spheroidal and polyhedral malignant cells displaying pronounced pleomorphism and numerous mitotic figures. Initially a diagnosis of Hodgkin's disease was considered, but on review it was decided that the appearances indicated an anaplastic secondary carcinoma compatible with a metastasis from a primary breast neoplasm.

Because of the absence of a palpable mass in the breast and in view of the patient's age it was decided that immediate mastectomy was not indicated. The right axilla and supraclavicular region were treated by radiotherapy (1,400 rads) but the breast itself was not irradiated. The patient was kept under regular observation.

She remained well until 1966, when a small mobile swelling was noted in the left breast. Mammography showed no abnormality in either breast. The lump was excised and on histological examination it was seen to be an area of fibroadenosis with no evidence of malignancy. She continued to be examined regularly in the breast unit.

No masses were palpable in either breast until December 1970, when a discrete hard nodule 1·5 cm in diameter was noted in the upper outer quadrant of the right breast. This was tethered slightly to skin but not to muscle. Axillary lymph nodes were not enlarged and there were no other abnormalities on examination. Chest *x*-ray film and skeletal survey showed no metastases. A carcinoma, with microcalcification, however, was found in the right breast on mammography. The mass was excised. Frozen-section histological examination showed a carcinoma 2 cm in diameter. A radical mastectomy was then done. Histological examination showed a poorly differentiated intraduct and infiltrating carcinoma. Several axillary lymph nodes contained metastatic tumour deposits.

Comment

Occult carcinoma of the breast is rare. Owen *et al.* (1954), in a study of the clinical and pathological material at the Mayo Clinic from 1907 to 1950, collected 5,451 cases of carcinoma of the breast in which there was axillary lymph node involvement. In 27 of these cases no tumour was palpable in the breast, giving an incidence of 0·5%.

In 1909 Cameron advocated early mastectomy for occult carcinoma of the breast. Since then most cases with axillary lymph node metastases have been treated by radical mastectomy after all other possible primary sites have been excluded by thorough investigation.

In cases not treated by immediate mastectomy the occult tumour has in most instances soon become palpable. Occasionally, however, a period of several months or even years has elapsed between the development of an axillary lymph node metastasis and the subsequent detection of the breast tumour. Klopp (1950) reported a latent period of four years, and Roux-Berger (1951) and Haagensen (1956) described cases where five years passed before the breast neoplasm became clinically evident. The latent period of 17 years in the present case appears to be unique in its length.

Bond (1968) postulated that metastasis formation in carcinoma of the breast may occur very early in the natural history of the condition. The present case shows that this can take place long before the tumour is clinically detectable. It also emphasizes that carcinoma of the breast may occasionally be very slow growing. Collins *et al.* (1956) suggested that at least half the duration of development of any cancer may occur before it enters the period of clinical observation. With breast tumours as slow growing as the tumour in the present case this interval can evidently be considerable.

I wish to thank Mr. W. P. Greening, director of the breast unit, for permission to report this case. Thanks are also due to Dr. N. F. C. Gowing, consultant pathologist, Royal Marsden Hospital, for the histological review.

References

Bond, W. H. (1968). In *Treatment of Carcinoma of the Breast*, ed. A. S. Jarrett. Amsterdam, Excerpta Medica.
Cameron, H. C. (1909). *British Medical Journal*, **1**, 577.
Collins, V. P., Loeffler, R. K., and Tivey, H. (1956). *American Journal of Roentgenology* **76**, 988.
Haagensen, C. D. (1956). *Diseases of the Breast*, p. 439. Philadelphia, Saunders.
Klopp, C. T. (1950). *Annals of Surgery*, **131**, 437.
Owen, H. W., Dockerty, M. B., and Gray, H. K., (1954). *Surgery Gynecology and Obstetrics with International Abstracts of Surgery*, **98**, 302.
Roux-Berger, J. L. (1951). *Mémoires de l'Académie de Chirurgie*, **77**, 436.

Pulmonary Aspergillomata in a Child Treated with Clotrimazole

E. G. V. EVANS, D. A. WATSON,
N. R. MATTHEWS

British Medical Journal, 1971, **4**, 599-600

Pulmonary aspergillosis, most frequently caused by *Aspergillus fumigatus*, has been classified into five clinical types (Pepys, 1966). One of the commonest is the aspergilloma (Hinson, 1958), where the fungus forms a discrete, often solitary mycetoma (fungal ball) in the lung tissue, usually in cavitating or necrotic areas in the upper lobes.

Generally speaking the treatment of aspergillomata has been unsatisfactory (*British Medical Journal*, 1971). An orally administered synthetic antifungal agent, BAYb 5097 (bis-phenyl-(2-chlorophenyl)-1-imidazolyl-methane), later named clotrimazole, has been described (Plempel *et al.*, 1969) and its possible value in treating fungal infections in man discussed (*British Medical Journal*, 1969). Clotrimazole has been approved by the Committee on Safety of Drugs for use in clinical trials under controlled conditions. It inhibits in vitro a large variety of yeasts and mycelial fungi at concentrations below 10 μg/ml and usually at concentrations of 1-2 μg/ml (Plempel *et al.*, 1969; Holt, 1970; Waitz *et al.*, 1970). The LD_{50} for animals is about 1,000 mg/kg body weight, and doses of 150 and 60 mg/kg/day given to animals and man respectively are well tolerated. A single oral dose of 40 mg/kg in man produces a blood level of 2-4 μg/ml after four hours. Oberste-Lehn *et al.* (1969) treated a patient with sycosis barbae from which *Candida albicans* had been isolated, a patient with pulmonary aspergilloma, and a patient with a pulmonary infection due to *C. krusei* with clotrimazole (60 mg/kg body weight) without serious toxic effects and with encouraging therapeutic results.

We report a case of multiple aspergillomata treated with clotrimazole and, later, surgical excision of the cavities.

University of Leeds and General Infirmary, Leeds LS1 3EX
E. G. V. EVANS, B.SC., Lecturer in Medical Mycology
D. A. WATSON, M.B., F.R.C.S., Honorary Senior Lecturer and Consultant Cardiothoracic Surgeon

General Infirmary, Leeds LS1 3EX
N. R. MATTHEWS, M.B., CH.B., Registrar in Thoracic Surgery

Case History

The patient, an 8-year-old boy, had had skin infections due to *Staphylococcus aureus* since the age of 2 weeks, and from the age of 4 months numerous chest infections and staphylococcal tension cysts in both lungs. When he was 6 years 5 months a further large tension cyst formed in the right upper lobe. After six months it was clear that the right upper lobe was destroyed and that lobectomy was necessary. There was no evidence of an immunological deficiency. *X*-ray examination showed what appeared to be a mycetoma in a cavity in the left lung (Fig. 1). The eosinophil count was greatly raised. There were numerous aggregations of fungal mycelium in the sputum and *A. fumigatus* was consistently isolated

in appreciable quantities on culture. Precipitin tests for aspergillosis* were strongly positive.

After lobectomy an irregular aspergilloma was found in the large cyst in the right upper lobe. It yielded *A. fumigatus* and histologically was a typical mycetoma (Fig. 2). A bronchopleural fistula occurred after lobectomy and *A. fumigatus* was recovered in large quantities from the pleural aspirate as well as from the sputum. Thoracotomy for closure of the fistula showed a previously undetected leak from a cyst in the apex of the right lower lobe. Nystatin inhalations (120,000 units/day) had been started before thoracotomy, and at operation the pleural space was irrigated with nystatin suspension (500,000 units) and a catheter inserted at the apex through which nystatin suspension (200,000 units/day) was given for six days. Nevertheless, viable mycelial aggregations persisted in the sputum and *A. fumigatus* was recovered from the pleural aspirate five days after closure of the fistula. Systemic antimycotic therapy was considered imperative, and since early reports had indicated that clotrimazole was relatively non-toxic it was chosen in preference to amphotericin B. Clotrimazole (70 mg/kg/day) was started and the nystatin discontinued. At this time the aspergillus precipitin reaction was still strongly positive.

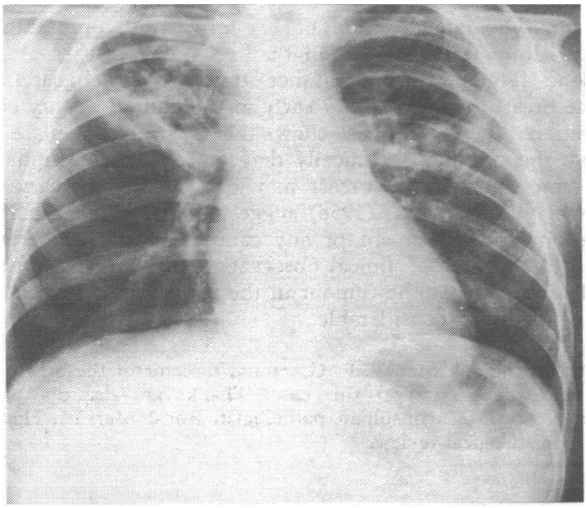

FIG. 1—X-ray picture showing enlargement of cavities in left lung; opacities within cysts were suggestive of a mycetoma.

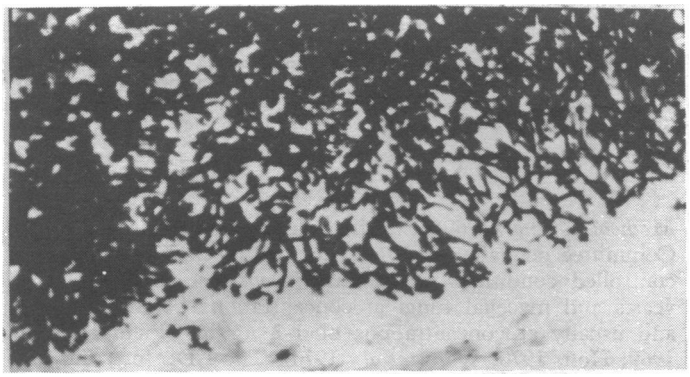

FIG. 2—Histological section of mycetoma showing typical branching fungal mycelium. (Grocott's methenamine-silver stain. ×160.)

*Bencard aspergillosis sero-diagnostic set, Bencard Ltd., Brentford, England.

One week after starting clotrimazole the sputum became culturally negative for *A. fumigatus*. Two days later macroscopic fragments of fungus were expectorated, which on microscopical examination showed compact masses of mycelium typical of mycetomata, indicating that aspergillomata remained in the lungs. The fungus was non-viable. After 45 days on clotrimazole the patient developed bronchopneumonia, which responded to antibacterial therapy. At this time an electrocardiogram showed electrical alternans and inverted T waves in all chest leads, and the clotrimazole was stopped because of possible toxicity. The E.C.G. changes, however, persisted for five weeks after stopping the clotrimazole.

Before, during, and after clotrimazole therapy an insignificant quantity of *C. albicans* persisted in the sputum. After discontinuing clotrimazole the amount of *C. albicans* noticeably increased and yeast mycelium was seen. Nystatin inhalations (120,000 units/day) reduced the amount of yeast but oral candidiasis developed. Fungal elements could still be seen in the sputum 17 weeks after discontinuing the clotrimazole, but cultures remained negative and the aspergillosis precipitin test was almost negative. Nystatin inhalations together with cephalexin (750 mg/day) were continued for nine months after lobectomy and the patient's condition remained stable. There was still a considerable amount of thick, purulent secretion but no evidence of aspergillus on microscopy or culture, and the precipitin test was negative. Bronchoscopy and bronchography confirmed that there were bronchiectatic segments in the left lower lobe as well as a large cavity; the rest of the lung appeared healthy. On left lower lobectomy one year after the first operation the abscesses were found mainly in the apical segment of the left lower lobe, and one particularly large cavity extended into the upper lobe. This cavity contained a mycetoma, and mycetomata were found in the smaller cavities. Microscopical examination showed that each consisted of typical interwoven masses of fungal mycelium but cultures yielded no growth.

Comment

Clotrimazole was well tolerated. There was no increase in the blood urea or serum creatinine, no electrolyte disturbance, and no abnormality of serum bilirubin, alkaline phosphatase, serum proteins, or serum transaminases. There was no depression of bone marrow, the total white cell count remained high, and the eosinophilia continued throughout. The continued presence of non-viable mycelial elements in the abscess cavities for a long period after the relatively short course of clotrimazole was stopped suggests that it has a fungicidal action. The nystatin aerosol therapy given after the clotrimazole was discontinued was not thought to have had an appreciable antifungal effect.

There has long been a need for an efficacious, non-toxic antifungal agent for the treatment of systemic fungal infections. The value of a new drug cannot be assessed on the evidence of one case, but the results in this case are encouraging.

We are grateful to Mr. R. A. Forster, chief technician of the mycology unit, for help with the diagnostic procedures.

References

British Medical Journal, 1969, **4**, 444.
British Medical Journal, 1971, **2**, 124.
Hinson, K. F. W. (1958). In *Fungous Diseases and their Treatment*, ed. R. W. Riddell and G. T. Stewart, p. 123. London, Butterworths.
Holt, R. J. (1970). Abstracts of 10th International Congress for Microbiology, Mexico City, p. 149.
Oberste-Lehn, H., Baggesen, I., and Plempel, M. (1969). *Deutsche medizinische Wochenschrift*, **94**, 1365.
Pepys, J. (1966). *Postgraduate Medical Journal*, **42**, 698.
Plempel, M., Bartmann, K., Buchel, K. H., and Regal, E. (1969). *Deutsche medizinische Wochenschrift* **94**, 1356.
Waitz, J. A., Moss, E. L., jun., Falco, F. G., and Weinstein, M. J. (1970). Abstracts of 10th International Congress for Microbiology, Mexico City, p. 149.