2 Jacobson H. WHO: medicine, regionalism and managed politics. In: Cox RW, Jacobson HK, eds. *The anatomy of influence: decision making in international organisations.* Princeton: Yale University Press, 1973.
3 World Health Organisation. *Global strategy for Health for All by the Year 2000. 16th plenary session of the World Health Assembly, 1981.* Geneva: WHO, 1981.
4 World Health Organisation/Unicef. *Alma-Ata declaration on primary health care.* Geneva: WHO, 1978.
5 World Health Organisation. Resolution 23. In: *34th session of the World Health Assembly. Handbook of resolutions and decisions of the World Health Assembly and the Executive Board 1973-84.* Geneva: WHO, 1985.
6 Walt G, Harnmeijer JW. Formulating an essential drugs policy: WHO's role. In: Kanji N, Hardon A, Harnmeijer JW, Mamdani M, Walt G. *Drugs policy in developing countries.* London: Zed Books, 1992.
7 New director general for the World Health Organisation. *Lancet* 1988;i:291.
8 Kanji N. Charging for drugs in Africa: Unicef's Bamako initiative. *Health Policy and Planning* 1989;4:110-20.
9 Unicef/HAI/Oxfam. *Report on the international study conference on community financing in primary health care, Freetown, 23-30 September 1989.* Amsterdam: HAI/Unicef, 1990.
10 World Bank. *World development report 1993.* Oxford: Oxford University Press, 1993:4.

Grand Rounds—Hammersmith Hospital

Nocardia pericarditis

A rare opportunistic infection

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Case history

A 71 year old woman was treated for an uncomplicated haemorrhage from an intracerebral aneurysm in 1987. She recovered completely but was noted to be hypertensive. Her blood pressure was subsequently controlled with hydralazine and atenolol. She remained well until March 1993, when she presented with a four month history of weight loss, malaise, and shortness of breath. Investigations showed severe renal impairment, and renal biopsy showed a focal necrotising glomerulonephritis with crescents. She also had high titres of perinuclear autoneutrophil cytoplasmic antibodies. Microscopic polyarteritis, possibly precipitated by hydralazine, was diagnosed. The hydralazine was therefore discontinued. Her polyarteritis was treated with high dose prednisolone, with cyclophosphamide for the first three months and azathioprine subsequently. She was discharged well after seven weeks.

Three months later, she was admitted to her local hospital with presumed bacterial pneumonia. No pathogen was isolated. She was treated with antibiotics and transferred to our hospital. Further investigations included a bronchoscopy, which showed no infectious agent, computed tomography of the thorax, and tests of pulmonary function, which suggested early fibrosing alveolitis. She improved clinically with appropriate antibiotics.

Two months later she presented with a seven week history of bilateral pleuritic chest pain, increasing shortness of breath, and generalised weakness. Her drugs included prednisolone (17·5 mg per day) and azathioprine (75 mg per day). She had a temperature of 38·3°C and was centrally cyanosed and dyspnoeic. Her heart rate was 92 beats/min and blood pressure 120/70 mm Hg. Auscultation of the chest showed bilateral coarse inspiratory crepitations posteriorly. Examination found no other abnormalities. She had normochromic anaemia (haemoglobin 84 g/l), a neutrophil leucocytosis (white cell count $14{\cdot}0\times10^9$/l, 96% polymorphs) and raised platelet counts (577×10^9/l). Her urea concentration was 16·5 mmol/l and creatinine was stable at 164 μmol/l. C reactive protein concentration was raised at 242 mg/l (normal 0-10 mg/l), and perinuclear antineutrophil cytoplasmic antibodies were still detectable. She was hypoxaemic on air with an arterial oxygen pressure of 6·5 kPa, improving to 9·6 kPa on 60% oxygen. Chest radiography showed fine interstitial shadowing throughout both lung fields. Electrocardiography, Doppler ultrasonography of the legs, and a ventilation and perfusion scan gave normal results, and cultures of blood, sputum, and urine were sterile.

She was started on intravenous cefotaxime and oral erythromycin. Over the next few days her clinical condition deteriorated and she required continuous positive airway pressure ventilation to maintain oxygenation. High dose co-trimoxazole was started to treat possible *Pneumocystis carinii* pneumonia, and her immunosuppressive treatment was increased because of concern about continuing alveolitis. Computed tomography of the chest showed, as an incidental finding, loculated thickening of the pericardium (fig 1).

At this stage *Nocardia asteroides* was grown from a blood culture. She was already taking appropriate antibiotic treatment. The next day the patient collapsed and was found to be tachycardic at 130 beats/min and hypotensive (90/40 mg Hg) with 15 mm Hg

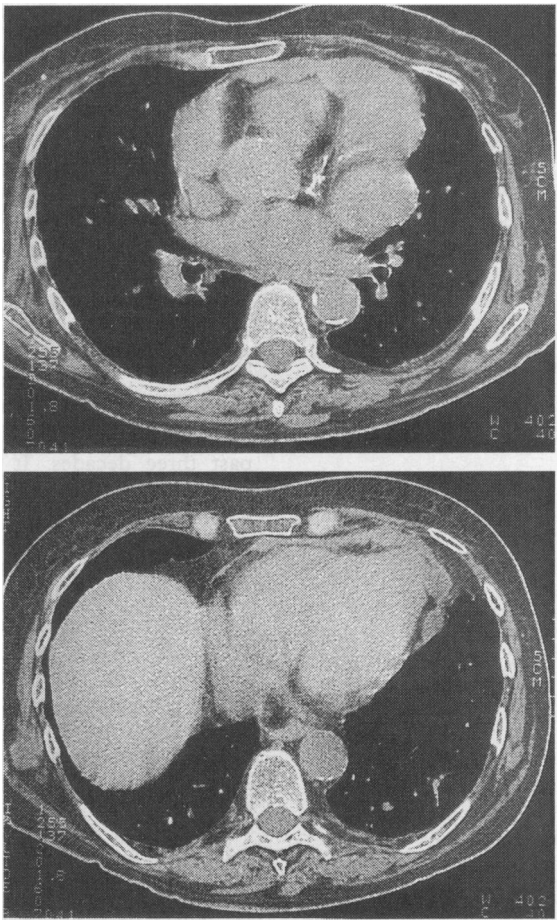

FIG 1—*Computed tomograms taken with mediastinal window setting at level of left atrium (top) and ventricles (bottom). The pericardium is greatly thickened and lobulated predominantly along the anterior and left lateral cardiac borders*

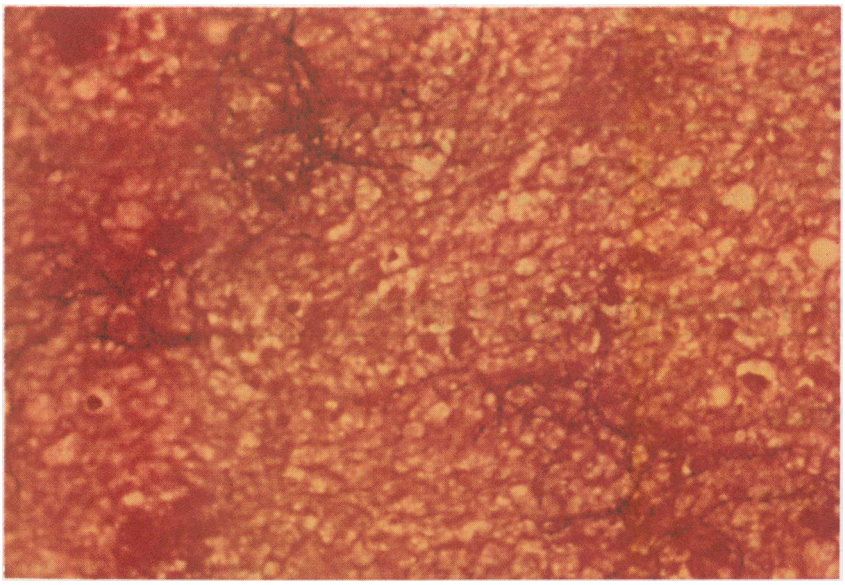

FIG 2—*Gram stain of the pericardial biopsy specimen showing branching, filamentous, "beaded" Gram positive rod typical of Nocardia asteroides. The organism also stained acid fast*

paradox, central venous pressure was 1·86 kPa. Echocardiography showed right ventricular end diastolic collapse confirming cardiac tamponade. Pericardial aspiration was done urgently, and 50 ml of pus withdrawn. Sternotomy showed a tense pericardium from which 500 ml of pus was drained and she had a pericardiectomy. Gram stain and culture of the pericardium and aspirate confirmed infection with *Nocardia asteroides* (fig 2).

Treatment with co-trimoxazole and ciprofloxacin was continued. She initially made a good recovery with no evidence of recurrence of nocardiosis or of pericardial constriction. However, she later developed nosocomial bacterial septicaemia with subsequent multiorgan failure. Despite best medical treatment she died three months later.

Comment

Nocardia spp are free living, aerobic, Gram positive actinomycetes. They are natural soil saphrophytes that are often found in decaying organic matter. Nocardia was identified by Nocard in 1888 from cattle with "farcin du boeuf," an emaciating disease.[1] Eppinger described the first human illness in 1891.[2] The predominant human pathogen is *N asteroides*. Other less common human pathogens are *N brasiliensis* and *N caviae*.

CLINICAL MANIFESTATIONS OF NOCARDIOSIS

The incidence of nocardiosis has increased over the past three decades. It is now most often seen in immunocompromised patients, particularly in those who have deficiencies in cell mediated immunity or chronic chest disease. Infection has been reported in several clinical contexts (box).

Nocardia infection is difficult to diagnose. It produces a wide spectrum of disease with few specific symptoms. There are no pathognomonic clinical, laboratory, or radiological features. Infection may follow an acute, subacute, or chronic course with a tendency to remissions and exacerbations. Men are affected three times more commonly than women. Infection has occurred in patients as young as four weeks.

In humans infection with *Nocardia spp* usually occurs through the respiratory tract, although percutaneous inoculation is recognised. The lungs are affected, resulting in focal acute pneumonitis, multiple nodules, miliary abscesses, or cavitation. Non-specific symptoms include anorexia, weight loss, cough, pleuritic pain, dyspnoea, and occasionally haemoptysis. Untreated pulmonary nocardiosis usually runs a chronic course similar to tuberculosis. Spread may be local, with empyema, or metastatic. Haematogenous dissemination occurs in about half of patients after pulmonary infection. Dissemination is commonest in the central nervous system, with the formation of intracerebral abscesses; or skin and subcutaneous tissues, producing suppurative necrosis and abscesses. Rare manifestations include peritonitis, endocarditis, osteomyelitis, and septic arthritis.

Nocardia pericarditis is extremely rare. Only nine cases of proved infection have been reported worldwide,[4-11] and this is the first case reported in the United Kingdom. The patients reported on were aged 34-57 years (six men, three women). Four were immunocompromised (one patient had leprosy and trachoma,[5] one had emphysema and alcoholism,[8] one was receiving immunosuppressive treatment for mixed connective tissue disease,[9] and one had syphilis and alcoholism.[10]) Five presented with cardiac tamponade. Three patients died of constrictive pericarditis and metastatic abscess. The six survivors all had pericardiectomy as well as treatment with antibiotics. This emphasises the importance of a combined surgical and medical treatment to treating Nocardia pericarditis.

MEDICAL TREATMENT

No large clinical trials have been done of antimicrobial treatment because of the rarity and heterogeneity of the disease. Antibiotic regimens are therefore based on in vitro testing and animal models. Sulphonamides are the drugs of choice, although resistance has occasionally been reported.[12] Standard treatment has been with sulphadiazine 4-6 g/day in combination with chloramphenicol or streptomycin. Co-trimoxazole is a suitable alternative therapy (10 mg/kg trimethoprim and 50 mg/kg sulphamethoxazole daily), but treatment failures have been reported.[12] When these drugs fail or are not applicable other suitable drugs with in vitro activity include minocycline, imipenem, amikacin, ciprofloxacin, or the combination of amoxycillin and erythromycin.

The optimal duration of treatment is debated. A minimum of six weeks is recommended because of the tendency to relapse and the risk of metastatic abscess formation. Wallace *et al* treated 34 patients with co-trimoxazole and found that relapse was rare when patients were treated for three months or longer.[14] The mortality is increased in three groups: patients receiving corticosteroids or antineoplastic drugs, those who have symptoms of visceral nocardiosis for less than three months, and those with disseminated infection affecting two or more non-contiguous organs. Mortality is 10-15% in immunocompetent patients with pulmonary disease but higher in patients with serious underlying disease.

Discussion

CP: This woman's case was extremely interesting even before she developed nocardia infection. It is

Clinical contexts in which infection with nocardia has been reported

- Immunosuppressive therapy including corticosteroids and antineoplastic chemotherapy
- Organ transplantation
- Splenectomy
- AIDS
- Tuberculosis
- Chronic obstructive airways disease
- Pulmonary alveolar proteinosis
- Diabetes mellitus
- Alcoholism

unusual to see hydralazine induced polyarteritis, and it is unusual for polyarteritis to cause fibrosing alveolitis. Immunosuppressive drugs, particularly steroids, are known to predispose to infections with nocardia. The fibrosing alveolitis may be important as other chronic lung diseases are associated with nocardia infection. It is clear, however, that nocardia can infect people without obvious risk factors.

Nocardiosis is a rare infection, with an incidence in a United States series of only 500-1000 cases/year, although this may be an underestimate. In treating over 200 people with systemic vasculitis with similar immunosuppressive therapy over the past 10 years, we have seen only two cases.

It is unclear whether this organism is transmissible among immunocompromised people. Certainly, it is generally acquired from the environment, but there was a small outbreak in the transplant unit at the Institute of Urology in the late 1970s.

SL: As far as I know the organism is not transmitted person to person. The best documented outbreak is from the liver unit at King's College Hospital, and there the number of cases were thought to have come from a common source from nearby building work. The hospital typed the strains and found them all different, suggesting that a common source was more likely than person to person spread.

JS: Nocardia is a bacterium but it looks like a fungus. What is it related to phylogenetically?

SL: It is related to *Mycobacterium* spp.

JS: Is polyarteritis different from lupus in these hydralazine induced cases?

KD: Systemic lupus erythematosus-like illnesses can be provoked by many drugs including hydralazine and also procainamide, certain anticonvulsants, isoniazid, chlorpromazine, and a range of antibiotics and anti-inflammatories. The disease induced by hydralazine, procainamide, and isoniazid (which have a primary amine or hydrazine moiety that is acetylated by the hepatic *N*-acetyltransferase system) occurs more commonly in people who are genetically slow acetylators.

Specific patterns of autoantibodies are associated, typically antibodies to histones H2A-H2B in patients taking hydralazine, and antibodies to double stranded DNA are rare. An increased prevalence of HLA-DR4 is also found in these patients, which makes them immunogenetically dissimilar to patients with idiopathic lupus. It should also be noted that while patients taking hydralazine commonly develop antinuclear antibodies, the overt disease is much rarer. One theory which Dr Sim's group in Oxford has adduced to explain the way in which hydralazine causes disease, is that by inducing nucleophilic activation of C4, hydralazine causes acquired C4 deficiency. There is also evidence that the drug may interact directly with DNA, modifying its antigenicity, or may inhibit DNA methylation, altering T cell reactivity.

AJR: Though there are some similarities between hydralazine induced polyarteritis and hydralazine induced lupus, some important differences exist. Patients who develop hydralazine induced polyarteritis are not slow acetylators. They have a different immunogenetic background, and they have entirely different morphological findings with a different set of autoantibodies so that, although the two seem to be provoked by the same drug, they are not necessarily related.

HB: And renal disease in hydralazine induced lupus is extremely rare.

CO: Was the hydralazine relevant? I thought that when the drug was stopped the disease got better.

CP: In general, if you are dealing with a patient without such severe clinical features you can just stop the drug and see what happens; but in this case with severe crescentic nephritis we had to add immunosuppressive drugs. But from a purist's point of view, we should have just stopped the drug to see what happened.

I thank Dr Nicola Strickland for radiological help, Dr Sandra Lacey, Mr Philip Hornick, and Dr Gill Gaskin and Dr William Lynn. I also thank Dr Lindsey Rolfe for her help with preparation of the article.

1 Nocard ME. Note sur la maladie des boeufs de la Guadeloupe connue sous le nom de farcin. *Annales de l'Institute Pasteur* 1888;2:293-302.
2 Eppinger H. Über eine neue, pathogene *Cladothrix* und eine durch sie hervorgerufene Pseudotuberculosis (cladothrichica). *Beitrage zur Pathologie Anatomische Allgemeine Pathologie* 1891;9:287-328.
3 Curry WA. Human nocardiosis—a clinical review with selected case reports. *Arch Intern Med* 1980;140:810-26.
4 Briceno MT, Pollak L. Nocardiosis y actinomicosis pulmonares. *Mycopathologia* 1961;15:358-66.
5 Smith WG, McAleer R, Laurie W. Nocardiosis in Australia. *Med J Aust* 1963;2:534-6.
6 Susens GP, Al-Shamma A, Rowe JC, Herbert CC, Bassis ML, Coggs GC. Purulent constrictive pericarditis—caused by Nocardia asteroides. *Ann Intern Med* 1967;67:1021-32.
7 Chavez CM, Causey WA, Conn JH. Constrictive pericarditis due to infection with Nocardia asteroides. *Chest* 1972;61:79-81.
8 Poland GA, Jorgensen CR, Sarosi GA. Nocardia asteroides pericarditis—report of a case and review of the literature. *Mayo Clin Proc* 1990;65:819-24.
9 Leung WH, Wong KL, Lau CP, Wong CK. Purulent pericarditis and cardiac tamponade caused by Nocardia asteroides in MCTD. *J Rheumatol* 1990;17:1237-9.
10 Clenney TL, Hammond MD, McKeown PP. Holt DA, Wallach PM. Cardiac tamponade due to Nocardia asteroides. *Chest* 1993;103:641-2.
11 Kessler R, Follis F, Daube D, Wernly J. Constrictive pericarditis from Nocardia asteroides infection. *Ann Thoracic Surg* 1991;52:861-2.
12 Stamm AM, McFall DW, Dismukes WE. Failure of sulphonamides and trimethoprim in the treatment of nocardiosis. *Arch Intern Med* 1983;143:383-5.
13 Dewsnup DH, Wright DN. In vitro susceptibilty of Nocardia asteroides to 25 antimicrobial agents. *Antimicrob Agents Chemother* 1984;25:165-7.
14 Wallace RJ, Septimus EJ, Williams TW, Conklin RH, Satterwhite TK, Bushby MB, *et al.* Use of trimethoprim-sulphamethoxazole for treatment of infections due to Nocardia. *Rev Infect Dis* 1982;4:315-25.

Correction

Cardiology—I: Treatment of myocardial infarction, unstable angina, and angina pectoris

An editorial, an authors', and a printer's error occurred in this Recent Advances article by John McMurray and Andrew Rankin (19 November, pp 1343-50). The first category under ACE inhibition in table VI should have read, "Infarction complicated by left ventricular failure [not fibrillation]." The first sentence on p 1347 should have read, "Mortality [not survival] five years after a myocardial infarction is about 17% in those who stop smoking and 30% in those who do not." The last bullet in the summary box on p 1349 should have read, "Use of platelet monoclonal antibodies and intracoronary stents as adjuncts to angioplasty [not angiography]."

ABC of Breast Diseases: Role of systemic treatment for primary operable breast cancer

A printer's error occurred in this paper by M A Richards and colleagues (19 November, pp 1363-6). In the box of definitions of risk groups and associated risk of relapse (p 1365) the sizes of tumours for node negative patients of intermediate risk and high risk were omitted. The size was >1 cm in diameter for both groups of patients.