strated at all in five, six, and four animals of the respective dietary groups 2, 3, and 4, even after reinoculation with the blood of a fresh "acme" passage mouse. In mice given diet 2, 3, or 4 infection followed a much milder course than in those given diet 1. This was true in all mice not reaching or dying at the acute stage, as judged by the total numbers of trypanosomes in the blood of the animals over the period of the experiment. When the persistent chronic stage was reached, however, death was often rapid (cf. Table II and Tables III, IV, and V).

The results of Experiment I are supported by those of Experiment II. The mice fed on the casein diet 3 showed only the slightest evidence of blood-stream invasion by parasites during the 23-day period of observation. The infection followed an acute course in both the natural diets, Nos. 1 and 5, and this course was that normally recorded in this laboratory over many years.

Macraith *et al.* (1952) concluded that milk probably contains something that can inhibit or restrict the development of the asexual phase of blood-transmitted *Plasmodium berghei* in the rat and the mouse. Another possibility is that milk may be deficient in certain nutrients required by the parasite (*British Medical Journal*, 1952). The second explanation would fit the results observed in the present experiments with *T. congolense* in mice given diets with milk casein as the source of protein. It is clear that parasitaemia developed much more rapidly and attained a higher level in mice given diets 1 and 5, which were nutritionally more complex than the casein diets. Moreover, since diet 5 also contained milk, inhibition of parasite growth from the absence of undefined nutrients rather than from an anti-parasitic effect of milk might appear to be the more tenable explanation. It may be of importance to note that the mice made good gains of weight on all diets, especially on diet 4, which contained a high proportion of carbohydrate (Table X).

TABLE X.—Weekly Mean Weights (g.) of Uninfected Mice Given Experimental Diets 1-4

Diet No.*	Age of Mice (Weeks)								
	4	5	6	7	8	9	10	12	17
1	19	24	29	30	31	32	34	36	39
2	17	25	30	30	32	32	33	35	35
3	20	24	30	33	33	35	37	37	37
4	18	25	32	34	36	37	39	41	44

* Each dietary group comprised 4 males and 4 females; litter mates were evenly distributed.

Summary

Mice fed on five different diets were experimentally infected with *T. congolense*.

Parasitaemia with acute followed by chronic infection developed as expected in mice fed on two of the diets, which were diets of the type normally employed in laboratories for rearing and maintenance of mice.

In mice fed on three of the diets in which milk casein was the source of protein the parasitaemia was either delayed or prevented.

Since one of the two "normal" diets contained milk but permitted normal development of the infection it might appear that failure of the incomplete diets to nourish the parasite is the explanation of the observed results, rather than that milk itself contains an anti-parasitic agent.

REFERENCES

- British Medical Journal*, 1952, 2, 1405.
 Browning, C. H., Calver, K. M., and Adamson, H. (1948). *J. Path. Bact.*, 60, 336.
 Howie, J. W. (1951). *J. Anim. Tech. Ass.*, 2, 7.
 Macraith, B. G., Deegan, T., and Jones, E. S. (1952). *British Medical Journal*, 2, 1382.

HISTOPLASMOSIS IN GREAT BRITAIN

DESCRIPTION OF A SECOND CASE OF DISSEMINATED HISTOPLASMOSIS; TREATMENT BY ETHYL VANILLATE

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Work in the past few years on human infections by the *Histoplasma capsulatum* has emphasized certain features. Generalized dissemination (disseminated histoplasmosis) is common and usually fatal. Infection confined to the skin is frequent, though, unlike cutaneous blastomycosis, the skin lesion is usually within a short while followed by manifestations of dissemination (Curtis and Grekin, 1947) and is therefore often fatal. Infection can be confined to a single organ or viscus—usually the lung—with at no time evidence of dissemination and often no past history of even mild illness. These cases are identified usually after recovery by a positive intradermal histoplasmin test or by complement fixation.

Only one other case of disseminated histoplasmosis has been reported in Great Britain, and this occurred in 1940 (Derry, Card, Wilson, and Duncan, 1942). A regular soldier aged 30 developed his illness in France in 1940 and the diagnosis was eventually made at necropsy in Great Britain. He had been resident in India in 1932-6 and in the Sudan in 1936-7; this gives a possible incubation period of three years at least (assuming the disease is not indigenous to France).

In the second case, which we report below, the patient had not been out of England for seven years. Symptoms first appeared about a year before admission to hospital, and we must therefore assume either that the disease has an incubation period of at least six years or that he contracted his illness in England. We regard the first of these suggestions as the more probable.

Arblaster (1950) and Crofton (1950) report three cases of pulmonary calcification in England in which the diagnosis of "healed" histoplasmosis was suggested because of a positive histoplasmin intradermal test. All three patients had been resident in the U.S.A. or Canada. Duncan (1945, 1947) isolated an atypical organism from a skin lesion in a man from West Africa.

In 1951 Limerick described the development of a retrocaecal abscess occurring after appendicectomy in 1947 in a man aged 35. The abscess cleared up in three weeks with drainage and was said to be due to *H. capsulatum*. No further details are given.

The cases of Duncan, Arblaster, and Limerick, however, do not conform in many ways to the usually accepted criteria and must be regarded as very doubtful. Hutchison (1952) reported a localized laryngeal lesion due to *H. capsulatum* in a fit man of 72 who had lived

in Hyderabad for 30 years and had spent some time in Malaya. He had, however, been resident in Great Britain since 1934 (six years in Sussex and eight years in Dumfriesshire until the diagnosis in 1948). He was fit and well in 1951.

These cases are particularly interesting on two counts: (1) the three patients, not from the American continent, had all been to India; and (2) in view of the prolonged incubation period it is likely that further cases may now be expected to occur in this country in soldiers who had been resident in endemic areas during the war.

Case History

The patient, a man aged 32, had been in H.M. Forces for six years and was discharged in England in 1945. He had spent most of his time at Alexandria and Port Said, but had visited Durban for three weeks, had spent three weeks in Tobruk, and had stayed at Bombay for two months. He visited numerous places in the Near East, including Cyprus, Aden, and Malta, but never went ashore.

He began to complain of peptic-ulcer-like abdominal pain at the end of 1951. On October 14, 1952, he first attended this hospital, and he was seen by one of us (S.L.) on December 17. On examination he was pyrexial, with obvious loss of

FIG. 1.—Granulomatous ulcer inside right cheek.

weight, a large spleen, a large liver, a few small axillary glands, pallor, marked tenderness over the sternum, and two large ulcers in the mouth (see Fig. 1). Examination of the central nervous system was normal; the blood pressure was 125/75 mm. Hg. The ulcers (about 2 cm. in diameter) were situated on the hard palate and the inside of the right cheek. They were granulomatous in appearance, with a raised rolled edge. The patient was admitted to the medical wards.

On December 19 a blood count showed: haemoglobin, 58%; red cells 3,300,000; white cells, 3,000 (72% polymorphs, 1% metamyelocytes, 1% eosinophils, 11% lymphocytes, 8% monocytes, 7% stab cells). A marrow puncture was normal and did not favour the diagnosis of leukaemia. W.R. and Kahn test were negative. It was felt that the only alternative diagnosis now possible was that of disseminated histoplasmosis.

Penicillin in large doses and the local application of an antibiotic to the ulcers was ineffective, and was discontinued after ten days. An x-ray film of the chest on December 29 showed the presence of a small opacity in the right costophrenic angle. Intravenous hydroxy-stilbamidine for ten days was ineffective. On January 7, 1953, his haemoglobin was 54% and the blood count was unchanged. Repeated estimations of plasma proteins, serum bilirubin, thymol turbidity, and cephalin-cholesterol flocculation were unchanged and normal. Blood urea was 26 mg. per 100 ml. A histoplasmin intradermal test was negative (no wheal or

erythema). An electrocardiogram on January 14 was within normal limits.

An x-ray film of the chest on January 21 showed extensive spread of the pulmonary lesion (see Fig. 2). On the 24th small ulcers of the skin were appearing and doses of sulphadiazine were started with no improvement. On the 29th ethyl vanillate was given.

On February 1 he was having great difficulty in keeping down the capsules of ethyl vanillate, and from February 5 it was given in an emulsion. The emulsion was made up to contain 12.5 g. of ethyl vanillate in 200 ml., and this was dripped into the stomach through a Ryle's tube, the gastric drip lasting for 50 minutes and being given every six hours.

On February 9 he said he felt very much better, but was even more wasted. His blood pressure was 115/70 mm. Hg. There had been no improvement in any of his physical signs, and his clinical condition had grossly deteriorated. He died suddenly on the evening of that day.

FIG. 2.—Chest x-ray film two weeks before death, showing extensive bilateral lung involvement.

Post-mortem Findings

The liver weighed 1,552 g., and a large number of pale slightly raised nodules up to 1.5 cm. in diameter could be seen through the capsule. Enlargement of lymph nodes was general, but was especially marked in the abdomen. The suprarenals showed enormous enlargement, presenting as yellowish rounded masses 6 by 6 by 4 cm., on each side deforming the upper pole of each kidney. On section the suprarenals had a cream-coloured honeycombed appearance with some liquefaction. The kidneys and bowel showed no detectable lesions. The spleen weighed 430 g., with a splenunculus the size of a walnut. The lungs each weighed just over 600 g., all lobes showing very numerous white solid areas 1-5 mm. in diameter, sometimes coalescing into larger masses with central necrosis.

Histological evidence of histoplasmosis was found in sections from the liver, spleen, lymph nodes, lungs, bone marrow, thyroid, and suprarenals. Very scanty parasites were detected in sections of skin lesions. In each case distension of reticulo-endothelial cells by large numbers of capsulated yeasts was evident (Fig. 3). Goodpasture's stain gave clearer definition of the parasites than Schiff's periodic acid or phloxine tartrazine. In the suprarenals there was extensive involvement of the cortex as well as the medulla, with a very small outer fringe of unaffected cells.

H. capsulatum was cultivated from the spleen, suprarenals, liver, lung, and bone marrow.

FIG. 3.—Section of lymph node showing endothelial cells engorged with the parasites.

Bacteriology

Examination of the first biopsy (December 29) was so suggestive of histoplasmosis that a second biopsy was carried out (January 21) in order to isolate the parasite. An impression smear (January 21) showed an abundance of oval capsulated yeasts (Fig. 4), and cultures were made on Sabouraud's and glucose agar (pH 7.4) at room temperature and at 37° C. On 1% glucose agar after seven days at room temperature there appeared a profuse growth of small fluffy white colonies adherent to the medium. A few days later typical tuberculate chlamydospores of *H. capsulatum* were found in the centre of the colonies. No growth occurred on Sabouraud medium, and it appears that, from subculturing, this strain grows very slowly at a low pH. On glucose agar, growth was best at room temperature at a pH approaching neutrality. The colonies become brownish, with the appearance of chlamydospores. The chlamydo-

FIG. 4.—Showing organisms with characteristic unstained capsules obtained by direct contact smear from biopsy of cheek ulcer. ($\times 2,000$.)

spores (Fig. 5) are of two types—a large tuberculated thick-walled structure 14–16 μ in diameter and a small smooth pear-shaped form 4–5 μ in diameter. From the mycelial growth cultures were made on sealed blood-agar slants at 37° C., and after a fortnight smooth creamy colonies of the yeast form were produced. The yeast cells were of varying shape, about 2–3 μ in diameter, and about half appeared oval with pointed ends. The yeast form did not

ferment glucose, maltose, saccharose, or lactose after 14 days' incubation at 37° C.

With the use of the slide-cell technique and 1% glucose agar the control cell showed a good growth in six days, but no growth occurred in concentrations of 4.2 mg. of ethyl vanillate or greater. Similar tests carried out with "cuprimyl" (tetradiethylamine salt of cupric-bis-8-hydroxyquinoline 5:7 disulphonic acid) showed no inhibition in a concentration of 10 mg. per 100 ml.

Discussion

In this case there did not appear to be any evidence of adrenal failure, though a close watch was kept for this both biochemically and clinically; nevertheless the sudden death was very suggestive of this.

The diagnosis of the disseminated disease can in most cases be suspected on the clinical picture: irregular fever, ulceration of the mouth and palate of a peculiarly granulomatous type (Fig. 1), ulceration of the skin, enlargement of the liver and spleen, lymph-node enlargement, developing pulmonary lesions which may show a localized consolidation with or without cavitation (Fig. 2), or, more commonly, generalized miliary opacities in the lungs. Anorexia and much loss of weight, to eventual gross cachexia, are the rule. Abdominal pain and discomfort is common, and intestinal ulceration with diarrhoea not infrequent. The diagnosis can be confirmed, however, only by identification of the organism in the tissues (Fig. 3) and positive culture.

FIG. 5.—Characteristic "cog-wheel" appearance of chlamydospores seen on culture of *H. capsulatum*. ($\times 2,000$.)

Treatment

Clinical experience has shown the complete failure of promanide (promin in U.S.A.), "actidione" (an antibiotic from *Streptomyces griseus*), penicillin, streptomycin, aureomycin, chloramphenicol, sulphonamides, iodides, arspenamine, mercurials, stilbamidine, and antimonials to affect the course of the disease and its fatal termination, and to this list we would add hydroxy-stilbamidine. Two cases have been reported in which pulmonary resection has apparently resulted in survival for two years and for six months respectively (Hodgson, Weed, and Claggett, 1950).

Ethyl vanillate, obtained by oxidizing lignin in the spent liquor from the sulphur pulp manufacturing process, has been used in disseminated histoplasmosis (Christie, Middleton, Peterson, and McVickar, 1951; Ellis, Scott, and Miller, 1952), being at the moment the drug of choice in treating histoplasmosis and coccidioidomycosis. In concentrations of 10 to 30 mg. per 100 ml., it has a marked inhibiting effect on *Blastomyces dermatitidis*, *Coccidioides immitis*, and *H. capsulatum* (information provided by Messrs. Squibb). However, a difference in susceptibility to ethyl vanillate has been demonstrated for different strains of *H. capsulatum* which may be of significance in treatment. It is, however, rather surprising that the organism in our case did not grow in ethyl vanillate at a concentration of 4.2 mg. per 100 ml., yet, in spite of blood levels well above this for 10 days (see Table), the disease here showed no signs of regression.

Ethyl Vanillate Levels in Blood and Urine (24-hour Collections)

Day	Plasma Vanillic Acid (Corrected for Normal Phenolic Substances in Blood) (mg./100 ml.)	Urine Vanillic Acid (Calculated as Vanillic and Phenolic Substances Excreted (g.))
28/1/53		1.70
29/1/53		0.88
30/1/53	6.8	5.70
31/1/53		16.50
1/2/53		14.40
2/2/53	3.3	5.75
3/2/53	18.6	26.10
4/2/53	15.8	
5/2/53	20.5	11.40
6/2/53		4.83
7/2/53		6.42
9/2/53	21.5	

Blood levels of over 30 mg. per 100 ml. are apt to cause toxic phenomena (coma with or without convulsions), and if the level exceeds 50 mg. the toxic phenomena can be lethal (Christie *et al.*, 1951). To maintain this blood level in an adult requires about 40 to 50 g. of ethyl vanillate daily by mouth, and in a child 0.75 to 2.5 g. per kg. of body weight a day. More recently, Christie (1952) said that ethyl vanillate was the only therapeutic agent of any value in histoplasmosis, though it was not satisfactory.

The patient here described received 45 g. daily from February 2, but part of this was vomited. From February 5 he received and retained 50 g. daily.

Summary

After a brief review of the cases of histoplasma infection previously published in Great Britain the second case of disseminated histoplasmosis to be reported is described. This case was fatal in spite of treatment with 45–50 g. of ethyl vanillate daily. Some information is included on culture of the organism, as in this case it showed certain cultural peculiarities.

We are grateful for the help we received from many sources in the treatment of this case. We would particularly like to thank Dr. A. S. Osborne, of the American Embassy, Dr. W. P. Kennedy, of the Ministry of Health, and Mr. C. B. Sitterson, jun., of the Institute of Paper Chemistry, Wisconsin, U.S.A., for their advice; Dr. Harvey Blank and Messrs. E. R. Squibb and Sons, New York, U.S.A., for the prompt dispatch to us of ethyl vanillate and appropriate information adequate for the treatment of this case; Dr. R. Forgan, Dr. John Harper, and Messrs. May and Baker, of Dagenham, for their advice and for supplying us with the hydroxy-stilbamidine and "cuprimyl" used by us; Mrs. E. D. Price for her patience and careful secretarial work; and Mr. E. Sheppard for his most excellent photography. Finally, we are most grateful to the nursing staff for the great care with which treatment was carried out, and to Dr. G. H. Cranswick and Dr. P. G. Swann for their many helpful suggestions.

Since this paper was completed we understand that a case of disseminated histoplasmosis in a young woman was transferred to this country from South Africa, where the diagnosis was made. Unfortunately the patient died two days after arrival.

REFERENCES

- Arblaster, P. G. (1950). *Thorax*, **5**, 333.
 Christie, A. (1952). *Lancet*, **1**, 1011.
 — Middleton, J. G., Peterson, J. C., and McVickar, D. L. (1951). *Pediatrics*, **7**, 7.
 Crofton, J. (1950). *Thorax*, **5**, 340.
 Curtis, A. C., and Grekin, J. N. (1947). *J. Amer. med. Ass.*, **134**, 1217.
 Derry, D. C. L., Card, W. I., Wilson, R., and Duncan, J. T. (1942). *Lancet*, **1**, 224.
 Duncan, J. T. (1945). *British Medical Journal*, **2**, 715.
 — (1947). *Trans. roy. Soc. trop. Med. Hyg.*, **40**, 364.
 Ellis, F. F., jun., Scott, R. J., and Miller, J. M. (1952). *Antibiot. and Chemother.*, **2**, 347.
 Hodgson, C. H., Weed, L. A., and Clagett, O. T. (1950). *J. thorac. Surg.*, **20**, 97.
 Hutchison, H. E. (1952). *J. Path. Bact.*, **64**, 309.
 Limerick, C. B. (1951). *British Medical Journal*, **1**, 885.

THE MECHANISM OF SYNCOPE AFTER COUGHING

BY

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Syncope from coughing has been considered a rare condition; thus Whitty (1943) and Baker (1949) could collect only about 100 cases from the literature. Charcot (1876) thought it was a form of epilepsy, and by coining the term "laryngeal vertigo" made it the province of neurology and throat surgery. McCann *et al.* (1949) obtained some continuous records during coughing in two subjects with the syndrome. They believed that syncope was not primarily epileptic but circulatory in origin, and that pulmonary arterial vasoconstriction or pathologically sensitive "vascular reflexes" might be responsible. Correspondence in the *British Medical Journal* resulted in no factual data, but suggested that the condition might be commoner than supposed.

Material and Methods

The patients were 27 middle-aged or elderly males who gave a history of syncopal attacks on coughing. In many it was found possible to provoke an attack by asking the patient to give a few strong coughs. Inhaling cigarette smoke or irritation of the nose was used in a few. Pressures were recorded continuously by capacitance manometers (Hansen, 1949): intrathoracic by means of a water-filled oesophageal tube (Dornhorst and Leathart, 1952); intracardiac by catheter; and intra-arterial and venous by needles or fine catheters. Fore-arm flow was measured with a plethysmograph and recorded on the same photographic paper (Davies, 1953).

Results

The data obtained in the 27 subjects with syncope were compared with similar measurements in about 40 other subjects of all ages and both sexes. There was no qualitative difference in the effects of coughing in the two groups. A single "ahem" produced an intrathoracic pressure rise of 20 to 30 mm. Hg, ordinary coughing in both groups 50 to 100 mm. Hg, and coughing leading to syncope 150 to 300 mm. Hg. The circulatory effects were proportional to the violence and duration of the coughing attacks. All subjects performed the Valsalva manoeuvre. There was no difference in circulatory effects after the Valsalva manoeuvre between those with cough syncope and those without cough syncope.

Continuous records of syncopal attacks were obtained on fifteen occasions, and many minor attacks causing dizziness or "blackout" were also recorded. The subjects coughed in two ways, continuous or intermittent, with different circulatory effects. Both, when violent, resulted in syncope.

Continuous Coughing

The subjects coughed continuously in prolonged paroxysms lasting many seconds without drawing breath. Often the intrathoracic pressure reached 300 mm. Hg and was maintained at this level until a breath was taken or the paroxysm ended. The circulatory effects were essentially similar to those of the Valsalva manoeuvre, but more pronounced owing to the greater rise of intrathoracic pressure. When asked to perform their maximum Valsalva manoeuvre it was found that few could reach and maintain an intrathoracic pressure of 100 mm. Hg. This conspicuous