The pathogenic potential of commensal species of *Neisseria*

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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 discussion 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 Smith³ 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

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
<i>N gonorrhoeae</i>	<i>N gonorrhoeae</i>
<i>N meningitidis</i>	<i>N meningitidis</i>
<i>N flava</i>	<i>N subflava</i>
<i>N perflava</i>	<i>N sicca</i>
<i>N subflava</i>	<i>N mucosa</i>
<i>N sicca</i>	<i>N flavescens</i>
<i>N catarrhalis</i>	
<i>N flavescens</i>	
<i>N haemolysans</i>	
<i>N caviae</i>	<i>Species incertae cedis</i>
	<i>N animalis</i>
	<i>N canis</i>
	<i>N cinerea</i>
	<i>N denitrificans</i>
	<i>N lactamica</i>
	<i>N suis</i>

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 defect¹⁰ and Marfan's syndrome²¹ 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
		G	M	F	S			
7th (1957)	<i>N gonorrhoeae</i>	+	—	—	—	—	ND	—
	<i>N meningitidis</i>	+	+	—	—	—	ND	—
	<i>N flava</i>	+	+	+	—	+	ND	+
	<i>N perflava</i>	+	+	+	+	+	ND	+
	<i>N subflava</i>	+	+	—	—	+	ND	+
	<i>N sicca</i>	+	+	+	+	—	ND	+
	<i>N catarrhalis</i>	—	—	—	—	—	ND	+
	<i>N flavescens</i>	—	—	—	—	+	ND	+
	<i>N haemolysans</i>	+	+	+	+	—	ND	+
	<i>N caviae</i>	—	—	—	—	+	ND	+
8th (1974)	<i>N gonorrhoeae</i>	+	—	—	—	—	—	—
	<i>N meningitidis</i>	+	+	—	—	—	V	—
	<i>N subflava</i>	+	+	V	V	+	V	d
	<i>N sicca</i>	+	+	+	+	d	+	d
	<i>N mucosa</i>	+	+	+	+	—	+	+
	<i>N flavescens</i>	—	—	—	—	+	—	+

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		
<i>N. flava</i>	20	F	Connaughton and Rountree ⁸	1939
	14	F	Matlage <i>et al</i> ⁹	1950
	5	F	Scott ¹⁰	1971
<i>N. perflava</i>	45	M	Major and Johnson ¹¹	1945
	44	M	Breslin <i>et al</i> ¹²	1967
	47	M	Clark and Patton ¹³	1968
<i>N. sicca</i>	12	M	Shaw ¹⁴	1949
	60	F	Gay and Sevier ¹⁵	1978
	21	M	Ghoneim and Tandon ¹⁶	1979
<i>N. catarrhalis</i>	15	F	Clarke and Haining ¹⁷	1936
	21	M	Clarke and Haining ¹⁷	1936
	69	F	Pollock and Holzmänn ¹⁸	1976
	45	F	Douer <i>et al</i> ¹⁹	1977
<i>N. mucosa</i>	9	M	Brodie <i>et al</i> ²⁰	1971
	19	M	Dowling <i>et al</i> ²¹	1974
	54	M	Drapkin ²²	1977
	40	M	Hennessey <i>et al</i> ²³	1981
<i>N. pharyngis</i>	21	F	Goldstein ²⁴	1934
	26	M	Shilling ²⁵	1939
	21	F	Hudson ²⁶	1957
	15	M	Linde and Heins ²⁷	1960
<i>Micrococcus pharyngis siccus</i>	27	M	Graef <i>et al</i> ²⁸	1932
	14	F	Weed <i>et al</i> ²⁹	1943
<i>Micrococcus pharyngitidis-sicca</i>	25	M	Schultz ³⁰	1918
Unidentified	45	M	Coulter ³¹	1915
	25	M	Shilling 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 endocarditis¹³—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		
<i>N. flava</i>	8 days	M	Noguchi <i>et al.</i> ³⁴	1963
<i>N. perflava</i>	31	M	Sophian ³⁵	1944
<i>N. subflava</i>	7 months	M	Benson <i>et al.</i> 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
	6½	M	Bansmer and Brem ³⁸	1948
Organism resembling				
<i>N. catarrhalis</i>	45	F	Newing and Christie ³⁹	1947
<i>N. catarrhalis</i>	2½	M	Pfister <i>et al.</i> ⁴⁰	1965
	14 months	F	Cocchi and Olivelli ⁴¹	1968
	36	M	Elston <i>et al.</i> ⁴²	1970
	3	M	Arora and Chitkara ⁴³	1973
<i>Micrococcus catarrhalis</i>	3 months	—	Wilson ⁴⁴	1908
	5	F	Garland ⁴⁵	1923
	31	F	Moersch ⁴⁶	1928
<i>N. mucosa</i>	5	F	Berger <i>et al.</i> ⁴⁷	1974
<i>Diplococcus mucosus</i>	—	—	Cowan ⁴⁸	1938
	29	M	Bray and Cruickshank ⁴⁹	1943
	3 months	F	Bishop and Randell ⁵⁰	1947
<i>N. lactamica</i>	7 months	F	Lauer and Fisher ⁵¹	1976
	6	M	Hansman ⁵²	1978
<i>N. flavescens</i>	—	—	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 <i>et al.</i> 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		
<i>N. flava</i>	10 months	F	Kostmann*	1939
	21	M	Hillemand <i>et al.</i> *	1951
<i>N. catarrhalis</i>	6 months	—	Mayerhofer-Lateiner*†	1918
	—	M	Cot and Robert†‡	1921
	35	M	Gaupp and Axen*†	1933
	—	—	Zoeller <i>et al.</i> *†	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 <i>et al.</i> *	1960
	—	—	Cassoute and Gibaud‡	1920
<i>N. mucosa</i>	7 weeks	—	Neal‡	1922
	12	F	Véron <i>et al.</i> §	1961
	6 months	—	Sirot and Cluzel§	1972
	3	—	Sirot and Cluzel§	1972
<i>N. pharyngis</i>	22	M	Engel and Löfgren*	1941
	49	F	Engel and Löfgren*	1941
<i>Diplococcus pharyngis flavus</i> II	52	F	Emile-Weil <i>et al.</i> *	1933
<i>Diplococcus pharyngis flavus</i> III	20	M	Brunel and Dérobert*	1937
'Meningococcus-like' organism	8½	M	Reuss†	1922
<i>N. capsulata</i>	—	—	Courtois <i>et al.</i>	1954

*For reference see Noguchi *et al.*³⁴†For reference see Beason *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				Author(s)	Year published
	No of inflammatory cells (cells/litre)	Glucose (mmol/l)	Protein (g/l)	Gram-negative diplococci seen in smear		
<i>N. perflava</i>	1.5×10^{10}	NR	NR	+	Sophian ³⁵	1944
<i>N. subflava</i>	4.8×10^9	0.17	1.9	+	Lewin and Hughes ³⁷	1966
	1.9×10^9	0.22	1.4	+	Lewin and Hughes ³⁷	1966
	4.0×10^6	1.7	0.4	+	Lewin and Hughes ³⁷	1966
<i>N. sicca</i>	4.2×10^9	4.6	0.8	—	Bansmer and Brem ³⁸	1948
<i>N. catarrhalis</i>	3.0×10^9	NR	NR	+	Pfister <i>et al.</i> ⁴⁰	1965
	1.2×10^9	1.7	0.7	+	Cocchi and Olivelli ⁴¹	1968
	7.6×10^9	2.1	3.5	+	Elston <i>et al.</i> ⁴²	1970
	10–12 HPF	1.4	0.7	+	Arora and Chitkara ⁴³	1973
<i>M. catarrhalis</i>	1.5×10^9	1.9	increased	+	Garland ⁴⁵	1923
<i>N. mucosa</i>	2.3×10^9	Normal	Normal	—	Berger <i>et al.</i> ⁴⁷	1974
(<i>D. mucosus</i>)	3.3×10^8	NR	2.4	+	Bray and Cruickshank ⁴⁹	1943
	2.0×10^8	1.9	1.9	+	Bishop and Randall ⁵⁰	1947
<i>N. lactamica</i>	1.3×10^{10}	Not detected	2.5	—	Lauer and Fisher ⁵¹	1976
<i>N. flavescens</i>	2.6×10^7	4.4	0.5	+	Prentice ⁵⁴	1957
Undescribed	2.9×10^8	Not detected	2.0	+	Christie and Cook ⁵⁷	1947
	1.1×10^8	4.3	0.3	NR	Kippax <i>et al.</i> 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 $1.2 \times 10^9/l$ 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 ≤ 1.7 mmol/l, and about half had protein concentrations > 1.5 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				
<i>N subflava</i>	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 ⁵⁷	1966
<i>N subflava</i>	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 ⁵⁷	1966
<i>N subflava</i>	10	M	Fever, nausea, stomach ache, mild pharyngitis, macular-purpuric skin rash, patient recovered.	Bacteria isolated from blood	Muchmore and Venters ⁵⁹	1968
<i>N catarrhalis</i>	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 <i>et al</i> ⁶⁰	1969
<i>N catarrhalis</i>	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 <i>et al</i> ⁶¹	1975
<i>N pharyngis</i>	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
<i>N lactamica</i>	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
<i>N flavescens</i>	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 cough³⁷⁻⁶⁰ (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 <i>N catarrhalis</i> (<i>Branhamella catarrhalis</i>)	Predisposing host factor	Author(s)	Year published
Maxillary sinusitis	Complement-fixing antibodies present in sera of some patients.	ND	Brorson <i>et al</i> 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 <i>et al</i> ⁶⁶ Coffey <i>et al</i> ⁶⁷ Kamme <i>et al</i> ⁶⁸ Lee <i>et al</i> ⁶⁹ Leinonen <i>et al</i> ⁷⁰	1966 1967 1971 1981 1981
Laryngitis	Organisms isolated as sole pathogen from nasopharynx in 55% of patients studied.	None	Schalén <i>et al</i> ⁷¹	1980
Bronchitis or pneumonia	Predominant organisms in sputum.	All patients had chronic underlying lung disease.	Johnson <i>et al</i> 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. One patient had chronic lymphocytic leukaemia and another was an alcoholic with chronic obstructive pulmonary disease. Patients were miners with altered pulmonary function; they all suffered from repeated respiratory tract infections and many had received corticosteroids.	McNeely <i>et al</i> ⁷³ Srinivasan <i>et al</i> ⁷⁴ Ninane <i>et al</i> ⁷⁵ Ninane <i>et al</i> ⁷⁶ Ninane <i>et al</i> ⁷⁷	1976 1981 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), tetracycline⁷² or a combination of amoxycillin and clavulanic-acid⁷⁷ (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 lactamica* 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 lactamica* 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
<i>N flava</i>	Carpenter ⁸³	1943
	Wax ⁸⁴	1950
	Wilkinson ⁸⁵	1952
<i>N subflava</i>	Johnston ⁸⁶	1951
	Wax ⁸⁴	1950
<i>N sicca</i>	Wax ⁸⁴	1950
	Weaver ⁸⁷	1950
	Wilkinson ⁸⁵	1952
<i>N catarrhalis</i>	Wax ⁸⁴	1950
	Wilkinson ⁸⁵	1952
	Graber <i>et al</i> ⁸⁸	1963
	McCague <i>et al</i> ⁸⁹	1976
	Blackwell <i>et al</i> ⁹⁰	1978
	Jephcott and Morton ⁹¹	1972
<i>N lactamicus</i>	Brunton <i>et al</i> ⁹²	1980
<i>N lactamica</i>	Wax ⁸⁴	1950
<i>N flavescens</i>		
Aberrant strain of <i>N catarrhalis</i> or <i>N gonorrhoeae</i>	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 ago⁵³) 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 gonococci 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*.

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Doern GV, Blacklow NR, Gantz NM, Avcoin P, Fischer RA,

Parker DS. *Neisseria sicca* osteomyelitis. *J Clin Microbiol* 1982; 16:595-9.

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