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The pathogenic potential of commensal species of *Neisseria*

AP JOHNSON

From the Division of Communicable Diseases, MRC Clinical Research Centre, Watford Road, Harrow, Middlesex, HA1 3UJ

SUMMARY Although *Neisseria* species other than *N gonorrhoeae* and *N meningitidis* normally comprise part of the commensal bacterial flora of the oropharynx, they may occasionally act as opportunistic pathogens. Infections in which these organisms have been implicated include cases of endocarditis, meningitis, septicaemia, otitis, bronchopneumonia and possibly genital tract disease. In this paper, the clinical and pathological features of such infections are described, together with a discusssion of factors that may contribute to their development.

In most textbooks of medical microbiology, the genus *Neisseria* is considered to contain only two pathogenic species, namely, *N gonorrhoeae* and *N meningitidis*. The other members of the genus are generally regarded as harmless inhabitants of the oropharynx. There is ample evidence in the literature, however, that these normally non-pathogenic species are capable of producing infection in a variety of anatomical sites including the heart, nervous system, bloodstream, respiratory tract and possibly the genital tract. Although the pathogenesis of gonococcal and meningococcal infections has been investigated extensively and is well documented,[1 2] there is little collated information concerning infections produced by other *Neisseria* spp. This article is an attempt to remedy this deficiency.

Classification of the genus Neisseria

Any review of *Neisseria* infections is complicated by the fact that the classification of the organisms comprising the genus has undergone a number of changes over the years. A detailed discussion of the evolution of the taxonomy of the genus is beyond the scope of this article, but a brief outline, which conveys some idea of the degree of change is presented below. In the early part of this century, Gram-negative cocci were allocated a variety of generic and specific names including *Micrococcus catarrhalis, M cinereus, M flavus,* i, ii and iii, *M pharyngis siccus, Diplococcus mucosus* and *D crassus*. In an early review, Wilson and Smith[3] considered the classification of these organisms to be unsatisfactory and suggested that apart from the meningococcus, all Gram-negative cocci found in the oropharynx should be classified as a single group called either *D pharyngis* or *N pharyngis*. This suggestion was not, however, generally adopted. In the 7th edition of *Bergey's Manual of Determinative Bacteriology*[4] published in 1957, the genus *Neisseria* comprised 10 species (Tables 1 and 2). On the basis of subsequent studies of genetic homology between organisms,[5 6] however, several of the species were reclassified, and the 8th edition of *Bergey's Manual*[7] published in 1974, lists only six main species (Tables 1 and 2). The former species *N flava* and *N perflava* have been incorporated into the species *N subflava,* while the former species *N catarrhalis* and *N haemolysans* have been transferred to the genera *Branhamella* and *Gemella* respectively. In addition, 10 species are mentioned, but because of the lack of relevant genetic data they are currently listed as *species incertae cedis* (Table 1).

In this review no attempt has been made to reclassify organisms described in early papers in terms of the currently used taxonomic scheme. Rather, the specific names used in each paper are given. However, the reader must bear in mind that the specific names used were determined by the classification scheme in vogue at the time each paper

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Table 1 *Species of Neisseria listed in the 7th (1957)[4] and 8th (1974)[7] editions of Bergey's Manual of Determinative Bacteriology*

1957 classification[4]	*1974 classification*[7]
N gonorrhoeae	*N gonorrhoeae*
N meningitidis	*N meningitidis*
N flava	*N subflava*
N perflava	*N sicca*
N subflava	*N mucosa*
N sicca	*N flavescens*
N catarrhalis	
N flavescens	
N haemolysans	
N caviae	
Species incertae cedis	
N animalis	*N canis*
N caviae	*N cinerea*
N cuniculi	*N denitrificans*
N elongata	*N lactamicus*
N ovis	*N suis*

was published, and that different authors who appear to be discussing the same species may not necessarily be referring to identical organisms.

Infections produced by Neisseria organisms

HEART INFECTIONS

Recorded cases of endocarditis produced by *Neisseria* organisms together with their clinical and pathological features are presented in Tables 3 and 4 respectively. A variety of *Neisseria* spp are documented as having caused endocarditis, although there are no recorded cases involving *N flavescens* or *N lactamica*, despite the fact that these organisms can cause meningitis and septicaemia (discussed below). As with endocarditis produced by other micro-organisms—for example, *Streptococcus viridans*—patients generally presented with fever and malaise. Cardiac murmurs were nearly always present and the diagnosis was established by the repeated isolation of the micro-organism from the blood stream. Many patients developed petechiae, splinter haemorrhages and Osler's nodes (small tender nodules most frequently found on the finger or toe pads) which were probably manifestations of allergic vasculitis. Embolic episodes involving the right brachial and femoral arteries,[25] the brain,[18 20 21] and the toe,[15] were also noted. Some patients exhibited haematuria which may have been due to renal emboli, focal embolic glomerulitis or diffuse glomerulonephritis.

Several of the patients had a history of underlying heart disease. Rheumatic fever was a common feature,[8 11 28 32] but patients with ventricular septal defect[10] and Marfan's syndrome[21] have also been reported. Four patients had previously received prosthetic heart valves,[13 16 18 23] a procedure which is now known to predispose towards the development of bacterial endocarditis. One patient developed

Table 2 *Characteristics used to differentiate Neisseria species in the 7th and 8th editions of Bergey's Manual of Determinative Bacteriology*[4 7]

Edition of Bergey (year)	*Species listed*	*Differential characteristics*							
		Acid from				*Pigment*	*Capsule*	*Growth at 22°C*	*Polysaccharide from 5% sucrose*
		G	*M*	*F*	*S*				
7th (1957)	*N gonorrhoeae*	+	−	−	−	−	ND	−	ND
	N meningitidis	+	+	−	−	−	ND	−	ND
	N flava	+	+	+	−	+	ND	+	ND
	N perflava	+	+	+	+	+	ND	+	ND
	N subflava	+	+	−	−	+	ND	+	ND
	N sicca	+	+	+	+	−	ND	+	ND
	N catarrhalis	−	−	−	−	−	ND	+	ND
	N flavescens	−	−	−	−	+	ND	+	ND
	N haemolysans	+	+	+	+	−	ND	+	ND
	N caviae	−	−	−	−	+	ND	+	ND
8th (1974)	*N gonorrhoeae*	+	−	−	−	−	−	−	O
	N meningitidis	+	+	−	−	−	V	−	O
	N subflava	+	+	V	V	+	+	d	d
	N sicca	+	+	+	+	d	V	d	+
	N mucosa	+	+	+	+	−	+	+	+
	N flavescens	−	−	−	−	+	−	+	+

G = glucose
M = maltose
F = fructose
S = sucrose
ND = not discussed
O = no growth on medium with 5% sucrose
V = character inconsistent and in one strain may sometimes be positive, sometimes negative.
d = some strains positive, some strains negative

Table 3 *Cases of endocarditis caused by Neisseria organisms*

Organism	*Patient*		*Author(s)*	*Year published*
	Age (yrs)	*Sex*		
N flava	20	F	Connaughton and Rountree[8]	1939
	14	F	Matlage *et al*[9]	1950
	5	F	Scott[10]	1971
N perflava	45	M	Major and Johnson[11]	1945
	44	M	Breslin *et al*[12]	1967
	47	M	Clark and Patton[13]	1968
N sicca	12	M	Shaw[14]	1949
	60	F	Gay and Sevier[15]	1978
	21	M	Ghoneim and Tandon[16]	1979
N catarrhalis	15	F	Clarke and Haining[17]	1936
	21	M	Clarke and Haining[17]	1936
	69	F	Pollock and Holzmann[18]	1976
	45	F	Douer *et al*[19]	1977
N mucosa	9	M	Brodie *et al*[20]	1971
	19	M	Dowling *et al*[21]	1974
	54	M	Drapkin[22]	1977
	40	M	Hennessey *et al*[23]	1981
N pharyngis	21	F	Goldstein[24]	1934
	26	M	Shiling[25]	1939
	21	F	Hudson[26]	1957
	15	M	Linde and Heins[27]	1960
Micrococcus pharyngis siccus	27	M	Graef *et al*[28]	1932
	14	F	Weed *et al*[29]	1943
Micrococcus pharyngitidis-siccae	25	M	Schultz[30]	1918
Unidentified	45	M	Coulter[31]	1915
	25	M	Shiling[25]	1939
	66	M	Dammin[32]	1941

Table 4 *Clinical and pathological features of endocarditis caused by Neisseria organisms*

Clinical or pathological feature reported	*Reference*	*Clinical or pathological feature reported*	*Reference*
Fever	8,9,10,11,12,13,15,16,17,18,19,20,21, 22,23,24,25,27,28,29,30,31,32	Abdominal pain	9,10,13,17,24,25,28
Headache	9,10,12,14,17,20,21,24,29,30	Splinter haemorrhages	9,11,16,29
Chills	10,11,13,17,19,21,22,23,24,25,29,31,32	Osler's nodes	16
Vomiting	8,9,20,28,29,31	Janeway's lesions	22
Muscular aches	8,9,24	Embolic episodes	15,16,18,20,21,25,26
Enlargement of heart	8,10,11,17,24,25,28,31,32	Clubbing of fingers	14,25
Heart murmurs	8,9,10,11,12,13,15,17,19,20,21,22,25, 28,29,30,31,32	History of rheumatic fever	8,11,28,32
Conjunctival petechiae	8,9,10,11,13,20,28,29,30,32	Pre-existing heart valve abnormality	10,14,21
Petechiae on skin	11,14,16,17,24,28,30,32	Intracardiac prosthesis	13,16,18,23
Haematuria	8,10,13,15,18,19,21,22,25,28,29,30,32	Recent history of dental procedure	8,18,21,26
Arthralgia/arthritis	8,9,15,22,24,31	Patient died	8,17,18,24,25,28,30,31,32

early onset endocarditis[13]—that is, onset within two months of valve replacement—while the other three patients[16 18 23] developed late onset disease.

Although the portal of entry for the initiating episode of bacteraemia which resulted in infection of the endocardium was often not apparent, it was thought that the oropharynx was the source of infection in a number of instances. In four patients, endocarditis developed after dental extractions,[8 18 21 26] and in one patient, bacteraemia was believed to have occurred following the use of an oral irrigation device.[22] In at least two other patients poor oral hygiene was noted.[10 32] It was suggested that in one patient the source of bacteraemia may have been a genital tract infection,[9] while in another patient the development of endocarditis was thought to be possibly related to a prior gynaecological operation.[19]

In addition to endocarditis, one case of purulent pericarditis due to a *Neisseria* organism *(N mucosa)* has been described.[33] A 51-year-old man with chronic renal failure developed purulent pericarditis and *N mucosa* was isolated from pericardial tissue and fluid.

MENINGITIS

Documented cases of meningitis produced by

Table 5 *Cases of meningitis caused by Neisseria organisms*

Organism	*Patient*		*Author(s)*	*Year published*
	*Age**	*Sex*		
N flava	8 days	M	Noguchi *et al*[34]	1963
N perflava	31	M	Sophian[35]	1944
N subflava	7 months	M	Benson *et al*[36]	1928
	7 months	F	Lewin and Hughes[37]	1966
	2½	F	Lewin and Hughes[37]	1966
	9 months	F	Lewin and Hughes[37]	1966
N sicca	6½	M	Bansmer and Brem[38]	1948
Organism resembling				
N catarrhalis	45	F	Newing and Christie[39]	1947
N catarrhalis	2½	M	Pfister *et al*[40]	1965
	14 months	F	Cocchi and Ulivelli[41]	1968
	36	M	Elston *et al*[42]	1970
	3	M	Arora and Chitkara[43]	1973
Micrococcus catarrhalis	3 months	–	Wilson[44]	1908
	5	F	Garland[45]	1923
	31	F	Moersch[46]	1928
N mucosa	5	F	Berger *et al*[47]	1974
Diplococcus mucosus	–	–	Cowan[48]	1938
	29	M	Bray and Cruickshank[49]	1943
	3 months	F	Bishop and Randell[50]	1947
N lactamica	7 months	F	Lauer and Fisher[51]	1976
	6	M	Hansman[52]	1978
N flavescens	–	–	Branham[53]	1930
	10	M	Prentice[54]	1957
Unidentified	7	F	Reimann and Koucky[55]	1939
	31	M	Edwards[56]	1944
	25	F	Christie and Cook[57]	1947
	4	M	Kippax *et al*[58]	1968

*Age in years unless stated otherwise.

Table 6 *Cases of meningitis caused by Neisseria organisms reported in languages other than English*

Organism	*Patient*		*Author(s)*	*Year published*
	Age	*Sex*		
N flava	10 months	F	Kostmann*	1939
	21	M	Hillemand *et al**	1951
N catarrhalis	6 months	–	Mayerhofer-Lateiner*†	1918
	–	M	Cot and Robert†‡	1921
	35	M	Gaupp and Axen*†	1933
	–	–	Zoeller *et al**†	1933
	4½	M	Zinke*†	1936
	1½	M	Zinke*†	1936
	5 months	F	Bergqvist*†	1940
	4	F	Savini*†	1957
	5	F	Savini*†	1957
	13	M	Bentegeat *et al**	1960
	–	–	Cassoute and Gibaud‡	1920
	7 weeks	–	Neal‡	1922
N mucosa	12	F	Véron *et al*§	1961
	6 months	–	Sirot and Cluzel§	1972
	3	–	Sirot and Cluzel§	1972
N pharyngis	22	M	Engel and Löfgren*	1941
	49	F	Engel and Löfgren*	1941
Diplococcus pharyngis flavus II	52	F	Emile-Weil *et al**	1933
Diplococcus pharyngis flavus III	20	M	Brunel and Dérobert*	1937
'Meningococcus-like' organism	8½	M	Reuss†	1922
N capsulata	–	–	Courtois *et al*‖	1954

*For reference see Noguchi *et al.*[34]
†For reference see Benson *et al.*[36]
‡For reference see Garland.[45]
§For reference see Berger *et al.*[47]
‖For reference see Kippax *et al.*[58]

Table 7 *Clinical and pathological features of meningitis caused by Neisseria organisms*

Clinical or pathological feature reported	*Reference*	*Clinical or pathological feature reported*	*Reference*
Fever	35,36,37,38,40,41,42,43,44,45,46,47,49,50, 51,54,57,58	Maculo-papular or purpuric rash on skin	49,52,57
Headache	38,45,46,49,55,57	Neck stiffness	35,38,40,41,42,45,47,49, 52,54,55,58
Vomiting	36,37,38,39,41,44,45,46,47,54,55,58	Positive Kernig's sign	35,36,38,40,41,45,54,55, 57,58
Lethargy/drowsiness	37,38,39,40,43,45,47,51,52,57,58	Positive Babinski's sign	35,47
Altered state or loss of consciousness	37,39,40,42,43,57	Positive Brudzinski's sign	35,36,40,41,47
Confusion	35,39,49,57	Positive Oppenheim's sign	35
Convulsions	37,40,43,44,58	Positive Gordon's sign	35
Bulging fontanelle	36,44,50	Cloudy cerebro-spinal fluid	35,36,38,39,40,41,44,45,46, 49,50,51,55
Inflammation or infection of upper respiratory tract	36,37,38,39,41,42,45,47,49,51,56,57	Cerebral-spinal fluid under increased pressure	35,38,39,45,49,50,57,58
Petechiae on skin	35,37,40,41,44,47,49	Patient died	35,36,37,39,44,45,46,56,57

Table 8 *Pathological findings in cerebro-spinal fluid from patients with meningitis caused by Neisseria organisms*

Organism	*Findings in cerebrospinal fluid*					
	No of inflammatory cells (cells/litre)	*Glucose (mmol/l)*	*Protein (g/l)*	*Gram-negative diplococci seen in smear*	*Author(s)*	*Year published*
N perflava	$1{\cdot}5 \times 10^{10}$	NR	NR	+	Sophian[35]	1944
N subflava	$4{\cdot}8 \times 10^{9}$	0·17	1·9	+	Lewin and Hughes[37]	1966
	$1{\cdot}9 \times 10^{9}$	0·22	1·4	+	Lewin and Hughes[37]	1966
	$4{\cdot}0 \times 10^{6}$	1·7	0·4	+	Lewin and Hughes[37]	1966
N sicca	$4{\cdot}2 \times 10^{9}$	4·6	0·8	−	Bansmer and Brem[38]	1948
N catarrhalis	$3{\cdot}0 \times 10^{9}$	NR	NR	+	Pfister *et al*[40]	1965
	$1{\cdot}2 \times 10^{9}$	1·7	0·7	+	Cocchi and Ulivelli[41]	1968
	$7{\cdot}6 \times 10^{9}$	2·1	3·5	+	Elston *et al*[42]	1970
	10–12 HPF	1·4	0·7	+	Arora and Chitkara[43]	1973
M catarrhalis	$1{\cdot}5 \times 10^{9}$	1·9	increased	+	Garland[45]	1923
N mucosa	$2{\cdot}3 \times 10^{9}$	Normal	Normal	−	Berger *et al*[47]	1974
(D mucosus)	$3{\cdot}3 \times 10^{8}$	NR	2·4	+	Bray and Cruickshank[49]	1943
	$2{\cdot}0 \times 10^{8}$	1·9	1·9	+	Bishop and Randall[50]	1947
N lactamica	$1{\cdot}3 \times 10^{10}$	Not detected	2·5	−	Lauer and Fisher[51]	1976
N flavescens	$2{\cdot}6 \times 10^{7}$	4·4	0·5	+	Prentice[54]	1957
Undescribed	$2{\cdot}9 \times 10^{8}$	Not detected	2·0	+	Christie and Cook[57]	1947
	$1{\cdot}1 \times 10^{8}$	4·3	0·3	NR	Kippax *et al*[58]	1968

HPF = high power field.
NR = not reported.

Neisseria spp other than the gonococcus and the meningococcus are listed in Tables 5 and 6. Most patients presented with meningeal symptoms such as headache, vomiting, lethargy, neck stiffness, and positive Kernig's and Brudzinski's signs (Table 7) which are common to many types of meningitis. Interestingly, several patients had a petechial, maculo-papular or purpuric rash (Table 7) which is a feature commonly associated with cases of meningococcal meningitis. Gram-negative cocci were frequently seen in smears of cerebrospinal fluid (CSF) (Table 8) and in all cases the diagnosis was confirmed by isolation of the organisms from the CSF and occasionally from the blood.

The findings in the CSF were generally consistent with those seen in other forms of bacterial meningitis (Table 8). The white blood cell count was commonly, though not invariably, greatly than $1{\cdot}2 \times 10^{9}$/l with a predominance of polymorphonuclear leucocytes. In the cases where glucose and protein concentrations in CSF were recorded, about half the patients had glucose concentrations $\leq 1{\cdot}7$ mmol/l, and about half had protein concentrations $>1{\cdot}5$ g/l.

SEPTICAEMIA

The clinical and microbiological features of documented cases of *Neisseria* septicaemia are shown in Table 9. It must be remembered, however, that invasion of the blood stream by bacteria occurs also in cases of endocarditis and meningitis (see above), and that there is an overlap with regard to the clinical features of these conditions. In all the reported cases

Table 9 *Clinical and pathological features of septicaemia caused by Neisseria organisms*

Organism	Patient		Clinical features	Bacteriological features	Author(s)	Year published
	Age*	Sex				
N subflava	3 months	M	History of coryza and cough 1 wk prior to admission, fever, loss of consciousness, generalised petechial rash, pupils unresponsive to light, deep tendon reflexes absent, right upper lobe pneumonia, patient died.	Bacteria isolated from blood	Lewin and Hughes[37]	1966
N subflava	2	F	History of coryza and cough 1 wk prior to admission, fever, generalised petechial rash, tonsillar fauces inflamed, haematuria, patient recovered.	Bacteria isolated from blood	Lewin and Hughes[37]	1966
N subflava	10	M	Fever, nausea, stomach ache, mild pharyngitis, macular-purpuric skin rash, patient recovered.	Bacteria isolated from blood	Muchmore and Venters[59]	1968
N catarrhalis	6 months	M	History of fever and vomiting 2 days before admission, sudden onset of purpuric lesions, few spontaneous movements, pupils sluggish to light, CSF clear and colourless, patient recovered.	Bacteria isolated from blood, CSF and bone marrow	Feigin *et al*[60]	1969
N catarrhalis	8	M	History of immunosuppressive therapy for acute lymphoblastic leukaemia, fever, malaise, nausea, abdominal distension, purpuric rash, pain and swelling in both knees, extensive oropharyngeal ulceration, patient died.	Bacteria isolated from blood. Bacteria seen in Gram-stain of material obtained by needling from cutaneous lesions	Burnett *et al*[61]	1975
N pharyngis	24	F	Patient collapsed at work. Evidence of disseminated intravascular coagulation. Patient died.	Bacteria isolated from blood and from heart swab taken at autopsy	Thomson and Gopaul[62]	1973
N lactamica	23 months	F	Patient had chromosomal defect and suffered from patent ductus arteriosus with pulmonary hypertension. Patient found lifeless in bed but resuscitated. On admission, patient had inflamed and dull right tympanic membrane.	Bacteria isolated from blood. Bacteria seen in Gram-stain of fluid from middle ear.	Wilson and Overman[63]	1976
N flavescens	20	F	Fever, chills, headache, vomiting, myalgia, arthralgia, maculopapular and pustular skin lesions, third right metacarpophalangeal joint inflamed, CSF clear, patient recovered.	Bacteria isolated from blood. Bacteria seen in Gram-stain of pustular skin lesion, but cultures were negative.	Wertlake and Williams[64]	1968

*Age in years unless otherwise stated.

of *Neisseria* septicaemia organisms were isolated from the blood, but additionally in one case, organisms were isolated from the CSF and bone marrow,[60] while in two other cases organisms were seen in Gram-stained materials from skin lesions.[61 64] The cases described here are of particular interest in that they resemble the clinical picture generally seen in meningococcal septicaemia, with the development of a maculo-papular, petechial or purpuric rash. Other similarities include fever,[37 59 60 61 64] joint involvement,[61 64] and, in one patient, evidence of disseminated intravascular coagulation.[62]

In some of the patients, septicaemia may have followed an upper respiratory tract infection. Three patients had a history of either coryza and cough[37 60] (although relevant microbiological data were not available) or pharyngitis,[59] and in one patient, organisms were detected microscopically in fluid from the middle ear.[63] One other patient was predisposed to infection as a result of receiving immunosuppressive drugs.[61]

RESPIRATORY TRACT INFECTIONS

Although Koch's postulates have not been fulfilled, the isolation of *Neisseria* organisms in pure culture from the heart, CSF or blood (organs and tissues which are normally sterile) provides strong circumstantial evidence that these organisms are the aetiological agents in the cases of endocarditis, meningitis and septicaemia described above. With regard to respiratory tract infections, however, the interpretation of bacteriological findings is more difficult as *Neisseria* organisms are known to exist as harmless inhabitants of the upper respiratory tract. With this proviso in mind, there is, nevertheless, an accumulating body of evidence which suggests that one particular species—namely *N catarrhalis* (recently renamed *Branhamella catarrhalis*)—can cause infections in both the upper and lower respiratory tract (Table 10). There is only serological evidence to support an aetiological role for *N catarrhalis* in some cases of sinusitis,[65] but the evidence for it causing otitis media in children is stronger, the organisms having been isolated in pure culture from middle ear exudates and having been seen associated with polymorphonuclear leucocytes in Gram-stained smears.[66-70] Moreover, it is unlikely that these isolates were simply contaminants from the oropharynx, since other organisms also found normally in the oropharynx were not isolated. In a study of acute

Table 10 *Evidence for aetiological role of Neisseria catarrhalis (Branhamella catarrhalis) in respiratory tract infections*

Infection	*Evidence for aetiological role of N catarrhalis (Branhamella catarrhalis)*	*Predisposing host factor*	*Author(s)*	*Year published*
Maxillary sinusitis	Complement-fixing antibodies present in sera of some patients.	ND	Brorson *et al*[65]	1976
Otitis media	Organisms isolated in pure culture from middle ear exudate; Organisms seen in association with PMN leucocytes in middle ear exudate; antibodies detected in serum and/or middle ear fluid of patients from whom organisms were isolated.	ND	Coffey *et al*[66] Coffey *et al*[67] Kamme *et al*[68] Lee *et al*[69] Leinonen *et al*[70]	1966 1967 1971 1981 1981
Laryngitis	Organisms isolated as sole pathogen from nasopharynx in 55% of patients studied.	None	Schalén *et al*[71]	1980
Bronchitis or pneumonia	Predominant organisms in sputum.	All patients had chronic underlying lung disease.	Johnson *et al*[72]	1981
Pneumonia	Organisms isolated in pure culture from sputum and transtracheal aspirate; organisms seen associated with PMN leucocytes in Gram-stained sputum and transtracheal aspirate; positive correlation between disappearance of organisms and clinical improvement.	Patient received immunosuppressive therapy for multiple myeloma.	McNeely *et al*[73]	1976
		One patient had chronic lymphocytic leukaemia and another was an alcoholic with chronic obstructive pulmonary disease.	Srinivasan *et al*[74]	1981
		Patients were miners with altered pulmonary function; they all suffered from repeated respiratory tract infections and many had received corticosteroids.	Ninane *et al*[75] Ninane *et al*[76] Ninane *et al*[77]	1977 1978 1978

ND = not done

laryngitis in non-compromised adults, *B catarrhalis* was isolated as the sole pathogen in 55% of the patients, a figure significantly higher than that for the control group.[71]

There is also fairly convincing evidence that *N catarrhalis* may cause bronchopneumonia, these organisms having been isolated in pure culture from bronchial secretions obtained by transtracheal puncture,[72-77] which is widely accepted as the procedure of choice for collecting uncontaminated material from the lower respiratory tract. Moreover, in the studies reported by Ninane and colleagues,[76] transtracheal aspirates containing epidermoid cells were discarded thus reducing the possibility that the aspirates were contaminated with oropharyngeal secretions.

Further evidence for the pathogenic role of *N catarrhalis* in cases of pneumonia was a correlation between the disappearance of the organisms and the resolution of clinical symptoms. Generally, treatment with ampicillin or other antibiotics resulted in the disappearance of the organisms and clinical improvement.[76] However, in some patients treated with ampicillin or amoxycillin, the organisms persisted as did signs and symptoms of infection.[72 75 76] Laboratory investigation showed the persistent strains to produce β-lactamase.[72 76 77] When the patients were treated subsequently with either cefuroxime,[75 76] (a cephalosporin active against β-lactamase-producing organisms), tetracycline[72] or a combination of amoxycillin and clavulanic-acid[77] (a β-lactamase inhibitor) the organisms were eliminated and the condition of the patients improved.

Neisseria catarrhalis (occasionally producing β-lactamase) was also recorded as a respiratory tract pathogen by Percival and colleagues.[78] Interestingly, these workers noted that although *N catarrhalis* was the sole pathogen isolated from some patients, it was more frequently isolated together with *Haemophilus influenzae* and pneumococci. All the patients from whom *N catarrhalis* was isolated were chronic bronchitics or had bronchiectasis.

In addition to *N catarrhalis,* three other *Neisseria* organisms have been reported as being associated with infections related to the respiratory tract. *Neisseria sicca* has been isolated in pure culture from the transtracheal aspirate of an elderly patient suffering from pneumonia,[79] and *N mucosa* has been isolated from the pleural space of a patient suffering from empyema a year after pneumonectomy.[80] *Neisseria lactamicus* was isolated from the pharynx of a man suffering from fever, chills, and pharyngitis,[81] but the role that the organism played in the disease is questionable since *N lactamicus* may be isolated from the healthy nasopharynx.[82]

GENITAL TRACT INFECTIONS

It is frequently thought that the observation of Gram-negative diplococci in genital tract smears is evidence of a gonococcal infection. However, as shown in Table 11, several species of *Neisseria* other than the gonococcus have been isolated from the genital tract. It should also be mentioned that meningococci have similarly been isolated.[90]

While it is now clear that *Neisseria* organisms other

Table 11 *Occurrence of Neisseria organisms in the genital tract*

Organism	*Author(s)*	*Year published*
N flava	Carpenter[83]	1943
	Wax[84]	1950
	Wilkinson[85]	1952
N subflava	Johnston[86]	1951
	Wax[84]	1950
N sicca	Wax[84]	1950
	Weaver[87]	1950
	Wilkinson[85]	1952
N catarrhalis	Wax[84]	1950
	Wilkinson[85]	1952
	Graber *et al*[88]	1963
	McCague *et al*[89]	1976
	Blackwell *et al*[90]	1978
N lactamicus	Jephcott and Morton[91]	1972
N lactamica	Brunton *et al*[92]	1980
N flavescens	Wax[84]	1950
Aberrant strain of *N catarrhalis* or *N gonorrhoeae*	Coleman[93]	1946

than the gonococcus may be isolated from the genital tract, it is not clear whether these organisms cause pathological changes. In some cases it was suggested that the organisms isolated were acting as pathogens, while in other instances the evidence suggested that they were not directly involved in the disease process. However, the results of these studies are difficult to interpret for several reasons. Firstly, the isolation of organisms from patients with no evidence of genital tract disease does not negate the possibility that the organisms may be pathogenic, as the gonococcus (a known genital tract pathogen) frequently produces asymptomatic infections. Secondly and more importantly, some of the patients described in the papers listed in Table 11 may also have been infected with genital pathogens such as *Chlamydia trachomatis* or *Ureaplasma urealyticum* which would not have been detected by conventional bacteriology. If non-gonococcal *Neisseria* species are to be shown to be pathogenic for the genital tract, they must first be isolated from patients from whom no other genital pathogens can be recovered. Until such studies are carried out, the relevance of non-gonococcal *Neisseria* species to the aetiology of genital tract disease will remain purely speculative.

Factors possibly influencing the development of infection with Neisseria organisms

From the epidemiological standpoint, most of the reports of non-gonococcal non-meningococcal *Neisseria* infection take the form of case histories rather than reports of outbreaks (although one mild epidemic of meningitis due to *N flavescens* was reported 50 years ago[53]) suggesting minimal person to person transmission. As *Neisseria* organisms other than the gonococcus or meningococcus normally exist as inhabitants of the oropharynx, development of disease is probably due in most instances, to endogenous spread of infection and probably reflects either reduced resistance to infection on the part of the host or enhanced virulence of the infecting strain. In some of the reported cases it was evident that the patients were prone to infection as a result of immunosuppressive therapy or because of chronic lung disease, but in the majority of cases the underlying cause of disease was not known. In view of our current lack of knowledge concerning the pathogenesis of these infections it must be stressed that much of what follows is speculative.

The first stage in the development of diseases such as endocarditis, meningitis or septicaemia must involve the haematogenous spread of organisms from the oropharynx. Micro-organisms in the oropharynx enter the blood stream following oral trauma, which may be severe—for example dental extraction—or relatively mild—for example tooth brushing, chewing. Micro-organisms that enter the blood stream are usually eliminated within a short time, but the isolation of *Neisseria* organisms from blood in cases of endocarditis, meningitis or septicaemia suggests that they may be resistant to the bactericidal activity of human serum. Strains of gonococci vary in their susceptibility to killing by serum when cultured in vitro, with strains associated with disseminated infection being generally more serum-resistant than strains isolated from cases of localised infection.[94] It would clearly be of interest to see if other species of *Neisseria* isolated from blood were similarly serum-resistant in comparison with commensal strains of the same species which appear to be serum-susceptible.[95] An alternative explanation for the ability of *Neisseria* organisms to survive in the blood stream is that the patient's serum may be defective in killing micro-organisms. It is now known that deficiency of terminal components of the complement system predisposes to repeated systemic infection with *N gonorrhoeae* and *N meningitidis*.[96] It would be of value to know if such complement deficiencies are present in the sera of patients infected with other *Neisseria* species.

After invading the blood stream, the micro-organisms must be capable of colonising appropriate anatomical sites such as the heart or nervous system if they are to produce infection. If they are to colonise the heart effectively, for example, they must be capable of attaching to valve leaflets or other areas of the endocardium. Gould *et al*[97] reported that species of bacteria commonly associated with bacterial endocarditis adhered in significantly higher numbers

to the endothelial surfaces of human and canine aortic valve leaflets in vitro, than did bacteria not associated with this disease. In view of these findings, it would be of interest to determine if *Neisseria* organisms isolated from cases of endocarditis adhered to heart tissue more readily than organisms isolated from the healthy oropharynx. Attachment would also be an important prerequisite for the successful colonisation of the genital tract, either as the first step in the process of infection, or simply in the establishment of a commensal genital tract flora.

Once established at a potential site of infection, *Neisseria* organisms must be capable of resisting host defences. As with gonococcal and meningococcal infections, the host appears to respond to an opportunistic *Neisseria* infection with an acute inflammatory reaction. The persistence of *Neisseria* organisms in the presence of large numbers of polymorphonuclear leucocytes implies either that the bacteria are capable of resisting to some extent the bactericidal activity of these phagocytic cells, or that the polymorphonuclear leucocytes from patients with opportunistic *Neisseria* infections are defective at killing these organisms. This question could be resolved perhaps by performing in vitro phagocytosis studies with polymorphonuclear leucocytes from patients and from healthy donors, and by using *Neisseria* organisms of apparently differing virulence. Such studies have been reported previously for *N gonorrhoeae*.[98]

Conclusions

The great interest shown by researchers during the last few decades in the study of gonoccoci and meningococci has resulted in a steady increase in our knowledge and understanding of the diseases produced by these organisms. By way of contrast relatively little attention has been paid to the other *Neisseria* species, as they have generally been regarded as harmless organisms of little clinical importance. While it is true to say that the latter bacteria do not rank among the major pathogens encountered in the field of infectious diseases, it would appear that they may cause infections more frequently than is commonly appreciated, and microbiologists should guard against dismissing too readily as normal flora, *Neisseria* species isolated from clinical material.

Addendum After this paper was submitted for publication, a report appeared in the literature describing a case of osteomyelitis due to *N sicca*.

Reference

Doern GV, Blacklow NR, Gantz NM, Avcoin P, Fischer RA, Parker DS. *Neisseria sicca* osteomyelitis. *J Clin Microbiol* 1982; **16**:595–9.

References

[1] Brooks GF, Gotschlich EC, Holmes KK, Sawyer WD, Young FE, eds. *Immunobiology of Neisseria gonorrhoeae*. Washington DC: American Society for Microbiology, 1978.

[2] Danielsson D, Normark S, eds. *Genetics and immunobiology of pathogenic Neisseria*. Umea, Sweden 1980: University of Umea Press.

[3] Wilson GS, Smith MM. Observations on Gram-negative cocci of the nasopharynx, with description of *Neisseria pharyngis*. *J Pathol Bacteriol* 1928;**31**:597–608.

[4] Branham SE, Pelczar MJ, Family VIII. Neisseriaceae Prévot, 1933. Genus I. *Neisseria Trevisan* 1885. In: Breed RS, Murray EGD, Smith NR, eds. *Bergey's manual of determinative bacteriology* 7th ed. Baltimore: The Williams and Wilkins Co, 1957: 480–5.

[5] Kingsbury DT. Deoxyribonucleic acid homologies among species of the genus *Neisseria*. *J Bacteriol* 1967;**94**:870–4.

[6] Henriksen SD, Bøvre K. The taxonomy of the genera *Moraxella* and *Neisseria*. *J Gen Microbiol* 1968;**51**:387–92.

[7] Reyn A, Family I. Neisseriaceae Prévot 1933. Genus I. Neisseria Trevisan 1885. In: Buchanan RE, Gibbons NE, eds. *Bergey's manual of determinative bacteriology*, 8th ed. Baltimore: The Williams and Wilkins Co, 1974; 427–32.

[8] Connaughton FW, Rountree PM. A fatal case of infective endocarditis due to *Neisseria flava*. *Med J Aust* 1939;**2**:138–9.

[9] Matlage WT, Harrison PE, Greene JA. *Neisseria flava* endocarditis: With report of a case. *Ann Intern Med* 1950:**33**:1494–8.

[10] Scott RM. Bacterial endocarditis due to *Neisseria flava*. *J Pediatr* 1971;**78**:673–5.

[11] Major RH, Johnson EW. *Neisseria perflava* endocarditis; Recovery. *JAMA* 1945;**127**:1051–2.

[12] Breslin AB, Biggs JC, Hall GV. Bacterial endocarditis due to *Neisseria perflava* in a patient hypersensitive to penicillin. *Aust Ann Med* 1967;**16**:245–9.

[13] Clark H, Patton RD. Postcardiotomy endocarditis due to *Neisseria perflava* on a prosthetic aortic valve. *Ann Intern Med* 1968;**68**:386–9.

[14] Shaw FW. The pathogenicity of *Neisseria sicca*. *Science* 1949;**75**:488.

[15] Gay RM, Sevier RE. *Neisseria sicca* endocarditis: report of a case and review of the literature. *J Clin Microbiol* 1978;**8**:729–32.

[16] Ghoneim ATM, Tandon AP. Prosthetic valve endocarditis due to *Neisseria sicca*: a case report. *Indian Heart J* 1979;**31**:246–8.

[17] Clarke RM, Haining RB. *Neisseria catarrhalis* endocarditis. *Ann Intern Med* 1936–37;**10**:117–21.

[18] Pollock AA, Holzman RS. *Neisseria catarrhalis* endocarditis. *Ann Intern Med* 1976;**85**:206–7.

[19] Douer D, Danziger Y, Pinkhas J. *Neisseria catarrhalis* endocarditis. *Ann Intern Med* 1977;**86**:116.

[20] Brodie E, Adler JL, Daly AK. Bacterial endocarditis due to an unusual species of encapsulated *Neisseria: Neisseria mucosa* endocarditis. *Am J Dis Child* 1971;**122**:433–7.

[21] Dowling JN, Lee W-S, Sacco RJ, Ho M. Endocarditis caused by *Neisseria mucosa* in Marfan's syndrome. *Ann Intern Med* 1974;**81**:641–3.

[22] Drapkin MS. Endocarditis after the use of an oral irrigation device. *Ann Intern Med* 1977;**87**:455.

[23] Hennessey R, Reinhart JH, McGuckin MB. Endocarditis caused by *Neisseria mucosa* in a patient with a prosthetic heart valve. *Am J Med Technol* 1981;**47**:909–11.

[24] Goldstein JD, Endocarditis due to a *Neisseria pharyngis* organism. *Am J Med Sci* 1934;**187**:672–7.

[25] Shiling MS. Bacteriology of endocarditis with report of two unusual cases. *Ann Intern Med* 1939;**13**:476–86.

[26] Hudson R. *Neisseria pharyngis* bacteriaemia in a patient with subacute bacterial endocarditis. *J Clin Pathol* 1957;**10**:195–6.

[27] Linde LM, Heins HL. Bacterial endocarditis following surgery for congenital heart disease. *N Engl J Med* 1960;**263**:65–9.

[28] Graef I, De La Chapelle CE, Vance MC. *Micrococcus pharyngis siccus* endocarditis. *Am J Pathol* 1932;**8**:347–54.

[29] Weed MR, Clapper M, Myers GB. Endocarditis caused by the *Micrococcus pharyngis siccus:* Recovery after treatment with heparin and sulfapyridine. *Am Heart J* 1943;**25**:547–52.

[30] Schultz OT. Acute vegetative endocarditis with multiple secondary foci of involvement due to *Micrococcus pharyngitidis—siccae. JAMA* 1918;**71**:1739–41.

[31] Coulter CB. Gram-negative micrococcus causing fatal endocarditis. *Proc NY Pathol Soc* 1915;**15**:7–12.

[32] Dammin GJ. Subacute bacterial endocarditis caused by a hitherto undescribed Gram-negative coccus. *Ann Intern Med* 1941;**15**:756–65.

[33] Fainstein V, Musher DM, Young EJ. Purulent pericarditis due to *Neisseria mucosa. Chest* 1978;**74**:476–7.

[34] Noguchi TT, Nachum R, Lawrence CA. Acute purulent meningitis caused by chromogenic *Neisseria. Med Arts Sci* 1963;**17**:11–8.

[35] Sophian LH. A case of acute meningitis caused by *Neisseria perflava. Am J Med Sci* 1944;**207**:376–8.

[36] Benson H, Brennwasser R, D'andrea D. *Neisseria subflava* (Bergey) meningitis in an infant. *J Infect Dis* 1928;**43**:516–24.

[37] Lewin RA, Hughes WT. *Neisseria subflava* as a cause of meningitis and septicemia in children. *JAMA* 1966;**195**:821–3.

[38] Bansmer C, Brem J. Acute meningitis caused by *Neisseria sicca. N Engl J Med* 1948;**238**:596–7.

[39] Newing WJ, Christie R. Meningitis: Isolation of an organism resembling *Neisseria catarrhalis* from cerebrospinal fluid. *Med J Aust* 1947;**1**:306–7.

[40] Pfister LE, Gallagher MV, Potterfield TG, Brown DW. *Neisseria catarrhalis* bacteremia with meningitis. *JAMA* 1965;**193**:399–401.

[41] Cocchi P, Ulivelli A. Meningitis caused by *Neisseria catarrhalis. Acta Paediatr Scand* 1968;**57**:451–3.

[42] Elston HR, Quigley HJ, Fitch DM. Meningitis due to *Neisseria catarrhalis. Nebraska State Med J* 1970;**55**:369–71.

[43] Arora S, Chitkara NL. Non-pathogenic Neisserian *Neisseria catarrhalis* as cause of meningitis. *J Assoc Physicians India* 1973;**21**:255–7.

[44] Wilson WJ. A contribution to the bacteriology of cerebrospinal meningitis. *Lancet* 1908;i:1686–7.

[45] Garland J. A case of meningitis due to *Micrococcus catarrhalis. Am J Dis Child* 1923; **26**:600–2.

[46] Moersch FP. Meningitis due to *Micrococcus catarrhalis. Staff Meetings of the Mayo Clinic* 1928;**3**:238–9.

[47] Berger U, Aboulkhair I, Rottmann W. Septicaemia and meningitis caused by *Neisseria mucosa varietas heidelbergensis. Infection* 1974;**2**:108–10.

[48] Cowan ST. Unusual infections following cerebral operations: with a description of *Diplococcus mucosus. Lancet* 1938;ii:1052–4.

[49] Bray PT, Cruickshank JC. Meningitis due to *Diplococcus mucosus. Br Med J* 1943;i:601–2.

[50] Bishop LK, Randall CC. *Diplococcus mucosus* meningitis successfully treated with sulfadiazine and penicillin. *Am J Dis Child* 1947;**74**:725–9.

[51] Lauer BA, Fisher CE. *Neisseria lactamica* meningitis. *Am J Dis Child* 1976;**130**:198–9.

[52] Hansman D. Meningitis caused by *Neisseria lactamica. N Engl J Med* 1978;**299**:491.

[53] Branham SE. A new meningococcus-like organism *(Neiseria flavescens nsp)* from epidemic meningitis. *Public Health Rep* 1930;**45**:845–9.

[54] Prentice AW. *Neisseria flavescens* as a cause of meningitis. *Lancet* 1957;i:613–4.

[55] Reimann HA, Koucky RW. Meningitis caused by atypical Gram-negative cocci. *J Bacteriol* 1939;**37**:401–10.

[56] Edwards JL. An atypical *Neisseria* causing meningitis. *J Hyg* 1944;**43**:328–9.

[57] Christie ALM, Cook GT. Fatal meningitis due to a capsulated *Neisseria. J Hyg* 1947;**45**:149–50.

[58] Kippax PW, Saeed N, Pamplin WAV. An unusual *Neisseria* isolated from a case of meningitis. *J Clin Pathol* 1968;**21**:440–2.

[59] Muchmore HG, Venters HD. Purpura and septicemia due to *Neisseria subflava. N Engl J Med* 1968;**278**:1166–7.

[60] Feigin RD, Joaquin VS, Middelkamp JN. Purpura fulminans associated with *Neisseria catarrhalis* septicemia and meningitis. *Pediatrics* 1969;**44**:120–3.

[61] Burnett AK, Easton DJ, Gordon AM, Rowan RM. *Neisseria catarrhalis* septicaemia in acute lymphoblastic leukaemia. *Scott Med J* 1975;**20**:37–8.

[62] Thomson S, Gopaul D. *Neisseria pharyngis* septicaemia with associated disseminated intravascular coagulation. *Can J Med Technol* 1973;**35**:6–7.

[63] Wilson HD, Overman TL. Septicemia due to *Neisseria lactamica. J Clin Microbiol* 1976;**4**:214–5.

[64] Wertlake PT, Williams TW. Septicaemia caused by *Neisseria flavescens. J Clin Pathol* 1968;**21**:437–9.

[65] Brorson J-E, Axelsson A, Holm SE. Studies on *Branhamella catarrhalis (Neisseria catarrhalis)* with special reference to maxillary sinusitis. *Scand J Infect Dis* 1976;**8**:151–5.

[66] Coffey JD, Booth HN, Martin AD. Otitis media in the practice of paediatrics: Bacteriological and clinical observations. *Pediatrics* 1966;**38**:25–32.

[67] Coffey JD, Martin AD, Booth HN. *Neisseria catarrhalis* in exudate otitis media. *Arch Otolaryngol* 1967;**86**:403–6.

[68] Kamme C, Lundgren K, Mårdh P-A. The aetiology of acute otitis media in children. *Scand J Infect Dis* 1971;**3**:217–23.

[69] Lee W-S, Fordham T, Alban J. Otitis media caused by beta-lactamase-producing *Branhamella (Neisseria) catarrhalis. J Clin Microbiol* 1981;**13**:222–3.

[70] Leinonen M, Luotonen J, Herva E, Valkonen K, Mäkelä PH. Preliminary serologic evidence for a pathogenic role of *Branhamella catarrhalis. J Infect Dis* 1981;**144**:570–4.

[71] Schalén L, Christensen P, Kamme C, Miörner H, Pettersson K-I, Schalén C. High isolation rate of *Branhamella catarrhalis* from the nasopharynx in adults with acute laryngitis. *Scand J Infect Dis* 1980;**12**:277–80.

[72] Johnson MA, Drew WL, Roberts M. *Branhamella (Neisseria) catarrhalis*—A lower respiratory tract pathogen? *J Clin Microbiol* 1981;**13**:1066–9.

[73] McNeely DJ, Kitchens CS, Kluge RM. Fatal *Neisseria (Branhamella) catarrhalis* pneumonia in an immunodeficient host. *Am Rev Respir Dis* 1976;**114**:399–402.

[74] Srinivasan G, Raff MJ, Templeton WC, Givens SJ, Graves RC, Melo JC. *Branhamella catarrhalis* pneumonia. *Am Rev Respir Dis* 1981;**123**:553–5.

[75] Ninane G, Joly P, Piot P, Kraytman M. *Branhamella (Neisseria) catarrhalis* as pathogen. *Lancet* 1977;ii:149.

[76] Ninane G, Joly J, Kraytman M. Bronchopulmonary infection due to *Branhamella catarrhalis:* 11 cases assessed by transtracheal puncture. *Br Med J* 1978;i;276–8.

[77] Ninane G, Joly J, Kraytman M, Piot P. Bronchopulmonary infection due to β-lactamase-producing *Branhamella catarrhalis* treated with amoxycillin/clavulanic acid. *Lancet* 1978;ii:257.

[78] Percival A, Corkill JE, Rowlands J, Sykes RB. Pathogenicity of and β-lactamase production by *Branhamella (Neisseria) catarrhalis. Lancet* 1977;ii:1175.

[79] Alcid DV. *Neisseria sicca* pneumonia. *Chest* 1980;**77**:123–4.

[80] Thorsteinsson SB, Minuth JN, Musher DM. Postpneumonectomy empyema due to *Neisseria mucosa. Am J Clin Pathol* 1975;**64**:534–6.

[81] Fisher LS, Edelstein P, Guze LB. *Neisseria lactamicus* pharyngitis. *JAMA* 1975;**233**:22.

[82] Pykett AH. Isolation of *Neisseria lactamicus* from the nasopharynx. *J Clin Pathol* 1973;**26**:399–400.

[83] Carpenter CM. Isolation of *Neisseria flava* from the genitourinary

tract of three patients. *Am J Public Health* 1943;**33**:135–6.

[84] Wax L. The identity of *Neisseria* other than the gonococcus isolated from the genito-urinary tract. *J Vener Dis Inform* 1950;**31**:208–13.

[85] Wilkinson AE. Occurrence of *Neisseria* other than the gonococcus in the genital tract. *Br J Vener Dis* 1952;**28**:24–7.

[86] Johnston J. Nongonococcal Neisserian strains isolated from the genitourinary tract. *Am J Syph* 1951;**35**:79–82.

[87] Weaver JD. Nongonorrheal vulvovaginitis due to Gram-negative intracellular diplococci. *Am J Obstet Gynecol* 1950;**60**:257–60.

[88] Graber CD, Scott RC, Dunkelberg WE, Dirks KR. Isolation of *Neisseria catarrhalis* from three patients with urethritis and a clinical syndrome resembling gonorrhea. *Am J Clin Pathol* 1963;**39**:360–3.

[89] McCague JJ, McCague NJ, Altman CC. *Neisseria catarrhalis* urethritis: a case report. *J Urol* 1976;**115**:471.

[90] Blackwell C, Young H, Bain SSR. Isolation of *Neisseria meningitidis* and *Neisseria catarrhalis* from the genitourinary tract and anal canal. *Br J Vener Dis* 1978;**54**:41–4.

[91] Jephcott AE, Morton RS. Isolation of *Neisseria lactamicus* from a genital site. *Lancet* 1972;ii:739–40.

[92] Brunton WAT, Young H, Fraser DRK. Isolation of *Neisseria lactamica* from the female genital tract. *Br J Vener Dis* 1980;**56**:325–6.

[93] Coleman MB. An unusual strain of *Neisseria* isolated from the cervix uteri. *J Vener Dis Inform* 1946;**27**:159–60.

[94] Schoolnik GK, Buchanan TM, Holmes KK. Gonococci causing disseminated gonococcal infection are resistant to the bactericidal action of normal human sera. *J Clin Invest* 1976;**58**:1163–73.

[95] Johnson AP, Osborn MF, Taylor-Robinson D. Iron-mediated protection of *Neisseria gonorrhoeae* against killing by normal human serum. *Fems Microbiol Lett* 1978;**4**:225–7.

[96] Lee TJ, Schmayer A, Snyderman R, Yount WJ, Sparling PF. Familial deficiences of the sixth and seventh components of complement associated with bacteremic *Neisseria* infections. In: Brooks GF, Gotschlich EC, Holmes KK, Sawyer WD, Young FE, eds. *Immunobiology of Neisseria gonorrhoeae*. Washington DC: American Society for Microbiology, 1978:204–6.

[97] Gould K, Ramirez-Ronda CH, Holmes RK, Sanford JP. Adherence of bacteria to heart valves *in vitro*. *J Clin Invest* 1975;**56**:1364–70.

[98] Veale DR, Penn CW, Smith H. Capacity of gonococci to survive and grow within human phagocytes. In: Brooks GF, Gotschlich EC, Holmes KK, Sawyer WD, Young FE, eds. *Immunobiology of Neisseria gonorrhoeae*. Washington DC: American Society for Microbiology, 1978:227–31.

Requests for reprints to : Dr AP Johnson, Division of Communicable Diseases, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ. England.