Histoplasmosis in the Cape Province

A Report of the Second Known Outbreak

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SUMMARY

Histoplasmosis is a rare disease in the Cape Province. The diagnosis of acute disseminated histoplasmosis in a patient who presented at Groote Schuur Hospital 3 weeks after a caving expedition, led to the identification of acute benign pulmonary histoplasmosis in 9 other people who had explored the same cave. Possible explanations for this outbreak are discussed.


The fungus *Histoplasma capsulatum* is endemic in many tropical and subtropical areas of the world, including the southern USA, Central America, South America, Central Africa, Indochnia and Indonesia. The soil is its natural habitat, and human infection occurs by inhalation of spores liberated into the atmosphere. This occurs particularly in areas inhabited by chickens, birds and bats, as the organism flourishes in their droppings. The high nitrogen content of bat droppings in caves is known to be particularly favourable for the growth of *H. capsulatum*.

Histoplasmosis is well known in the Transvaal and in Rhodesia, but there has been only one reported outbreak in the Cape, despite the fact that the members of the South African Spelaeological Association (SASA), who have undertaken organized cave exploration in the Cape for 25 years, are well aware of the existence of the condition. A detailed and comprehensive review of histoplasmosis the interested reader is referred to a recent publication.

CASE REPORT

A 66-year-old man presented at hospital with a history of fever, nausea, vomiting and progressive weakness for the previous 6 days. The onset of symptoms was acute, and they had failed to respond to treatment with dihydroxylate, oral neomycin and ampicillin from his general practitioner. Prior to this illness he had been perfectly well, and was a fit man whose hobby was mountaineering. On examination at the time of admission he was pyrexic, dehydrated, weak and had an erythematous skin rash. His respiratory rate was 18/min. There was good chest expansion; the only abnormality was a few bilateral basal crepitations. The cardiovascular, gastro-intestinal and central nervous systems were normal. Chest radiography showed a normal heart, but nodular shadowing throughout both lung fields (Fig. 1). Several blood and sputum cultures were negative and no organisms were seen in the sputum.

The following haematological results were obtained: haemoglobin 10.8 g/100 ml, with normal red cell indices; leucocytes 4.8X10⁹/l, neutrophils 63%, lymphocytes 27%, monocytes 1%, eosinophils 6%, basophils 1%, band cells 1%, myelocytes 1%; serum urea and electrolytes were normal, as was serum bilirubin. Alkaline phosphatase was 199 U (normal 30 - 85 U); SGOT 92 U/l (normal 10 - 50 U); pH 7.45; Pco₂, 4.13 kPa; and Po₂, 8.4 kPa.

Total protein was 51 g/l, albumin 24 g/l, α₁-globulin 3.5 g/l, α₂-globulin 9 g/l, β-globulin 6.4 g/l, and γ-globulin 7 g/l. Immunoglobulin measurements showed an IgG of 49 U (normal 90 - 110 U), IgA 97 U (normal 55 - 70 U), and IgM 182 U (normal 70 - 230 U).

Shortly after admission to hospital, the patient volunteered that 2 weeks before the onset of the illness he had been into the De Hoop cave near Bredasdorp. This cave is about 400 m long, with a bat nursery chamber halfway in, and is situated about 35 m above sea-level above the eastern bank of De Hoop vlei at 20°21'30"E, 34°25'15"S. At the time of his visit, the nursery chamber...
Fig. 1. Typical chest radiograph showing the bilateral nodular shadowing.

contained an estimated 80,000 pregnant *Miniopterus schreibersi* bats. The temperature all year is 29° - 30°C, and the humidity is 100%.

During this expedition, which was the patient's first into a bat-containing cave, he had walked through a 'rain' of bat guano. A tentative diagnosis of histoplasmosis was made, and the severity of his illness suggested that this may have been disseminated. In view of the fact that histoplasmosis is exceedingly rare in the Cape, and that alternative diagnoses such as miliary tuberculosis needed to be considered, he was submitted to thoracotomy and open lung biopsy in order to rapidly establish a definitive diagnosis. A bone marrow aspirate and bone marrow trephine specimen were taken at the same time. The lung biopsy specimen showed several yellow nodules 3 - 6 mm in diameter which histologically were composed of numerous lymphocytes and histiocytes, the latter undergoing epithelioid cell transformation. A few giant cells were also present. Inflammatory exudate filled the alveoli, but no tissue necrosis was seen. Moderate numbers of small budding fungal organisms were scattered throughout the lesions (Fig. 2), and the diagnosis of histoplasmosis was thus confirmed. The results of blood tests for *Histoplasma* antibody at that time were negative.

The degree of systemic illness and the presence of granulomas in the bone marrow suggested disseminated histoplasmosis, and he was, therefore, treated with amphotericin B. This was given in small intravenous doses initially (with 25 - 50 mg promethazine), and the dose was gradually increased to a maximum of 35 mg/d. The erythematous skin rash progressed to pustular lesions, but subsequently regressed on treatment with amphotericin B. A total dose of 1 g was given over 6 weeks.

The patient's course was one of gradual improvement, but complicated by an episode of staphylococcal septicaemia which was successfully treated, and by a renal tubular leak of potassium which resulted in hypokalaemia and necessitated large doses of potassium replacement. He was discharged from hospital quite well 8 weeks after admission, with no obvious cause for immune incompetence, and has been well during the subsequent 9 months of follow-up. His chest radiograph cleared completely, histoplasma antibody tests became positive, and IgG levels returned to normal.

The identification of this index case led to the investigation of 18 members of a rambling club who had explored the De Hoop cave.

**Investigation of Other Cavers**

The clinical, radiological and serological features of the ramblers (including the index case) are summarized in Table 1. The leader (patient 5) and 4 others visited the nursery chamber on 17 September 1977. The leader had explored the cave on several previous occasions. None had any clinical or radiological evidence of ABPH after this visit, although patient 3 did have antibodies in his blood. He had previously spent 10 years as a mining geologist in the Transvaal, South West Africa, Rhodesia, Zambia and Mozambique, and could well have had unrecognized ABPH then.

Four members of the club visited the cave on 10 October 1977 and turned back just inside the entrance. None had any evidence of histoplasmosis (patients 15 - 18).

The leader (patient 5) and 9 others (including the index case who will be excluded from further discussion here) visited the nursery chamber on 10 October 1977. Exactly 14 days later, all developed mild dyspnoea and non-productive cough, fever, anorexia, skin rashes, lassitude, transient mild headache and other aches, i.e. symptoms compatible with ABPH. The diagnosis was confirmed by chest radiographs showing bilateral nodular shadowing which cleared spontaneously in the subsequent months. One patient (No. 12), who in 1976 had an aortic valve replacement, was admitted for observation. He showed no evidence of histoplasmosis endocarditis and was discharged after 5 days. None received or required specific...
### TABLE I. SUMMARY OF THE VISITORS TO THE DE HOOP CAVE

<table>
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<tr>
<th>Patient</th>
<th>Date in cave</th>
<th>? Guano chamber</th>
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*Index case.
†Leader.

3 divers with no previous caving experience, visited some caves north of Oudtshoorn. The 3 divers were afterwards found to have ABPH, while those with previous caving experience remained well.\(^5\) Macpherson\(^6\) concluded that the divers had probably become infected by spores brought to the Cape in the accompanying Transvaal cavers' unwashed overalls and equipment.

The circumstantial evidence presented in Table I suggests that the De Hoop cave may have become infected between 17 September and 10 October 1977. However, since 5 cavers can be expected to raise less dust than 10 cavers, the cave may equally well have become infected before 17 September 1977. The existence of this cave has been known for many years. It was mined for bat guano during the 1939-1945 war,\(^7\) and it is clear from the ‘tide mark’ on the walls, and from the remains of a light railway inside, that considerable quantities were removed. There are no 'stories' in the area of respiratory illnesses during the period of mining activity.

More recently, the cave has been visited regularly by university students, Boy Scouts and school parties. The latter two groups are notorious for raising dust! Again, there have been no reports of respiratory illness following these visits.

After the Second World War, the land on which the cave is situated was bought by the Cape Provincial Administration (CPA) for use as a nature reserve. During the last 3 years the cave has been regularly visited by CPA research workers who are interested in, inter alia, the bats. After the recent histoplasmosis outbreak, all those CPA employees who had been in the cave were examined by Dr J. R. Joubert at Tygerberg Hospital.

treatment. Skin tests could not be done reliably because of lack of availability of histoplasmin. Histoplasma antibodies were sought and found in all but 2 of these patients. None of the subjects had been caving in endemic areas, and none kept pigeons, chickens or other birds. All made a complete recovery.

### DISCUSSION

Histoplasmosis resembles tuberculosis in that exposure to the pathogen does not always cause clinical symptoms, but usually stimulates antibody formation and cell-mediated immunity. In the endemic areas of the USA, asymptomatic histoplasmosis, as shown by large-scale skin testing, can affect up to 80% of the population. On the other hand, acute disseminated histoplasmosis is reported to be very rare, affecting between 1 in 100 000 and 1 in 500 000 infected persons per year.\(^7\) One-third of these infections occur in the first year of life and the remainder in adult life, the greatest incidence being in the 6th and 7th decades. There is a large male predominance in adults. Some idea of the rarity of histoplasmosis in the Cape can be gained from the observation that a computer search of 139 120 inpatient records at Groote Schuur Hospital over the past 7 years revealed only 2 other cases of histoplasmosis. Bank et al.\(^8\) reported a histologically proven case of chronic histoplasmosis of the small bowel in a woman who lived at Napier, a small town about 50 km from the De Hoop cave.

The first reported outbreak of ABPH in the Cape affected 3 visitors from the Transvaal in March 1963.\(^8\) Several members of the Transvaal branch of SASA, and
Apparently none had any evidence of histoplasmosis.

There are three possible explanations for the outbreak reported here. Firstly, the spores may have been in the cave for a long time without causing symptomatic disease until now. There is no evidence to support this theory, which implies that the spores may be distributed all over the southern Cape. The rarity of histoplasmosis is against it. There is no good reason why the spores should suddenly have become more virulent, nor why the leader (patient 5) should suddenly have become more susceptible. Lurie12 performed skin tests on 140 South Africans, 17 (i.e. 12%) had positive or equivocal reactions, but none of these came from the Cape Province. Jackson,13 wondering if he was confusing tuberculosis with histoplasmosis, skin-tested 453 patients of all races attending tuberculosis clinics in Cape Town. Only 3 (i.e. 0,66%) had positive results, all having come from the Transkei.

As part of their investigation into ABPH in the Transvaal, Murray et al.14 had skin-tested 20 members of the Cape Town section of SASA. Only 3 had caved outside the Cape. None had a history compatible with ABPH and none was histoplasmin-positive.15

We are looking for histoplasmosis antibodies in the current generation of SASA members who have caved only in the Cape. So far, we have tested 8 — all were negative.

A second possibility is that the spores may have been introduced by a migrating bat. This theory would require a bat to have moved almost 1 600 km from the Transvaal. Such long migrations have been reported from the USA and from Russia,16 but the longest reported migration in South Africa is 500 km from the Eastern Transvaal to St Lucia in Natal (L. R. Wingate — personal communication). Bats in the Americas have been shown to be infected with histoplasmosis.17 In South Africa, Murray et al.18 were unable to isolate H. capsulatum from bats in infected Transvaal caves. Furthermore, Herselman and Hanekom19 have no evidence that the bats of the southern Cape move more than 230 km within that area.

A third possibility is that the spores may have been introduced on the clothes, boots or equipment of a visitor from an infected cave. This theory is impossible to prove or disprove, but by elimination of the first two theories, and by consideration of the circumstantial evidence given below, is not unattractive. As mentioned, the 1963 outbreak of ABPH was considered to have been caused by spores unwittingly introduced from the Transvaal. The CPA bat banders visit caves all over the Cape Province in the course of their field work. During the period 8 - 22 June 1977 they visited 'a few dry, small caves with practically no droppings and very few bats' in the northern Cape. They subsequently visited the De Hoop cave on 3 - 8 July 1977, August 1977 and 21 September 1977. The September visit was the only one to the De Hoop cave between the visits of the ramblers. The northern Cape caves are in the area bounded by Vryburg, Kuruman and Campbell — not far south of, and more or less at the same altitude as, the histoplasmosis-infected caves of the Transvaal. It may be that these caves have H. capsulatum spores in the dust, and that they were unwittingly brought to the De Hoop cave by the bat researchers. Unfortunately, no work has been done on these remote and little-visited caves.

One of us (S.A.C.) first visited the De Hoop cave in January 1978 to collect guano samples for analysis for H. capsulatum, and has returned for further samples each month thereafter. Samples were collected at 1-m intervals along the path through the guano chamber taken by the ramblers. Those collected in January were all negative; the later specimens are still being processed.

CONCLUSION

We believe that the De Hoop cave became infected with H. capsulatum spores introduced from a distant cave — but we have been unable to identify the source or the vector. Since there have been no subsequent reports of ABPH from the caves north of Oudtshoorn which were infected in 1963, since the guano samples taken from the De Hoop cave in 1978 have failed to grow H. capsulatum, and since subsequent visitors to the De Hoop cave have failed to develop ABPH, we further believe that the spores have died or will die, and that ABPH will not become established in the Cape.

Despite this, we recommend three simple precautions to be taken by visitors to infected or possibly infected caves: (i) take care not to raise the dust; (ii) wear a respirator or other mask to prevent the dust from entering the lungs; (iii) after leaving the cave, thoroughly wash and dry all boots, clothing, helmets, lights, ropes, ladders and other equipment which may have become contaminated.

We acknowledge with grateful thanks the assistance of Dr P. J. Botha and Mrs J. Hyland of the Department of Bacteriology, University of Cape Town, for the histoplasmosis screening tests; Dr N. G. Hofmeyr, Department of Radiology, Groote Schuur Hospital, for reporting most of the chest radiographs; Dr C. N. Young of the South African Institute for Medical Research, Johannesburg, for analysing the guano samples; the Department of Nature Conservation of the Cape Provincial Administration for access to the De Hoop cave, and for other co-operation; members of the South African Spelaeological Association (Cape Section) for collecting guano samples; and the patients for cheerfully attending for radiographs and blood tests.

REFERENCES