residents in any of the 14 British towns that were studied, where the rates ranged from 4·2% to 7·5%.[2]

The decline in prevalence that accompanies migration to Australia points to environmental influences in causing the disease. The rates among immigrants do not, however, fall to the levels of natives of Australia. There are two possible explanations for this. Firstly, some people who have already developed the disease while living in the UK may be included among the immigrants. Secondly, there may be a latent period between inception of the disease and its first radiological manifestation, so that, progression being to some extent irreversible, migrants carry with them the higher UK risk of developing the disease. It seems likely that both explanations apply.

Since Paget's disease is uncommon before the age of 45 the reduction in risk among migrants in comparison with those who remain in the UK is probably related to the age at migration. Those who migrate as children will have had cumulatively less exposure to adverse influences in the UK environment, and there may be some critical age range below which migrants take on the lower risk of Australia rather than taking with them the higher risk of the UK. A study of variations in prevalence among immigrants according to the age at migration is being carried out to explore this. This study will also provide detailed data on the place of origin of migrants in the UK. There is, in England, an apparent area of high prevalence in the Lancashire towns, and the prevalence among migrants to Australia may also be related to the prevalence in their place of origin.

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Antibiotic resistance in Streptococcus pneumoniae and Haemophilus influenzae

Report of a study group on bacterial resistance*

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Summary and conclusions

Twenty laboratories in England and Scotland took part in 1977 in a survey of antibiotic resistance in Streptococcus pneumoniae and Haemophilus influenzae. In Str pneumoniae 59 (6·8%) of the 866 strains studied were resistant to tetracycline and three to chloramphenicol, and one strain showed a decreased susceptibility to penicillin. The prevalence of resistance to tetracycline was lower than that found in a similar study performed in 1975. Nine hundred and fifty-two strains of H influenzae were examined: 15 (1·6%) were resistant to ampicillin (all were beta-lactamase producers) and 26 (2·7%) to tetracycline. Only two strains were resistant to chloramphenicol and two to trimethoprim. Sixty-three H influenzae strains were capsulated. Thirty-four of these were of Pittman type b, and antibiotic resistance, particularly to ampicillin, was more common in these than in other serotypes or non-typable strains.

Some variation was seen in the resistance rate of both H influenzae and Str pneumoniae to tetracycline in strains from different centres, but too few were isolated to assess whether this represented a true geographical difference.

Introduction

Both *Streptococcus pneumoniae* and *Haemophilus influenzae* are among the more antibiotic susceptible of bacterial species, but resistance in both to all the commonly used antibiotics in respiratory infections has now been described. In *Str pneumoniae*, for example, sulphonamide resistance was described at an early date by Ross.[1] Tetracycline resistance was described in 1963[2]; penicillin,[3] erythromycin, and lincomycin[4 5] resistance in 1967; and chloramphenicol resistance in 1970.[6] Recently strains showing multiple resistance to several antibiotics, including penicillin, have been reported from South Africa.[7-9] In *H influenzae* sporadic isolates resistant to tetracycline had been described by 1970,[10] chloramphenicol resistance was reported in 1972,[11] and in 1974 ampicillin-resistant Pittman type b strains were reported by several workers in different parts of the world.[12-14]

In 1975 a study group was established in the United Kingdom to investigate the prevalence of tetracycline resistance in *Str pneumoniae* and *Str pyogenes*.[15] At the beginning of 1977 it was

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The report was prepared by the following staff of the Department of Medical Microbiology, London Hospital Medical College: A J Howard, lecturer; C J Hince, research assistant; J D Williams, professor.

decided that the group should take part in a study of antibiotic resistance in *Str pneumoniae* and *H influenzae*. We report the findings.

Methods

All strains of *H influenzae* and *Str pneumoniae* isolated from 31 January to 29 April 1977 in the laboratories listed in table I were sent to the London Hospital Medical College (LHMC), except Newcastle, which sent only *Str Pneumoniae*, and Portsmouth, which sent only *H influenzae*.

For transport specimens of *Str pneumoniae* were inoculated into semi-solid blood agar (0·4% nutrient agar plus 5% horse blood) and the haemophili on to chocolate agar slops. Both species were dispatched after overnight incubation at 37°C. A standard form bearing limited clinical details and the results of routine antimicrobial susceptibility testing accompanied each strain. On receipt at LHMC the identity of each isolate was confirmed and antimicrobial susceptibility testing repeated.

At LHMC Gram-positive cocci showing α-haemolysis on horse blood agar and sensitivity to optochin (ethyl hydrocuprein) were accepted as *Str pneumoniae* and serotyped using antisera obtained from the State Serum Institute, Copenhagen.[16] Non-CO_2-requiring, non-haemolytic organisms dependent on X and V factors for growth were accepted as *H influenzae*, and capsulated strains, recognised by their iridescence on transparent media, were serotyped using agglutinating antiserum (Wellcome Reagents Ltd).

Sensitivity testing of Str pneumoniae at LHMC—Antibiotic susceptibility was initially determined by disc diffusion methods. These were performed by seeding a 1/100 dilution of a five- to six-hour broth culture (Todd-Hewitt broth plus 1% glucose plus 10% horse serum) on to Oxoid DST agar (plus 4% lysed horse blood) using sterile cotton-wool swabs. Filter paper discs, 6 mm in diameter, containing either 2 units of penicillin, 10 μg of chloramphenicol, 10 μg of tetracycline, or 10 μg of erythromycin were then applied to the surface of the agar and the zones of inhibition measured after overnight incubation at 37°C. The minimum inhibitory concentration (MIC) of an antibiotic for any strain showing a zone of inhibition equal to or less than 20 mm in diameter was later determined by an agar dilution technique. This necessitated preparing serial double dilutions of antibiotic in Oxoid DST agar (plus 4% lysed horse blood) to provide a range of concentrations from 128 mg/l to 0·015 mg/l and applying a bacterial inoculum of about 10^4 colony-forming units to the agar surface using a Denley multipoint inoculator.

Sensitivity testing of H influenzae at LHMC—All strains were screened by a disc diffusion method. Dilutions of 1/100 of five- to six-hour broth cultures (nutrient broth plus 5% Fildes extract) were prepared and seeded on to the surface of Oxoid DST agar supplemented with 0·25% lysed horse blood and 10 mg/l nicotinamide-adenine dinucleotide (BDH Chemicals Ltd).[17] Filter paper discs, 6 mm in diameter, containing either 2 μg of ampicillin, 1·25 μg of trimethoprim, 10 μg of tetracycline, or 100 μg of sulphamethoxazole were then applied to the surface and the plates incubated without added carbon dioxide at 37°C. The MIC of an antibiotic for any strains showing a zone of inhibition equal to or less than 20 mm in diameter was determined by the agar dilution method described above, substituting the haemophilus sensitivity agar for the pneumococcal one. Any strain showing decreased susceptibility to ampicillin was tested for β-lactamase production using the chromogenic cephalosporin 87/312.[18]

Results

RESISTANCE TO STR PNEUMONIAE

Tetracycline—For analysis strains were considered to be resistant if susceptibility testing at LHMC showed them to need over 2 mg/l of tetracycline for inhibition. Altogether 866 isolates were examined and table I illustrates the prevalence of tetracycline resistance in strains from the various centres. The overall prevalence was 6·8%. The MICs of tetracycline for the resistant strains ranged from 4 mg/l to 64 mg/l. In the previous survey in 1975[15] the overall prevalence of tetracycline resistance was 13%—a significantly higher level of resistance than found in the present study ($\chi^2 = 19{\cdot}25$; $P < 0{\cdot}0005$). The reduction in the prevalence of resistance was reflected in the fact that in nearly all centres the resistance rate was lower in the present survey than in the former one. The results from different centres varied, low rates of resistance being found in Aberdeen (3·3%), Birmingham (2·7%), Bristol (2·3%), Edinburgh (0%), and Plymouth (3·2%) and higher rates recorded for Ayr (12·3%), Glasgow (14·2%), and the London Hospital (9·2%). Two laboratories, University College Hospital and Inverness, did not send their isolates to LHMC but only the results of their routine sensitivity testing of *Str pneumoniae* to tetracycline. The reported incidence of resistance in these laboratories was 13·3% (18 out of 135 strains) and 0% (0 out of 69 strains) respectively.

Chloramphenicol—Three strains were resistant to this drug, the MICs being 16 mg/l (sensitive strains were inhibited by 4 mg/l or less). Two of the chloramphenicol-resistant strains were also resistant to tetracycline.

Erythromycin—No strain resistant to this agent was received.

Penicillin—With a 2-unit disc no strain with a decreased susceptibility could be identified in the strains received at LHMC. It was thought that low degrees of resistance may have been missed, so all strains were further screened by inoculating 10^4 colony-forming units of each on to plates containing 0·05 mg/l of benzylpenicillin. Only one strain, a type 22 pneumococcus, was found to have a reduced sensitivity to penicillin, the MIC being 0·12 mg/l. All other strains tested were inhibited by a concentration of 0·03 mg/l of penicillin or less.

RESISTANCE IN H INFLUENZAE

Ampicillin—Fifteen strains out of 952 received at LHMC (1·6%) needed over 2 mg/l of ampicillin for inhibition and were considered to be resistant (table I). All the resistant strains were β-lactamase producing, and the MICs for ampicillin ranged from 4 mg/l to 16 mg/l. Four strains were received with an intermediate level of resistance (MICs for ampicillin of 1 and 2 mg/l). None of these,

TABLE I—*Antibiotic resistance in Str pneumoniae and H influenzae*

Centre	*Str pneumoniae*		*H influenzae*		
	No of isolates	No (%) resistant to tetracycline	No of isolates	No (%) resistant to tetracycline	No (%) resistant to ampicillin
Aberdeen	61	2 (3·3)	34	3 (8·8)	0
Ayr	63	8 (12·7)	29	2 (6·9)	0
Birmingham	37	1 (2·7)	69	3 (4·3)	0
Bristol	43	1 (2·3)	79	6 (7·6)	3 (3·8)
Edinburgh	42	0	106	2 (1·9)	3 (2·8)
Epping	20	2 (10)	47	2 (4·3)	2 (4·3)
Glasgow	34	5 (14·7)	28	1 (3·6)	0
London:					
Guy's	46	3 (6·5)	33	1 (3·0)	1 (3·0)
The London	130	12 (9·2)	139	1 (0·7)	2 (1·4)
St Thomas's	81	7 (8·6)	53	1 (1·9)	0
Liverpool	41	3 (7·3)	49	0	0
Newcastle	81	6 (7·4)			
Nottingham	27	4 (14·8)	94	3 (3·2)	1 (1·1)
Plymouth	125	4 (3·2)	141	0	1 (0·7)
Portsmouth			13	0	0
Stockport	7	1 (14·2)	16	0	0
High Wycombe	13	0	15	1 (6·7)	2 (13·3)
York	15	0	7	0	0
Total	866	59 (6·8)	952	26 (2·7)	15 (1·6)

TABLE II—*Antibiotic susceptibility of 874 strains of H influenzae to trimethoprim and sulphamethoxazole. Inoculum: 10^4 colony-forming units*

MIC (mg l):	0·015	0·03	0·06	0·12	0·25	0·5	1	2	4	8	16	32
Trimethoprim	525	240	88	10	5	2	2					2
Sulphamethoxazole						162	183	173	123	101	63	69

however, could be shown to produce a β-lactamase by our screening procedure. All other strains received were inhibited by 0·5 mg/l of ampicillin or less. There was little geographical variation in resistance, the rate varying from 0% in eight centres to only 4% in two.

Tetracycline—Organisms tested at LHMC which were inhibited by 2 mg/l of drug or more were considered to be resistant. The overall incidence was 2·7% (table I). The MICs of tetracycline for the resistant strains ranged from 4 mg/l to 32 mg/l.

Chloramphenicol—Only two strains resistant to this agent were received, each requiring 8 mg/l of chloramphenicol for inhibition (sensitive strains were inhibited by 1 mg/l or less). Both were also resistant to tetracycline and neither was capsulated. Using the method described by Manten *et al*,[19] both of the chloramphenicol-resistant strains could be shown to inactivate the drug in vitro.

Trimethoprim—Resistance to this agent was also found to be rare and to be present in only two of the strains received at LHMC (MICs of trimethoprim for these two organisms were equal to or greater than 32 mg/l). Both strains also showed decreased susceptibility to ampicillin (MICs of 2 mg/l), though neither could be shown to produce a β-lactamase.

Sulphamethoxazole—The results provided by disc testing at LHMC for this agent were found to be inconsistent and to correlate poorly with the results of MIC testing. The MICs of sulphamethoxazole were therefore determined for many of the strains. The results are presented in table II together with the corresponding MICs of trimethoprim. Sixty-nine out of 874 strains (7·9%) required 32 mg/l or more of sulphamethoxazole for inhibition. But repeating the sulphamethoxazole MICs of these more resistant strains with the lower inoculum of 10^3 colony-forming units showed that all but seven were inhibited by 16 mg/l or less of drug and of these seven strains, none required more than 64 mg/l for inhibition.

SEROTYPES OF H INFLUENZAE

Sixty-three capsulated strains were received. The serotypes comprised 3 type a, 34 type b, 6 type d, 16 type e, and 4 type f strains.

Table III shows that resistance to antibiotics, in particular to ampicillin, was more common in strains of Pittman type b than in other serotypes or in non-typable strains ($\chi^2 = 16{\cdot}01$; $P < 0{\cdot}0005$).

TABLE III—*Antibiotic resistance among typable and non-typable strains of H influenzae*

	Type b	Other serotypes	Non-typable
No of strains tested	34	29	889
No resistant to:			
Ampicillin	4*	1*	10*
Tetracycline	2	0	24
Chloramphenicol	0	0	2
Trimethoprim	1	0	1
Total resistant	7 (20·6%)	1 (3·4%)	37 (4·2%)

*β-Lactamase-producing strains.

Discussion

In the survey carried out in 1975[15] the analyses were performed using the results of each laboratory's routine antibiotic susceptibility testing. For this present study it was thought that greater uniformity would be achieved, particularly in testing *H influenzae*, if all the results were confirmed by one laboratory. Thus, except when otherwise indicated, all the results discussed in this paper refer to results obtained at LHMC.

It might be argued that the apparent fall in tetracycline resistance in *Str pneumoniae* since 1975 simply reflects differences in methods between the two studies. The results of each laboratory's routine antimicrobial susceptibility testing were, however, again available for analysis in this study, and, for tetracycline resistance in *Str pneumoniae*, the overall incidence they reported (7·1%) corresponded closely to the result obtained at LHMC (6·8%). Tetracycline resistance in this species has therefore probably genuinely fallen. Tetracycline use has declined in England and Scotland over the past few years—from 14·5 million prescriptions in 1969 to 10·1 million in 1976 (figures obtained from the Department of Health and Social Security)—and this change in prescribing habits may have contributed to the fall in resistance.

The resistance of *H influenzae* to ampicillin and tetracycline remains similar to that reported by Cavanagh *et al*[17] in 1975. The finding that antibiotic resistance, in particular to ampicillin, was more prevalent in type b than in other strains of *H influenzae* was unexpected. Only a few type b strains were isolated in the study (34), and a larger survey is needed to show how widespread resistance to ampicillin is in this serotype in the community at large. The results of previous surveys have been conflicting. In the United States two small studies by Khan *et al*[20] and Smith[21] reported resistance rates among type b strains as being 7% and 11% respectively. But a larger study by Brotherton *et al*[22] in Boston showed resistance in only four of 209 type b strains isolated between 1974 and 1976.

Although there were variations in the incidence of tetracycline resistance in the strains of both *Str pneumoniae* and *H influenzae* received from different centres, the numbers received from each were too low to assess whether these results represented true geographical variations.

The MICs of sulphamethoxazole for *H influenzae* agreed well with those of previous studies,[23-25] which had used low inocula for testing, and little increase seems to have occurred in resistance to the sulphonamides. The difficulties experienced in sulphamethoxazole disc sensitivity testing were emphasised by the finding that the overall incidence of sulphonamide resistance reported by sending laboratories was around 20%. For sulphonamides the results of in-vitro testing correlate better with in-vivo results if low inocula are used,[26] and routine disc sensitivity testing seems to overestimate sulphonamide resistance in this species.

Our results indicate that ampicillin and tetracycline still retain their usefulness in the management of respiratory tract infections. But the possibility that ampicillin resistance may be more common among type b strains of *H influenzae* suggests that this agent is unsuitable as first-line treatment for severe haemophilus infections in children before sensitivities are known. In the present study 14 strains of *H influenzae* were received from blood cultures or cerebrospinal fluid and two were ampicillin resistant. Perhaps it would be judicious to start treatment of type b *H influenzae* infections with chloramphenicol.

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Norethisterone oenanthate as an injectable contraceptive: use of a modified dose schedule

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Summary and conclusions

Norethisterone oenanthate (NET-OEN) was given as an injectable contraceptive to 295 healthy women over 1606 woman-months. A modified injection schedule was used. There were no pregnancies, and the 12-month, life-table, use-related discontinuation rate was 39·1/100 users. Menstrual disturbance (10·8/100 women), minor side effects (13·5/100 women), and personal reasons (12·0/100 women) were the main causes of use-related discontinuation. There was no difference in use-related discontinuation rates between women receiving their first injection during a normal menstrual period and those receiving it immediately after a pregnancy. There were no serious side effects.

The use of NET-OEN in certain groups of women is recommended, particularly in those in need of highly effective contraception, who cannot or do not wish to take oral contraceptives, who are lactating, or who are awaiting hospital admission for sterilisation.

Introduction

The discovery by Junkman that the esterification of a progestogen alcohol produced a systematically active long-acting progesten led to the synthesis of a series of long-acting fertility-regulating agents.[1] During the past 15 years several of these drugs have been investigated,[2 3] although only two of them—depot-medroxyprogesterone acetate (DMPA) and norethisterone oenanthate (NET-OEN)—have reached large-scale human trials.[4-6] In the United Kingdom experience with injectable contraceptives is limited and DMPA is the only such preparation currently licensed by the Committee on Safety of Medicines, and that only for short-term use.[7] DMPA is effective in preventing pregnancy, with quoted failure rates of 0-1·2/100 woman-years and over 77 000 woman-years of experience reported worldwide. It may not be the drug of choice for long-term use owing to a high incidence of amenorrhoea and irregular bleeding patterns. In a multinational study[8] comparing DMPA with NET-OEN given at 12-weekly intervals, patients using NET-OEN were found to have less amenorrhoea but significantly more pregnancies.

NET-OEN has been the subject of clinical trials in England for the past two and a half years. We report our experience with the drug given on a modified injection schedule.

Patients and methods

Patients were recruited from the family planning clinics, gynaecology wards, and postnatal wards of King's College Hospital. Informed consent was obtained from all. Only healthy women aged 18-45 years were admitted to the study. Unless they had recently delivered or been pregnant they were required to have a history of regular menstrual cycles, with a variation of not more than 10 days between the longest and the shortest menstrual cycles in the last three months. Patients who normally used hormonal contraceptives stopped using them for at least four weeks before the study.

Injection schedule—NET-OEN was supplied in ampoules containing 200 mg of the steroid in 1 ml of an oily solution. The ampoule was warmed in hot tap water and the drug given as an intramuscular injection into the gluteal muscles. A modified injection schedule was used. The first injection was given during days 1-5 of a normal menstrual period or before discharge from hospital after confinement or termination of pregnancy. The second, third, and fourth injections were given at eight-week intervals. Subsequent injections were given at 12-week intervals.

Follow-up—At each visit weight and blood pressure were recorded and menstrual details obtained. Complaints and any possible adverse effects were noted. All injections were given within seven days of the scheduled day. Patients who did not attend for injection on schedule were sent written reminders or contacted by telephone or home visit. If no response was obtained or the patient did not attend within seven days of a scheduled visit she was recorded as lost to follow-up. Patients who discontinued treatment were asked the reason for doing so. When a doctor discontinued treatment the reason for doing so was also recorded. The absence of periods for 90 days or more was recorded as "amenorrhoea," while continuous vaginal bleeding for more than 10 days was recorded as "prolonged bleeding." Patients discontinuing treatment because of the absence of regular vaginal bleeding, including those who discontinued because of vaginal bleeding requiring no sanitary protection (spotting), were recorded as having "irregular bleeding."

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