stances, when the alcoholic is also depressed and has suicidal tendencies, it would seem wise to avoid the drug altogether.

I should like to thank HM Coroner for Bedfordshire for permission to publish details of these cases; the scientific officers at the Home Office Forensic Science Laboratory, Aldermaston, Reading, who performed the analyses; and Dr J C Valentine, consultant pathologist, who performed the post-mortem examination in cases 1 and 5.

¹ *Data Sheet Compendium*. London, Association of the British Pharmaceutical Industry, 1977.

² Glatt, M, *The Alcoholic and the Help He Needs*, part II. London, Priory Press, 1972.

³ Jakobsson, S, and Möller, M, in *Abstracts of the Sixth International Meeting of Forensic Sciences*, Edinburgh, 1972, p 150. London, Association of the British Pharmaceutical Industry, 1972.

⁴ Personal communication from chairman of the Local Pharmaceutical Committee, Bedfordshire.

(Accepted 30 January 1978)

Department of Histopathology, Bedford General Hospital, Bedford MK42 9DJ

JOAN M HORDER, MRCPATH, DMJ(PATH), senior registrar

Meningitis due to chloramphenicol-resistant *Haemophilus influenzae* type b

Two strains of *Haemophilus influenzae* resistant to chloramphenicol have been reported from the USA,¹ and a resistant non-typable strain has been isolated in Holland.² We report here a case of meningitis due to chloramphenicol-resistant *Haemophilus influenzae* type b that occurred in Oxfordshire in July 1977.

Case report

A 19-month-old girl presented after two days' illness with drowsiness, irritability, stiff neck, and vomiting. Cerebrospinal fluid (CSF) showed 8.5×10^9 /l white cells, mainly polymorphs, and numerous pleomorphic Gram-negative rods on microscopy. The peripheral blood showed a neutrophil leucocytosis of 17.8×10^9 /l. Both CSF and blood grew *Haemophilus influenzae* type b.

Immediate treatment was begun with chloramphenicol 150 mg intravenously every 4 hours (90 mg/kg/24 h). After 72 hours the level of consciousness, tachycardia, and fever had not improved and a further CSF specimen showed 2.0×10^9 white cells/l, with organisms still present on microscopy. This CSF specimen and a further blood culture also grew *Haemophilus influenzae*.

The original sensitivity plate was then reappraised and the zone of inhibition around the 25- μ g chloramphenicol disc was shown to be slightly smaller than that given by a control strain. A test for penicillinase production by the organism gave a negative result. Chloramphenicol was therefore stopped and treatment changed to ampicillin 10 mg intrathecally once, and 400 mg intravenously every 4 hours (250 mg/kg/24 h).

Steady clinical improvement followed. The CSF was sterile after three days and pyrexia and tachycardia resolved after 10 days. Oral amoxycillin was substituted after seven days in doses up to 2 g/24 h and stopped after 14 days, since when the child has remained well.

The minimum inhibitory concentration of chloramphenicol for this organism was 8 mg/l (control strain 0.5 mg/l) and that of tetracycline 32 mg/l (control strain 1.0 mg/l), using the agar plate incorporation method.

A strain of *Haemophilus influenzae* type b resistant to chloramphenicol and tetracycline was isolated from the throat of the 4-year-old brother, but non-typable strains from the mother, father, and babysitter were sensitive to both antibiotics.

The patient had been previously well, apart from otitis media four months earlier, which had been treated with penicillin. The rest of her family had also been well and had used neither chloramphenicol nor tetracycline in the previous five years.

Comment

The only other strain of chloramphenicol-resistant *Haemophilus influenzae* type b so far reported caused meningitis in a 9-month-old

infant from Philadelphia; it was also tetracycline resistant. This resistance was probably plasmid-mediated, as in the non-typable strain isolated in Holland.² This has grave implications for future treatment. Ampicillin has been considered to be a safe and effective antibiotic for treating infections caused by *Haemophilus influenzae*, but increasing numbers of treatment failures have been reported; these are explained by inadequate doses, relatively poor penetration of meninges, or bacterial resistance due to the production of β -lactamase.³ Intravenous chloramphenicol penetrates readily into the CSF and has previously been considered to be active against all strains of *Haemophilus influenzae*. The possibility of resistance to either or both these antibiotics emphasises the importance of performing sensitivity tests whenever invasive strains are isolated and of reculturing CSF and blood when early clinical response is unsatisfactory. A less potent chloramphenicol disc—for example, 5 μ g—might facilitate recognition of resistant strains. As advocated by the American Academy of Pediatrics,⁴ combination of chloramphenicol and ampicillin as initial treatment for *Haemophilus influenzae* meningitis may be considered. Antibiotic antagonism is, however, a theoretical objection and combination therapy may actually increase the risk of long-term complications.⁵

We are grateful to Dr J D Baum for permission to report details of this case.

¹ Centre for Disease Control, *Morbidity and Mortality Weekly Report*, 1976, **25**, 386.

² van Klingeren, B, van Embden, J D A, and Dessens-Kroon, M, *Antimicrobial Agents and Chemotherapy*, 1977, **11**, 383.

³ Smith, A L, *New England Journal of Medicine*, 1976, **294**, 1329.

⁴ American Academy of Pediatrics, Committee on Infectious Disease, *Pediatrics*, 1976, **57**, 417.

⁵ Lindberg, J, *et al*, *Pediatrics*, 1977, **60**, 1.

(Accepted 10 November 1977)

Departments of Paediatrics and Pathology, Churchill Hospital, Oxford

ANN-LOUISE KINMONTH, MB, senior house physician

C N STORRS, MRCP, DCH, paediatric senior registrar

R G MITCHELL, DM FRCP, consultant microbiologist

Psittacosis masquerading as rheumatic fever

It is now generally accepted that the diagnosis of rheumatic fever is based on the modified Jones's criteria,¹ in which evidence of a preceding streptococcal infection is paramount. We record a case in which an initial clinical diagnosis of rheumatic fever was made but in which subsequent serological evidence indicated infection by *Chlamydia psittaci* rather than streptococci.

Case report

A 39-year-old salesman was admitted with a two-week history of general malaise, sweating, and shivering associated with a sore throat and an unproductive cough. Three days before admission he had developed acute pain and swelling and redness of the wrist, metacarpophalangeal, and proximal interphalangeal joints. This developed into a fitting arthritis, which affected the elbow, knee, ankle, shoulder, and temporomandibular joints. Two days before admission he had developed a red, patchy rash proximally on all limbs, which subsequently spread on to the trunk. Four days before admission his GP had prescribed oxytetracycline and soluble aspirin. He had no relevant medical history apart from longstanding, recurrent low back pain.

On admission the abnormal findings were that he was clammy, febrile (38.5°), and peripherally cyanosed, with signs of acute arthritis affecting carpal and metacarpophalangeal joints. He had a rash with the typical appearance of erythema marginatum affecting his trunk and proximal aspects of limbs. His pulse was 108/min and regular; the respiratory rate was 20/min; and there was a soft systolic ejection murmur over the aortic area. An electrocardiogram showed sinus tachycardia with right bundle-branch block. A chest x-ray film showed minor patchy shadowing at the right lung base. The results of routine biochemical tests were all normal, but he had a mild normochromic normocytic anaemia of 12.6 g/dl, with a WBC 13×10^9 /l (neutrophilia) and ESR 116 mm in first hour (Westergren). Treatment with penicillin V 500 mg six-hourly and soluble aspirin 600 mg four-hourly with bed

rest was instituted and the temperature resolved in 24 hours, while all signs and symptoms disappeared in five days. Subsequent investigations showed no evidence of streptococcal infection (a throat swab grew no pathogens and the antistreptolysin titre was < 125 units/ml both one day after admission and six weeks later). The antibody titre for psittacosis LGV was $> 1/1000$ on admission and six weeks later was still raised at $1/128$. Inquiry later showed that before his illness he had visited regularly a neighbouring house in which a healthy, psittacine bird was kept.

Discussion

In this case there are two major and three minor criteria of rheumatic fever present, but without evidence of a recent streptococcal infection. On the contrary, the presence of a cough and constitutional disturbance associated with patchy shadowing on the chest x-ray film and a significant and changing antibody titre all support a diagnosis of psittacosis. The rashes described in association with this disease include "rose spots,"² erythema nodosum,² and a macular scaly rash.³ We could find no reports of an exanthem resembling erythema marginatum. Arthritis, which may be migratory,⁴ is a rare complication of psittacosis in man, though in sheep and cattle polyarthritis it is well recognised.⁵

This case shows that psittacosis may present with minimal respiratory disturbance and with a clinical picture resembling rheumatic fever with erythema marginatum and polyarthritis.

¹ American Heart Association, *Circulation*, 1965, **32**, 664.

² Sarner, M. and Wilson, R. J., *British Medical Journal*, 1965, **2**, 1469.

³ Harrison, D. L., *Practitioner*, 1963, **190**, 245.

⁴ Favour, C. B., *American Journal of the Medical Sciences*, 1943, **205**, 162.

⁵ Cutlip, R. C., Smith, P. C., and Page, L. A., *Journal of the American Veterinary Medical Association*, 1972, **161**, 1213.

(Accepted 8 December 1977)

Nuffield Department of Clinical Medicine and Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford

R. W. SIMPSON, BA, MRCP, senior house officer

C. HUANG, BA, MB, house officer

D. G. GRAHAME-SMITH, PHD, FRCP, professor of clinical pharmacology and consultant physician

Identification of *Clostridium difficile* as a cause of pseudomembranous colitis

The demonstration of a toxin¹ in the stool of patients with pseudomembranous colitis and neutralisation of the toxin by *Clostridium sordellii* antitoxin² has provided a valuable tool in the search for the cause of this disease. These findings also implicate *Cl. sordellii*, or an organism producing an antigenically similar toxin, as the causal agent. We tested all clostridial species isolated from patients with pseudomembranous colitis for toxin production and neutralisation by *Cl. sordellii* antitoxin.

Patients, methods, and results

Eight patients with pseudomembranous colitis³ were studied together with 20 patients with postoperative diarrhoea without evidence of colitis, all of whom had undergone major gastrointestinal surgery within 10 days and had three or more bowel actions each day. Clostridia were isolated on lysed blood agar containing kanamycin sulphate (70 mg/l) or nalidixic acid (10 mg/l). Broth cultures of clostridia and faeces from patients were tested for toxin on monolayers of HeLa cells. Toxin was neutralised by incubating samples with antitoxin to *Cl. perfringens* types A, B, C, D, E; *Cl. oedematiens* type A (Wellcome Reagents Ltd); and *Cl. sordellii* (Wellcome Research Laboratories) for one hour at room temperature.

In all patients with pseudomembranous colitis high titres of toxin were detected in faeces (see table). The toxic activity caused a diffuse rounding of the HeLa cells, which became refractile and separated from the glass. In seven patients with postoperative diarrhoea a second type of cytopathic effect was observed: irregular patchy areas of separation appeared, leaving islands of deformed cells. This effect was present only at low levels after 48 hours' incubation, in contrast to the toxin associated with pseudomembranous colitis, which was evident after 18 hours. The toxic effect of

faeces from all patients with colitis was neutralised at 18 hours by *Cl. sordellii* antitoxin but not by the other antisera. After further incubation up to 48 hours the second patchy type of cytopathic effect developed in several cases (see table). None of the antisera neutralised the patchy type of cytopathic effect.

Toxic cytopathic effects of faecal fluid from patients with pseudomembranous colitis

Case No	Highest toxin titre	Neutralisation by <i>Cl. sordellii</i> antitoxin	2nd cytopathic effect at 48 h
1	$> 5 \times 10^3$	+	+
2	4×10^3	+	+
3	4×10^3	+	+
4	2×10^3	+	+
5	1×10^3	+	+
6	8×10^2	+	+
7	8×10^2	+	+
8	3×10^4	+	+

We isolated *Cl. perfringens*, *Cl. innocuum*, *Cl. paraputrificum*, *Cl. tertium*, *Cl. sporogenes*, and *Cl. sphenoides* from faeces of patients with pseudomembranous colitis. *Cl. difficile* was isolated from all patients with colitis and from six with postoperative diarrhoea. A cytopathic effect identical with that seen with faeces was produced by cultures of two strains of *Cl. difficile* isolated from patients with colitis but not by other clostridia. This toxin produced by *Cl. difficile* was neutralised by *Cl. sordellii* antitoxin. As with the faeces, incubation for 48 hours showed the second cytopathic effect, which was also produced by cultures of three other strains of *Cl. difficile*. Seven strains of *Cl. difficile* were sensitive to metronidazole, sulphonamide, and vancomycin and resistant to penicillins, cephalosporins, aminoglycosides, lincomycins, tetracycline, and erythromycin.

Comment

The demonstration that the cytopathic effect of *Cl. difficile* is indistinguishable from that produced by faeces and is neutralised by *Cl. sordellii* antitoxin suggests that *Cl. difficile* is the causative agent of pseudomembranous colitis. The production of toxin by *Cl. difficile* is not a new observation⁴: on subcutaneous injection into guinea-pigs it causes oedema, respiratory arrest, and death and is inactivated by heat.⁵ These properties resemble the toxic effects of faecal extract from patients with pseudomembranous colitis. The finding of a second, milder cytopathic effect produced by faeces from some patients with postoperative diarrhoea and by three strains of *Cl. difficile* indicate the possibility of a second pathogenic role for this organism in postoperative diarrhoea.

Little is known about the distribution of *Cl. difficile* in populations, but Hall and O'Toole⁴ found it in the faeces of 40% of infants. Careful search will probably disclose small numbers of *Cl. difficile* in the intestinal tract of healthy adults. Under appropriate conditions these may multiply and cause postoperative diarrhoea or pseudomembranous colitis according to their potential for toxin production.

We are grateful to Dr P. D. Walker of Wellcome Research Laboratories for supplying *Cl. sordellii* antitoxin, and to Dr H. E. Larson and Dr A. B. Price for helpful discussion.

Requests for reprints should be addressed to Dr D. W. Burdon.

¹ Larson, H. E., et al., *British Medical Journal*, 1977, **1**, 1246.

² Rifkin, G. D., Fekety, F. R., and Silva, J., *Lancet*, 1977, **2**, 1103.

³ Kappas, A., et al., *British Medical Journal*, 1978, **1**, 675.

⁴ Hall, I. C., and O'Toole, E., *American Journal of Diseases of Children*, 1935, **49**, 390.

⁵ Snyder, M. L., *Journal of Infectious Diseases*, 1937, **60**, 223.

(Accepted 16 February 1978)

Department of Microbiology, Birmingham Children's Hospital, Birmingham

R. H. GEORGE, MB, MRCPATH, consultant microbiologist

JANE M. SYMONDS, MB, BS, senior registrar in microbiology

Departments of Microbiology and Surgery, General Hospital, Birmingham B4 6NH

FRANCES DIMOCK, FIMLS, research technician

J. D. BROWN, FIMLS, senior chief technician

Y. ARABI, FRCS, senior registrar

N. SHINAGAWA, MD, senior registrar

M. R. B. KEIGHLEY, MS, FRCS, consultant surgeon and senior lecturer

J. ALEXANDER-WILLIAMS, MD, FRCS, consultant surgeon

D. W. BURDON, MB, MRCPATH, consultant microbiologist