that smoking habit might determine which of the two diseases develops.⁷ They also observed that cigarette smoking is associated with increased consumption of refined sugar and that such consumption has consistently been associated with Crohn's disease. Studies of diet have not, however, shown any association between consumption of refined sugar and ulcerative colitis. Furthermore, Thornton *et al* recently provided evidence that smoking and a high consumption of refined sugar show independent positive associations with the development of Crohn's disease.⁶

With regard to use of oral contraceptives our data on Crohn's disease, indicating a possible increased risk of the disease in those taking the pill, are consistent with the findings of others.^{8-10,11} In our study the use of oral contraceptives was, however, more strongly associated with ulcerative colitis than with Crohn's disease, though even this association fell just short of conventional levels of significance in the adjusted analysis (see table III). The only other studies of the relation between the use of oral contraceptives and ulcerative colitis have been performed by the Royal College of General Practitioners, which found a positive association,⁸ and by Rhodes *et al*, who did not.¹⁰

It might be argued that women developing such a disabling condition as chronic inflammatory bowel disease would want to avoid pregnancy at all costs and might, therefore, switch to oral contraception, thus producing a spurious positive association between the pill and disease. This argument does not, however, explain our observations. Firstly, as far as was possible, we identified the date of onset of disease in each woman and related use of contraceptives to that date. Secondly, the association between use of the pill and disease was stronger in those who had been using oral contraceptives for a long time than in those who had recently started this method of birth control.

If oral contraceptives do have an aetiological role in chronic inflammatory bowel disease (and this cannot yet be regarded as established) the mechanism of their action is obscure. The suggestion, however, that colonic Crohn's disease is particularly associated with use of the pill points towards a possible vascular basis for the lesion, as there have been several cases of acute

segmental colitis associated with the oral contraceptive pill that have been interpreted as having an ischaemic aetiology.^{18,19}

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Increase in bronchopulmonary infection due to *Branhamella catarrhalis*

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Abstract

In a six month prospective study during the winter *Branhamella catarrhalis* was isolated from the sputum of 63 patients with symptoms of bronchopulmonary infection: 49 isolates were in pure culture and 14 were with another pathogen, *Haemophilus influenzae* being the commonest (found with 10 of the 14 *B catarrhalis* isolates). Of 36 patients infected in the community, 26 required admission to hospital. The remaining 27 patients

were infected while in hospital. Forty four of the 63 isolates produced β lactamase; 26 of these had been acquired in the community. As a result 29 patients were treated inappropriately with ampicillin and did not respond to this treatment. β Lactamase produced by *B catarrhalis* may also protect other pathogens normally susceptible to β lactam antibiotics. Most patients had chronic lung diseases or lung cancer, but three otherwise healthy patients who did not smoke developed bronchitis. *B catarrhalis* contributed to the death of five patients.

A survey of the antibiotic prescribing habits of the referring general practitioners together with the sensitivity results of *B catarrhalis* suggest that changes in antibiotic prescribing habits in the community may be responsible for the increase in *B catarrhalis* infection.

Introduction

Branhamella catarrhalis, previously considered to be a harmless oropharyngeal commensal, is being recognised increasingly as an important pathogen. Its presence in the oropharynx lends itself to

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endogenous spread, most commonly to the middle ear causing otitis media¹ or by aspiration causing bronchopulmonary disease.^{2,3} Patients with such infections have previously responded to treatment with ampicillin, but the organism's capacity to produce β lactamase, first noted in 1977,⁴ has conferred penicillin resistance, thus complicating what was a simple choice of antibiotic. In less than a decade the proportion of strains producing β lactamase has risen to over a half.

In Edinburgh significant growth of *B catarrhalis* from purulent sputum is always reported; a noticeable increase in the rate of isolation from patients suffering from bronchopulmonary infection admitted to the medical wards has thus been noted.⁵ The reason for this increase is obscure. To study possible factors contributing to this increase in the rate of isolation and also the increase in the proportion of strains producing β lactamase a prospective six month study was conducted from November 1983 to April 1984.

Methods

All sputum samples from hospital wards, outpatient departments, and local general practices received by the bacteriology laboratory at the City Hospital, Edinburgh, during November 1983 to April 1984 were studied. Our method of bacteriological screening of sputum has not altered for several years.⁶ Sensitivity tests to penicillin, ampicillin, chloramphenicol, erythromycin, co-trimoxazole, trimethoprim, Augmentin (clavulanate potentiated amoxycillin), cefotaxime, and cefuroxime were performed by the disc diffusion method. Clinical details, findings of chest radiography, and virological titres were reviewed in all patients whose sputum yielded a pure culture of *B catarrhalis* or a mixed culture with other respiratory pathogens in which *B catarrhalis* was the predominant organism. Previous antibiotic treatment and the initial antibiotic chosen on admission to hospital were recorded. A simple questionnaire sent to all general practitioners who had referred patients in whom *B catarrhalis* had been isolated from sputum samples requested details of their preference for antibiotics in the treatment of chest infections among ampicillin, amoxycillin, co-trimoxazole, erythromycin, a cephalosporin, tetracycline, and "other."

Results

During the six months of the study *B catarrhalis* was isolated from the sputum of 48 men and 15 women (mean age 69 years, range 21-88) (table). *B catarrhalis* was isolated in pure culture from the sputum of 49 patients. The

examined during the corresponding six months from November to April in the previous five years was constant at roughly 3000 specimens.

Chronic pulmonary diseases in the 63 patients included chronic bronchitis and emphysema (in 33 patients), carcinoma bronchus (13), asthma (eight), congestive cardiac failure (five), pulmonary fibrosis or bronchiectasis (four), and polymyalgia rheumatica (one). Pneumonia occurred in three patients. Respiratory syncytial virus may have predisposed one otherwise healthy non-smoking octogenarian to infection. Two previously healthy non-smoking junior hospital doctors developed tracheobronchitis with β lactamase negative strains of *B catarrhalis*, one after infection with *Mycoplasma pneumoniae* and the other after a coryzal illness. The 63 patients comprised 40 smokers, 12 ex-smokers (who had not smoked for at least one year), six non-smokers, and five patients whose smoking state was unknown.

Of 36 patients infected in the community, 26 had *B catarrhalis* in their sputum on admission to hospital, seven were attending hospital outpatient departments, and three were attending general practices. Among these 36 patients, 26 had strains of *B catarrhalis* that produced β lactamase and 10 had been treated unsuccessfully with ampicillin. None had received treatment with trimethoprim.

Twenty seven patients became infected with *B catarrhalis* in hospital; in 18 β lactamase production was present. Overall, 44 out of the 63 strains produced β lactamase.

All the isolates were sensitive to Augmentin, erythromycin, chloramphenicol, co-trimoxazole, cefotaxime, and cefuroxime, but all were resistant to trimethoprim. The 19 β lactamase negative strains were uniformly sensitive to penicillin and ampicillin.

Forty seven of the 49 GPs, in 31 practices, responded to the questionnaire. Thirty seven GPs stated ampicillin or amoxycillin as their antibiotic of first choice, five tetracycline, three erythromycin, three cephradine, and one co-trimoxazole.

The hospital doctors' first choice of antibiotic for patients subsequently found to have bronchopulmonary infection due to *B catarrhalis* included ampicillin (20 doctors), Augmentin (for patients who had not responded to ampicillin before admission) (eight), erythromycin (one), chloramphenicol (one), and flucloxacillin (one). Overall, 26 patients had received ampicillin inappropriately in the presence of β lactamase producing strains of *B catarrhalis*. When the results of antibiotic sensitivity tests were available the alternatives to ampicillin treatment chosen by the hospital doctors were Augmentin (14 doctors), co-trimoxazole (six), erythromycin (two), chloramphenicol (one), and cephradine (one).

B catarrhalis contributed to the deaths of five patients: three had carcinoma bronchus, one chronic bronchitis, and one cerebrovascular accident. Five patients with mild symptoms recovered without antibiotic treatment. The hospital stay of two patients was prolonged because of recurrent infection with β lactamase producing *B catarrhalis* as a result of doctors initially ignoring the bacteriological report and continuing treatment with ampicillin. They all responded promptly to Augmentin treatment.

Number of isolates of *B catarrhalis* causing bronchopulmonary infection from January 1981 to April 1984

	1981		1982		1983		1984	
	Total No of isolates	No of isolates producing β lactamase	Total No of isolates	No of isolates producing β lactamase	Total No of isolates	No of isolates producing β lactamase	Total No of isolates	No of isolates producing β lactamase
January	1	1	13	6	22	14	14	9
February	5	2	9	3	14	5	5	4
March	4	2	5	2	15	7	14	12
April	2	1	1	0	4	4	11	9
May	0	0	0	0	14	11		
June	1	0	3	2	11	9		
July	2	0	3	1	8	4		
August	4	3	2	0	2	1		
September	3	1	1	0	4	2		
October	2	1	1	0	3	1		
November	4	2	8	3	14	8		
December	4	1	18	11	5	2		

Gram stain of these sputum samples showed numerous neutrophils with many intracellular and extracellular Gram negative diplococci. In the remaining 14 patients *B catarrhalis* was isolated with one other pathogen: β lactamase producing strains of *B catarrhalis* were present with eight of the 10 strains of *Haemophilus influenzae* isolated, one of the two strains of *Staphylococcus aureus*, and one strain of *Streptococcus pneumoniae*. A β lactamase negative strain of *B catarrhalis* was isolated with one strain of *Pseudomonas aeruginosa*. The strains of *B catarrhalis* producing β lactamase may have protected the strains of *H influenzae*, all of which were β lactamase negative, from ampicillin. The total number of routine sputum samples

Discussion

H influenzae and *Strep pneumoniae* are responsible for most infective exacerbations of chronic bronchitis. During the past two years, however, *B catarrhalis* has become an important pathogen in the winter months as over 70% of strains produce β lactamase and thus do not respond to treatment with ampicillin, the standard drug of first choice. Moreover, as *B catarrhalis* is not a fastidious organism (it can survive in dried sputum for 27 days⁷) nosocomial spread may

result⁷; almost half of our patients acquired their infection in hospital.

Previous reports accept that *B catarrhalis* infection occurs in immune compromised hosts^{8,9} or in patients with chronic pulmonary disorders,^{2,3} but our finding of infection in otherwise healthy non-smoking adults, supported by others,³ suggests that there may be an increase in the number of more virulent strains. Historically, the virulence of *B catarrhalis* seems to have fluctuated. In the early part of this century it was associated with epidemics of severe "flu like" illness.¹⁰ Thereafter its appearance in reports, usually in cases of meningitis, endocarditis, or conjunctivitis, was sporadic until the mid-1970s. Since then the number of reports from different countries suggests that more virulent organisms are appearing rather than simply reflecting an increased tendency to report them.

The pathogenic mechanisms of *B catarrhalis* are still poorly understood. Its deoxyribonuclease production enables it to inflame mucous membranes. Unlike *Neisseria gonorrhoeae* and *Neisseria meningitidis*, *B catarrhalis* does not produce IgA1 proteases, which cleave IgA1 into Fab and Fc portions and thus breach the protective immunoglobulin barrier of the mucous membrane.¹¹

Other members of the family Neisseriaceae have not been studied as extensively as *N gonorrhoea* and *N meningitidis* as generally they have been regarded as harmless organisms of little clinical import. As *B catarrhalis* has recently been causing disease more often than is normally expected microbiologists and clinicians should not dismiss it too readily as normal flora.

The reason for this resurgence is obscure, though the role of antibiotic pressure warrants careful scrutiny. Ampicillin has been used widely in the Edinburgh area, and this may have played a part in increasing the number of strains of *B catarrhalis* producing β lactamase. Similarly, trimethoprim, though not used as extensively in Edinburgh, has been shown to induce bacterial resistance to

itself.¹² The increasing use of such antibiotics may alter the nasopharyngeal flora sufficiently to lead to an increased incidence of infections with *B catarrhalis*. Further studies are required to test this hypothesis.

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SHORT REPORTS

Metabolic acidosis due to D-lactate

Metabolic acidosis caused by D(-)-lactic acid has been well documented in patients after bowel surgery.¹ I describe a patient who had not undergone bowel surgery but developed D(-)-lactic acidosis; this has not been reported before.

Case report

A 60 year old man had a 10 year history of chronic pancreatitis; he had undergone cholecystectomy nine years previously and a Peustow procedure (filleting of the pancreatic duct and jejunal anastomosis) seven years previously. He had also been treated with pancreatic enzymes and cimetidine. He developed chronic renal failure (interstitial nephritis), and haemodialysis was started when he was 59; shortly afterwards he received a cadaveric renal allograft. Immunosuppression with azathioprine and prednisolone was started. The early course after transplantation was complicated by four episodes of rejection, each treated with methylprednisolone, and by the development of diabetes mellitus, which was treated with insulin.

Two months after transplantation he had been well with stable but poor graft function until he was readmitted after a week of lethargy and nausea and vomiting. On examination he did not have a fever but was poorly perfused, cyanosed, tachypnoeic (48 breaths/min) and hypotensive. His haemoglobin concentration was 125 g/l, white cell count $3.4 \times 10^9/l$, sodium concentration 141 mmol(mEq)/l, potassium 4.4 mmol(mEq)/l, chloride 103 mmol(mEq)/l, bicarbonate 13 mmol(mEq)/l, urea 21 mmol/l (126 mg/100 ml), and creatinine 193 μ mol/l (2.2 mg/100 ml). He also had acidosis with pH 7.3, oxygen tension 11.4 kPa (86 mmHg), carbon dioxide tension 2.7 kPa (20 mmHg), standard bicarbonate 14 mmol(mEq)/l, and base excess -16 mmol(mEq)/l; the anion gap was 29 mmol(mEq)/l, and L(+)-lactate concentration was low at 1.1 mmol/l (9.9 mg/100 ml). There was no evidence of salicylates, β -hydroxybutyrate, or ketones in the blood, and the glucose concentration was 6.8 mmol/l (123 mg/100 ml). The D(-)-lactate concentration was 6.8 mmol/l (61 mg/100 ml) (normal <0.2 mmol/l (<1.8 mg/100 ml)).

He was treated for suspected sepsis (subsequent blood cultures grew *Escherichia coli*) with broad spectrum antibiotics (ampicillin, flucloxacillin, and

gentamicin) and was given sodium bicarbonate. After a respiratory arrest requiring ventilation he was given haemodialysis with bicarbonate dialysate. He deteriorated, became anuric and hypotensive, and developed progressive lung shadowing; he died two days later.

Method of measuring D(-)-lactate—The D(-)-lactate concentration was measured by substituting D(-)-lactate dehydrogenase (EC 1.1.1.28, Boehringer Mannheim Biochemicals, No 106941) for L(+)-lactate dehydrogenase (EC 1.1.1.27) in the kit for estimating lactate (Boehringer Mannheim Biochemicals test combination No 139084).

Comment

D(-)-lactic acidosis has been well described in association with the short bowel syndrome after jejunoileal bypass surgery, most commonly for obesity.¹⁻⁵ The syndrome has not been reported in patients who have not had bowel surgery. High concentrations of D(-)-lactate have been associated with dizziness, ataxia, dysarthria, fatigue, confusion, headache, and other neurological syndromes.^{1,3,4} The D(-)-lactate has been assumed to result from the metabolism of carbohydrate by bacteria abnormally found in the small bowel, or after the rapid transit of carbohydrate to the large bowel. If the amount of D(-)-lactate produced exceeds the capacity for further metabolism then it will be absorbed.

The acidosis in this patient was thought to be disproportionate to the degree of renal impairment. Blood was therefore screened for other possible acids, including D(-)-lactic acid, which is a cause of acidosis.¹ D(-)-Lactate is normally undetectable,⁴ and the measured concentration of 6.8 mmol/l (61 mg/100 ml) suggests that this contributed greatly to the acidosis. Unfortunately the organism cultured from his blood was not characterised for its ability to produce D(-)-lactate. *E coli* is not known to produce D(-)-lactate, and the source may have been another gut organism. This patient had not undergone surgery resulting in anatomical or functional bowel shortening, and, although the Peustow procedure may sometimes be associated with creation of a blind loop, he did not have a history of diarrhoea or other suggestive features. The source of the D(-)-lactate is therefore speculative.