over whole regions or several countries. Such epidemics with very high percentage of fatalities belong to the past, but epidemics still break out in small communities of people who live and eat together, particularly in the tropics. Although it seemed that with better control of food production epidemics of mycotoxicoses would eventually disappear, severe epidemics in the 21st century indicate that they will keep breaking out for as long as there is famine caused by wars and natural disasters.

NATURAL CAUSES

There is a theory that the tenth plague described in *Exodus* was caused by mycotoxins produced by moulds as the last phase of the ecological disaster that hit Egypt (5). According to this theory the first plague, red coloration of the river Nile was caused by ashes rich in sulphates brought by winds from the eruption of the volcano Santorini on the Mediterranean coast. Ashes from the Santorini volcano found in the sediments in the eastern part of the Nile Delta in Egypt originate from the eruption that happened during the 19th Egyptian dynasty (6). Paragraph 55 of the London Medical Papyrus, which was completed in the Late Middle Bronze Age (when the exodus occurred according to the Bible), describes the treatment of caustic wounds caused by the contact with red water from the Nile (7). The Egyptian doctor recommends bandaging the burns with alkaline substances collected far from the river without rinsing with water. This indicates that water from Nile could not be used, because it was acid. According to the theory of natural disaster as the cause of the plagues (5), acid water killed the fish and the frogs left the shores of Nile covering the country. The plagues that followed, including the appearance of all kinds of pests, were most probably the consequence of abundant available flesh, either the carcasses of frogs and domestic

animals or the wounds caused by caustic water from the Nile. Acid mud from the Nile could not fertilise the fields which resulted in food shortages. In ancient times, first-born sons were particularly respected and even during food shortages they were not starving. In fact, consuming higher quantities of cereals, they were more exposed to cereals contaminated with mycotoxins than the rest of the population. This may explain the last plague - the death of first-born sons. After the tenth plague which caused the death of all first-born sons, the pharaoh (probably Ramses II from the 19th Egyptian dynasty, who ruled from 1301-1234 BC) granted Jewish exodus to the Holy Land which, according to the Bible resulted in the emigration of 600.000 men, excluding women and children (1).

The only mycotoxicosis of huge proportions that occurred occasionally in Europe was ergotism caused by toxins produced by the genus *Claviceps* (*C. purpurea* and *C. fusiformis*). This mycotoxicosis, which would often spread across rye-producing countries in the Middle Ages (France, Germany) was called *ignis sacer* (holy fire) or St Anthony's fire, because of the burning sensations in the legs of affected persons (8). Although some authors believe they have recognised the symptoms of ergotism in classical Greek and Roman literature (9), a more thorough analysis has revealed that these symptoms do not correspond to mycotoxicosis but have another aetiology (10).

Rye-infesting ergot looks like a violet or black sclerotium and has the form of cockspear (*argot* in old French) that falls on the ground and remains inactive during winter. If the spring is moist and warm, spherical heads develop on stalks (Lat. *clavus* – nail) containing ascospores that infest flowering rye (4). It takes eight days for the spherical heads to secrete the so-called honey-dew, which contains asexual spores. From these spores develop mycelia and afterwards sclerotia. There are about 40 ergot alkaloids which may disturb the nervous system or lead to peripheral vasoconstriction with fasciculation, pain, and gangrene.

Gangrenous ergotism was first described mentioned in *Annales Xantenses* in 857 AD, which refers to the Norse sacking of the church of Xanten in the lower Rhine area, Germany (11). This is what the chronicle reports: "A great plague of swollen blisters consumed the people by a loathsome rot so that limbs were loosened and fell off before death". During the epidemic of ergotism around Paris (945 AD), people who reached the church of St Mary in Paris were

received by Duke Hugh the Great, Count of Paris, who fed and treated them. It seems that the Duke fed them with uncontaminated grains. Once they recovered, they would return home and relapse, but return to St Mary's would restore their health (11). In the famine of 994 AD, ergotism broke out in Aquitaine and Limousin with more than 40,000 fatalities. Due to continuous wars before the Crusades, fields were neglected and ergotism was common north of the Alps, where rye was staple food (8). It is not surprising that poor people consumed ergot-contaminated rye because food shortage was such that even cannibalism was reported.

In the 11th century, after epidemics of gangrenous ergotism that regularly hit various French counties, the relics of St Anthony were brought from Constantinople. This patron saint of fire became the patron against *ignis sacer* (holy fire), or ergotism (12). The order of St Anthony was soon founded in Vienne, France (in 1093 AD) and after having been recognised by Pope Urban II (in 1095), the devotion to St Anthony spread over the whole Catholic Europe. A visit to the Shrine of St Anthony was considered to be the best remedy for ergotism, probably because the trip to the sanctuary ended exposure to ergot-contaminated food.

Another therapy against ergotism was based on the medieval theory that diseases reflect misbalance between hot and cold, dry and wet fluids in the organism. Ergotism, which included burning sensation in the limbs, was treated with various cooling drinks containing wine poured over the relics of saints, fish and water, thistle, and mandrake (4). Mandrake juice contains hallucinogen alkaloids and so does bread baked with ergot-contaminated dough, as baked ergot may transform into lysergic acid diethylamine (LSD). This is why this therapy only added to the hallucinogenic symptoms of ergotism.

After the Renaissance, large-scale epidemics of ergotism disappeared and were replaced by small epidemics breaking out in France, Germany, Norway, Sweden, Finland, England, Ireland, Hungary, and Russia (8). An outbreak of symptoms similar to convulsive ergotism (disordered speech, odd postures and gestures and convulsive fits) was started in December 1691 and ended in the late autumn of 1692 in the Puritan settlement of Salem near Boston, affecting mostly women and young girls. It was preceded by early rains and warm weather in spring and hot and stormy summer, which favoured infestation of rye that was consumed until the next

crop grown in drought conditions (13). The victims were processed at Salem witchcraft trials that ended in the late autumn of 1692; 20 persons were executed on the gallows and two died in prison. In Russia ergotism was endemic and present until 1926 (8).

WARS

Wars usually bring the greatest shortage of food, but until the Second World War there are no data regarding possible war-related mycotoxicoses, either among soldiers or civilians. During the spring months of the Second World War, some regions of the USSR saw outbreaks of a haemorrhagic disease associated with the consumption of bread prepared from grains that remained in the fields and were gathered after snow thawed (14). The disease was first described in 1932 as "septic angina". Later on it was realised that angina was only the final phase of mycotoxicosis caused by trichothecenes, produced by *Fusarium* moulds (mostly *F. poae* and *F. sporothrichoides*). As the most prominent symptom of this mycotoxicosis is a significant drop in leukocytes, it was renamed "alimentary toxic aleukia" (ATA). The clinical course of ATA consists of four phases, and each phase depends on the length and severity of exposure. In the first phase, which may develop immediately or a few hours after the ingestion of toxins, mucous membranes of the upper digestive system (oral cavity and pharynx) become irritated. The most frequent symptoms are the burning sensation in the oral cavity and pharynx and pain with a "peppery" sensation while swallowing. Nausea and vomiting, weakness, excessive perspiration, and sleep disturbances may last for two to three days. If exposure continues, or the dose is large, the disease progresses to the second, leukopenic phase that lasts two to four weeks. Patients have minimal clinical symptoms, but haematological examination shows leukopenia, granulopenia, trombocytopenia, and relative lymphocytosis. The third phase that follows in the case of continued exposure is characterised by severe angina and haemorrhages with red petechial rash on the chest, lateral surface of the trunk, and inner surfaces of arms and hips, usually sparing the face. Together with the rash or a few days later, swallowing becomes painful due to catarrhal, diphtheric, necrotic or gangrenous pharyngitis. In severe cases, the gangrenous process in the larynx results in aphonia and death due to strangulation. In the last phase, a

severe haemorrhagic diathesis with nasal, oral, gastric and intestinal bleedings is the consequence of a severe drop in all peripheral blood cells.

Although the first outbreak of ATA was recorded in East Siberia in 1913, it did not receive attention it deserved (15). After several years it reoccurred in Western Siberia and in 1942 the disease became widespread with the highest frequency in latitudes between 50° and 60° and longitudes between 40° and 140°. In some agricultural regions of this area, ATA appeared every year for 14 years, and in some districts such as Orenburg (south of Ural) whole villages were affected. In 1943 and 1944, the outbreak spread in the Orenburg district over 30 and 47 out of 50 counties, respectively. In some counties, more than 10 % of the population was affected and the mortality was up to 60 %. The last cases of ATA were recorded in 1947, and since 1948 it did not reappear. In the years of ATA outbreaks, late harvesting of wheat and common millet (*Panicum miliaceum*) coincided with unusually mild winters (mean January temperature -8 °C as compared with ten-year mean of -14 °C), so that soil did not freeze as the usual 80 cm to 120 cm in depth.

One of the greatest outbreaks of disease caused by mycotoxins in modern times occurred during the Second World War (1944) Japanese invasion of Manipur in India, near the border with Burma (16). Japanese soldiers arriving from Burma and bringing with them food supply for one month only occupied Indian Army Supply Depots containing damp grain spoiled by monsoon rain. One month later, 65,000 Japanese unwounded soldiers died withdrawing to Burma. On the other side, after the battle of Kohima, the turning point of the Second World War in this part of the World, 30 % of the 7th Division of Indian army suffered a number of symptoms such as pain in the back of the head, parchment-like skin, furred tongue with a red edge, cracks in the corner of the mouth, sores on the lower lip, hardened liver, sore kidneys, severe diarrhoea, and poor coordination of the limbs. In those time diagnostics did not include determination of mycotoxins, but it may be assumed that soldiers on both sides were poisoned with *Aspergillus*, *Penicillium*, and *Fusarium* toxins. Symptom treatment in hospitals was not successful and they died within four days of the so-called mouldy grain disease. In contrast, recovery was complete wherever they were on a diet with fresh food.

One of the large-scale mycotoxicosis may have happened in Bengal after the Japanese attack on Kolkata (16, 17). In 1942, East Bengal was

overpopulated as a result of wartime industrial development, but civil disobedience and non-cooperation created by Gandhi resulted in a shortage of supplies. When the Japanese attacked Kolkata, local merchants who had stocked up grain before the war broke out, fled the city. The government of Bengal took their stocks and distributed them to the hungry population, although it was visibly spoiled. Grain was spoiled by moulds, and estimates say that acute mycotoxicoses combined with hunger took their toll in three million lives. Some authors (16) claim that the so-called Bengal famine of 1943 was not caused by the shortage of grains, but rather by the spoilage of grains with insects and moulds.

OTHER SUPPOSED MYCOTOXICOSES

There are other diseases that are believed to be associated with mycotoxin poisoning, such as slow nervous fever (England, Germany and France from 1650 to 1740) and putrid malignant fever (England 1700 to 1750) (18).

Slow nervous fever appeared in the summer and autumn after a very severe and cold winter, which favours the growth of *Claviceps purpurea*. The symptoms are hot and cold sensations, headache and dizziness, depression, sensitivity to light and noise, nausea and vomiting, quick and weak pulse, tremor and convulsions, diarrhoea, delirium, stupor, and coma (19). If the symptoms of convulsions, epilepsy, hallucinations, deafness, temporary blindness, speechlessness, insanity and gangrene also occurred, such cases were reported in court records because these were considered symptoms of bewitchment. The outbreaks of slow nervous fever occurred repeatedly in England, regularly after very cold winters. In the first part of the 18th century, it was the most common cause of child death in London (20). In England, the most severe outbreak occurred in 1740-1741, the same year as in Northern Germany and France. In England, rye production decreased gradually from 1700 to 1750, and higher consumption of wheat resulted in the drop and eventually disappearance of slow nervous fever (19). Slow nervous fever was the leading cause of child mortality during its peak, and when it disappeared life expectancy increased considerably.

Children also suffered putrid malignant fever, which would break out in the late spring and early summer after a warm, moist winter. Symptoms such as bleeding, rash, angina with ulceration of the

pharynx and putrid smell with a “pepperish” sensation in the mouth, are similar to the trichothecenes mycotoxicosis, later known as ATA. Putrid malignant fever disappeared, child mortality significantly decreased, and mean survival increased when potatoes became staple food in the second part of the 18th century. This was the century of the highest demographic increase in Ireland (300 %), where potatoes were adopted much more readily than in England and Scotland where the increase was 50 %.

CONCLUSION

Nowadays we can only suppose which disease outbreaks in the history of mankind were in fact caused by mycotoxins. We mostly rely on the descriptions of symptoms which are often very meticulous, because the diagnostic methods were quite poor and the analysis of mycotoxins nonexistent. It seems strange that until recently people did not look for natural cause of the disease but believed that gods, demons, and other supernatural forces brought diseases and death.

Acknowledgment

This work has been financially supported by the Ministry of Science, Education and Sports of the Republic of Croatia (grant No. 0022-0222148-2142).

REFERENCES

1. Jeruzalemska Biblija. Zagreb: Kršćanska sadašnjost; 2004.
2. Vergilius PM. *Georgike*. Velika Gorica: Papir; 1994.
3. Ovidius. *Opera omnia*. III Fasti, Tristia, Epistolae ex ponto. Leipzig: Nova Editio Sterotypa; 1845.
4. Van Dongen PWJ, de Groot ANJA. History of ergot alkaloids from ergotism to ergometrine. *Eur J Obstet Gynecol Reprod Biol* 1995;60:109-16.
5. Marr JS, Malloy CD. An epidemiologic analysis of the ten plagues of Egypt. *Caduceus* 1996;12:7-24.
6. Stanley DJ, Sheng H. Volcanic shards from Santorini (Upper Minoan ash) in the Nile Delta, Egypt. *Nature* 1986;320:733-5.
7. Trevisanato SI. Ancient Egyptian doctors and the nature of the biblical plagues. *Med Hypotheses* 2005;65:811-3.
8. Barger G. *Ergot and ergotism*. London, Gurney and Jackson 1931. p. 20-84.
9. Biggs RD. Ergotism and other mycotoxicoses in ancient Mesopotamia? *Aula Orientalis* 1991; 9:15-21.
10. Neuburger M. *Handbuch der Geschichte der Medizin*. Zweiter band. Jena: Verlag von Gustav Fischer; 1903.
11. *Annales Xantenses et Annales Vedastini*. Hannoverae: Typis Culemannorum; 1909.
12. Gorys E. *Lexikon der Heiligen*. Muenchen: Deutscher Taschenbuch Verlag GmbH; 2004.
13. Caporael LR. Ergotism: The Satan loosed in Salem? *Science* 1976;192:21-6.
14. Gajdušek DC. *Acute Infectious Hemorrhagic Fevers and Mycotoxicoses in the Union of Soviet Socialist Republics*. Washington: Walter Reed Army Medical Center; 1953.
15. Joffe AZ. *Fusarium poae* and *F. sporotrichoides* as principal causal agents of alimentary toxic aleukia. In: Wyllie T, Morehouse LG, editors. *Mycotoxic fungi, mycotoxins, mycotoxicoses*. Vol. 3. *Mycotoxicoses of man and plants: mycotoxin control and regulatory practices*. New York: Marcel Decker, Inc.; 1978. p. 21-86.
16. Tainsh RA. Hunger in India: the human factor. *Int Relations* 1981;7:1053-62.
17. Brett-Crowther MR. The waste and spoilage of food. *Int Relations* 1977;5:162-79.
18. Meggs WJ. Epidemics of mold poisoning past and present. *Toxicol Ind Health* 2009;25:571-6.
19. Matossian MK. Mold poisoning: an unrecognized English health problem, 1550-1800. *Med Hist* 1981;25:73-84.
20. Appleby AB. Nutritional disease: the case of London 1550-1750. *J Interdiscip Hist* 1975;6:1-22.

Sažetak**UTJECAJ MIKOTOKSIKOZA NA POVIJEST**

Mikotoksikoze su akutne i kronične bolesti ljudi i životinja koje uzrokuju mikotoksini, toksični produkti plijesni. Poznato je oko 400 mikotoksina, no za samo malen broj mikotoksina dokazano je da uzrokuju mikotoksikoze u ljudi. Ciljni organi djelovanja mikotoksina najčešće su jetra i bubrezi gdje se metaboliziraju, no oštećenja mogu zahvatiti živčani, respiratorni, probavni, krvotvorni, endokrini i imunski sustav.

Epidemije mikotoksikoza obično nastaju u vrijeme nestašice hrane zato što stanovništvo konzumira hranu koju ne bi jelo u normalnim okolnostima. Mikotoksikoze koje su tijekom povijesti zahvatile velika područja uzrokovale su demografske promjene, migracije i utjecale su na ishod ratova te su time promijenile tijek povijesti. Takvih golemih epidemija mikotoksikoza danas više nema zbog toga što je prehrana raznovrsna, žitarice više nisu osnovna hrana, a proizvodnja i skladištenje žitarica znatno su napredovali. U razvijenim zemljama znanstvenici su zabrinutiji zbog trajne izloženosti ljudi niskim koncentracijama mikotoksina koji mogu imati kancerogeni učinak jer se njihova prisutnost u žitaricama i drugoj hrani ne može izbjeći. Mikotoksikoze se danas javljaju većinom u tropskim i suptropskim područjima, i to u malenim zajednicama ljudi koje se hrane zajedno (tvornice, škole i sl.).

U radu su prikazane mikotoksikoze koje su utjecale na povijest čovječanstva.

KLJUČNE RIJEČI: *alimentarna toksična aleukija, deseto biblijsko zlo, ergotizam, gnojna maligna vrućica, spora bolest živčanog sustava*

CORRESPONDING AUTHOR:

Maja Peraica, MD, PhD
Unit of Toxicology
Institute for Medical Research and Occupational Health
Ksaverska c. 2, 10000 Zagreb, Croatia
E-mail: mperaica@imi.hr