Degrees of Atmospheric Pollution with Halothane during Dental Anaesthesia. Results expressed as Parts per Million. (Figures in Parentheses are Range and Number of Patient:)

	With Room Ventilation Off	With Room Ventilation On	With Room Ventilation and Local Fan On	With Room Ventilation and Scavenging Device
Anaesthetist's level	23.1 (3.1-58.4; n=6)	56.8 (16.7-118.1; n=18)	46.3 (2.7-296.8; n=56)	25.2 (1.9-110.0; n=56)
Dental surgeon's level	68.3 (2.7-941.0; n=37)	73.77 (3.1-566.7; n=19)	45.6 (4.5-310.7; n=58)	18.5 (1.6-122; n=60)
Two metres from expiratory valve	13.8 (3.1-36.4; n=24)	4.3 (1.6-7.1; n=5)	6.0 (1.6-17.2; n=73)	5.5 (1.5-12.2; n=53)

on and a scavenging device attached to the expiratory valve of the nasal mask.

Results

The degrees of atmospheric pollution so measured are presented in the table. The values obtained with the two scavenging devices were similar and are grouped together.

Discussion

This study shows that the anaesthetist and the dental surgeon are exposed to high concentrations of halothane in the atmosphere during procedures under general anaesthesia in the dental chair. These levels are greatly in excess of those occurring in general surgical operating theatres. Though scavenging devices reduced the contamination considerably it remained relatively high. It should be noted that there are no recommendations on acceptable levels of pollution of the atmosphere with volatile anaesthetics. It has, however, proved possible in surgical operating theatres to reduce halothane levels to the order of 1 p.p.m. by using scavenging devices (Witcher *et al.*, 1971; Pfäffli *et al.*, 1972). If 1 p.p.m. is taken as an acceptable level it is obvious that scavenging devices alone will not prove successful during dental anaesthesia. It is interesting to note that the use of the air-changing system and a local fan had little effect on contamination, perhaps as a result of local air eddies.

The evidence that exposure to low concentrations of volatile anaesthetics is harmful remains circumstantial (Spence, 1973). It seems reasonable, however, to take steps to exclude a possible

hazard to staff during dental extractions. Unfortunately no other method of general anaesthesia is entirely suitable for the present number of patients, many of whom are children, requiring treatment. The morbidity and mortality record of inhalation anaesthesia for dental outpatients is extremely good, and the method should not be abandoned lightly. Until the association between pollution and toxic effects on exposed personnel is clearly established, it may be better to support long-term measures for the prevention of dental decay than increase the hazard for patients who require general anaesthesia for their dental extractions.

We should like to thank Dr. C. J. F. Potter for his kind donation of one of his devices for use in this study. We also thank our colleagues in the anaesthetic department and the dental surgeons and nurses in the outpatient anaesthetic department at Kings' College Hospital Dental School for their kind co-operation.

References

- Askrog, V. F., and Harvald, B. (1970). *Nordisk Medicin*, 83, 498.
- Cohen, E. N., Bellville, J. W., and Brown, B. W. (1971). *Anesthesiology*, 35, 343.
- Knill-Jones, R. P., Rodrigues, L. V., Moir, D. D., and Spence, A. A. (1972). *Lancet*, 1, 1326.
- Pfäffli, P., Nikko, P., and Ahlman, K. (1972). *British Journal of Anaesthesia*, 44, 230.
- Sniper, W., and Murchison, A. G. (1972). *British Journal of Anaesthesia*, 44, 1220.
- Spence, A. A. (1973). *Annals of the Royal College of Surgeons of England*, 52, 360.
- Vaisman, A. I. (1967). *Ekspperimental'naya Khirurgiya i Anesteziologiya*, No. 3, 44.
- Witcher, C. E., Cohen, E. N., and Trudell, J. R. (1971). *Anesthesiology*, 35, 348.

Amphotericin Pharmacophobia

W. ST C. SYMMERS, SEN.

British Medical Journal, 1973, 4, 460-463

Summary

Five cases are described in which fear of the possibly hazardous effects of giving amphotericin to patients with kidney disease resulted in death from progressive infection by an amphotericin-sensitive fungus (*Cryptococcus neoformans* in three cases, *Blastomyces dermatitidis* in one case, and *Histoplasma capsulatum* in one case).

Department of Histopathology, Charing Cross Hospital and Medical School, London W6 8RF

W. ST C. SYMMERS, SEN., M.D., Pathologist

Introduction

A pathologist is sometimes in the position of seeming to be wise after an event that at the time of its currency was an equivocal and difficult clinical responsibility. The cases described in this paper could not have been recorded without the collaboration of the doctors who were concerned with the diagnosis and treatment of the patients' illnesses. It is my privilege to have the task of presenting their observations. No one should read these case reports without a thought of how he himself might have dealt with the situation at the time when his peers had to do so.

Amphotericin is a nephrotoxic drug (Siegel *et al.*, 1970) and some degree of renal damage is almost inevitable when the drug is given intravenously. It has a sinister reputation in patients known to have kidney disease, and in the series of five fatal cases of fungal infection described in this paper the antibiotic was withheld or prescribed in too low a dosage be-

cause the patients had or were believed to have organic renal disease. No effective alternative antifungal drug was available. As the result, four of the patients died of their fungal infection; the fifth, as the insensitive jargon of the day phrased it, was "salvaged" by starting antifungal treatment when he was already in extremis—he recovered from the infection, though only to survive for a year in the decerebrate state that indicated the extent of the damage to the brain by the fungus before it was exterminated. There was a postmortem examination in four of the five cases: only in one was there significant renal disease (chronic pyelonephritis).

Case Reports

CASE 1. SARCOIDOSIS AND CRYPTOCOCCAL MENINGOENCEPHALITIS

A house physician, 26 years old, had been known to have sarcoidosis for three years when he began to develop symptoms of meningitis. The sarcoidosis had been manifested by lupus pernio, generalized lymph node enlargement, splenomegaly, and focal osteitis. Lymph node biopsy had shown the classic picture of sarcoidosis; the Kveim-Siltzbach test was positive; the serum IgG was consistently raised; the tuberculin skin test was negative, and was known to have been positive four years before the onset of sarcoidosis, when his class at school had been screened in order that those who should be immunized with Bacille Calmette-Guérin (B.C.G.) might be identified (he was not given B.C.G.). As he was without symptoms it was not thought advisable to put him on any treatment for sarcoidosis. Until the onset of meningitis he never felt ill and he was never away from his studies.

The meningitis was at first thought to be tuberculous. This clinical impression was supported by the laboratory reports on the cerebrospinal fluid, though tubercle bacilli were never found. It was later clear that cryptococci in the fluid had been mistaken for red blood cells. Streptomycin was given intrathecally and intramuscularly and isoniazid and sodium aminosalicylate by mouth, without effect. Eventually, a registrar on another firm asked whether cryptococcosis was a possibility. It was then realized not only that cryptococci were to be seen in the cerebrospinal fluid but that yeasts that had been regarded as contaminants of the cultures of the fluid were pathogenic cryptococci. In the absence of the consultant in charge of the firm his deputy prescribed amphotericin, with early and sustained improvement.

The consultant returned a week later, and being unfamiliar with amphotericin he read about it and noted its reputation for nephrotoxicity. The patient had a history of scarlatinal nephritis 20 years before. There was a trace of albumin in his urine, and a few hyaline casts and some red blood cells (could these have been cryptococci?). The consultant stopped amphotericin. There was an immediate rapid advance of the meningocerebral infection, with no response to any of the drugs that were tried in place of amphotericin (various antibiotics and chemotherapeutic agents with little or no antifungal activity). Three weeks later amphotericin was again ordered, and given by intraventricular, intracisternal, intrathecal, and intravenous injection. It was too late to do more than delay death by a few days.* There was no necropsy.

CASE 2. HODGKIN'S DISEASE AND CRYPTOCOCCAL MENINGOENCEPHALITIS

The patient, a housewife, was 24 when she was found to have classic Hodgkin's disease involving several groups of lymph nodes and presumptively the spleen and liver. Her condition was fairly well controlled by radiotherapy and courses of cyclophosphamide until she suffered concussion in a fall while skiing. After this a slow but progressive worsening of her general condition culminated in the development of meningitis. Cryptococci were recognized in the first sample of cerebrospinal fluid examined and she was immediately put on a course of treatment with flucytosine (Roche). At first the response was promising but the cryptococcus became resistant to the drug and the infection again began to

progress. The physician was aware that the patient had been compelled to resign from her place in a school of nursing because of "orthostatic albuminuria," which, though symptomless and generally regarded as a trivial anomaly, was thought to be incompatible with a vocation as ambulatory as nursing. Unfortunately, as he later stated, he "dared not give amphotericin because of the renal history." He tried a range of other antifungal drugs, including saramycetin, hydroxystilbamidine, natamycin, and hamycin, as well as various other antibiotics and sulphonamides, without effect. She died of the meningocerebral infection 23 weeks after the first symptom. There was no evidence of significant renal disease at necropsy, only such changes being found as would accompany the closing stages of any fatal illness.

CASE 3. CRYPTOCOCCAL MENINGITIS AFTER EXCISION OF CRYPTOCOCCAL PULMONARY GRANULOMA

A medical student suggested to his fiancée that she should have her chest x-rayed, on the principle that it is sensible to have such an examination from time to time, even in the absence of symptoms. Totally unexpectedly a "coin shadow" was found in the middle lobe of the right lung. Further investigation showed no evidence of the nature of this lesion. It was decided, therefore, to do a lobectomy, essentially as a diagnostic procedure. The lesion proved to be a solitary, well-encapsulated cryptococcal granuloma, 1.5 cm in diameter, and apparently healing. Antifungal therapy was thought to be unnecessary as it was intended to keep the patient under observation. Within two weeks of the operation a small ulcer developed on the upper lip. *Cryptococcus neoformans* was grown from this and, shortly afterwards, as signs of incipient meningitis appeared, from the cerebrospinal fluid.

There was a family history of polycystic kidneys. The patient was found to have an inconstant trace of protein in the urine. There was no other urinary abnormality; renal function tests and intravenous pyelography gave normal results. Amphotericin was given, starting with particularly small doses and keeping a careful check on renal function. A slight rise in the serum non-protein nitrogen and creatinine levels, and a slight fall in the serum potassium were soon noted, along with the presence of occasional red blood cells in the urine and more proteinuria than before. The dose of amphotericin was substantially lowered, with the intention of protecting the kidneys but with the effect that the concentration of the drug fell well below an adequate anticryptococcal level. The infection of the meninges progressed and cryptococcal ulcers appeared in many parts of the skin. She died of the meningoencephalitis and haematogenous dissemination of the infection. Necropsy showed no definite evidence of any organic renal disease.

Her case was written up for publication as an instance of "amphotericin-resistant cryptococcosis." In fact, the in-vitro sensitivity of the cryptococcus responsible was well within the average range and remained essentially unchanged throughout the course of the illness. The original authors withdrew their paper and have suggested that I include this summary of the history here.

CASE 4. SPINAL CARIES DUE TO BLASTOMYCES DERMATITIDIS

A South African, resident in London, developed herpes zoster three weeks after visiting a nephew who had chickenpox. She was 66 years old. Persistent pain in the distribution of the affected nerve (the seventh right thoracic nerve) after healing of the skin lesions was thought at first to be postherpetic neuralgia. Its increasing severity was soon noticed to be associated with increased prominence of the corresponding spinous process, which was painful on percussion. Radiography showed an ill-defined osteolytic lesion in the body of the seventh thoracic vertebra. As there was no clinical evidence of a tumour elsewhere, and as the carious destruction of the bone was progressing rapidly, with incipient collapse of the vertebral body, an exploratory operation was carried out. A poorly walled off abscess was found in the costovertebral region, external to the parietal layer of the pleura and communicating with a subperiosteal abscess lateral to the body of the seventh thoracic vertebra, which was itself partly excavated by an abscess lined by caseous material. *B. dermatitidis* was isolated from the pus.

The patient had a history of recurrent pyelonephritis since a pregnancy 28 years before. She was also said to have had acute glomerulonephritis in childhood, with slight persistent proteinuria

*Case 5 illustrates a different outcome of delayed treatment of fungal meningoencephalitis—cure of the infection but a decerebrate state resulting from the damage already caused.

since that time. Because of the history of renal disease, amphotericin was thought to be contraindicated. A course of a long-acting sulphonamide (sulphamethoxypyridazine) was started, on the mistaken assumption that blastomycosis acquired presumably in South Africa must, though caused by *B. dermatitidis* (the fungus of North American blastomycosis), be essentially the same as South American blastomycosis, which in fact is an altogether different disease, caused by *Paracoccidioides brasiliensis* and—unlike North American blastomycosis—commonly amenable to treatment with sulphonamides. Soon after starting this treatment it was recognized that the infection was spreading through the blood stream. In spite of the known occasional potential of sulphadiazine to cause renal failure, this drug was given in place of sulphamethoxypyridazine, again on the grounds that it has a special reputation for control, though not cure, of South American blastomycosis.

When it became clear that the patient's condition was not responding to sulphonamides, hydroxystilbamidine was given, this drug being in fact known to suppress *B. dermatitidis* though it does not destroy it and lacks the potentially curative action of amphotericin. The patient collapsed with acute hypotension as a result of the too rapid administration of a dose of 250 mg of hydroxystilbamidine intravenously. This recognized hazard is ordinarily avoided by giving the drug well diluted over a period of an hour or two. The house physician who gave the injection said that he had dissolved the dose in only 10 ml of saline and taken about half a minute to give the injection. Myocardial infarction was found to have occurred and the patient died 18 hours later. Necropsy confirmed the presence of well-marked chronic pyelonephritis with scarring of both kidneys.

CASE 5. ADRENAL FAILURE AND DECEREBRATE STATE DUE TO HISTOPLASMOSIS

An engineer who had spent many years in south-eastern Asia retired to Europe. Eight years later, aged 66, he developed two very painful ulcers, one on the dorsum of the tongue and one on the inner aspect of a cheek. Biopsy of the lingual ulcer was thought to show a "granular cell myoblastoma" and the whole lesion was then excised. The ulcer recurred at the site of excision and a further biopsy specimen was taken; the buccal ulcer was biopsied at the same time. Both specimens were reported as showing a malignant granular cell myoblastoma. The buccal ulcer was widely excised, the greater part of the cheek being removed. The lingual ulcer was treated by implantation of radium needles: it continued to enlarge and the tongue was therefore excised.

A few months later a fresh ulcer appeared on the hard palate. The biopsy specimen from this lesion was examined by a different group of pathologists, who diagnosed leishmaniasis. They reviewed sections of the earlier ulcers and concluded that the granularity of the cytoplasm of the cells that had led to the diagnosis of granular cell myoblastoma was in fact due to the presence of leishmaniasis, and that the cells were parasitized macrophages and not tumour cells. A course of sodium stibogluconate was given, without effect. In the belief that the parasite might be antimony-resistant, amphotericin—which has antileishmanial as well as antifungal activity—was prescribed. The ulcer on the palate disappeared within two weeks. It was noticed during this course of amphotericin that the patient had a persistent trace of proteinuria. A history of nephritis in childhood was then recalled.

Three months later an ulcer began to develop at the anus. At this time the patient was on a visit to a son who lived in Britain. The latter was friendly with a pathologist, whose interest was roused by the patient's history, which suggested to him the possibility of histoplasmosis, as he had been to a talk on fungal diseases during which a similar syndrome had been described. When the anal ulcer was biopsied the sections were found to contain histoplasmas; *Histoplasma capsulatum* was isolated from the lesion. The pathologists in the patient's own country could not be prevailed on to make the sections of the earlier ulcers available for review; they maintained that there was no possibility that they had mistaken histoplasmas for leishmaniasis.

On his return home the patient began to develop symptoms of Addison's disease. It was realized that this was probably due to histoplasmosis. Because of the renal history it was felt that further administration of amphotericin, which had been started in England, was out of the question, though there seems to have been no evidence of deficient renal function, apart from the slight pro-

teinuria. The adrenal insufficiency seemed to be responding satisfactorily to substitution treatment. The infection became generalized and histoplasmic meningitis set in. The patient's family was told that the "kidney disease" resulting from the childhood nephritis precluded the use of amphotericin and that he must die of the infection. No other antifungal drugs were available in those days that could have been used effectively against generalized histoplasmosis.

The doctors were directed by the family to give amphotericin. They refused. After an interval of five days a fresh team of physicians took over and agreed to use the drug. The infection ceased to progress. Eventually, the cerebrospinal fluid returned to normal and all evidence of active histoplasmosis disappeared. The patient survived in a decerebrate state, on substitution therapy for Addison's disease, until his death from staphylococcal pneumonia a year later. There was no evidence of significant renal disease at necropsy. Extensive cerebral atrophy, affecting particularly the underside of the frontal and temporal lobes, was associated with pronounced cortical gliosis and loss of neurons, and many small pseudocysts and scars resulting from infarction due to arterial obliteration. These changes were presumed to be the outcome of a widespread histoplasmic infection of the meninges, brain, and cerebral vasculature. No organisms were recognizable in the tissues.

Discussion

The discussion of these cases will be divided into two sections, the first dealing with particular points relating to the individual cases and the second to the doctors' attitude to the use of amphotericin.

THE CASES

Cases 1 to 3

Only in one of these three instances of fatal infection of the central nervous system by *C. neoformans* was the mycosis recognized before there was evident involvement of the brain. Two of the cases illustrate the role of classic Hodgkin's disease and sarcoidosis in predisposing to cryptococcosis (Symmers, 1973). When such longstanding diseases of the lymphoreticular system have this effect on the body's defences the resulting infection is usually rapidly progressive, with generalized haematogenous dissemination rather than the more characteristic localized visceral disease. However, the specific organ affinities of the fungus are still apparent in the course of the disseminated infection. Therefore, when cryptococcosis develops in the course of, say, Hodgkin's disease, meningoencephalitis is usually the major clinical manifestation. Other mycoses, including dormant histoplasmosis, coccidioidomycosis, and the blastomycoses, may likewise become rapidly disseminated as a complication of chronic diseases of the lymphoreticular system, as may tuberculosis and herpesvirus infection. The lymphoreticular diseases thus tend to weaken immunity to those frankly pathogenic organisms that, having previously attacked the body and been checked by its defences, may persist in dormant fashion. This is in contrast to the effects on resistance of immunosuppressive drugs and cancer chemotherapy—they tend to predispose to infections that are caused not by conventional pathogens but by commensals and saprophytes, such as the moulds.

Case 3 is a classic example of the chance radiological discovery of a symptomless pulmonary focus of cryptococcosis. The diagnostic problem posed by a "coin shadow" in a lung is sometimes solved by examination of the sputum or by the recognition of a neoplasm elsewhere in the body. Failing such evidence, resection of the affected segment or lobe may be necessary for identification of the nature of the lesion. It is not usual for resection of cryptococcal granulomas that present as "coin" shadows to be followed soon by further signs

of the infection. When this happens, as in this case and in two others that I have seen, it may take the form of extraordinarily rapid haematogenous dissemination of the infection. In other cases there may never be further evidence of the latter, or its reappearance may be delayed for many years. I have seen cryptococcal meningoencephalitis appear 16 years after resection of a pulmonary granuloma.

Case 4

This was a characteristic instance of mycotic spondylitis with caries and incipient vertebral collapse. A similar case, but due to cryptococcal infection, was reported recently (Balasubramaniam and Silva, 1973), and I have referred briefly elsewhere to a series of 24 cases of mycotic disease of the spine, including six caused by *B. dermatitidis* (case 4 among them) and five caused by *C. neoformans* (Symmers, in press). It is still far from generally recognized that infection by *B. dermatitidis*, the cause of North American blastomycosis, occurs throughout the African continent, including South Africa (Osmond *et al.*, 1971), where this patient may well have acquired her infection. Evidence is accumulating that this form of blastomycosis is not only frequent and widespread in Africa but that it may even have originated there. "North American" proves not to be an appropriate epithet for the disease.

The doctors who were looking after this patient seem to have been confused geographically and terminologically, equating blastomycosis in a woman from South Africa with South American blastomycosis, and prescribing treatment that, while appropriate for the latter, is of no value against "North American" blastomycosis. Infection by *P. brasiliensis*, the cause of South American blastomycosis, does not occur naturally outside America.

Case 5

This case illustrates a syndrome of histoplasmosis that is becoming familiar in Europe among returned expatriates whose infection was acquired in southern or south-eastern Asia. A study of 48 such cases was published last year (Symmers, 1972). The infection in these patients typically presents with painful ulceration at mucocutaneous junctions or within body orifices. There is a high liability to the development of Addison's disease in consequence of the heavy histoplasmic infection of the adrenals, the cortical parenchymal cells of which, unlike the cells of other parenchymatous organs, are specially prone to be parasitized by the fungus. This exposes the patients to a particular risk of rapidly fatal adrenocortical failure if the initial dosage with antifungal drugs is too high, an occurrence reminiscent of the Jarisch-Herxheimer reaction during treatment of syphilis.

A long interval between leaving the area of indigenous histoplasmosis and the first clinical manifestation of the infection is typical of this syndrome and adds to the difficulty in recognizing its nature promptly.

H. capsulatum and leishmania are notoriously liable to be mistaken for one another in histological sections, being of the same order of size and present in comparable numbers as obligate intracytoplasmic parasites in macrophages in infected tissues (Woo and Reimann, 1957). It is likely that the oral ulcers in this case were histoplasmic and not leishmanial. There are also recorded precedents for the initial misinterpretation of the parasitized macrophages as cells of a "granular cell myoblastoma." This diagnosis had been made elsewhere in a case that was recognized by Earle and his colleagues (1960) to be histoplasmosis. The tongue is one of the more

frequent sites of this tumour, a circumstance that facilitates the error made in case 5. Once made, the mistake was compounded by regarding recurrence of the lingual ulcer and the presence of the buccal lesion as evidence of malignancy; in fact, malignant granular cell "myoblastomas" are very rare (Cappell, 1948).

AMPHOTERICIN PHARMACOPHOBIA

Common to all five cases was the fear that amphotericin is particularly dangerous to patients with renal disease. This fear was so great that the chance that the drug might cure the infection without inducing fatal renal failure was not taken. In the three cases that occurred within reach of facilities for treatment by dialysis the possibility that this procedure might tide the patient over in the event of severe renal damage by amphotericin was not considered. Nobody seems to have considered that the loss of both kidneys is not necessarily fatal or incompatible with a useful life nowadays.

It is true that amphotericin is nephrotoxic. It is no less true that amphotericin is a life-saving drug and sometimes the only means of preventing death from fungal infection. Sometimes the physician must balance the therapeutic necessity for the drug against its ingravescent side effects, including renal damage: in some of these cases he will, with skill, bring his patient through both dangers—in others he will lose his patient to the side effects of the drug or to its failure to prove effective against the infection. At least he should surely give his patient the chance of overcoming the latter.

Today, amphotericin has been joined by other valuable antifungal drugs that may be used reasonably safely in treating severe and progressive infections. Flucytosine and clotrimazole (Bayer b 5097) are now widely available. Their effectiveness and their substantial margin of freedom from serious side effects, as well as their ease of administration (both are active by mouth), make them welcome additions to the small range of antifungal drugs that are of use against systemic infections. But these new drugs are not substitutes for amphotericin. They are not always as effective, they sometimes inhibit progression of infection but do not eradicate it, and they seem to have more tendency to induce resistance of the fungi to their action.

In sum, there are still patients whose fungal infection can be cured only by amphotericin. A small proportion of these patients may be endangered by the nephrotoxicity of the drug. This danger is less with modern, more modest concepts of amphotericin dosage, which have strengthened the curative reputation of the drug while substantially improving on its earlier record in terms of undesirable side effects. Those few patients who suffer renal damage as the price of recovering from an otherwise fatal infection may at least have the benefit of modern means of overcoming the effects of renal failure.

References

- Balasubramaniam, P., and Silva, J. F. (1973). *British Medical Journal*, 2, 27.
- Cappell, D. F. (1948). *Annals of the Royal College of Surgeons of England*, 2, 80.
- Earle, J. H. O., Highman, J. H., and Lockey, E. (1960). *British Medical Journal*, 1, 607.
- Osmond, J. D., Schweitzer, G., Dunbar, J. M., and Villet, W. (1971). *South African Medical Journal*, 45, 431.
- Siegel, R. R., Hellebusch, A., and Saliba, N. (1970). *Clinical Research*, 18, 447.
- Symmers, W. St C. (1972). *Annales de la Société Belge de Médecine Tropicale*, 52, 435.
- Symmers, W. St C. (1973). *British Medical Journal*, 2, 423.
- Symmers, W. St C. (In press.). *Curiosa—A Miscellany of Clinical and Pathological Experiences*, chap. 21. London, Baillière Tindall.
- Woo, Z.-P., and Reimann, H. A. (1957). *Journal of the American Medical Association*, 164, 1092.