Clinical Microbiology of Coryneform Bacteria

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INTRODUCTION

During the last few years, we have witnessed a massive increase in the number of publications related to the clinical microbiology of coryneform bacteria. There are many reasons for this: (i) there are a large number of immunocompromised patients whose diagnosis and treatment have become ever more intensive and invasive, resulting in better growth conditions for microbial aggressors; (ii) up to now, the pathogenic potential of coryneform bacteria has been underestimated; and (iii) there has been an increased interest in taxonomy, resulting in the reclassification of taxa defined earlier and in precise descriptions of both established and entirely new taxa. From our daily work in reference laboratories, we know that many colleagues are still confused by all these dramatic changes. Therefore, we thought it appropriate to present a comprehensive review of the clinical microbiology of coryneform bacteria with an emphasis on the developments within the last 6 years. Lipsky et al. (254) and Coyle and Lipsky (91) had reviewed this topic in 1982 and 1990, respectively. The present review aims at continuing this tradition.

When clinical microbiologists refer to coryneform bacteria, they often use terms like "gram-positive rods," "diphtheroids," and "*Corynebacterium* species." The authors of this review prefer the term "coryneform bacteria," which comprises aerobically growing, asporogenous, non-partially-acid-fast, irregularly shaped gram-positive rods. It is acknowledged that the term "coryneform" does not entirely characterize the bacteria discussed here, since some bacteria covered are not club-shaped and may even exhibit branching filaments, characters that are never observed for true *Corynebacterium* species. However, to facilitate the description and to summarize the bacteria reviewed in a single term, the expression "coryneform" will be used throughout.

Based on the given definition of coryneform bacteria, several genera will be excluded from this review; these include *Bacillus*, *Kurthia*, *Listeria*, *Lactobacillus*, and *Erysipelothrix*. In addition, *Gardnerella vaginalis* and the long-established *Actinomyces* species (except *A. pyogenes*) will not be covered by this review. For aerobic, non-partially-acid-fast actinomycetes (*Actinomadura* spp., *Dermatophilus congolensis*, *Amycolata* spp., *Micromonospora* spp., *Nocardiopsis dassonvillei*, and *Streptomyces* spp.), the reader is referred to the excellent review by McNeil and Brown (283). *Oerskovia* spp. and *Rothia dentocariosa* will also be discussed here. Medically relevant genera covered by the present review are listed in Table 1.

Identification of coryneform bacteria to the species level often causes problems but should be performed whenever they grow in pure culture from clinical specimens and/or when they represent the predominant organisms in normally sterile samples. According to von Graevenitz et al., it is worthwhile to identify coryneform bacteria to the species level in order to detect unsuspected species, to ascribe potential pathogenicity to species so far thought to be nonpathogenic, and to outline hitherto undescribed species (441).

During the last few years, there has been an increased number of case reports claiming an association of coryneform bacteria with disease. Coyle and Lipsky clearly stated that the "recognition of infections caused by coryneform bacteria is highly dependent on the laboratorian's ability to identify these species" (91). We completely agree with their statement and believe that many case reports claiming an association of coryneform bacteria with disease were inappropriate or simply wrong. Again, there are many reasons: (i) the laboratorian cannot rely entirely on the databases of commercial identification systems, because they may be incorrect or cover a limited

number of taxa only; (ii) the methods used for identification were inappropriate (e.g., because of lack of chemotaxonomic investigations); (iii) there have been significant changes in the taxonomy of coryneform bacteria; and (iv) the distinction between colonization and infection has not been made in every case. Therefore, we will also critically review recent case reports claiming an association of certain coryneform bacteria with disease. Finally, we will present the minimal microbiological requirements for publications on associations of coryneform bacteria with disease.

To facilitate comprehension, identification of and infections caused by certain taxa of coryneform bacteria will be discussed together. The sequence in which the different taxa are discussed does not reflect their prevalence or their clinical importance but is based on historical, biochemical, and chemotaxonomic features.

IDENTIFICATION OF CORYNEFORM BACTERIA

D. G. Hollis and R. E. Weaver, Special Bacteriology Laboratory, Centers for Disease Control and Prevention (CDC), Atlanta, Ga., were the first to systematically examine the full range of coryneform bacteria isolated from clinical specimens (204). Their guide for the identification of gram-positive rods turned out to be an invaluable source for clinical microbiologists aiming to identify clinical isolates and became the basis for later taxonomic investigations on coryneform bacteria. It is worth noting that the last edition of *Bergey's Manual of Systematic Bacteriology*, vol. 2, in 1986 lists 17 *Corynebacterium* species (not all medically relevant) (76), whereas between 1987 and 1995, 11 new *Corynebacterium* species have been established (see below), many of them representing previous CDC coryneform groups defined by Hollis and Weaver (204) (Table 2).

In general, most coryneform taxa can be identified to the species level by methods that are also used in the differentiation of other medically important bacteria. We wish to emphasize the value of a Gram stain for the differentiation of coryneform bacteria (72). The Gram stain appearance may even serve as an adjunct in the assignment to a certain genus (e.g., club-shaped rods are observed in true members of the genus *Corynebacterium* only). Clinical microbiologists, however, must not misidentify rapidly growing, partially or even fully acid-fast

TABLE 1. Genera of aerobically growing gram-positive rods

Low G+C content	High G+C content (medically relevant coryneforms)	High G+C content (medically nonrelevant coryneforms)	High G+C content (partially acid fast or acid fast)
Bacillus	*Actinomyces*	*Agrococcus*	*Dietzia*
Clostridium	*Arcanobacterium*	*Agromyces*	*Gordona*
Erysipelothrix	*Arthrobacter*	*Brachybacterium*	*Mycobacterium*
Gardnerella	*Aureobacterium*	*Clavibacter*	*Nocardia*
Lactobacillus	*Brevibacterium*	*Curtobacterium*	*Rhodococcus*
Listeria	*Cellulomonas*	*Jonesia*	*Tsukamurella*
	Corynebacterium	*Rathayibacter*	
	"*Corynebacterium aquaticum*"	*Renibacterium*	
	Dermabacter	*Sanguibacter*	
	Exiguobacterium	*Terrabacter*	
	Microbacterium		
	Oerskovia		
	Propionibacterium		
	Rothia		
	Turicella		

TABLE 2. Chronology of the definitions of new
Corynebacterium species

Status in 1986 (76)[a]	Status in 1996		
	Yr of definition	Species defined (reference)	Previous designation
C. diphtheriae	1987	*C. jeikeium* (214)	CDC JK
C. pseudotuberculosis	1988	*C. amycolatum* (75)	CDC F-2, I-2
C. xerosis	1991	*C. accolens* (309)	CDC G-1
C. pseudodiphtheriticum	1992	*C. urealyticum* (336)	CDC D-2
(*C. kutscheri*)	1993	*C. afermentans* (360)	CDC ANF-1
C. minutissimum	1993	*C. propinquum* (357)	CDC ANF-3
C. striatum	1995	*C. macginleyi* (362)	CDC G-1
(*C. renale*)	1995	*C. ulcerans* (365)	"*C. ulcerans*"
(*C. cystitidis*)	1995	*C. argentoratense* (363)	
(*C. pilosum*)	1995	*C. glucuronolyticum* (142)	
(*C. mycetoides*)	1995	*C. auris* (148)	CDC ANF-1
C. matruchotii			
(*C. flavescens*)			
(*C. vitarumen*)			
(*C. glutamicum*)			
(*C. callunae*)			
(*C. bovis*)			

[a] The use of parentheses indicates a species that, at present, is not recognized as medically relevant.

organisms as coryneform bacteria solely on the basis of their Gram stain appearance. For example, Barnass et al. reported on a vancomycin-resistant "*Corynebacterium*" species growing on MacConkey agar (19), which we could later identify as *Mycobacterium fortuitum* (141). Characteristics such as colony size, pigmentation, odor of colonies, and presence of hemolysis are also useful for the identification of coryneform bacteria.

The following features are key reactions for the differentiation of coryneform bacteria: catalase, fermentative or oxidative metabolism, and motility (439). The initial screening reactions should also include nitrate reduction; urea production; esculin hydrolysis; acid production from glucose, maltose, sucrose, mannitol, and xylose; and the CAMP reaction with a β-hemolysin-producing strain of *Staphylococcus aureus* (ATCC 25923) (439). This system is a modified and shortened version of the Hollis and Weaver system which dominated the identification of coryneform bacteria during the 1980s. However, in the early 1990s, the API (RAPID) Coryne strip (API bioMérieux, La-Balme-les-Grottes, France) became available and is now widely used. This system includes enzymatic tests as well as carbohydrate fermentation reactions and is read normally after 24 h but in certain cases after 48 h of incubation. Freney et al. found that the API Coryne system identified about 98% of 240 isolates correctly to the species level, with 32% of the total strains requiring additional tests to arrive at a final identification (140). However, this study was problematic as the authors did not include coryneform bacteria which were not included in the database. Gavin et al. observed that after 24 h of incubation, the API Coryne system identified about 84% of 177 strains tested to the correct species with no additional tests and that the majority of misidentified and unidentified isolates belonged either to species not included in the database or to certain CDC coryneform groups (169). The evaluation of the API Coryne system by Soto et al. showed that about 88% of the 160 strains tested were correctly identified (including a total of 22% of all strains for which additional tests had to be performed) and that 11% of the unidentified rods were not included in the system's database (410). Work is currently in progress to update and extend the API Coryne database (141).

The only other commercially available identification system for coryneform bacteria is the Biolog system (Biolog, Hazelwood, Calif.). This system uses a different approach for the identification of coryneform bacteria than the API Coryne system as it is based on utilization reactions only. Lindenmann et al. found that the Biolog system (release 3.50) identified only about 60% of all 174 strains tested to the correct genus or to genus and species after 24 h of incubation (251). However, Biolog's database for coryneform bacteria has now been significantly improved (release 3.70) and, in contrast to the API Coryne system, may provide reliable identifications for some taxa (e.g., *Arcanobacterium haemolyticum*) after only 4 h of incubation (251). The Biolog system may serve as a useful adjunct in taxonomic investigations of coryneform bacteria.

Kämpfer demonstrated the use of glycosidase tests by using fluorogenic substrates with high separation values at the genus level for coryneform bacteria (223). The same author has published on numerical classification of coryneform bacteria (225, 226). However, this approach using hundreds of phenotypic tests for identification of a coryneform bacterium is not applicable in the routine clinical laboratory.

For the identification of some coryneform bacteria, chemotaxonomic investigations (e.g., cell wall analyses) have to be performed. However, these techniques are reserved for the reference laboratory and will not be discussed in detail here (Table 3). The analysis of cellular fatty acid (CFA) patterns by means of the Sherlock system (MIDI Inc., Newark, Del.) is an extremely useful method for identification of coryneform bacteria (30, 440). In our experience, CFA analyses can clearly confirm the assignment of a strain to a particular genus but identification of coryneform bacteria to species level with the Sherlock system is problematic because species of the same genus very often exhibit very similar patterns and quantitative CFA patterns are strongly dependent on incubation conditions. Nevertheless, the Sherlock system supplements the identification of coryneform bacteria in the reference laboratory, in particular when the laboratory has created its own database. Identification to species level within the genus *Corynebacterium* can, in some cases, be accomplished by high-performance liquid chromatography of mycolic acids (102, 103). Molecular genetic techniques for species identification of *Corynebacterium* strains include restriction analysis of amplified 16S rDNA (434) and repetitive extragenic palindromic PCR typing (70).

von Graevenitz et al. evaluated a polyphasic approach for the identification of coryneform bacteria based on biochemical characteristics, CFA patterns, and cell wall analyses (441). With this system, they were able to identify 76% of 202 consecutive clinical isolates to the species level; 21% of the isolates could be identified to the genus level only, and 3% remained unidentified. von Graevenitz et al. recommended their multisystem approach for the identification of coryneform bacteria until the databases of commercial systems (API Coryne, Sherlock TSBA and CLIN databases) are broader and more indepth.

SUSCEPTIBILITY TESTING OF CORYNEFORM BACTERIA

Thus far, the National Committee for Clinical Laboratory Standards (NCCLS) has not published specific guidelines for susceptibility testing of coryneform bacteria, in particular for fastidious organisms like lipophilic corynebacteria. This may reflect the underrecognition or underestimation of coryneform bacteria isolated from clinical specimens. Presently, it is not clear which medium should be used for growing the inoculum for susceptibility testing, which medium to use for broth microdilution or agar dilution techniques, or which incubation

TABLE 3. Some characteristics of coryneform genera

Characteristic	Value for:						
	Corynebacterium	*Turicella*	*Arthrobacter*	*Brevibacterium*	*Dermabacter*	*Oerskovia*	*Cellulomonas*
G+C (mol%)[a]	46–74	65–72	59–70	60–64	62	71–75	71–76
Mycolic acids	v[b] (C_{22-38})	−	−	−	−	−	−
CFA							
Rank	18:1 ωc9	18:1 ωc9	15:0ai	15:0 ai	17:0 ai	15:0 ai	15:0 ai
	16:0	16:0	17:0ai	17:0 ai	15:0 ai	15:0 i	16:0
	18:0	18:0	15:0i	15:0 i	16:0 i	17:0 ai	
TBSA[c]	v	+	−	−	−	−	−
Diamino acid[d]	*m*-DAP	*m*-DAP	L-Lys	*m*-DAP	*m*-DAP	L-Lys	L-Orn
Arabinogalactan	+	+	−	−	−	−	−
Major menaquinones	MK-9 (H_2), MK-8 (H_2)	MK-10, MK-11	MK-9 (H_2), MK-8, MK-9	MK-8 (H_2)	MK-9, MK-8, MK-7	MK-9 (H_4)	MK-9 (H_4)
Microscopy	Irregular, V forms, clubbing, palisading	Irregular, long rods	Rod-coccus cycle, "jointed rods"	Rod-coccus cycle	Short to coccoid	Coccoid to rudimentary filaments, vegetative hyphae	Short, thin, branching

[a] G+C, guanine + cytosine.
[b] v, variable.
[c] TBSA, tuberculostearic acid (10-methyl-octadecanoic acid).
[d] *m*-DAP, *meso*-diaminopimelic acid; Lys, lysine; Orn, ornithine; DAB, diaminobutyric acid.

conditions should be used. For fastidious organisms such as lipophilic corynebacteria, the supplementation of media with sheep blood or Tween 80 seems to be advisable, and some *Actinomyces* spp. grow best aerobically in an atmosphere enriched with CO_2. In our experience, most disk diffusion tests as well as tests of MICs for coryneform bacteria are readable after 24 h of incubation; for a few strains, 48 h is required. Finally, the interpretive categories for breakpoints and zone diameters need to be established, in particular for penicillins. In a pragmatic approach, the NCCLS categories for staphylococci have been applied when testing coryneforms for susceptibility to penicillin (156), whereas other authors recommend the use of the *Streptococcus* interpretive criteria instead of those for *Listeria monocytogenes* when assessing the activity of penicillin against *Corynebacterium* spp. (454).

The E-test showed a good correlation of MICs with both broth microdilution and agar dilution in tests with *Corynebacterium* spp. (269, 469). To our knowledge, no data have been published on the use of commercial panels or automated methods for susceptibility testing of coryneform bacteria.

Antimicrobial susceptibility patterns of coryneform bacteria have not been studied systematically. Only very few comprehensive studies on this subject are extant (154, 408, 457). A few other studies have focused on particular organisms such as *Corynebacterium jeikeium*, *C. urealyticum* (166, 334, 406), *C. striatum* (270), and *A. haemolyticum* (53) or on selected antibiotics (272). Known susceptibility patterns for coryneform bacteria are given in the text for each single taxon.

CORYNEFORM BACTERIA

Nonlipophilic, Fermentative Corynebacteria

***C. diphtheriae* group.** Recent 16S rRNA gene sequence analysis and DNA-DNA hybridization studies have shown that the *C. diphtheriae* group of organisms includes not only *C. diphtheriae* (with the four biotypes gravis, mitis, belfanti, and intermedius, which are highly related) and *C. pseudotuberculosis* but also *C. ulcerans* as a valid independent species (326, 365, 376). Colonies of all of these form grey-brown haloes on Tinsdale medium (due to the action of cystinase) and contain large amounts (23 to 29%) of a fatty acid that is unusual for *Coryne-*

bacterium spp., i.e., $C_{16:1\omega9cis}$ (30). However, in the recent MIDI software (version 3.9), this peak, at equivalent chain length 15.817, represents part of the so-called "summed feature 4" (i.e., $C_{16:1\omega7cis}/C_{15iso2}OH$).

The *C. diphtheriae* group of organisms and *C. macginleyi* are among the few corynebacteria that are consistently pyrazinamidase negative (Table 4). Based on these tests, screening significant corynebacterial isolates for cystinase and pyrazinamidase production has been proposed (84). *C. diphtheriae* (all biotypes), *C. ulcerans*, and *C. pseudotuberculosis* are also similar in that all can harbor the phage-borne diphtheria toxin gene. However, *C. ulcerans* and *C. pseudotuberculosis* can be distinguished from *C. diphtheriae* because both are positive for urease and in the reverse CAMP test. In addition, *C. ulcerans* ferments glycogen, starch, and trehalose.

16S rRNA gene analysis revealed that *C. kutscheri* and *C. argentoratense* are closely related to *C. diphtheriae* although they are biochemically less similar (326, 376).

There are four biotypes of *C. diphtheriae*: gravis, mitis, belfanti, and intermedius. Previously, *C. diphtheriae* biotype belfanti was considered a variant of *C. diphtheriae* biotype mitis. Historically, the biotypes of *C. diphtheriae* were defined by differences in both colony morphology and biochemical tests (237). In practice, only *C. diphtheriae* biotype intermedius can be easily distinguished on the basis of colony morphology (92, 237). It forms small grey or translucent colonies that are typical of the lipophilic strains (see below), whereas biotypes mitis and gravis both produce larger, whiter, and more opaque colonies that are essentially indistinguishable. *C. diphtheriae* biotype intermedius can be distinguished from *C. diphtheriae* biotype mitis because the former is dextrin positive. *C. diphtheriae* biotypes mitis and gravis can be distinguished by their glycogen and starch reactions (*C. diphtheriae* biotype gravis is positive for both). *C. diphtheriae* biotype belfanti is nitrate negative but otherwise resembles *C. diphtheriae* biotype mitis. The API Coryne system, which includes glycogen and nitrate, can distinguish *C. diphtheriae* biotypes belfanti and gravis but lumps together *C. diphtheriae* biotypes mitis and intermedius. Coyle and colleagues have examined ATCC reference strains of *C. diphtheriae* and found the intermedius strains had been mistyped and were actually mitis types (92). *C. diphtheriae*

TABLE 3—*Continued*

				Value for:				
Sanguibacter	*Microbacterium*	*Aureobacterium*	"*C. aquaticum*"	*Propionibacterium*	*Propioniferax*	*Rothia*	*Actinomyces*	*Exiguobacterium*
69–70	69–75	67–70	73	57–68	59–63	47–53	55–69	47
—	—	—	—	—	—	—	—	—
16:0	15:0 ai	15:0 ai	17:0 ai	15:0 i	15:0 ai	15:0 ai	16:0	17:0 i
15:0 ai	17:0 ai	17:0 ai	15:0 ai	15:0 ai	15:0 i	17:0 ai	18:1 ω9c	15:0 i
14:0	16:0 i	16:0 i	16:0 i	16:0	16:0 i	16:0	18:0	16:0
—	—	—	—					
L-Lys	L-Lys	Orn	DAB	LL-DAP, *m*-DAP	LL-A$_2$ pm	L-Lys	L-Lys, L-Orn	L-Lys
—							—	
MK-9 (H$_4$)	MK-12, MK-11	MK-11, MK-12	MK-10, MK-11	MK-9 (H$_4$)	MK-9 (H$_4$)	MK-7	MK-10 (H$_4$)	MK-7
Irregular, short	Short, thin	Irregular, V forms, coccoid	Short, irregular, slender	Irregular, sometimes coccoid, bifid, branched	Irregular, clusters, V forms	Diphtheroid, filamentous, or coccoid	Variable, often branching	Rod-coccus cycle

biotype intermedius seems to be the least common biotype. A specific Gram stain morphology for each biotype has been described (315): *C. diphtheriae* biotype mitis as long, pleomorphic, but rigid club-shaped rods; *C. diphtheriae* biotype intermedius as highly pleomorphic, ranging from very long to very short rods; and *C. diphtheriae* biotype gravis as usually short, coccoid, or pyriform rods morphologically resembling *C. pseudodiphtheriticum*. However, Gram stain morphology of organisms grown on sheep blood Trypticase soy agar does not seem to be distinctive for type (70). It is interesting that colonial morphotypes are stable even after extensive subculturing and consistent during an epidemic, although colony types have not been associated with distinct genotypes (237). However, different biotypes can be present during a single epidemic and can, in fact, be isolated from the same individual (62). For patient care, the differentiation of colonial types may have lost its relevance, since a relationship between severity of disease and biotype can no longer be recognized (237). However, typing can have epidemiological significance (see below).

Isolation of *C. diphtheriae* from traditional sites, i.e., pharynx and skin lesions, is facilitated by plating on a selective medium such as cystine tellurite blood agar or by picking multiple coryneform colonies from a semiselective medium such as colistin-nalidixic acid blood agar. Wilson et al. recommended that all colonial types recovered on Hoyle's selective medium be identified, as they found that the throat swab of one asymptomatic carrier who had contact with a patient with diphtheria grew both *C. pseudodiphtheriticum* and a nontoxigenic strain of *C. diphtheriae* (458). Clinical suspicion of diphtheria must be conveyed to the laboratory for initiation of proper procedures (130). Recognition of *C. diphtheriae* as a significant pathogen from blood or other unusual sites is usually related to complete identification of the organism.

C. diphtheriae strains isolated from different epidemics and geographical regions can vary in biotype, in the proportion of toxinogenic strains, and in clonal origin. Recent clinical strains that were submitted for toxin testing in the United Kingdom included 31 nontoxinogenic *C. diphtheriae* strains (19 *C. diphtheriae* biotype gravis, 9 *C. diphtheriae* biotype belfanti, and 3 *C. diphtheriae* biotype mitis) and 19 toxinogenic *Corynebacterium* strains (2 *C. diphtheriae* biotype gravis, 15 *C. diphtheriae* biotype mitis, and 2 *C. ulcerans*) (320). In Switzerland, all of the isolates from drug abusers were nontoxinogenic *C. diphtheriae* biotype mitis (179, 183), whereas in the former Soviet Union, a majority of the strains were toxinogenic *C. diphtheriae* bio-

type gravis and the rest were toxinogenic *C. diphtheriae* biotype mitis (59, 110, 264). Regarding the epidemiology of *C. diphtheriae*, the reader is also referred to the recent reviews by Efstratiou and George (119), Hardy et al. (194), and workers of the World Health Organization (163, 164) and to the more historical one by Saragea et al. (383).

There are several useful techniques for strain tracking or for the determination of clonal origin that are more discriminatory than colony type or toxin testing. In the past, phage typing and serotyping have been used but were limited because many strains were untypeable. These methods have been superseded by molecular techniques such as analysis of whole-cell peptide, genomic DNA restriction fragment length polymorphism (RFLP), and ribotyping (93, 110, 183, 237, 351, 379, 444). Recently, Nakao et al. demonstrated the usefulness of PCR single-strand conformation polymorphism analysis of diphtheria toxin gene and its regulatory element (*dtx*R) for epidemiological investigations of *C. diphtheriae* strains isolated during the ongoing epidemic in the former Soviet Union (303). The molecular epidemiology of 106 strains of *C. diphtheriae* (81 *C. diphtheriae* biotype gravis and 25 *C. diphtheriae* biotype mitis) from Russia, Estonia, and Finland were examined by ribotyping and pulsed-field gel electrophoresis (110). De Zoysa et al. (110) found five distinct strains with one predominant strain of *C. diphtheriae* biotype gravis (64 of 81 strains) and one predominant strain of *C. diphtheriae* biotype mitis (24 of 25 strains) associated with the epidemic. A single clonal group comprised increasingly larger proportions of isolates as the outbreak progressed (444). The other *C. diphtheriae* biotype gravis and *C. diphtheriae* biotype mitis ribotypes may have been endemic and caused sporadic disease.

In the Seattle outbreak of predominantly skin infections, toxinogenic *C. diphtheriae* biotype intermedius was the most common isolate, although all biotypes were responsible for consecutive, overlapping outbreaks (93). Molecular epidemiological techniques such as RFLP analysis have shown that *C. diphtheriae* biotype intermedius and *C. diphtheriae* biotype gravis may be more homogeneous than is *C. diphtheriae* biotype mitis. The greater heterogeneity may be because the mitis biotype is more broadly defined (93). Workers from Zürich found that all isolates from a group of intravenous drug abusers were nontoxinogenic *C. diphtheriae* biotype mitis, which were the same by biotyping, antimicrobial resistance patterns, and ribotyping, indicating infection by the same clone (179, 183, 471). They suggested that people with poor hygiene and

TABLE 4. Biochemical characteristics of *Corynebacterium* spp.

Species	Fermentation/ oxidation (F/O)	Lipo- philism	Nitrate	Urease	Esculin	Pyrazin- amidase	Alkaline phospha- tase	Acid production[a]					CAMP test	Other characteristics
								Glu	Mal	Suc	Man	Xyl		
C. accolens	F	+	+	−	−	V[b]	−	+	−	V	V	−	−	
C. afermentans subsp. *afermentans*	O	−	−	−	−	+	+	−	−	−	−	−	V	
C. afermentans subsp. *lipophilium*	O	+	−	−	−	+	+	−	−	−	−	−	V	
C. amycolatum	F	−	V	V	−	+	+	+	V	V	−	−	−	Mostly O/129 re- sistant
C. argentoratense	F	−	−	−	−	+	V	+	−	−	−	−	−	
C. auris	O	−	−	−	−	+	+	−	−	−	−	−	+	Dry, slight adher- ence
C. bovis	O	+	−	−	−	V	+	+	−	−	−	−	−	β-Galactosidase positive
C. cystitidis	F	−	−	+	−	+	+	+	−	−	−	−	−	Yellowish
C. diphtheriae gravis	F	−	+	−	−	−	−	+	+	−	−	−	−	See text
C. diphtheriae intermedius	F	+	+	−	−	−	−	+	+	−	−	−	−	See text
C. diphtheriae mitis	F	−	+/−[c]	−	−	−	−	+	+	−	−	−	−	See text
C. glucuronolyticum	F	−	V	V	V	+	V	+	V	+	−	V	+	β-Glucuronidase positive
C. jeikeium	O	+	−	−	−	+	+	+	V	−	−	−	−	Fructose-, no growth anaero- bically
C. kutscheri	F	−	V	+	+	V	−	+	+	+	−	−	−	
C. macginleyi	F	+	+	−	−	−	+	+	−	+	V	−	−	
C. matruchotii	F	−	+	V	+	+	−	+	V	V	−	−	−	"Whip handle"
C. minutissimum	F	−	−	−	−	+	+	+	+	V	−/(+)	−	−	Fructose positive
C. pilosum	F	−	+	+	−	+	+	+	−	−	−	−	−	Yellow pigment
C. propinquum	O	−	+	−	−	V	V	−	−	−	−	−	−	Tyrosine positive
C. pseudodiphtheriticum	O	−	+	+	−	+	V	−	−	−	−	−		
C. pseudotuberculosis	F	−	V	+	−	−	V	+	+	V	−	−	REV[d]	
C. renale	F	−	−	+	−	+	−	+	−	−	−	−	+	
C. striatum	F	−	+	−	−	+	+	+	−	V	−	−	V	Tyrosine positive
C. ulcerans	F	−	−	+	−	−	+	+	+	−	−	−	REV	Glycogen positive
C. urealyticum	O	+	−	+	−	+	V	−	−	−	−	−	−	
C. xerosis	F	−	V	−	−	+	+	+	+	+	−	−	−	O/129 susceptible
CDC Group F-1	F	+	V	+	−	+	−	+	+	+	−	−	−	
CDC Group G	F	+	V	−	−	+	+	+	V	V	−	−	−	Fructose positive, grows anaero- bically

[a] Glu, glucose; Mal, maltose; Suc, sucrose; Man, mannitol; Xyl, xylose.
[b] V, variable.
[c] Biotype belfanti is nitrate negative.
[d] REV, reverse CAMP reaction.

living conditions such as drug abusers may be a reservoir for *C. diphtheriae* infection. Using pattern analysis of DNA fragments probed with an insertion element, Rappuoli et al. showed that the toxinogenic *C. diphtheriae* biotype mitis strains responsible for a Swedish epidemic gave a similar pattern whereas all strains not involved in the epidemic gave unique patterns (351). In contrast, the strains of nontoxinogenic *C. diphtheriae* biotype gravis associated with sporadic endocarditis occurring in different locations in Australia were not related (120, 427).

A key advance in the diagnosis of diphtheria is the use of PCR to detect the toxin gene (10, 198, 268, 289, 320, 321). Pallen et al. and Aravena-Roman et al. used the same primer set and found 100% correlation with PCR product detection and lethality for guinea pigs (10, 320). Subsequent testing showed PCR to be useful for rapidly screening clinical *Coryne- bacterium* isolates, with a low rate of false positives (3%) (321). Hauser and colleagues showed excellent correlation of ampli- fication of a 0.9-kb segment of the *tox* gene, ADP-ribosylating activity, and guinea pig virulence (198). Using another set of primers within the *tox* gene, Martinetti-Lucchini et al. (268)

found the PCR test more accurate than the Elek test when the guinea pig virulence assay was taken as the "gold standard," possibly due to false-positive precipitin lines in the Elek test. However, Mikhailovich et al. found 100% agreement of PCR and the Elek test for 250 isolates from the former Soviet Union (289). There is also the rare possibility of a false-positive PCR assay in which the organism possesses the *tox* gene but is nontoxinogenic because it is unable to express the gene (176, 321). An in vitro method to measure the cytotoxicity of diph- theria toxin to Vero cells is as sensitive and specific as the in vivo guinea pig assay (206). *C. ulcerans* and *C. pseudotubercu- losis* may possess the diphtheria *tox* gene, whereas, as noted above, some clinical isolates of *C. diphtheriae* may not (198, 210, 320, 321). The percentage of toxinogenic *C. diphtheriae* isolates in any particular survey can vary widely.

The most common disease caused by *C. diphtheriae* is diph- theria, an acute communicable disease manifested by both local infection of the upper respiratory tract and the systemic effects of a toxin, which are most notable in the heart, periph- eral nerves, and the kidney (135). There are two phases of

diphtheria, the initial local presentation as a severe pharyngitis with or without (349) tough pharyngeal membranes that can grow over the air passage and cause suffocation and a later systemic phase caused by the effect of circulating exotoxin on tissues of the host. Death may result from respiratory obstruction by the membrane or myocarditis effected by the 58 kDa exotoxin. The gene for the exotoxin is carried on a family of closely related corynebacteriophages (177) and has been sequenced (174). It is this work that allowed specific primers for the PCR detection of the toxin to be selected.

The crystal structure of the exotoxin whose active form consists of two polypeptide chains linked by a disulfide bond reveals three domains, the catalytic domain, the transmembrane domain, and a receptor binding domain (26, 65). The process by which the toxin binds to specific receptors and enters susceptible cells has been defined as a five-step process (26): the disulfide bridge between the catalytic domain and the transmembrane domain is hydrolyzed, the receptor domain binds to the diphtheria toxin receptor on the cell, the transmembrane domain inserts into the endosomal membrane, the catalytic domain is translocated into the cytosol, and the catalytic domain stops protein synthesis by inactivating elongation factor 2 via ADP-ribosylation from NAD. The exotoxin crosses the membrane of endosomes of target cells in response to the low endosomal pH.

The regulation of toxin gene expression is controlled by a chromosome-encoded regulatory element, diphtheria toxin repressor (DtxR) (35), which is an Fe^{2+}-activated protein with sequence-specific DNA-binding activity for the diphtheria toxin operator. Under high-iron conditions in *C. diphtheriae*, the Fe^{3+}-DtxR complex assumes a configuration so that it binds to the diphtheria toxin operator and represses toxin biosynthesis (344, 423, 424). The sequence and the three-dimensional structure of DtxR has been described (35, 344). The gene encodes a 226-residue protein with domains for metal ion activation, DNA binding, and protein-protein interaction (35).

C. diphtheriae probably has additional virulence factors, as nontoxigenic strains are also associated with significant invasive disease. Their mechanisms of pathogenicity (adherence and possible invasiveness) are not known.

Although it was thought that diphtheria had almost been eliminated by widespread immunization practices, it has resurfaced with a vengeance in areas of political and socioeconomic changes, where it occurs in nonimmunized or partially immunized persons (163, 164). Cases in the former Soviet Union increased from 839 in 1989 to 47,808 in 1994, with 1,746 fatalities. In 1994, the case-fatality ratio ranged from 2.8% in the Russian Federation to 23.0% in Lithuania and Turkestan (59). The highest age-specific incidence rates were among persons aged 4 to 10, 15 to 17, and 40 to 49 years. The number of susceptible people has increased both because decreased numbers are being vaccinated and because natural immunity decreases as exposure to *C. diphtheriae* declines. Previous and recent serological studies (with different antitoxin detection systems) in the former Soviet Union, Western Europe, and the United States indicate that 20 to 70% of adults older than 20 years are susceptible to *C. diphtheriae* (41, 216, 229, 234, 308, 342). However, a recent study on diphtheria antitoxin levels in Massachusetts found that 98.4% of adult plasma donors had protective levels of antibodies (189). This difference might be explained by the use of a combined tetanus and diphtheria adult vaccine in the United States.

There is the expectation that the intense efforts to vaccinate the recommended 95% of the population of the former Soviet Union will bring the epidemic under control even though there were more reported cases in the first 6 months of 1995 than in

the comparable period in 1994. Although the source of the present epidemic in the former Soviet Union is not known, in the southern parts of the former Soviet Union as in many tropical areas throughout the world, endemic infection with *C. diphtheriae* is associated with cutaneous diphtheria (194). Sporadic cases of respiratory diphtheria in developed countries are usually imported or associated with poor living conditions (195, 293, 442).

Today, the main reservoir of *C. diphtheriae* is the human skin; transmission from this source is more effective than transmission from the throat. The initial event in the establishment of cutaneous diphtheria may be a break in the skin due to trauma or underlying dermatosis. The subsequent infection with *C. diphtheriae* and possibly other organisms can cause a chronic nonhealing ulcer. Outbreaks of cutaneous diphtheria which have been reported are often associated with poor socioeconomic conditions or travel to an area of endemic infection (8, 179, 192). However, outbreaks seem to be sporadic; the epidemic that occurred in Seattle in the 1970s and 1980s among an indigent population of alcoholics has not been repeated. All biotypes and both toxigenic and nontoxigenic types of *C. diphtheriae* have been isolated from various sporadic or epidemic cases of cutaneous diphtheria (8, 93, 110, 179, 192, 195). Cutaneous lesions may contribute to the spread of respiratory diphtheria and should be cultured for epidemiological and control measures (293).

With the wider identification of *C. diphtheriae* in diseases other than respiratory diphtheria and the more accurate and accessible testing for toxin production, the reported spectrum of disease caused by *C. diphtheriae* is changing. *C. diphtheriae*, usually nontoxigenic strains, has been associated with septicemia (15, 40, 183), endocarditis (40, 183, 202, 207, 298, 330, 427), septic arthritis (1, 16, 99, 298, 427), osteomyelitis (341), and cerebral abscess (298). Sequelae of septicemia with nontoxinogenic *C. diphtheriae* biotype mitis strains included endocarditis with the aortic and mitral valves being successfully replaced (33). A recent review of *C. diphtheriae* endocarditis included 49 cases (207). Salvanet-Bouccara et al. described *C. diphtheriae* biotype mitis as the causative agent of two cases of chronic endophthalmitis (380).

Carriage of *C. diphtheriae* has been studied. During a prospective study, 117 intravenous drug users were screened for infection with *C. diphtheriae*. Nontoxigenic *C. diphtheriae* was isolated from 5 of 132 throat swab specimens and 5 of 28 skin ulcer specimens, but disease was not clearly attributable to the isolates (179). When phenotypic and molecular typing methods were used, these 10 strains were shown to belong to a single clone. In the same study, no *C. diphtheriae* was isolated from 200 controls. In general, carriage rates are low in immunized populations (287). Isolations may represent the endemic presence of *C. diphtheriae* in parts of the population. However, it may be that host resistance factors, poor standards of hygiene, and low socioeconomic status have more importance for carriage of *C. diphtheriae*. Nieto et al. did not detect any *C. diphtheriae* strains in throat swabs from 186 human immunodeficiency virus-infected patients (311).

An increasing proportion of nontoxinogenic compared with toxinogenic *C. diphtheriae* strains has been observed. A possible explanation is that laboratories may increasingly identify coryneform organisms involved in diseases other than diphtheria. It has also been postulated that nontoxinogenic strains occur more often in people who have been previously immunized (427), since immunization selects against toxigenic strains.

Toxinogenic *C. ulcerans* can cause a disease indistinguishable from diphtheria. Recently, this organism was isolated

from the pharyngeal membrane of a patient with laryngeal diphtheria (210) and from patients with less severe nasopharyngeal disease (105, 331). Nontoxinogenic *C. ulcerans* has been associated with necrotic granulomas and pulmonary nodules in an immunocompetent host (108).

C. pseudotuberculosis has been reviewed in detail (91). In general, infections due to *C. pseudotuberculosis* are rarely seen in humans and usually present as caseous lymphadenitis acquired as occupational disease. *C. pseudotuberculosis* is a significant cause of morbidity in animals, mainly in sheep but also in goats and horses.

The phospholipase D (PLD) genes and gene products from *C. pseudotuberculosis* and *C. ulcerans* share 80% DNA homology, 87% amino acid sequence homology, and antigenic relationships (96). Interestingly, the PLDs from *C. pseudotuberculosis* and *C. ulcerans* share over 60% DNA and amino acid homology with the PLD of *A. haemolyticum* (282). Therefore, it is not unlikely that this highly conserved enzyme may represent a virulence factor.

Although immunization is the most important long-term factor for prevention of diphtheria, antibiotics play a major role in the treatment and control of diphtheria. They are used to prevent dissemination and toxin production in infected patients, clinical disease in and spread from asymptomatic carriers, and colonization of contacts. Recent in vitro susceptibility results on the isolates from the former Soviet Union confirm the older literature: all strains were susceptible to erythromycin, penicillin, ampicillin, cefuroxime, chloramphenicol, ciprofloxacin, gentamicin, and tetracycline, and 2 of 83 strains were resistant to trimethoprim and rifampin (264). Nontoxigenic *C. diphtheriae* strains isolated in France were susceptible to β-lactams (except cefixime and cefpodoxime), pefloxacin, and vancomycin when tested by the disk diffusion method, and resistance to minocycline, erythromycin, and rifampin was detected in a few strains only (327). In vitro susceptibility testing demonstrated that *C. pseudotuberculosis* strains are susceptible to β-lactams, macrolides, tetracyclines, chloramphenicol, and rifampin (221).

C. xerosis and C. striatum. Historically, *C. xerosis* and *C. striatum* were differentiated on the basis of relatively few tests. Both ferment glucose and sucrose and are negative in tests for urease production, esculin hydrolysis, and mannitol and xylose fermentation. They are distinguished primarily by fermentation of maltose by *C. xerosis* but not *C. striatum*. Thus, it is not too surprising that some strains have been misidentified. When 10 reference strains of *C. xerosis* were studied, 3 did not conform to the species description but were more closely related by DNA homology, CFA analysis, and biochemical testing to the type strain of *C. striatum* than to *C. xerosis* (90) and should be reclassified to this species. Coyle and colleagues found five different DNA homology groups among the remaining *C. xerosis* reference strains (90). Furthermore, Funke et al. recently demonstrated that nearly all isolates tentatively identified as *C. xerosis* in the routine clinical laboratory actually represent *C. amycolatum* strains (147). They concluded that true *C. xerosis* strains are extremely rare. This information makes us believe that most clinical isolates described as *C. xerosis* are probably *C. amycolatum*. However, for simplicity and historical continuity, we are reviewing information on isolates reported as *C. xerosis* in this section. Features differentiating *C. amycolatum* from *C. xerosis* include the following: *C. amycolatum* strains produce whitish-grayish colonies, lack mycolic acids, show weak or no leucine arylamidase activity, produce large amounts of propionic acid from glucose fermentation, and are mostly resistant to the vibriocidal agent O/129, whereas *C. xerosis* strains produce yellowish colonies, express mycolic ac-

ids and leucine arylamidase activity, produce lactic acid as a product from glucose fermentation, and are susceptible to O/129 (147). Wauters et al. also demonstrated that propionic acid-producing strains designated *C. xerosis* correspond to *C. amycolatum* (450).

Other characteristics may be helpful in identifying *C. xerosis* (probably *C. amycolatum*) and *C. striatum*. Martinez-Martinez et al. (273) confirmed previous information (76) that *C. striatum* hydrolyzes tyrosine. They stated that *C. striatum* ferments sugars rapidly (24 to 36 h) whereas *C. xerosis* does not hydrolyze tyrosine and ferments sugars slowly (72 to 96 h). The hydrolysis of tyrosine and the augmentation of brown pigment (possibly melanin) on tyrosine-supplemented medium are most probably related (247). Some strains of *C. striatum* are CAMP positive (247). It should be noted that the ATCC and NCTC *C. striatum* reference strains do not fit the descriptions in the original publications (89).

The characteristics usually listed for *C. xerosis* in Table 4 are based on strains ATCC 373 (the type strain) and ATCC 7711 (147). It is possible that some CDC group G strains will be confused with *C. xerosis* or *C. striatum* if lipophilia is not taken into account. de Briel et al. demonstrated that the former CDC coryneform group I-1 strains represented *C. striatum* strains (103).

As *C. xerosis* and *C. striatum* strains become defined better, it seems that colony morphology has become more useful in distinguishing species. *C. xerosis* and *C. striatum* grow well on laboratory media (the colonies may be small initially, but by 48 to 72 h on sheep blood agar, they are usually greater than 2 mm in diameter). True *C. xerosis* colonies appear yellowish, dry, and granular whereas *C. striatum* colonies are whitish, moist, and smooth (somewhat like coagulase-negative staphylococci). There are two reports of unusual *C. striatum*-like nitrite-reducing strains (247, 265).

As implied above, there is little understanding about the pathogenic role of *C. xerosis* and *C. striatum* as these species have not been clearly defined in the past, identification has not been dependable, and there is now strong evidence that the majority of strains identified as *C. xerosis* actually are *C. amycolatum* (147, 450). In addition, the organisms commonly occur in the normal flora on both skin and oropharynx, making it difficult to distinguish infection from contamination or colonization.

There are 12 recent reports of *C. xerosis* infections; eight of these infections occurred after surgery or antibiotic therapy (infections of protheses, postsurgical wound infection, nosocomial pneumonia, infection of a pancreatic pseudocyst, and spontaneous peritonitis) (11, 34, 167, 232, 238, 256, 437, 446, 461). In five cases, the isolates were described as multiply resistant (167, 232, 256, 446, 461), supporting the contention that the strains were *C. amycolatum*. Multiresistance is very common in *C. amycolatum* strains, whereas true *C. xerosis* strains are susceptible to nearly all antimicrobial agents tested (147, 154). There are four reported associations with endocarditis (60, 262, 371, 421), with the organisms being generally susceptible. In only one report (446), however, was there enough information on the identification. All others were said to be identified by either the Vitek system, API Coryne, or a reference laboratory, but insufficient biochemical descriptions of the organisms were given. The designation of *C. xerosis* by the Vitek system is not specific, because "*C. xerosis*" is one of the few coryneforms contained in the database. *C. xerosis* was a primary pathogen in only two of the nonendocarditis cases, and these were in alcoholic patients (437, 461). Most other cases probably represented colonization of a prosthetic device or a preexisting wound.

Although *C. striatum* is one of the more commonly isolated corynebacteria, there is not much documentation linking it unambiguously with infection. Recent reports of *C. striatum* infections (247, 328, 449) involve colonization of indwelling protheses, catheter tips, ventilator tubes (seven of these were from one study [247]), feeding tubes, previous chronic wounds (draining elbow sinus, finger granuloma), and the conjunctiva. Two isolates were from the female genital tract and were associated with premature rupture of amniotic membranes. However, in both cases either the validity of the identification (328) or the presence of other organisms (449) makes the causal link questionable. In the study showing nosocomial transmission of an unusual brown-pigmented strain of *C. striatum* (247) (in addition to related isolates from sputum, which were colonizing the respiratory tract), most of the specimens were from skin-associated sites, with the attendant possibility of contamination or colonization. Cases of endocarditis (261, 375), pacemaker-related endocarditis (with very few microbiological data) (286), and bacteremia (429) due to *C. striatum* have been described in the literature. *C. striatum* was also isolated from patients with chronic obstructive airway disease (88) and fatal pulmonary infection (271).

There are several reports on the susceptibility pattern of *C. striatum* (270, 273, 370, 408). A study of 86 strains found that all were susceptible to penicillin G, most were susceptible to other β-lactam antibiotics, and most were resistant to ciprofloxacin, erythromycin, rifampin, and tetracycline; susceptibility to aminoglycosides was variable (270). In contrast, many isolates from case reports showed resistance to β-lactam antibiotics, but only one showed high-level resistance and was susceptible to vancomycin and netilmicin only (328). Since the isolates were obtained after antibiotic treatment, this lends credence to the theory that most of the isolates were secondarily colonizing organisms. No vancomycin-resistant strain has been reported.

C. minutissimum. *C. minutissimum* was validly described in 1983 by Collins and Jones (80). The habitat of *C. minutissimum* is the human skin. Colonies of *C. minutissimum* are convex and circular, have entire edges, and are about 1 to 1.5 mm in diameter after 24 h of incubation. It is important to note that the surface of *C. minutissimum* colonies is shiny and moist. Gram stains show typical diphtheroids with single cells or V forms; palisades and clustering as "Chinese letters" can also be observed. *C. minutissimum* colonies were reported to exhibit a coral-red to orange fluorescence under Wood's light (365 nm) when cells were grown on rich media, e.g., media containing 20% (vol/vol) fetal calf serum (384). Some authors have also described this phenomenon for cells grown on plain Mueller-Hinton agar plates (73), whereas others could not confirm this observation (29, 470).

Originally, *C. minutissimum* was thought to cause erythrasma, an asymptomatic skin infection characterized by scaly, reddish, macular patches in intertriginous areas, but newer data question this association. Coyle and Lipsky have thoroughly discussed this possible disease association (91). Erythrasma is most probably a polymicrobial process.

The Special Bacteriology Reference Laboratory at CDC had earlier defined two different biotypes of *C. minutissimum* (204). Strain NCTC 10288 (ATCC 23348), the type strain, was the representative of biotype 1 of *C. minutissimum*, and strain ATCC 23346 was the representative of biotype 2; the major difference was the ability of strains of biotype 1 to ferment sucrose and the inability of strains belonging to biotype 2 to do so. Collins and Jones described sucrose fermentation by *C. minutissimum* strains as variable (80). Estrangin et al. found that one group of *C. minutissimum* produced propionic acid

and another group of *C. minutissimum* strains did not produce this end product of glucose metabolism (127).

When the API Coryne strip is used, *C. minutissimum* strains may be identified as *C. jeikeium* (numerical code, 2100324), producing acid from maltose; however, the aerobic and lipophilic *C. jeikeium* can easily be separated from the facultatively anaerobic, moist, and well-growing *C. minutissimum* strains. Furthermore, *C. minutissimum* strains ferment fructose and grow in 6.5% NaCl, whereas *C. jeikeium* strains are negative for these reactions (9, 358).

Recent biochemical and chemotaxonomic investigations of a collection of strains initially identified as *C. minutissimum* (470) revealed that some strains of *C. minutissimum* are actually able to ferment mannitol and that the most frequent misidentification of a strain as *C. minutissimum* occurs with *C. amycolatum* strains. In contrast to the moist *C. minutissimum* strains, however, *C. amycolatum* always shows dry, waxy colonies; *C. minutissimum* produces lactate and succinate as major end products of glucose metabolism, whereas *C. amycolatum* produces lactate and propionate; DNase activity is observed with *C. minutissimum* but not *C. amycolatum* strains; *C. minutissimum* strains are susceptible to the vibriocidal compound O/129, whereas most *C. amycolatum* strains are resistant; and some strains of *C. minutissimum* contain small amounts of tuberculostearic acid (TBSA) (30, 440), which is not detected in *C. amycolatum* strains.

There is a discrepancy between the large number of *C. minutissimum* strains isolated in the routine clinical laboratory and the relatively small number of publications claiming a disease association. The first deep tissue invasion by *C. minutissimum* was reported in a patient with recurrent breast abscesses and was microbiologically satisfactorily documented (27). In contrast, a case report of embolic retinopathy as a result of "*C. minutissimum*" endocarditis was insufficient, as it did not contain any information regarding the identification of the organism thought to be responsible for disease (201). The same was true for the identification of "*C. minutissimum*" causing bacteremia in a patient with chronic myeloid leukemia (184), since data for nitrate reduction were missing and the pinpoint colonies described were too small to be *C. minutissimum* but, rather, suggested that the strain may have belonged to CDC group G bacteria. Another case of *C. minutissimum* bacteremia and one of a postoperative neck abscess due to *C. minutissimum* were better documented, but the important description of the colony morphology was not included (172). The three strains causing opportunistic infections described by Vanbosterhout et al. (431) are without doubt *C. amycolatum* strains; these strains had a dry and waxy appearance and produced propionic acid. The role of *C. minutissimum* in a case of a central venous catheter sepsis involving four different bacteria is unclear, as is the report that this strain was multiresistant (58). It was resistant only to penicillin, erythromycin, and clindamycin, which is not an unusual finding for *Corynebacterium* spp. and especially *C. amycolatum* strains (154). In summary, there are at present only a few completely documented cases of *C. minutissimum* infections in humans.

C. amycolatum. *C. amycolatum* was established only in 1988 by Collins et al. (75), who recovered these coryneform isolates from swabs of the skin of healthy people. These bacteria were found to have characteristics compatible with an assignment to the genus *Corynebacterium* [*meso*-diaminopimelic acid as the diamino acid of the cell wall, arabinose and galactose as cell wall sugars, MK-9(H$_2$) as the principal menaquinone, and a G+C content in DNA of 61 mol%] except for the lack of detectable mycolic acids which at that time was considered a prerequisite for an assignment to the genus *Corynebacterium*

(76). However, it is now evident from phylogenetic analysis applying 16S rRNA gene sequencing that *C. amycolatum* clusters within the genus *Corynebacterium* (326). Cell wall analyses revealed that CDC coryneform groups F-2, I-2 and "*C. asperum*" are also lacking mycolic acids (21, 103), and Barreau et al. suggested that these taxa may be synonyms of *C. amycolatum* (21). CDC coryneform group F-2 and I-2 bacteria have been isolated from miscellaneous sources, whereas "*C. asperum*" has been isolated mainly from human respiratory specimens (21, 204).

Strains of *C. amycolatum* very typically produce dry colonies of about 1 to 1.5 mm in diameter after 24 h of incubation at 37°C. Gram stains show pleomorphic coryneform rods with single cells, V forms, or Chinese letters. The basic biochemical reactions of *C. amycolatum* are given in Table 4. Nitrate reduction was, unfortunately, not included in the original description of *C. amycolatum* (75). Because of the many variable biochemical reactions and its absence from the database of commercial identification systems (e.g., API Coryne), *C. amycolatum* is one of the most underdiagnosed taxa of coryneform bacteria. In fact, *C. amycolatum* is the most frequently encountered nonlipophilic *Corynebacterium* species in clinical specimens (141). In our experience, *C. amycolatum* strains are predominantly misidentified as *C. xerosis*, because both taxa have dry colonies and similar biochemical screening reactions (Table 4) (147). In addition, some strains of *C. amycolatum* may be identified as *C. minutissimum*, and a minority of *C. amycolatum* strains may be initially called *C. striatum* (see under those headings). Barreau et al. also indicated that *C. amycolatum* may be misidentified as *C. minutissimum* or *C. striatum* when the API Coryne system is used (21). Recently, Wauters et al. published a study based on quantitative DNA-DNA hybridizations indicating that previously designated strains of *C. xerosis*, *C. minutissimum*, *C. striatum*, and CDC coryneform group F-2 and I-2 which produce propionic acid belong to the species *C. amycolatum* (450).

For the routine laboratory, we recommend the following procedures for the identification of *C. amycolatum* strains: dry colonies of glucose-fermenting coryneforms should raise the suspicion of *C. amycolatum* (in contrast, *C. minutissimum* and *C. striatum* strains are always moist). Separation of *C. amycolatum* from *C. xerosis* is established by the lack of detectable (i.e., by thin-layer chromatography) mycolic acids in *C. amycolatum* strains. *C. amycolatum* strains may be multiresistant to antimicrobial agents, including β-lactams, macrolides, clindamycin, aminoglycosides, ciprofloxacin, and rifampin, but the majority are susceptible to tetracycline, and all isolates tested have remained susceptible to glycopeptides so far (154).

No case report explicitly describing *C. amycolatum* as a causative agent of infection can be found in the literature. However, it is most likely that some cases ascribed to *C. xerosis* (see above), *C. striatum*, and *C. minutissimum* (see above) may actually have been caused by *C. amycolatum*. Riche et al. reported a postoperative sternal wound infection due to CDC coryneform group I-2 bacteria (356). A strain belonging to this taxon was also described as the causative agent of a case of peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD) (109). As mentioned above, Vanbosterhout et al. reported three cases of opportunistic *C. amycolatum* infections (431): one of the strains came from blood cultures of a patient with a hematological neoplasia, one came from a pseudo-aneurysmal fistula as well as from a blood culture, and a third came from a patient with CAPD peritonitis.

C. glucuronolyticum. *C. glucuronolyticum* is a newly defined bacterium that has been isolated from male patients with genitourinary infections (142). It has also been independently described as "*C. seminale*" by another group of researchers (364). Colonies are white-yellowish, nonhemolytic, and convex, and the colony size is 1 to 1.5 mm in diameter after 24 h of incubation at 37°C on sheep blood agar (SBA). The Gram stain appearance of *C. glucuronolyticum* organisms is similar to that of many other *Corynebacterium* spp., coryneform rods of about 1 to 3 μm in length. *C. glucuronolyticum* strains are remarkable for their variability in basic biochemical reactions (Table 4). When urease activity is present in *C. glucuronolyticum* strains, it is abundant, with Christensen's urea broth becoming positive after only 5 min of incubation at room temperature. *C. glucuronolyticum* is one of the very few human pathogenic *Corynebacterium* species that is able to hydrolyze esculin. However, *C. glucuronolyticum* exhibits two other characteristic features: all strains tested so far show a strong CAMP reaction and strong β-glucuronidase activity. *C. glucuronolyticum* may be confused with *C. renale* (also positive for CAMP reaction and β-glucuronidase activity), but *C. renale* does not produce propionic acid as an end product of glucose metabolism (127, 142) as *C. glucuronolyticum* does, and leucine arylamidase activity is weak or absent in *C. renale* but strong in *C. glucuronolyticum*. Also, as far as is known, *C. renale* has caused genitourinary infections in animals only. Lactate and succinate are also produced by *C. glucuronolyticum*. A comparative phylogenetic analysis of the genes coding for 16S rRNA of *C. glucuronolyticum* revealed that this species showed no particular close affinity with any of the other presently defined *Corynebacterium* species (142).

C. glucuronolyticum strains are susceptible to β-lactams, gentamicin, rifampin, and vancomycin, but a relatively high proportion of strains are resistant to ciprofloxacin, clindamycin, erythromycin, and, in particular, tetracycline (154). The genetic basis of the resistance of some *C. glucuronolyticum* strains to these antimicrobial agents is not known.

C. glucuronolyticum may cause prostatitis or urethritis. The habitat of *C. glucuronolyticum* has not been fully defined, but the bacterium may be part of the normal genitourinary tract flora (141).

C. argentoratense. The species *C. argentoratense* was recently proposed for some strains isolated from the human throat (363). Colonies are cream colored, nonhemolytic, and 2 mm in diameter after 48 h of incubation at 37°C on SBA. Gram stains show typical coryneform bacteria. The biochemical characteristics are given in Table 4. The rare species *C. flavescens* and *C. mycetoides* (both probably nonpathogenic for humans) are readily distinguished from *C. argentoratense* by their yellow pigment and by their lack of pyrazinamidase activity (363). All three *Corynebacterium* species can also be distinguished by their distinct mycolic acid patterns (363). The few *C. argentoratense* strains that ferment glucose only weakly can be separated from *C. afermentans* by their α-chymotrypsin activity. Phylogenetically, *C. argentoratense* is closely related to *C. diphtheriae*, but the *tox* gene coding for the diphtheria toxin could not be detected in *C. argentoratense* strains (363). The isolates included in the study by Riegel et al. (363) were all from patients suffering from tonsillitis but the clinical significance of *C. argentoratense* is unclear at present. The authors of this review have only very few strains of *C. argentoratense* in their collections, and, again, all strains were isolated from the respiratory tract, and no obvious disease association of *C. argentoratense* was observed.

C. matruchotii. *C. matruchotii* was reclassified as a species in the genus *Corynebacterium* by Collins (74). The Gram stain appearance of *C. matruchotii* is unusual in that gram-positive bacilli with 'whip handles' are characteristically observed (72, 76, 91). Members of this species ferment glucose, have variable

reactions for maltose and sucrose, and are among the few coryneforms that ferment mannitol. Coyle et al. (91) have reviewed some of the discrepancies observed for biochemical reactions for this species as cited in *Bergey's Manual* (76) and the CDC guide (204). Nitrate reduction is variable. Products of glucose fermentation include propionate as well as acetate and lactate (106). The CFA composition is most like that of *C. minutissimum*, *C. afermentans* (ANF-1), and *C. striatum* (6, 30). *C. matruchotii* is thought to be an inhabitant of the oral cavity of animals and humans (106) but has only rarely been recovered from human infections (456).

Corynebacterium spp. pathogenic for animals but not for humans. The following bacteria are included in this review to emphasize and provide evidence that, as far as is known, they cause disease in animals only.

C. kutscheri is a frequent commensal in mice, rats, and voles, which may develop extensive pseudotuberculous lesions if they are immunocompromised. A case report of *C. kutscheri* causing chorioamnionitis and funisitis in humans is doubtful, because the strain described was nitrate negative (134), a trait not observed in true *C. kutscheri* strains (76). The data given in another report claiming septic arthritis due to *C. kutscheri* are also inadequate, because reactions for nitrate, urea, and esculin are not given and carbohydrate fermentation reactions are not specified (288). From a taxonomic point of view, *C. kutscheri* is remarkable in possessing a G+C content of 46 mol% (337), which is below the defined range for *Corynebacterium* spp. (51 to 63 mol%) (76).

Strains of the *Corynebacterium renale* group (*C. renale*, *C. pilosum*, and *C. cystitidis*) can cause genitourinary infections in animals, especially in cattle (76). It should be emphasized that the original descriptions of *C. pilosum* and *C. cystitidis* were each based on a single strain only (464). Again, case reports claiming an association of this group of bacteria with human disease are highly questionable. Chatelain et al. reported the isolation of *C. pilosum* from pus of a perianal abscess (64); today, this isolate would be identified as *C. amycolatum* (producing dry, cream-colored colonies, whereas the colonies of the type strain of *C. pilosum* are smooth and yellow-pigmented). Peloux et al. (329) described a human breast abscess due to a strain of the *C. renale* group with no species identification given. However, their isolate produced rough colonies with irregular edges, which, together with the biochemical characteristics given, is compatible with an identification of *C. amycolatum*. Finally, Sobrino et al. reported a case of prosthetic valve endocarditis caused by *C. pilosum* (397). It remains unclear why these authors did not identify their isolate as CDC coryneform group F-2, i.e., as *C. amycolatum*. The authors themselves described the typical morphology of *C. amycolatum*, which is in marked contrast to that of *C. pilosum* (see above).

Nonlipophilic, Nonfermentative Corynebacteria

***C. afermentans* subsp. *afermentans*.** *C. afermentans* first appeared in the literature as "CDC coryneform ANF (absolute nonfermenting)-1 bacteria" comprising gram-positive rods that did not produce acid from any sugars (204). In 1993, CDC coryneform group ANF-1 bacteria were shown to comprise the nonlipophilic, well-growing *C. afermentans* subsp. *afermentans* as well as the lipophilic *C. afermentans* subsp. *lipophilum* (see below) (360). The Special Bacteriology Reference Laboratory at CDC reported that the majority of their ANF-1 strains was isolated from ear samples as well as from blood cultures (204). In contrast, Riegel et al. described *C. afermentans* recovered from blood cultures only (360). Therefore, it is most likely that

the CDC collection also contained strains of *Turicella otitidis* (former CDC ANF-1-like bacteria) (155, 395) and *Corynebacterium auris* (148), which have so far been isolated exclusively from patients with ear infections or from healthy controls (141, 148, 155).

The concept that the species *C. afermentans* contains two subspecies was based on quantitative DNA-DNA hybridizations (360). Phenotypically, both subspecies can easily be differentiated by their colony size, which is about 1 to 2 mm in diameter after 24 h of incubation for *C. afermentans* subsp. *afermentans* and less than 0.5 mm in diameter for the grayish, glassy colonies of *C. afermentans* subsp. *lipophilum* when cells are grown on SBA plates. However, when *C. afermentans* subsp. *lipophilum* is grown on SBA plates containing 1% Tween 80, the colonies reach 2 to 3 mm diameter after 24 h of incubation whereas the growth of *C. afermentans* subsp. *afermentans* is not significantly influenced by Tween 80. Colonies of *C. afermentans* subsp. *afermentans* are nonhemolytic and whitish on SBA, and Gram stains show typical coryneform rods. Gram stains of *C. afermentans* subsp. *lipophilum* also reveal typical coryneform bacteria. The API Coryne numerical code for both subspecies of *C. afermentans* is 2100004. Some strains of *Brevibacterium* spp. and *Rhodococcus* spp. may give identical numerical codes; however, the large-colony-producing (>2 mm) and often cheeselike-smelling *Brevibacterium* spp. and the mucoid and/or yellow-pink-red pigmented *Rhodococcus* spp. can easily be distinguished from *C. afermentans*. It should be noted that some strains of *C. afermentans* subsp. *afermentans* exhibit a positive CAMP reaction (141, 393).

Taxonomically, *C. afermentans* is remarkable in possessing a G+C content of 66 to 68 mol% (360) which is above the presently defined range (in *Bergey's Manual*) of 51 to 63 mol% for *Corynebacterium* sensu stricto (76).

***C. auris*.** *C. auris* is another newly defined *Corynebacterium* species that was isolated from specimens of pediatric patients with otitis media (148). Colonies of *C. auris* are nonhemolytic, dry, and slightly adherent to agar, become slightly yellowish with time, and have diameters ranging from 1 to 2 mm after 48 h of incubation at 37°C on SBA. Biochemical screening reactions yield results similar to those for *C. afermentans* subsp. *afermentans* and *T. otitidis* (Table 4; also see Table 6), but all three taxa utilize different substrates when tested with the Biolog GP plate (148). All *C. auris* and *T. otitidis* strains have a strongly positive CAMP reaction, whereas *C. afermentans* subsp. *afermentans* is variable for this reaction. In contrast to *T. otitidis*, *C. auris* does not contain TBSA. Surprisingly, abundant degradation products of mycolic acids were observed when cellular fatty acids patterns of *C. auris* strains were analyzed with the MIDI system (148). The G+C content of *C. auris* is 68 to 74 mol%, which is above the presently defined range for *Corynebacterium* spp. (51 to 63 mol%) (76). However, phylogenetic analysis by 16S rRNA gene analysis revealed that *C. auris* is a true member of the genus *Corynebacterium* (148). Therefore, it has been proposed that the range of the G+C content of *Corynebacterium* sensu stricto should be extended from 46 mol% (in *C. kutscheri*) to 74 mol% (148). This large range is indicative of the considerable genotypic diversity within the genus *Corynebacterium*.

C. auris strains were susceptible to ciprofloxacin, gentamicin, rifampin, tetracycline, and vancomycin but resistant to penicillin G (when categories for staphylococci were applied according to the NCCLS method [305]). Susceptibility to clindamycin and erythromycin was variable (154).

So far, *C. auris* has been isolated exclusively from patients with ear infections (141). However, further prospective studies may reveal more about the clinical significance of *C. auris*.

C. pseudodiphtheriticum. Colonies of *C. pseudodiphtheriticum* are slightly dry and 1 to 2 mm in diameter after 48 h of incubation at 37°C. *C. pseudodiphtheriticum* is urease and nitrate positive (there is a typographical error in the 6th edition [first printing] of the *Manual of Clinical Microbiology*, where it is listed as nitrate negative [72]). Except for the nitrate reaction, it biochemically resembles *C. propinquum*. New 16S rRNA gene sequence data have shown that *C. pseudodiphtheriticum* is closely related to *C. propinquum* (326, 376).

C. pseudodiphtheriticum is part of the oropharyngeal bacterial flora and is therefore associated mainly with respiratory disease and less commonly with endocarditis, prostheses or wound infections or colonizations. Almost all the isolates in the CDC collection (204) were from respiratory specimens. Most of the reported respiratory diseases due to *C. pseudodiphtheriticum* occurred in immunosuppressed hosts (4, 67, 139, 263). Two recent cases of tracheitis and tracheobronchitis in immunocompromised hosts have been well documented (85, 94). Both cases revealed an inflammatory process partially occluding the tracheal lumen, and an essentially pure culture of the organism was isolated from this material. *C. pseudodiphtheriticum* may also cause pneumonia or bronchitis in nonimmunocompromised hosts (4, 263, 290). Many cases have involved patients with endotracheal intubation (with the possibility that the procedure introduced the organisms to the lower respiratory tract) or an inhibition of the cough response (139). *C. pseudodiphtheriticum* might be recovered from exudate of patients with suspected diphtheria (382).

C. pseudodiphtheriticum, similar to many oropharyngeal organisms of low virulence, may also cause endocarditis (197, 252, 254, 296, 459). A recent review of 18 cases of *C. pseudodiphtheriticum* endocarditis found that half (67% of the more recent ones) involved prosthetic valves (296). When *C. pseudodiphtheriticum* was associated with draining wounds (243), it seemed to have been a secondary colonizer. Although there are reports in the literature of *C. pseudodiphtheriticum* associated with urinary tract infection (304), it has not been substantiated by modern identification techniques that these strains were not, in fact, another urease-positive *Corynebacterium* spp., e.g., *C. amycolatum*, *C. urealyticum*, or CDC group F-1.

Susceptibility testing of nine well-identified *C. pseudodiphtheriticum* strains found uniform susceptibility to β-lactams, aminoglycosides, ciprofloxacin, rifampin, and tetracycline but mixed results for clindamycin and erythromycin (296); others have confirmed these results with 16 to 17 strain series for β-lactams, clindamycin, and erythromycin (4, 263). Other reports documented susceptibility to all drugs tested (94, 459), except when identification was doubtful or the organism may have been selected after strong antibiotic pressure (243).

C. propinquum. The name *C. propinquum* was proposed for CDC coryneform ANF-3 bacteria in 1993 (357). Strains of the Special Bacteriology Reference Laboratory at CDC were isolated mainly from respiratory tract specimens (204), and strains included in the study of Riegel et al. also came from these sources (357). As mentioned above, *C. propinquum* is phylogenetically closely related to *C. pseudodiphtheriticum*. It can be phenotypically differentiated from *C. pseudodiphtheriticum* by its negative urea reaction and is separated from *C. afermentans* by its ability to reduce nitrate (Table 4). Colonies are nonhemolytic, are 1 to 2 mm in diameter after 24 h of incubation on SBA, and have a matted surface. Gram stains show typical corynebacterial forms. It is noteworthy that unlike other nonfermenting corynebacteria, *C. propinquum* degrades tyrosine.

At present, only one case report claiming an association of *C. propinquum* with disease can be found in the literature.

Native valve endocarditis due to ANF-3 bacteria was reported by Petit et al. (333). However, there is reason to doubt their diagnosis, since they described the ANF-3 colonies as creamy and only 0.2 to 0.5 mm in diameter after 48 h of incubation on SBA, which is in contrast to the known features of *C. propinquum*. Unlike *C. pseudodiphtheriticum*, *C. propinquum* has not been described as a causative agent of lower respiratory tract infections so far.

Lipophilic Corynebacteria

Recent developments in the characterization of newer *Corynebacterium* species or as yet unnamed but closely related taxa have included more precise phenotypic, chemotaxonomic, and genetic descriptions of certain species whose growth is enhanced by the addition of lipids (e.g., Tween 80) to culture media. These species are referred to as lipophilic corynebacteria. Riegel et al. applied the term "lipid-requiring" rather than "lipophilic" for such taxonomic groups, since good growth was observed in brain heart infusion broth supplemented with 1% Tween 80 in comparison to no visible growth in brain heart infusion broth lacking lipid supplementation (358, 362). However, we prefer the term "lipophilic," because most media used in the routine laboratory contain at least minimal amounts of lipids and thus support growth of the lipophilic bacteria. They will produce small colonies unless they are grown on media enriched with a significant amount of lipids (e.g., 0.1 to 1% Tween 80), whereupon they will produce colonies like those of *C. diphtheriae* or *C. minutissimum*. Conventional methods involving the CDC protocol recommended the addition of 1 to 2 drops of sterile rabbit serum to broth as a standard lipid supplement (204).

Validated, lipophilic *Corynebacterium* species currently include *C. jeikeium*, *C. urealyticum*, *C. afermentans* subsp. *lipophilum*, *C. accolens*, the newly described *C. macginleyi* (362), *C. bovis*, and CDC groups F-1 and G. Lipophilic taxa whose status as *Corynebacterium* species have never been validated include "*C. genitalium*" (160), "*C. pseudogenitalium*" (161), and "*C. tuberculostearicum*" (45). At the genus level, the characteristics of most lipophilic strains are consistent with those of *Corynebacterium* spp., including short corynomycolic acids of C_{22} to C_{36} (103, 214), arabinogalactan and *meso*-diaminopimelic acid in the cell wall, and dihydrogenated menaquinones ($MK-9H_2$ and $MK-8H_2$) (72, 91). Lipophilic corynebacteria are usually fastidious and slower growing than nonlipophilic strains; most are nonhemolytic on blood agar (BA) and all are CAMP negative (441), except for some strains of *C. afermentans* subsp. *lipophilum* (141). Details pertaining to individual species and taxon groups are described below.

C. jeikeium. Bacteria later identified as *C. jeikeium* (formerly CDC group JK) were first characterized as diphtheroids associated with bacterial endocarditis following cardiac surgery; characteristically, these bacteria were resistant to penicillins, aminoglycosides, and cephalosporins but susceptible to vancomycin (214).

C. jeikeium has a CFA composition consistent with that of the genus *Corynebacterium*, with the majority of CFAs being of the straight-chain, monounsaturated types. TBSA has been found by Jackman et al. (214) but not by others (30, 440). *C. jeikeium* has a G+C content of 58 to 61 mol% and corynomycolic acids of 32 to 36 carbon atoms (103, 199).

C. jeikeium is considered part of the normal flora of the skin, particularly of inpatients (91, 244, 425). It can also be recovered from the inanimate hospital environment (346, 425). An early review of *C. jeikeium* infections by Lipsky et al. suggested that animal infections did not occur (254). In 1990, Coyle and

Lipsky published their comprehensive review of infections involving *C. jeikeium*, which were most frequently, although not exclusively, associated with immunocompromised hosts with malignancies, in-place medical devices, prolonged hospital stays, breaks in integument, and therapy with broad-spectrum antibiotics (91). Cutaneous manifestations of infection by *C. jeikeium* were described by Dan et al. (100). More recently, AIDS with (413) and without (381) neutropenia, neutropenia (373), neoplasms (25, 137), meningitis with transverse myelitis (217), cerebral ventriculitis (235), ventricular cerebrospinal fluid shunt infections (173), prosthetic and native heart valve endocarditis (432), osteomyelitis after total hip replacement (455), infectious arthritis after arthroplasty (465), and lymphadenopathy in a patient with Whipple's disease (339) have been reported as being associated with *C. jeikeium* infections. *C. jeikeium* was recently implicated as the cause of papular eruption with features histologically mimicking botryomycosis (220). In that publication, however, the brief microbiological description of the causative agent did not allude to a lipophilic bacterium (220). Pediatric *C. jeikeium* infections have only rarely been reported. Dietrich et al. reviewed the literature and described two cases in immunocompromised pediatric patients, with *C. jeikeium* being recovered from blood cultures from one patient and a blood culture and an abscess from the second (112). Clinical manifestations of *C. jeikeium* infections also include nosocomial septicemia, bacteremia, pulmonary infiltrates in patients with bone marrow disorders, cavitating pneumonia in a patient with chronic obstructive pulmonary disease, skin rashes, septic cutaneous emboli, meningitis, and soft tissue infections, particularly among granulocytopenic patients (91, 433).

Although *C. diphtheriae* is the most notable human pathogen in the genus *Corynebacterium*, the most frequently recovered clinically significant coryneform isolated in two prevalence studies at acute care facilities was *C. jeikeium* (267, 457).

C. jeikeium isolates are pleomorphic, occasionally club-shaped, gram-positive rods, arranged in V forms or palisades. After 24 h of growth on SBA at 37°C, colonies are nonhemolytic, small (0.5 to 1 mm), entire, low convex, and greyish-white (214, 367). Good growth occurs on blood agar at 30 to 42°C, but poor growth is obtained at 22°C. The organism is a strict aerobe, with no growth occurring anaerobically (214). Acidification reactions will probably not occur unless lipids are added to carbohydrate broths (204). The lipid requirement has also been shown when using SBA supplemented with 1% Tween 80, which is reported to give rise to large colonies (2 to 4 mm) in 48 h (358) compared with growth on unsupplemented SBA.

The CDC identification scheme identifies catalase-positive, oxidase-negative, penicillin-resistant (usually), lipid-requiring coryneforms that are nitrate and urea negative but able to ferment glucose, usually galactose, and sometimes maltose, as group JK (204, 214). These strains are otherwise biochemically inert (214). In our view, *C. jeikeium* has an oxidative metabolism. Recently, studies of *C. jeikeium* strains that had been precisely characterized by genetic, chemotaxonomic, enzymatic, and additional phenotypic criteria showed that *C. jeikeium* are strict aerobes that are unable to produce acid from fructose (358) but can produce pyrazinamidase and alkaline phosphatase (128, 362). In the API Coryne system, *C. jeikeium* may fail to demonstrate sufficient acid formation from glucose or maltose, resulting in incorrect identification (441). Simple and rapid biochemical methods to screen for *C. jeikeium* have been proposed (56). However, readers are cautioned that schemes such as the one described by Cartwright et al. (56) may not include sufficient differential tests or test sufficient numbers of lipophilic taxa (e.g., *C. afermentans* subsp.

lipophilum, *C. accolens*, *C. macginleyi*, CDC group F-1, and *C. bovis* are missing from the study of Cartwright et al.), and therefore, errors in identification may result.

C. jeikeium strains are often multiresistant to antibiotics (214, 334, 335, 358, 367, 425, 457) but are susceptible to glycopeptide antibiotics and pristinamycin, with variable susceptibility to erythromycin, tetracycline, rifampin, and quinolones (272, 408). Resistance to antibiotics is thought to be chromosomal rather than plasmid associated (231). Susceptibility studies of some of the newer quinolones toward *C. jeikeium* indicate that several of these agents demonstrated significant in vitro activity against members of this species (272). In fact, multiple resistance has been used as a screening test for this species. However, a resistant antibiotic profile alone cannot be used alone to identify *C. jeikeium* isolates, because other phenotypically similar taxa (CDC group G) express this feature and some *C. jeikeium* strains lack it (358, 457).

In a recent study (358), *C. jeikeium* was compared with "*C. genitalium*" (160) and "*C. pseudogenitalium*" (161), as well as with representative strains of five unidentified lipophilic coryneform bacteria (359), in DNA-DNA hybridization assays. That study confirmed that *C. jeikeium* is genomically diverse, with four homology groups at the species level, named DNA groups A, B, C, and D. The DNA of the type strain of *C. jeikeium* (DNA group A) was found to be less than 75% homologous to that of other study strains; the reference strain of "*C. genitalium*" biotype II was identifiable at the species level with *C. jeikeium* DNA group B. DNA groups A and B were associated with multiple resistance to antibiotics; strains falling into DNA groups C and D were found to be resistant to low levels of penicillin but otherwise were not multiresistant. The other isolates, found to be genetically unrelated to *C. jeikeium* in this report, ("*C. genitalium*" biotype I, "*C. pseudogenitalium*" all biotypes, and five strains of "LDC" [also discussed below]) were fully susceptible to penicillin and gentamicin. It was concluded that pending additional studies, bacteria with characteristic multiresistant antibiotic susceptibility profiles and phenotypic traits (including lack of the ability to produce acid from fructose and to grow anaerobically) could be placed in a single taxon as *C. jeikeium*.

Attempts have been made to track strains of *C. jeikeium* considered outbreak related as well as to study the habitat of this species on individual patients, in wards, and within hospitals. Pitcher et al. used plasmid profiling, antibiograms, and ribotyping (335). They found the last method to be a potentially useful typing tool, but plasmid profiling was of limited value due to the large number of plasmidless strains recovered in that environment (335). Khabbaz et al., using RFLP analysis of chromosomal DNA, concluded that patient-to-patient transmission of *C. jeikeium* did not occur (231).

C. urealyticum. *C. urealyticum* , formerly CDC coryneform group D-2, is a slow-growing, lipophilic *Corynebacterium* species like *C. jeikeium*, which characteristically expresses multiple resistance to antibiotics, is asaccharolytic, and is a urease producer (72, 91, 336).

A comprehensive series of publications by Soriano and colleagues from Madrid, Spain, established the role that *C. urealyticum* plays in urinary tract infections (UTI), primarily in association with alkali-encrusted cystitis (400, 401, 404, 405). Bacteria isolated from alkali-encrusted cystitis which were phenotypically consistent with *C. urealyticum* had been described in the literature as early as 1947 (399).

C. urealyticum bacteriuria occurs mainly in patients hospitalized for a long period, who are severely immunocompromised, urologically manipulated, and elderly (400). No deaths have been attributed to *C. urealyticum* infections to date (400).

Recovery of the organism from urine does not always signify UTI, however, and, like *C. jeikeium*, *C. urealyticum* is a frequent colonizer of the skin of hospitalized patients with or without UTIs (400, 407). Nieto et al. have recently presented evidence that *C. urealyticum* may be transmitted by air and suggested that skin colonization in compromised patients could occur by that route (312).

Recovery of *C. urealyticum* from urine is significantly associated with an alkaline pH and the presence of struvite crystals (138). *C. urealyticum* in urine can induce struvite crystal formation in vitro (405).

This organism has been documented to cause acute or chronic (encrusted) infections of the lower urinary tract if underlying renal or bladder disease is present (276, 400). *C. urealyticum* may cause infection in the upper part of the urinary tract, resulting in pyelonephritis or pyeloureteritis (3), particularly in immunocompromised or post-renal-transplant patients with surgical complications (2, 285, 302).

C. urealyticum has been considered an infrequent cause of infections other than UTI, including endocarditis (123, 242, 317), bacteremia (266, 403, 460), osteomyelitis (66), soft tissue infection (378), and wound infection (403).

Recovery of this bacterium in prevalence studies may be hindered unless prolonged (48 to 72 h) incubation times are used, as *C. urealyticum* is a fastidious, slow-growing pathogen in comparison to other bacteria that cause UTI (400). However, even when the growth characteristics of *C. urealyticum* are factored in, the incidence of *C. urealyticum* UTI in "normal patient populations" is very low. In five major studies, the prevalence rate of *C. urealyticum* UTI ranged from 0.5 to 2.5% for UTIs in nonselected populations (France [104], United Kingdom [267], South Africa [445], United States [377], and Spain [307]).

The use of selective media coupled with a prolonged incubation time, conditions directed toward isolating these bacteria from urine, has been attempted by several centers. One such medium (300), was useful in one Spanish investigation. Otherwise, the development and routine use of selective media are not cost-effective, and it was recommended that such media be used only in cases when *C. urealyticum* is clinically suspected (445). Soriano et al. (409) also recommended that selective media should not be used because additional bacteria recovered on them were not clinically relevant, and they advocated the use of both SBA and cystine lactose electrolyte-deficient agars to recover this organism. The prevalence of *C. urealyticum* was reported as 1% even when urine samples with neutral or alkaline pHs were preselected and incubation of cultures was prolonged (377). It was recommended that routine urine culture exclude assessment for *C. urealyticum* in the absence of alkaline pH, struvite crystals, leukocytes, and erythrocytes (377).

The name *Corynebacterium urealyticum* was proposed in 1986 (405) to describe *Corynebacterium* group D2, but this name was not validated until 1992 (336). The gram-positive rods may appear coccoidal after prolonged incubation and are arranged in V forms or palisades. After 48 h of growth on SBA under CO_2 at 25, 37, or 42°C, colonies are nonhemolytic, pinpoint, whitish, smooth, and convex. They grow in 48 h in 7% CO_2 as tiny, creamy-white colonies on chocolate agar and as greyish-white colonies on cystine lactose electrolyte-deficient agar when recovered on those media (which occurs for only about 50% of the strains [275]).

C. urealyticum strains are strict aerobes, with no growth occurring on BA plates incubated anaerobically (336). The CDC identification scheme identifies catalase-positive, oxidase-negative, penicillin-resistant, lipophilic coryneforms that are nitrate negative, asaccharolytic, and urease producers (most often very rapidly) as *C. urealyticum* (Table 4). These strains are nonreactive in other conventional CDC biochemical tests, but they produce leucine aminopeptidase (401), pyrazinamidase, and often alkaline phosphatase (362). They may be differentiated from *C. jeikeium* by their inability to oxidize sugars and by their urease production.

The majority of *C. urealyticum* strains, like *C. jeikeium*, are multiresistant to antibiotics. *C. urealyticum* is usually resistant to β-lactams and aminoglycosides, susceptible to vancomycin, and variably susceptible to quinolones, erythromycin, rifampin, and tetracyclines (3, 4, 104, 166, 274, 275, 334, 400, 402, 406, 408, 430). Some of the newer quinolones were found effective in vitro against *C. urealyticum* strains (272). The antidepressant drug sertraline significantly decreased the MIC of ciprofloxacin for *C. urealyticum* strains in vitro (301). Persistent infection is associated with the use of ineffective broad-spectrum antibiotics (104). Encrusted cystitis requires endoscopic resectioning of encrustations, in addition to antibiotic therapy, for permanent cure (3, 400).

C. urealyticum has a CFA composition consistent with that of the genus *Corynebacterium*, with the majority of CFAs being of the straight-chain, monounsaturated types; several studies have shown that strains consistently have trace to small amounts of TBSA (30, 86, 199, 440). Like *C. jeikeium*, *C. urealyticum* has a G+C content of 61 to 62 mol% (336) and corynomycolic acids of 26 to 36 carbon atoms (103, 200).

Pitcher et al. (336) and Riegel et al. (361) found by DNA-DNA hybridization analysis that although the *C. urealyticum* strains tested were sufficiently close to each other to be considered members of the same species, they were not closely related to other *Corynebacterium* species. By 16S rRNA sequence analysis, *C. urealyticum* was most closely related (98% homology) to *C. jeikeium* (326, 376).

There are few reports of epidemiological tracking of potentially related strains of *C. urealyticum*. Soto et al. (411) used ribotyping to investigate strains, isolated mainly from urine and skin infections, from patients at six hospitals in Spain and one in Britain, in addition to reference strains. The isolates were remarkably homogeneous and could be assigned to eight clusters only, despite the deliberate use of strains from a variety of sources. Garcia-Bravo et al. (165) investigated external factors in the antimicrobial resistance of *C. urealyticum* and concluded that resistant strains were likely to be acquired directly from a hospital environment.

***C. afermentans* subsp. *lipophilum*.** *C. afermentans* subsp. *lipophilum* was described by Riegel et al. in 1993 as consisting of poorly growing coryneforms (i.e., when cultured on blood agar for 48 h in the absence of lipid supplementation) which are biochemically nonreactive in all routine laboratory tests but produce detectable amounts of alkaline phosphatase, esterase, lipase, and acid phosphatase (360). The strains described by Riegel et al. were human blood culture isolates (360). Both subspecies of *C. afermentans* express corynomycolic acids and lack TBSA as a constituent CFA (30, 440). A lipid-requiring variant of CDC group ANF-1 was never described in the original CDC guide (204).

Only three reports of *C. afermentans* infections can be found in the literature. Dealler et al. reported a central venous line infection that was most probably caused by *C. afermentans* subsp. *lipophilum* (101). This report is remarkable insofar as the described strain of *C. afermentans* subsp. *lipophilum* was resistant to all β-lactams tested except imipenem, whereas Riegel et al. (360) found that all the isolates they tested were susceptible to these antibiotics (which is also our experience [141]). Sewell et al. described a prosthetic valve endocarditis

TABLE 5. Characteristics of lipophilic corynebacteria related
to *C. accolens* as described in the literature[a]

Characteristic	Value in taxon[b]:		
	C. accolens (309) (n = 78)	CDC group 6 (203) (n = 16)	Genomospecies II (362) (n = 15)
Satellitism	+	ND	+
Lipophilism	ND	+	+
Urea hydrolysis	V (32%)	−	−
Fermentation[c]			
Glucose	+ (100%)	+ (100%)	+ (100%)
Maltose	+ (90%)	V (57%)	− (7%)
Sucrose	V (45%)	−	V (40%)
Mannitol	−	−	"Occasionally fermented"

[a] We recommend that the results of Riegel et al. (362) for genomospecies II (which includes the type strain of the species) be used to identify *C. accolens*, as described in the text.

[b] +, 90 to 100% of strains positive; −, 0 to 10% of strains positive; V, variable (11 to 89% of strains positive); ND, no data.

[c] Fermentation of sugars by Neubauer et al. (309) and by Hollis (203) was measured by conventional methods, whereas Riegel et al. (362) used API Coryne strips.

with perivalvular abscess formation due to *C. afermentans* subsp. *lipophilum* (393). This case demonstrated that not all blood cultures drawn from patients with endocarditis caused by lipophilic corynebacteria may become positive and that blood cultures harboring lipophilic corynebacteria may become positive only after an extended period of incubation. Dykhuizen et al. described an immunocompetent patient who developed a brain abscess from which *C. afermentans* subsp. *lipophilum* grew (116).

C. accolens. *C. accolens* was first described by Neubauer et al. in 1991 as strains of gram-positive rods (Table 5) derived over a 30-year period from a variety of clinical infections. They exhibited satellitism when grown in the presence of staphylococcal colonies (309), which may be suggestive of their lipophilic nature. The phenotypic and chemotaxonomic characteristics of these bacteria were consistent with those of the genus *Corynebacterium*. However, genetic studies were not described in that report (309).

Concurrently, the CDC had collected strains that phenotypically resembled *C. accolens* and had been given the designation CDC coryneform group 6 (203). The property of satellitism was not described as being associated with that taxon group, but growth was enhanced by the addition of serum (203). Fifteen strains of lipophilic coryneforms recovered primarily from respiratory specimens and described as genomospecies II by Riegel et al. were also found to be related to *C. accolens* at the species level by DNA-DNA hybridization studies (362). In all three reports, all *C. accolens* strains were described as nitrate reducers; otherwise, descriptions of the biochemical results for *C. accolens* cited among these three publications are discrepant (Table 5). It is not unlikely that the *C. accolens* strains as defined by Neubauer et al. (309) included CDC coryneform group F-1 bacteria (see below), which are the only lipophilic fermentative corynebacteria that express urease activity. As the 15 strains characterized as genomospecies II by Riegel et al. undoubtedly belong to the same species, it is recommended that future identifications of *C. accolens* refer to the data given in their study (362). In particular, genomospecies II strains were described as being variable (53%) for pyrazinamidase production and negative (0%) for alkaline phosphatase activity when the API Coryne strip was applied (362) (Table 4).

C. accolens has been reported as causing endocarditis of native aortic and mitral valves in a patient without predisposing factors (68).

C. macginleyi. *C. macginleyi* was the name proposed for the tightly clustered genomospecies III of lipophilic coryneform bacteria (three strains only) recovered from eye specimens as reported by Riegel et al. (362). Like *C. accolens*, all strains reduce nitrate and ferment glucose. All strains exhibit alkaline phosphatase activity, ferment ribose and sucrose, but do not ferment maltose, lactose, xylose, trehalose, or glycogen; hippurate hydrolysis and mannitol fermentation are variable, whereas pyrazinamidase activity is not detected. The authors of this review have only a few *C. macginleyi* strains in their collections, nearly all of which also came from eye specimens.

CDC coryneform groups F-1 and G. CDC group F-1 and CDC group G (G-1 and G-2) were first described by the CDC in 1981 (204). CDC groups F-1 and F-2 are usually described together in the literature; they are urease-positive coryneforms that have variable reactions with respect to nitrate reduction. Both taxa usually ferment glucose, ribose, and maltose, and CDC group F-1 (but not group F-2) ferments sucrose. As described above, group F-2 is a synonym of *C. amycolatum*. The CDC guide had not referred to CDC group F-1 strains as being lipophilic, but this characteristic has been described more recently by both Coyle and Lipsky (91) and Riegel et al. (362), and so this taxon is included here with the discussion of lipophilic corynebacteria. Recent studies have clarified the taxonomy of these taxa somewhat. It is not unlikely that sucrose-fermenting *C. amycolatum* strains (see above) were identified as CDC group F-1 bacteria in the past. Lipophilic CDC group F-1 isolates, however, were found to contain corynomycolic acids (103) and thus were considered true corynebacteria. Strains studied by Riegel et al. (362) also were found to belong to two genomospecies (IV and V), but these authors recommended that the designation CDC group F-1 be retained until further investigations are done. There are no case reports in the literature in which CDC group F-1 strains are described as being the sole cause of infection.

CDC groups G-1 and G-2 are taxa which, as originally described by the CDC, ferment glucose, sucrose, and occasionally maltose; urease production is absent. CDC group G-1 reduce nitrate and thus can be differentiated from CDC group G-2 (nitrate negative) (204). Both groups were found to contain corynomycolic acids (103, 359), and their CFA compositions were found to be like those of true *Corynebacterium* species (30, 440).

Lipophilic, glucose-fermenting coryneforms, including CDC group G-1 and G-2 strains and reference strains of "*C. genitalium*," "*C. pseudogenitalium*," and "*C. tuberculostearicum*" (discussed below) obtained from several reference laboratory collections were studied by Riegel et al. using DNA-DNA hybridization analysis (362). They found that 17 strains of CDC group G-1 and G-2 could be grouped together by genetic means and therefore should no longer be differentiated based on the ability to reduce nitrate as G-1 (nitrate reducer) or G-2 (nitrate negative) and recommended the use of the term "CDC group G." Species determination of bacteria with characteristics most consistent with taxa called CDC group G-1 or G-2 by the CDC (i.e., genomospecies I of Riegel et al. [362]) remains difficult and requires further study. It is recommended that clinical microbiologists use the designation "CDC group G strains" for bacteria expressing characteristics of genomospecies I of Riegel et al. (362), including lipophilia, ability to grow anaerobically, ability to ferment glucose and fructose, production of pyrazinamidase and alkaline phosphatase, variable abilities to reduce nitrate and to ferment maltose or sucrose, and

TABLE 6. Biochemical and morphological characteristics of coryneform genera isolated from humans

Characteristic	Value in:						
	Corynebacterium	*Turicella*	*Arthrobacter*	*Brevibacterium*	*Dermabacter*	*Oerskovia*	*Cellulomonas*
Pigment[a]	− to w to y	w	w to g	w to g to sl y to t	− to w	w to y	sl y
Motility	−[b]	−	v	−	−	+[b] (pe)[c]	v[b] (p)[c]
$NO_3 \rightarrow NO_2$	v	−	v	v	−	+	+
Urea hydrolysis	v	−	v	−	−	−	−
Esculin hydrolysis	v	−	v	−	+	+	+
Gelatin hydrolysis	v	−	+	+	+	+	+
Casein hydrolysis	v	ND	ND	+	+	+	−
Starch hydrolysis	v	−	ND	−	+	+	+
DNA hydrolysis	v	−[d]	+	+	+	+	v
Sugars (acid production)	F/O[e]	O	O	O	F	F	F
Glucose	v	−	v	v	+	+	+
Maltose	v	−	v	v	+	+	+
Sucrose	v	−	v	v	+	+	+
Mannitol	v	−	−	−	−	−	v
Xylose	v	−	−	−	v	+	+
CAMP test	v	+	−	−	−	−	−
Others (unique)				Odor	Lysine positive, ornithine positive, arginine negative	Agar penetration; xanthine hydrolysis separates species	Cellulose hydrolysis positive

[a] Pigment abbreviations: g, greyish; o, orange; sl, slightly; t, tan; w, whitish; y, yellow.
[b] v, variable; −, negative in ≥90% of strains; +, positive in ≥90% of strains; ND, no data.
[c] p, polar; pe, peritrichous (in younger cultures monotrichous).
[d] Authors' experience.
[e] F, fermentative; O, oxidative.

inability to hydrolyze urea (in contrast, *C. jeikeium* is a strict aerobe and fructose non-fermenter [358]). CDC group G strains may be recovered from a variety of sources (blood, eye, skin, semen, mitral valve, abscesses, urethra) (362). In our experience, they are frequently isolated from eye specimens and intravascular catheters (141).

As discussed above for *C. jeikeium* strains, antibiograms cannot be used to separate these taxa. Clinically significant CDC group G strains, like those of *C. jeikeium* and *C. urealyticum*, are increasingly expressing multiple resistance to common antibiotics (457). In our experience, CDC group G strains are very often resistant to clindamycin and erythromycin (141).

CDC group G strains have only infrequently been reported as causative agents of disease, and the use of ad hoc nomenclature based on letters and numbers has contributed to confusion during reviews of the older literature on this topic (257). CDC group G-2 was responsible for a fatal endocarditis (12) and, among cases reviewed by Quinn et al., for septic arthritis and endocarditis in a patient with lupus erythematosus (345). Williams et al. found that CDC groups G-1 or G-2 were the second most common coryneforms isolated from clinically significant cultures (after *C. jeikeium*) in a study conducted in a large institution (457).

C. bovis. *C. bovis* was described as being derived from bovine sources and had been thought to be only an occasional human pathogen (254, 255) which fermented glucose, fructose, maltose, and glycerol, with significant amounts of the CFA TBSA being found in its cell wall (76). It has been questioned if this species, using current criteria for identifying corynebacteria, has indeed ever been recovered from cases of human disease (91). As reviewed by Coyle and Lipsky (91), two of four reference strains (NCTC 11914 and ATCC 13722) are thought to be incorrectly identified strains of *C. jeikeium* and plant coryneforms, respectively. The CDC has never had a human isolate of *C. bovis* in its collection (91). A recent review of the literature did not result in any description of cases of human

disease attributable to this species. It is evident from recent phylogenetic analysis that *C. bovis* is a true member of the genus *Corynebacterium* (326, 376), although it possesses an unusual mycolic acid structure (78).

By phenotypic means, *C. bovis* may be difficult to discern from other lipophilic taxa, *C. jeikeium*, and CDC coryneform group G bacteria. *C. bovis* may be initially distinguished from *C. jeikeium* and CDC coryneform group G bacteria by the source of specimen (animal and human disease association, respectively). *C. jeikeium* can be positive for maltose but negative for fructose and β-galactosidase production, whereas *C. bovis* is always maltose negative (Table 4) and has been described as positive for fructose and β-galactosidase (76, 362) (Table 4). CDC group G is often positive for maltose and/or sucrose but negative for β-galactosidase.

Other lipophilic coryneforms. Contemporary, precise phenotypic, chemotaxonomic, and genetic criteria have been used to analyze lipophilic coryneforms called "*C. genitalium*" (160), "*C. pseudogenitalium*" (161), and "*C. tuberculostearicum*" (45), taxa previously described but never validated as *Corynebacterium* species. Evangelista et al. (129) attempted to differentiate "*C. genitalium*" and "*C. pseudogenitalium*" from *C. jeikeium* but used only phenotypic criteria rather than chemotaxonomic and genetic methods to substantiate the taxonomic relationships. Some of these strains can now be assigned to valid species or placed within more precisely defined taxa (128). The taxonomy of others remains unclear.

"*C. genitalium*" CCUG 28786 (type II, ATCC 33031) was identified as a member of DNA hybridization group B of *C. jeikeium* (358). Riegel et al. (362) found that "*C. tuberculostearicum*" (ATCC 35521 [LDC 8]) and reference strains C-2, C-3, and C-4 of "*C. pseudogenitalium*" (CCUG 28788, CCUG 28789, CCUG 28790 [ATCC 33036, ATCC 33037, and ATCC 33038, respectively]) clustered with genomospecies I (CDC group G) (362). Type C-5 of "*C. pseudogenitalium*" (CCUG 27540 [ATCC 33039]) is related to genomospecies IV cluster

TABLE 6—*Continued*

				Value in:				
Sanguibacter	*Microbacterium*	*Aureobacterium*	"*C. aquaticum*"	*Propionibacterium*	*Propioniferax*	*Rothia*	*Actinomyces*	*Exiguobacterium*
y	y to o	y	y	y/sly	w	w	− to w	Golden
+	v (p)	v	+ (p)	−	−	−	−	+ (pe)
v	v	v	v	v	+	+	v	v
ND[b]	−	v	−	−	+	−	v	−
+	+	v	v	v	−	+	v	+
v	v	+	−	v	+	v	−	v
v	v	v	−		ND	−		+
ND	v	v	ND		+	−		+
ND	+	v	+		ND	−		ND
F	F	O	O	F	F	F	F	F
+	+	+	+	+	+	+	v	+
+	+	+	v	v	+	+	v	+
+	+	+/(+)	v	v	v	+	v	+
v	+	v	+	v	−	−	v	+
+	v	v	+	−	ND	−	v	−
ND	−	−	−	v	ND	−	v	ND

(i.e., CDC group F-1). "*C. genitalium*" CCUG 28784 (type V; ATCC 33034) and type C-1 "*C. pseudogenitalium*" (CCUG 28787 [ATCC 33035]) are not in a cluster, and their taxonomic status remains unclear (362). "*C. genitalium*" NCTC 11859 (ATCC 33030) and "*C. pseudogenitalium*" NCTC 11860 (ATCC 33039) are 97% homologous to *C. afermentans* DMMZ 525, and "*C. tuberculostearicum*" ATCC 35692 is 98% homologous to "*C. fastidiosum*," using 16S rRNA sequence analysis (326). Other lipophilic coryneforms, represented by single strains in the two studies by Riegel et al. (358, 362), could not be assigned to currently described taxa.

Genus *Turicella*

In 1993, two groups independently described coryneform bacteria isolated from patients with otitis media (153, 395). These organisms were nonfermentative and occurred either alone or together with gram-negative rods. Phenotypically, they resembled corynebacteria, but in contrast to most of these, they did not contain mycolic acids and always showed small amounts of TBSA (3 to 8%) (153). Distinct chemotaxonomic features (Table 3), as well as a phylogenetic analysis, defined these coryneform bacteria as members of a new genus and species, *Turicella otitidis* (155). Phenotypically, *T. otitidis* may be distinguished from *Corynebacterium* spp. by its longer cells. Biochemical reactions of *T. otitidis* are listed in Table 6. *T. otitidis* strains yield a numerical code of 2100004 in the API Coryne system (153). All *T. otitidis* strains examined so far exhibit a strongly positive CAMP reaction. The two research groups found different enzyme activities in the API Zym system, probably due to differences in incubation time and interpretation (155, 395). Remarkably, *T. otitidis* has not been isolated from any source other than from patients with ear infections and from ears of healthy control persons (141). The disease association of *T. otitidis* is currently under investigation. *T. otitidis* strains may be resistant to clindamycin and erythromycin, whereas the MICs of β-lactams are usually ≤0.03 μg/ml (154).

Genus *Arthrobacter*

Arthrobacter strains are widely distributed in the environment, especially in soil, but have only recently been described as being isolated from clinical specimens (146). Previously, clinical *Arthrobacter* strains may have been identified as CDC coryneform group B-1 and B-3 bacteria.

Colonies of *Arthrobacter* strains are whitish-grayish, 2 mm or greater in diameter, and slightly glistening after 24 h of incubation on SBA. Gram stains show coryneform bacteria after 24 h and mainly coccoid cells after 72 h of incubation. All *Arthrobacter* strains exhibit an oxidative metabolism, and DNase and gelatinase activity are detected within 10 days. *Arthrobacter* strains may be tentatively identified to the species level by means of carbohydrate assimilation tests (143), but building a reliable database is problematic because for many *Arthrobacter* species there is only a single described strain, the type strain.

$C_{15:0ai}$ is the predominant CFA in *Arthrobacter* spp., and lysine is the diamino acid of the cell wall. Analysis of the primary peptidoglycan structure may lead to species identification. Applying both chemotaxonomic and molecular genetic methods, Funke et al. proposed two new *Arthrobacter* species, *A. cumminsii* and *A. woluwensis*, for some of the clinical strains examined (146).

Members of the genus *Brevibacterium* may be readily confused with *Arthrobacter* species, since they have similar colony morphology and an oxidative metabolism. *Arthrobacter* strains may be motile, whereas *Brevibacterium* strains are always nonmotile. Many *Brevibacterium* strains give off a cheeselike odor, which is not observed for *Arthrobacter* strains. $C_{15:0ai}$ and $C_{17:0ai}$ are the predominant CFAs in *Brevibacterium* strains, whereas $C_{15:0ai}$ is the major CFA in *Arthrobacter* strains.

For *Arthrobacter* strains, penicillins showed markedly better activity than the cephalosporins. All *Arthrobacter* strains tested were susceptible to glycopeptide antibiotics (146).

Genus *Brevibacterium*

Brevibacteria are gram-positive rods that show a marked rod-coccus cycle when growing on complex media: young cultures (up to 24 h old) produce diphtheroidal rods with frequent V arrangements, while older cells (3 to 7 days old) in culture are mainly coccoid or coccobacillary and decolorize easily. Brevibacteria are nonmotile, nonfastidious, chemoorganotrophic, obligately aerobic (oxidative or indifferent toward sug-

ars), halotolerant (≥6.5% NaCl), and catalase positive. Other chemotaxonomic characteristics are listed in Table 6. Methanethiol formation from methionine, tested by the method of Pitcher and Malnick (338), is positive in most strains after 2 h, but the test loses its specificity for brevibacteria with longer incubation (143). Oxidation of sugars, if it occurs, may take up to 3 weeks in O/F media (182), but in our experience, it is mostly negative in cystine Trypticase agar media. In the API Coryne gallery, *Brevibacterium* may be confused with *R. equi*, *C. afermentans*, or *T. otitidis*, but the last three should be recognizable by their colonial morphology and lack of odor.

Colonies of brevibacteria on blood agar are opaque, grey-white, up to 2 mm or more in diameter after 24 h, and convex, and they show a smooth, shiny surface. Later, they become even larger and may turn slightly yellowish or greenish. They are nonhemolytic, and most give off a cheeselike odor. Human strains have growth optima between 30 and 37°C.

Habitats for nonhuman species (*B. iodinum*, *B. linens*) as well as for *B. casei* include raw milk and surface-ripened cheeses; animal sources have also been reported (77, 219). The first two species are of very limited importance to humans and will not be discussed further. The human skin has been the habitat of *B. casei* and *B. epidermidis*. Brevibacteria may contribute to the malodor of some people's feet.

The latest issue of *Bergey's Manual*, vol. 2, lists four species: *B. linens*, *B. iodinum*, *B. casei*, and *B. epidermidis* (219). Cai and Collins have shown by 16S rRNA gene sequencing that these four species form a distinct phylogenetic grouping (46). In 1993, a new species, *B. mcbrellneri*, which was found together with *Trichosporon beigelii* in patients with white piedra, was reported (277). Most recently, Pascual et al. described two *Brevibacterium* strains isolated from patients with otitis as *B. otitidis* (324). Taxa formerly described by the CDC as coryneform groups B-1 and B-3 were also later found to contain brevibacteria, although only half of one collection could be identified to the species level, i.e., as *B. casei* (182). The former *B. acetylicum* (219) has been shifted to the genus *Exiguobacterium* (131) (discussed below). Species differentiation was thought to be possible only by G+C determination, color of colonies, iodinine crystal formation, and temperature optima (219). It turns out, however, that human strains are by and large *B. casei* (>95% of all clinical isolates) and that these can be differentiated from *B. epidermidis* and *B. mcbrellneri* by carbohydrate assimilations (e.g., arabinose and mannitol) in the API 50CH gallery (143) or by restriction analysis of PCR-generated rDNA (48). The value of cellular protein profiles for the typing of brevibacteria has been demonstrated (224). Also mentioned have been the API Coryne gallery and tellurite reduction for separation of *B. epidermidis* from *B. mcbrellneri* (277) and cellular fatty acids for separation of *B. casei* from *B. epidermidis* (180), but the small numbers of non-*B. casei* strains investigated preclude a final judgment. In contrast, Funke and Carlotti found assimilation reactions more suitable for differentiation than was CFA analysis (143). Significantly, for brevibacteria the percentage of $C_{15:0ai} + C_{17:0ai}$ was greater than 75% of all CFAs (143).

Since 1984, many strains of brevibacteria have been reported from human sources, particularly from skin or structures adjacent to the skin (143, 182, 338). Diseases due to brevibacteria have also been described, e.g., osteomyelitis (310), CAPD peritonitis (180, 208), and septicemia (49, 230, 250, 354). The species identification of the strain described by McCaughey and Damani (278) as *B. epidermidis* is questionable, as the methods used in this study did not provide identification below the genus level (143). One report of a pleural empyema due to *B. linens* is also extant (292), although the species identification

is questionable because of its optimal growth temperature below 37°C. Bayston et al. reported a *Brevibacterium* strain colonizing a hydrocephalus shunt; extracellular slime production may have been a pathogenicity factor in this instance (23).

Many *B. casei* isolates have been resistant to β-lactams, ciprofloxacin, clindamycin, and erythromycin, whereas gentamicin, rifampin, and tetracycline have shown good activity against *B. casei* isolates (154). All isolates have also been susceptible to glycopeptide antibiotics.

Genus *Dermabacter*

In 1988, Jones and Collins described four strains of a gram-positive, asporogenous coryneform derived from the skin of healthy adults, which was assigned to a new genus and species, *Dermabacter hominis* (218). In retrospect, it was found that strains dating back to the 1970s and phenotypically resembling those of *D. hominis* had been referred to national bacteriology reference centers in Canada (Laboratory Centre for Disease Control) and the United States (CDC) (28). The CDC had provisionally assigned to these bacteria the names CDC coryneform group 3 (xylose fermenter) and group 5 (xylose nonfermenter) (203). These strains had been isolated primarily from blood cultures and less commonly from abscesses, wounds, skin lesions, eyes, and other body sites in patients in Canada, the United States, Belgium, and Sweden. In 1994, Funke et al. described the phenotypic and chemotaxonomic characteristics of 15 Swiss clinical isolates of CDC groups 3 and 5; they assigned these taxa to the genus and species *Dermabacter hominis* based on both chemotaxonomic and 16S rDNA sequence analyses when compared with the type strain of *D. hominis* NCFB 2769 (ATCC 49369) (156). Later, Gruner et al. (181) published similar results and found by means of DNA-DNA hybridization studies that 22 of 30 strains of CDC groups 3 and 5 could be classified as *D. hominis*; most of these clinical isolates demonstrated a higher degree of relatedness to one of the clinical strains (G4964, ATCC 51458) than to that of the type strain of the species. The eight remaining strains in that study, although identical to the others phenotypically and by CFA composition analysis, did not hybridize at the species level and were thought to represent additional species in that genus, but differentiating characteristics were not reported (181). By using partial 16S rRNA gene sequence analysis, strains ATCC 51323 (group 3), ATCC 51324 (group 3), ATCC 51325 (group 5), and ATCC 51326 (group 5) have been found to have 100% homology to the *D. hominis* type strain ATCC 49369 (29). Phylogenetic studies by Cai and Collins suggest that *D. hominis* is sufficiently distinct from the *Arthrobacter*/*Micrococcus* subline to merit separate genus-level status (46).

D. hominis strains have small, greyish-white convex colonies with a distinctive, pungent odor (28). They are nonmotile, catalase-positive, gram-positive bacilli, coccobacilli, or coccoidal forms that ferment glucose, lactose, sucrose, and maltose and hydrolyze esculin (Table 6). Xylose fermentation is variable, and mannitol is not fermented; nitrate is not reduced, and most strains are oxidase negative. *D. hominis* appear to be one of the very few taxa among coryneforms described to date which decarboxylate lysine and ornithine (28, 156, 203).

D. hominis has a CFA composition of the branched-chain type, with significant amounts of CFAs $C_{15:0ai}$, $C_{16:0i}$, and $C_{17:0ai}$ (28, 156, 218). The CFA composition is sufficiently unusual to be correctly identified at moderate to high confidence levels to specific library entries created for them by using the MIDI system and its library generation system software (28). *D. hominis* has a G+C content of 62 mol% and contains *meso*-diaminopimelic acid (156, 218). Mycolic acids are absent. *D.*

TABLE 7. Habitats and biochemical characteristics of human propionibacteria and *Propioniferax innocua*[a]

Habitat or characteristic	Value for:				
	P. acnes	*P. avidum*	*P. granulosum*	*P. propionicum*	*Propioniferax innocua*
Habitats	Skin[b], large intestine, mouth, conjunctiva	Skin (axilla, inguina, perianal area)	Skin	Mouth, eyelids, conjunctiva	Skin
Catalase	+	+	+	−	+
Optimal atmospheric growth conditions	Anaerobic	Anaerobic and aerobic	Anaerobic	Anaerobic	Aerobic
Indole	+	−	−	−	−
Nitrate to nitrite	+	−	−	+	+
Esculin (anaerobic)	−	+	−	−	−
Sucrose	−	+	+	+	+
Maltose	−	+	+	+	+
Beta-hemolysis	v[c]	+	+	−	ND[d]

[a] Modified from references 117 and 467.
[b] Including eyelids.
[c] v, variable.
[d] ND, no data.

hominis has major amounts of menaquinones MK-9 and MK-8 with MK-7, as well as the polar lipids diphosphatidylglycerol and phosphatidylglycerol (218). Acetate and lactate were detected as major end products of glucose metabolism (156).

The API Coryne system was found to be useful for identification of strains of *D. hominis*, with the caveat that *D. hominis* is not cited in the current edition of the API Code book (9) and may match with a high confidence level to "Coryneform group A" or "no match." The codes include 4470765, 4570165, 4570364, 4570365, and 4570765 (28, 156).

D. hominis strains are susceptible to cephalosporins, whereas the activities of ciprofloxacin, clindamycin, erythromycin, gentamicin, and tetracycline are limited, as revealed by their MIC_{90} values (MICs at which 90% of the isolates are inhibited) (154). In contrast, rifampin shows excellent activity on *D. hominis* isolates, with MICs of ≤ 0.03 μg/ml. MICs of glycopeptides are within the range of 0.06 to 0.5 μg/ml.

Case reports of *D. hominis* infections have not appeared in the literature to date.

Genus *Propionibacterium*

The literature on propionibacteria has become rather large, with two recent reviews (44, 117) covering the field extensively. This section will concentrate on the clinical microbiology aspects of the human (not veterinary or environmental) species.

Propionibacteria are diphtheroid organisms that may bifurcate or even branch. With the exception of *P. avidum* and *Propioniferax innocua* (this new genus was recently proposed for the former *Propionibacterium innocuum* [467]), they generally grow better under anaerobic than aerobic conditions, particularly on first isolation. Chemotaxonomic features are given in Table 3, and the differentiating biochemical ones are given in Table 7 (for a complete set of biochemical characteristics, see references 98, 204, 386, and 467). Propionibacteria form propionate and acetate as the main metabolites from glucose; smaller amounts of succinate, formate, lactate, and CO_2 may also be formed.

In many earlier publications, propionibacteria were misidentified as corynebacteria. The former *Corynebacterium parvum* has long been recognized as *P. acnes* (117), and the former *Arachnia propionica* was reclassified in 1988 as *P. propionicus* (correct naming *propionicum*) (63). *P. propionicum* is, however, catalase negative and may form filamentous forms and microcolonies resembling those of *Actinomyces* spp. It may also show a red fluorescence under long-wave UV light (38).

There are no reliable typing systems for *Propionibacterium* spp. at this time. *P. acnes*, *P. avidum*, and *P. granulosum* may be CAMP positive, but no data are available for the other species.

The habitats of propionibacteria are listed in Table 7. Propionibacteria not identified to the species level have also been found in the vagina (117). In the skin, *P. acnes* predominates over other constituents of the normal flora in the pilosebaceous follicles but colonizes only approximately 20% of the follicles (246). The organism appears at puberty and reaches approximately 10^5 CFU per follicle (246). In the large intestine, densities of 10^8 to 10^{10} CFU/g of stool may be observed but only in a minority of individuals (133).

P. acnes produces a number of extracellular factors like proteinases, hyaluronidase, lipase, PLC, neuraminidase, acid phosphatase, histamine, and tryptamine (117), some of which may participate in the pathogenesis of acne vulgaris, a disease whose etiological agent has still not been elaborated. *P. acnes* seems to play an important role in this disease, at least as far as duration and severity of inflammation are concerned (117).

P. acnes resists killing by phagocytes, is able to survive in macrophages (451), and is a well-known adjuvant, which nonspecifically activates macrophages. It also increases resistance to experimental tumors (372).

The role of propionibacteria in the etiology of human infections has been established without doubt, but their role in the pathogenesis of Kawasaki disease, sarcoidosis, and the syndrome "acne pustulose et hyperostose osteite" has not yet been elucidated (117). The literature on infections with propionibacteria comprises close to 100 case reports. This review attempts to summarize salient features of *Propionibacterium* infections, drawing upon the most recent publications.

Only a minority of clinical *Propionibacterium* isolates are clinically significant; in one series, it was 12% (44). There were, however, differences in the frequency of clinically significant strains among various specimens. In grafts, bone samples, cysts, bile, and lymph nodes, >20% were significant, and few of those strains were in mixed culture. *P. acnes* was isolated eight times more frequently than other *Propionibacterium* species (which parallels our own experience), but the percentage of significant isolates did not differ among the species. Experimental pathogenicity of *P. acnes* in a subcutaneous-abscess model was, however, erratic (43).

Predisposing conditions for *P. acnes*, *P. granulosum*, and *P. avidum* infections are the presence of foreign bodies, immunosuppression, preceding surgery, trauma, diabetes, and ob-

struction of sinuses or ducts. The incubation period may last from a few days to several months; occasionally, it lasts for more than 1 year. The prognosis is generally good if appropriate antibiotics are administered. Of note, the organisms are more likely to be isolated in anaerobic than in aerobic cultures (Table 7), and isolation may take from 1 to 14 days. In our experience, clinical significance is inversely proportional to the time of appearance in culture unless the patient has been pretreated with antibiotics.

Endocarditis occurs more often on prosthetic valves than on native valves (31, 188). Recently, we have been able to recover the organisms more often from infected valves if the latter were ground before culture (188). Septicemia without endocarditis is rare (37). Endophthalmitis occurs most frequently following extracapsular cataract extraction, with or without posterior chamber lens implantation, but may also follow trauma. Symptoms may appear 7 days to 11 months after the event, with signs of low-grade inflammation and later hypopyon, kerato-precipitates, plaques on the posterior capsule, and even abscess formation (211, 215). Vitreous culture may be positive or negative, but recently, PCR with *P. acnes*-specific primers from vitreous samples has proven successful in some cases (211). Central nervous system infections are most frequently shunt infections (possibly complicated by shunt nephritis [392]), brain abscesses (often with mixed cultures) and meningitis, and epidural or subdural empyema following neurosurgical procedures (350, 368). Arthritis may follow steroid injections or involve prosthetic joints (418). Osteomyelitis may follow surgery (314) or endocarditis (419). Surgical wound infections are rare. In one series, the organisms were isolated in mixed culture with coagulase-negative staphylococci from neurosurgical patients (126). Rare infections include bronchopneumonia (69, 294), botryomycosis (125, 175, 390), dental and parotid infections (171), and splenic abscess (115). In CAPD patients, propionibacteria have thus far been seen only as contaminants (398).

The spectrum of *P. propionicum* infections differs from that of the other propionibacteria and resembles, like its habitat, that of *Actinomyces israelii*. It comprises primarily canaliculitis and dacryocystitis (which occur mainly in elderly females [38]) but also abscesses and, rarely, pneumonia. Experimentally, *P. propionicum* also causes suppurative disease similar to that produced by *A. israelii* (118).

Propionibacteria are susceptible to most antibiotics except metronidazole and often to aminoglycosides (37, 107, 396, 447). A killing effect, however, was seen against only one of six strains for penicillin, against no strain for cefazolin, but against all six strains for vancomycin (191).

Genus *Rothia*

The genus *Rothia* contains *Rothia dentocariosa* as the only species. The minimal description previously accepted of *Rothia* as an irregular gram-positive rod which is fermentative, nitrate, esculin, glucose, maltose, and sucrose positive, and urease, mannitol, and xylose negative has run into difficulties. It would allow misidentification of some strains of *Dermabacter*, *Actinomyces viscosus*, *Propionibacterium avidum*, and *C. matruchotii* as *Rothia* (Tables 4, 6, and 7; also see Table 8), particularly because both *D. hominis* and *C. matruchotii* are unfamiliar to many clinical laboratories and the degree of aerotolerance of some *Actinomyces* and *Propionibacterium* spp. is not commonly appreciated. In fact, Bernard et al. (28) found that many of the strains eventually identified as *Dermabacter* (CDC group 3 and 5 strains) had been considered *Rothia* or *Actinomyces* spp. by the submitting laboratory. However, in contrast to *Actinomyces*

and *Propionibacterium* spp., *R. dentocariosa* colonies are larger (about 1 mm after 1 day) when incubated aerobically than when incubated anaerobically. Colonies of *R. dentocariosa* are white and raised, may be smooth and/or rough, and may have a spoked-wheel form. The Gram stain description of *Rothia* is confusing. Both CDC charts (204) and *Bergey's Manual* (170) describe *Rothia* as coccoid, diphtheroid-like or filamentous; however, the illustration in *Bergey's Manual* shows irregular rods with rudimentary branching. In the clinical laboratory, when taken from plates, *R. dentocariosa* tends to resemble the illustration in *Bergey's Manual* and when grown in broth, it is longer and shows more branching. The authors of this review have not seen filamentous or chaining forms (i.e., like *Lactobacillus*) with some organisms five or more times the length of the shorter forms or with bulbous ends up to 5 μm in diameter as described in *Bergey's Manual*.

Although *Rothia* is not in its database, API Coryne test strips yield codes of 7050125 or 7052125 (28). *Rothia* is distinct from *Dermabacter* in that it is nitrate and pyrazinamidase positive and alkaline phosphatase, β-galactosidase, sucrose, and ribose negative, and it differs from *A. viscosus* in the alkaline phosphatase, β-galactosidase, sucrose, ribose, and pyrrolidonyl arylamidase tests. *P. avidum* is β-hemolytic, and *C. matruchotii* has a distinctive Gram stain. However, CFA analysis allows easy discrimination, as both *Actinomyces* spp. and *C. matruchotii* have straight-chain CFAs whereas the others have branched-chain CFAs in different amounts: *R. dentocariosa* and *D. hominis* have mostly $C_{15:0ai}$ and $C_{17:0ai}$, and *Propionibacterium* spp. have mostly $C_{15:0i}$ and $C_{15:0ai}$ (30, 156).

The problem with many of the clinical reports is that not enough information is included to allow the reader to clearly distinguish the organism from the catalase-positive, aerotolerant strains of *Actinomyces* and *Propionibacterium* that could be encountered in similar clinical settings. Even though the identification is often performed at a reference laboratory, misidentifications may occur if some identification schemes are used and CFA chromatography is not done. At this time, there are enough data only to suggest an association of *R. dentocariosa* with endocarditis and occasionally with brain abscess. There are eight reports of *R. dentocariosa* causing endocarditis (7, 42, 213, 322, 388, 394, 417, 452). Most of these describe the organism as branching, having smooth and rough colonies, and growing better in air (42, 322, 452). There is one report each of *R. dentocariosa* associated with pilonidal abscess (identified by the CDC with specific fluorescent antibodies; branching was not noted [258]), bacteremia (340), and septicemia in a compromised host (332). The isolate described by Nivar-Aristy et al., associated with an arterial fistula, may have been an *Actinomyces* species (the organism grew best anaerobically and was nitrate and catalase negative [313]).

There are few data on the susceptibility of *R. dentocariosa*. It seems universally susceptible to penicillin and to other antibiotics, except for one report each of resistance to trimethoprim-sulfamethoxazole (42) and to both aminoglycosides and trimethoprim-sulfamethoxazole (374), but the identification of the latter organism could not be confirmed.

The phylogenetic position of CDC coryneform group 4 bacteria (203) has not been established so far. Phenotypically, these bacteria are closely related to *R. dentocariosa* (203). In contrast to *R. dentocariosa*, CDC coryneform group 4 strains show characteristic charcoal-gray to black colonies. In addition, the majority of CDC coryneform group 4 bacteria grow in nutrient broth containing 6% NaCl whereas only 3% of all *R. dentocariosa* strains tested did (203, 204). Only 7% of CDC coryneform group 4 strains degraded gelatin, whereas 58% of *R. dentocariosa* strains did (203, 204). CDC coryneform group

4 bacteria were isolated mainly from females with genitourinary infections (203). The CFA patterns of *R. dentocariosa* and CDC coryneform group 4 bacteria are very similar, with $C_{15:0ai}$, $C_{17:0ai}$, $C_{16:0i}$, and $C_{16:0}$ as the major acids (29, 141). It is to be expected that CDC coryneform group 4 strains will be validly described in the near future. At the time of this writing, no case reports on CDC coryneform group 4 bacteria could be found in the literature.

Genus *Exiguobacterium*

The genus *Exiguobacterium* was first described by Collins et al. in 1983 (83); it contained as its only species *E. aurantiacum*, an alkalophilic bacterium isolated from potato-processing effluent. In 1994, Farrow et al. included the former species incertae sedis, *Brevibacterium acetylicum*, in the genus *Exiguobacterium* (131). The chemotaxonomic differences between the two genera are considerable (Table 3). *E. acetylicum* has an almost unique CFA pattern, with $C_{13:0i}$ and $C_{13:0ai}$ each representing about 10% of the total CFAs (30). *Exiguobacterium* strains are motile (Table 6) by peritrichous flagella and facultatively anaerobic with a fermentative carbohydrate metabolism. Colonies of *E. acetylicum* exhibit a golden-yellow pigment, and most of the strains have a positive oxidase reaction (204). *E. acetylicum* strains may be misidentified as former CDC coryneform group A-5 bacteria, but cell wall and CFA analyses clearly separate *E. acetylicum* and *Microbacterium* spp. (see below) (Table 3).

The CDC has reported a number of strains from various clinical sources (e.g., skin, wounds, cerebrospinal fluid) (204), but case reports are not extant.

Genus *Oerskovia*

Members of the genus *Oerskovia* belong to the "nocardioform" bacteria. This term does not refer to a close phylogenetic relationship between certain genera (e.g., *Nocardia* and *Oerskovia*) but, rather, to certain common features such as gram positivity and formation of temporary mycelia breaking up into rod-shaped or coccoid rods (245). The *Oerskovia* mycelium is an extensively branching substrate hypha which breaks up into rod-shaped motile (first monotrichous, later peritrichous) or nonmotile (NMO [nonmotile oerskoviae]) elements. Strains are non-acid fast, catalase positive, and fermentative, and most are yellow pigmented. No aerial hyphae are formed. The main taxonomic features are listed in Table 3. The controversy over the taxonomic position of *Oerskovia* has continued, with the proposal of assigning the genera *Oerskovia*, *Cellulomonas*, *Pseudomicromonospora*, and *Jonesia* to a new family, *Cellulomonadaceae* (415), but recent molecular investigations applying 16S rDNA cataloging have revealed that the genera *Cellulomonas* and *Oerskovia* are phylogenetically intermixed (132), that the genera *Terrabacter* and *Sanguibacter* are more closely related to *Oerskovia* than are *Pseudomicromonospora* and *Jonesia* (132), and that *Promicromonospora enterophila* and *P. citrea* probably represent *Oerskovia* strains (348). The current opinion, based on chemotaxonomic features, is that *Oerskovia* and *Cellulomonas* represent separate genera (416). The taxonomic status of NMO is unclear at this time. In their biochemical characteristics, they resemble *Cellulomonas* (they are also cellulolytic), but chemotaxonomically and morphologically, they resemble the motile oerskoviae (245).

The normal habitats of *Oerskovia* spp. are soil, decaying plant material, brewery sewage, and aluminum hydroxide gels (245). Two species, *O. turbata* and *O. xanthineolytica* (both included in former CDC coryneform groups A-1 and A-2 [412]), have been described (245). The most important reactions are listed in Table 6; the main differences between the species lie in the hydrolysis of xanthine and hypoxanthine (positive in *O. xanthineolytica*, negative in *O. turbata*). In our experience, *Oerskovia* spp. are identified well by the API Coryne system.

Case reports of human infections include endocarditis (*O. turbata* [355]), meningitis (*O. xanthineolytica* [222]), endophthalmitis (*O. xanthineolytica* [209]), infection of a prosthetic joint (*O. xanthineolytica* [196]), catheter-related bacteremia (*O. turbata*, *O. xanthineolytica* [248, 260, 279, 428]), bacteremia caused by contaminated total parenteral nutrition solution (*Oerskovia* sp. [190]), gangrenous cholecystitis after endoscopic retrograde cholangiopancreaticography (*O. xanthineolytica* [150]), CAPD peritonitis (*O. xanthineolytica* [366]), pyonephrosis (NMO [95]), and soft tissue infection (*O. xanthineolytica* [150]).

Recently, *O. turbata* but not *O. xanthineolytica* was demonstrated to exhibit neuraminidase (sialidase) activity, which may be effective in vivo by destroying glycoproteins, glycolipids, gangliosides, and mucins (299).

Therapeutically, removal of the foreign body associated with *Oerskovia* infection is most often helpful. Antibiotics have variable effects on *Oerskovia* spp.; the most effective one in vitro has been vancomycin (150, 366). In a recent report, the *vanA* gene, mediating vancomycin resistance, was demonstrated in an *O. turbata* strain recovered from a patient's feces after a hospital outbreak of an infection due to vancomycin-resistant enterococci (343). Unfortunately, no details were given on the identification of the isolate.

Ribotyping has been successfully used to type a small number of clinically relevant *O. turbata* strains (284).

Genus *Cellulomonas*

The genus *Cellulomonas* contains eight validly described species (13, 151, 414). The habitat of *Cellulomonas* strains is usually the soil. Members of the genus *Cellulomonas* differ from *Oerskovia* species in lacking hyphal growth, in the presence of L-ornithine (instead of L-lysine) in the cell wall, and in the main CFAs (Table 3). Most strains described by Hollis and Weaver as CDC coryneform group A-3 and part of A-4 (204) belong to the genus *Cellulomonas* (151).

A-3 strains are first white and turn yellow within 3 days, whereas A-4 strains start out yellow. A-3 strains are mannitol negative and are able to ferment β-methylxyloside, whereas A-4 strains ferment mannitol but not β-methylxyloside (151, 204). A distinct feature of all *Cellulomonas* strains is their ability to hydrolyze cellulose (416). However, the recently proposed *C. hominis* strains (for the previous CDC A-3 bacteria) did not hydrolyze cellulose in the test system used (151). The two CDC A-4 strains isolated from blood cultures and included in the study by Funke et al. did not fit any species description of the eight presently defined *Cellulomonas* species. Their precise taxonomic position remains to be established by quantitative DNA-DNA hybridizations. It must be emphasized that many species descriptions of members of the genus *Cellulomonas* are based on single strains only.

All *Cellulomonas* strains tested so far were susceptible to rifampin, tetracycline, and vancomycin (151).

Genus *Sanguibacter*

The genus *Sanguibacter* was recently described by Fernandez-Garayzabal et al. (132). Strains were isolated from blood of healthy cows. This genus is mentioned here because it is phylogenetically closely related to *Oerskovia* and *Cellulomonas* (132) and because *Sanguibacter* strains may be isolated from

humans in the future. Phenotypically, *Sanguibacter* resembles *Oerskovia* in many respects, but its colonies are pale yellow, circular, and convex and have entire edges. Three species, *S. suarezii*, *S. keddieii*, and *S. inulinus*, have been described (132, 325). Chemotaxonomic differences from *Oerskovia* and *Cellulomonas* can be found in Table 6.

Genus *Microbacterium*

The genus *Microbacterium*, proposed in 1919, had undergone a number of changes until 1983, when Collins et al. (81) redefined it. Recently, based on nucleotide sequencing of 5S rRNA, Park et al. proposed the family *Microbacteriaceae* to accommodate the genera *Agromyces*, *Aureobacterium*, *Clavibacter*, *Curtobacterium*, and *Microbacterium*, i.e., the peptidoglycan group B actinomycetes (323). The prime chemotaxonomic criteria of *Microbacterium* are listed in Table 3. The organisms grow only weakly under anaerobic conditions. Six species have been described thus far (81, 468). Rainey et al. (347) and Takeuchi and Yokota (422) have demonstrated that the genera *Microbacterium* and *Aureobacterium* are phylogenetically intermixed. L-Lysine is present in position 3 in the peptide subunit (B1α) in *M. lacticum*, *M. laevaniformans*, and *M. dextranolyticum*, whereas the diamino acid in position 3 is replaced by the monoamino acid L-homoserine (B1β) in *M. imperiale*, *M. arborescens*, and *M. aurum* (81, 389, 468). Variation of the peptidoglycan within one genus is also known for the genera *Arthrobacter* and *Cellulomonas* (389). *M. imperiale* and *M. arborescens* share over 99% 16S rDNA homology (347, 422) and may be representatives of the same species, as has been suggested previously (144).

Recently, Funke et al. (144) have found microbacteria in environmental and clinical samples, mostly blood cultures. These strains resembled organisms described earlier by Hollis and Weaver (204) as CDC coryneform group A-4 and group A-5 bacteria, which mainly differ in xylose fermentation (A-4 is positive, and A-5 is negative). Most of these strains were yellow pigmented; orange pigment has been found only in *M. arborescens* and *M. imperiale*. A phenetic separation from *Cellulomonas* spp., may, in some cases, be possible by biochemical tests (Table 6), but cell wall analysis with the detection of L-lysine as the diamino acid is more reliable. Furthermore, *Microbacterium* spp. can be separated from *Cellulomonas* spp. by CFA analysis, which reveals significantly larger amounts of $C_{17:0ai}$ in *Microbacterium* spp. whereas $C_{15:0ai}$ is dominant in *Cellulomonas* spp. (144, 151). For the differentiation of yellow- or orange-pigmented coryneform bacteria, the reader is referred to an identification scheme outlined previously (144).

One clinically significant A-4 strain (although data for pigment and motility were missing) isolated from a patient with endocarditis (249), one A-4 strain from a patient with septicemia (32), and one A-5 strain from a patient with catheter-related septicemia (47) are extant in the literature. Notable is the isolation of microbacteria (group A-4) from eye specimens of patients with exogenous endophthalmitis (17, 145, 193). It was experimentally demonstrated that a clinical *Microbacterium* strain fulfilled the Koch-Henle postulates for causing endophthalmitis (193).

Microbacteria are susceptible to most antimicrobial agents except penicillin G (NCCLS categories for staphylococci); a significant number of strains are also resistant to aminoglycosides in vitro (144, 145).

Genus *Aureobacterium* and "*C. aquaticum*"

The genus *Aureobacterium* and "*C. aquaticum*" are discussed together because of their phenetic closeness. Only a few tests differentiate them, e.g., gelatin hydrolysis, casein hydrolysis, and a more rapidly appearing yellow pigment in *Aureobacterium* spp., whereas "*C. aquaticum*" strains exhibit a more rapid DNA hydrolysis (159). Chemotaxonomically, however, the two taxa clearly differ (Table 3); in addition, the interpeptide bridge consists of D-aminobutyric (DAB) acid in "*C. aquaticum*" and of (glycine)-D-ornithine in *Aureobacterium* (159). The name "*C. aquaticum*" is, thus, a misnomer, as *meso*-diaminopimelic acid represents the diamino acid in *Corynebacterium* sensu stricto. CFA analysis does not provide a clear-cut distinction between *Aureobacterium* and "*C. aquaticum*" strains (159).

Collins et al. reclassified strains belonging to six different taxa to the newly created genus *Aureobacterium* (82), and Yokota et al. added seven further species to this genus (466). Unfortunately, many species descriptions are based on one strain only, so that phenotypic species level identification within the genus *Aureobacterium* is almost impossible at present.

Aureobacterium spp. have been found in dairy products and in the environment (82, 466). At least some of the human strains seem to have been clinically significant (159). They were susceptible to many antibiotics, although some were resistant to clindamycin, ciprofloxacin, and gentamicin.

"*C. aquaticum*" is a water organism. Remarkably, "*C. aquaticum*" ranks third (after *C. diphtheriae* and *L. monocytogenes*) in the Hollis-Weaver charts with regard to the number of isolates tested for each taxon (204), but this may be due to referral bias. It has been reported to be an agent of meningitis (24), bacteremia (227, 295, 453), CAPD peritonitis (57, 297), and UTI (426) and has caused pseudobacteremia due to contamination of blood collection tubes as well (352). However, at least some of these case reports are doubtful from a diagnostic standpoint, as none of them included the above biochemical tests and/or chemotaxonomic investigations (especially detection of DAB), so that it remains unclear whether the strains were actually "*C. aquaticum*" or *Aureobacterium* spp. The identity of the "yellow motile group E coryneform bacteria" which caused empyema in five Egyptian children (122) remains unresolved. Of note, "*C. aquaticum*" frequently shows "intermediate" susceptibility to vancomycin (159). Nolte et al. reported a case of lethal *Aureobacterium* bacteremia in an immunocompromised patient (316). The MIC of vancomycin for this particular *Aureobacterium* strain was 32 µg/ml. Saweljew et al. also reported a fatal systemic infection with an *Aureobacterium* sp., but their patient was immunocompetent (385).

Recently, the DAB-containing "*Corynebacterium mediolanum*" was reclassified as *Agromyces mediolanus* (420), and Groth et al. proposed the new genus *Agrococcus* (containing coryneform bacteria) with DAB as diamino acid in its cell wall (178). Whether these two taxa possess any clinical relevance is unknown.

Genus *Arcanobacterium*

A. haemolyticum is a catalase-negative, gram-positive or -variable rod whose morphology is dependent on the growth media and conditions (71, 97). Phylogenetically, it clusters within the genus *Actinomyces* (152). Its CFA patterns are also closely related to those of *Actinomyces* spp. (30).

Although the Gram stain and colony morphology of *Actinomyces pyogenes* and *A. haemolyticum* are similar, they can be distinguished. Colonies of *A. pyogenes* tend to be larger and to exhibit a stronger beta-hemolysis than those of *A. haemolyticum*, whose hemolysis is more pronounced on human and rabbit blood agar than on SBA. The majority of *A. haemolyti-*

TABLE 8. Biochemical characteristics of aerobically growing *Actinomyces* spp. and *A. haemolyticum*[a,b]

Species	Catalase	Nitrate	Urease	Esculin	Production of:					CAMP test	Other characteristics
					Glu	Mal	Suc	Man	Xyl		
A. bernardiae	−	−	−	−	+	+	−	−	−	−	Most produce acid from glycogen
A. haemolyticum	−	−	−	−	+	+	V	−	−	Reverse	Beta-hemolysis
A. israelii	−	V	−	+	+	+	V	V	V	−	
A. naeslundii genospecies I	−	V	+	+	+	+	+	−	V	−	
A. naeslundii genospecies II	+	V	+	+	+	+	+	−	V	−	
A. neuii subsp. *neuii*	+	+	−	−	+	+	+	+	+	+	
A. neuii subsp. *anitratus*	+	−	−	−	+	+	+	+	+	+	
A. odontolyticus	−	+	−	V	+	V	+	−	V	−	Brown-red pigment (late)
A. pyogenes	−	−	−	V	+	V	V	V	+	−	Beta-hemolysis
A. radingae-turicensis (ART)[c]	−	−	−	V	+	+	+	V	+	−	
A. viscosus	+	+	V	V	+	+	+	−	V	−	

[a] All with fermentative metabolism, none of them motile, and none of them lipophilic.
[b] +, positive; −, negative; V, variable.
[c] For differentiation of *A. radingae* and *A. turicensis*, see the text.

cum isolates produce small, dark pits under colonies growing on ordinary BA medium (97). In addition to the β-hemolysin, *A. haemolyticum* secretes another protein that possesses PLD activity similar to that of *C. pseudotuberculosis* and *C. ulcerans* (282), resulting in a positive reverse CAMP test (Table 8). Strains of *A. haemolyticum* exhibit binding activities for several human plasma proteins (239).

Two different biotypes of *A. haemolyticum*, one smooth type isolated mainly from wounds and one rough type isolated mainly from respiratory tracts, have been reported (54). Although it was reported that a rapid α-mannosidase test can differentiate *A. haemolyticum* and *Listeria* spp. (both positive) from *A. pyogenes* and other corynebacteria tested (51), other investigators find that the test method is substrate dependent and is not specific for *A. haemolyticum*, as other systems, e.g., API ZYM, show *A. haemolyticum* and *Listeria* spp. to be negative and other coryneforms to be positive (438). Of course, *Listeria* spp. and *A. haemolyticum* can be distinguished by the catalase test. The API Coryne system correctly identifies *A. haemolyticum* and *A. pyogenes*, while the RapId ANA system identifies *A. haemolyticum* as *A. pyogenes* (22, 36, 72). API ZYM distinguishes *A. haemolyticum* and *A. pyogenes* on the basis of a positive acid phosphatase test for the former and β-glucuronidase test for the latter (36, 241). The Biolog system can correctly identify *A. haemolyticum* in 4 h (251). *A. haemolyticum* does not cross-react with *Streptococcus pyogenes* or group G streptococcal antiserum (240).

Because of the difficulties in recognizing *A. haemolyticum* in throat cultures, selective plates are thought to be necessary, and a variety of these have been described (39, 55, 259, 448). In general, these contain a nutrient base, rabbit or horse blood, and antibiotics. A CO_2-enriched atmosphere and tryptic soy agar with sheep blood were the best conditions to demonstrate growth and hemolysis of *A. haemolyticum* (97).

A. haemolyticum is associated primarily with pharyngitis (particularly in young adults) and with mixed wound infections (55, 61, 168, 259, 443). The clinical significance of *A. haemolyticum* in respiratory specimens has been difficult to assess both because the organism can be isolated in the absence of disease and because it is often isolated in association with beta-hemolytic streptococci or other pathogens. In a study of 3,922 throat cultures from patients with symptoms, *A. haemolyticum* was recovered from only 0.5% of patients overall but in 2% of those 15 to 25 years old. It was recovered as the only pathogen in about half of the patients and with beta-hemolytic

streptococci in the remainder, whereas *S. pyogenes* was recovered as the sole pathogen in about 16% of all patients (55). Similarly, Mackenzie et al., in a study of 11,620 throat cultures, found an incidence of 2.5% in those isolated from the 15- to 18-year-old group with pharyngitis while there were no isolations of *A. haemolyticum* from healthy controls (259), and Chalupa et al. found an 0.75% overall isolation rate (61). Even in younger children (average age, 7 years), there was a higher rate of recovery (10%) of *A. haemolyticum* from patients with infections compatible with *S. pyogenes* infections (228). *A. haemolyticum* was isolated with *Fusobacterium* species in a fulminant tubo-ovarian soft tissue infection (22) and with *Staphylococcus aureus*, *S. epidermidis*, and *P. acnes*, or with *Haemophilus parainfluenzae* in two cases of soft tissue infection (124). Traumatic wound infections involving *A. haemolyticum* and other organisms continue to be reported (18, 205, 369). The causative role of *A. haemolyticum* in dermatological lesions such as pompholyx eruptions, which occur on the hands and feet, is unclear. A pathogenic potential is suggested, as *A. haemolyticum* (together with group G streptococci) has been isolated from such lesions. A rash accompanied the infection, and the lesions resolved with erythromycin treatment, although simple overgrowth of these organisms has not been ruled out (436). Cellulitis and subperiosteal abscess formation (136), peritonsillar abscess (233, 291, 391), osteomyelitis, endocarditis (5), and septicemia (136) due to *A. haemolyticum* have also been reported.

Although *A. haemolyticum* is susceptible (thus far universally) to penicillins by in vitro MIC testing, treatment failure despite adequate doses of phenoxymethylpenicillin has been documented (14, 318). Two causes for this, analogous to those trying to explain therapeutic failures in *S. pyogenes* tonsillitis, have been proposed. (i) The organisms could be "tolerant" as indicated in vitro by their initial inhibition in the presence of penicillin and subsequent growth when penicillin is removed or destroyed by β-lactamase (318). (ii) Penicillin treatment failures could also be explained by the ability of *A. haemolyticum* to invade HEp-2 cells and survive internally (319). Erythromycin, which has good cell-penetrating ability, and gentamicin seem to be good treatment alternatives (318, 319). Carlson et al. (53) found that 138 *A. haemolyticum* strains tested were uniformly susceptible to β-lactams, erythromycin, azithromycin, clindamycin, doxycycline, ciprofloxacin, and vancomycin but resistant to trimethoprim-sulfamethoxazole. Plasmids encoding genes identical to *vanA* of *Enterococcus faecium* have

been recovered from a clinical strain of *A. haemolyticum* associated with an outbreak of infection due to vancomycin-resistant enterococci (343). Unfortunately, no data regarding the identification of the organism were given in that report.

Genus *Actinomyces*

A. pyogenes. *A. pyogenes* was transferred from the genus *Corynebacterium* independently by two groups of authors in 1982 (79, 353). After 24 h of incubation on SBA in a CO_2-enriched atmosphere, *A. pyogenes* shows weak hemolysis and pinpoint colonies, which increase to 1 mm in diameter after 48 h of incubation. Colonies of *A. pyogenes* are by then surrounded by a sharp zone of beta-hemolysis, which is usually stronger when the strains are incubated aerobically rather than anaerobically. Gram stains show straight to slightly curved rods with some branching.

A. pyogenes is a well-established cause of pyogenic infections in animals. Flies are thought to be the vectors of transmission (236). *A. pyogenes* can also be isolated from healthy animals, but it has not been described as part of the normal human flora. It is not surprising that most published cases of human *A. pyogenes* infections were acquired in a rural setting. The Special Bacteriology Reference Laboratory at CDC reported the receipt of 35 *A. pyogenes* strains by 1981, but at least 24 of these strains were of animal origin (204). The identification service of the National Type Culture Collection in the United Kingdom has received an average of only one *A. pyogenes* strain per year isolated from humans in the 1970s and 1980s (20). Isolates from blood cultures, abscesses, infected wounds, and respiratory specimens were predominant (20). *A. pyogenes* was shown to be involved in epidemic leg ulcers of schoolchildren in rural districts in Thailand (236). A case of *A. pyogenes* bacteremia in a patient with colon carcinoma was reported, but the original source of infection remained unidentified (20). Another blood culture isolate of *A. pyogenes* was reported from a patient with an infected diabetic foot ulcer from which *A. pyogenes* was also isolated (114). We observed a patient with an infected diabetic lower leg ulcer from which *A. pyogenes* grew in mixed culture and who developed spondylodiscitis and a psoas abscess; from several blood cultures as well as from an aspirate of the intramuscular abscess, *A. pyogenes* grew in pure culture (141). Another patient presented with a large subcutaneous abscess of the lumbar area due to *A. pyogenes* (114), and yet another patient had a subcutaneous abscess of her hand (111). Finally, a report presented data on 11 patients who were seen over a 20-year period in Denmark (162). In 7 of the 11 patients, *A. pyogenes* was isolated in pure culture, and five of these seven isolates came from patients with abdominal infections.

There have been several reports from a group in Finland (50–52) focusing on the differentiation of *A. pyogenes* and *A. haemolyticum*. However, in our hands, differentiation between these two taxa is easy. We recommend observation of the CAMP reaction, which shows an inhibition of the *S. aureus* β-hemolysin by *A. haemolyticum* whereas *A. pyogenes* shows a slight enhancement of the *S. aureus*-induced hemolysis. Other easy-to-perform tests include the fermentation of xylose (Table 8) and the hydrolysis of gelatin, which are positive for *A. pyogenes* but not *A. haemolyticum*. It is interesting that *A. pyogenes* may agglutinate with streptococcal group G antiserum and—although more weakly—with streptococcal group B antiserum (240, 462). Therefore, *A. pyogenes* may be misidentified as a *Streptococcus* species if Gram stains of beta-hemolytic colonies are not performed. In contrast, "*A. pyogenes*-like" bacteria, now referred to as *A. radingae-A. turicensis* complex (see below), do not agglutinate with streptococcal B

and G antisera (462). The API Coryne system can identify *A. pyogenes* isolates; however, some authors have demonstrated that the system database does not contain all numerical profiles including those derived from veterinary *A. pyogenes* strains (113, 186).

Workers from France demonstrated that ribotyping was superior to sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis or RFLP analysis for the typing of *A. pyogenes* isolates (185).

A. neuii. *A. neuii* first appeared in 1985 in the literature as "atypical CDC A-4 strains" causing endophthalmitis (87). In 1987, the Special Bacteriology Reference Laboratory of CDC reported the receipt of 13 strains of CDC coryneform group 1 bacteria (former "atypical A-4") (306), and by 1992, 21 strains had been received by the same laboratory (203). Funke et al. described seven further strains of group 1 bacteria and added eight strains of group 1-like bacteria (149). These bacteria were soon defined as *A. neuii* subsp. *neuii* and *A. neuii* subsp. *anitratus* (157). Recently, Funke and von Graevenitz summarized the clinical data of 67 patients from whom *A. neuii* strains were isolated during a 4½-year period (158).

The Department of Medical Microbiology, University of Zürich, reported that between April 1990 and September 1994 *A. neuii* strains represented 17% of all *Actinomyces* isolates recovered from clinical material (158). Sixty-one percent of the *Actinomyces* isolates belonged to the *A. radingae-A. turicensis* complex (see below), but *A. neuii* was significantly more frequently isolated than was *A. odontolyticus* (9%) or *A. israelii* (4%).

A. neuii grows well under aerobic conditions as white colonies of 0.5 to 1 mm in diameter on SBA after 48 h of incubation under a 5% CO_2 atmosphere. Gram stains of clinical material as well as of pure cultures show diphtheroids, but branching filaments, which are typical for many other *Actinomyces* species, are not observed (158). The basic biochemical characteristics of *A. neuii* are given in Table 8. It should be emphasized that all *A. neuii* strains show a strongly positive CAMP reaction with a β-hemolysin-producing strain of *S. aureus* on SBA plates (149). *A. neuii* subsp. *neuii* can be separated from *A. neuii* subsp. *anitratus* by its ability to reduce nitrate, to produce alpha-hemolysis on human BA plates, by its lack of alkaline phosphatase activity, and by its inability to produce acid from adonitol in a certain basal medium (149). By using the API Coryne identification system, *A. neuii* strains can be identified because they give typical numerical codes (2410735, 2510735, and 3410735) (149); however, *A. neuii* is presently not included in the database. CFA profiles of *A. neuii* were reported (30, 149), and $C_{16:0}$, $C_{18:1\omega9cis}$, and $C_{18:0}$ were the major components. This pattern is also observed in *Corynebacterium* sensu stricto, but $C_{10:0}$, $C_{12:0}$, and $C_{14:0}$, which are also present in *A. neuii* (as well as in other *Actinomyces* species), are usually not detected in *Corynebacterium* species (30, 440).

A. neuii does not cause typical actinomycosis with discharge of sulfur granules (158). In the study by Funke and von Graevenitz, *A. neuii* was isolated from nearly half of the patients with abscesses, many of which were recurrent ones. Approximately 25% of the patients had infected atheromas. In many of the patients with abscesses or infected atheromas, *A. neuii* was associated with a mixed anaerobic flora but was the only aerobically growing rod. *A. neuii* was also isolated from patients (many of whom were immunocompromised) with skin lesions and genitourinary infections as well as from blood cultures. One case of a fatal septicemia due to *A. neuii* was observed. The outcome of the patients with abscesses and infected atheromas who were treated by either surgery only or by surgical drainage and antimicrobial chemotherapy was favorable. Gen-

itourinary infections responded clinically very well to therapy with β-lactams (158). The literature also contains one case of an acute native-valve endocarditis due to CDC group 1 bacteria (121). As already outlined (149), it was most likely that the authors had mistaken CDC group 1 strains for CDC group I strains. Two cases of endophthalmitis caused by *A. neuii* can be found in the literature, although these strains were designated CDC A-4 strains (280, 281). It remains unclear why the authors designated their strains CDC A-4 in 1990 and 1991 although the strains described had been previously shown to belong to CDC group 1 (*A. neuii*) (87, 306).

As known for other *Actinomyces* species (387), *A. neuii* is generally susceptible to β-lactams, clindamycin, and vancomycin; good activity of erythromycin, rifampin, and tetracycline against *A. neuii* isolates was also demonstrated, whereas the MIC_{50}s of ciprofloxacin and gentamicin were above the breakpoints recommended by NCCLS (158, 305).

A. bernardiae. The name *A. bernardiae* has recently been proposed for CDC coryneform group 2 bacteria (152). These bacteria were first described in the literature in 1987, when the Special Bacteriology Reference Laboratory of the CDC reported on 11 strains of a catalase-negative, gram-positive rod that could be separated biochemically from previously established taxa (306). By 1992, the same institution had received no further isolates (203). Funke et al. described six isolates derived mainly from blood cultures and abscesses, whereas the CDC strains came from a variety of clinical sources (152, 306). The Department of Medical Microbiology, University of Zürich, has continued to isolate *A. bernardiae* from clinical samples and at present has 15 strains in its collection, the majority of which were isolated from abscesses.

Gram stains of *A. bernardiae* reveal relatively short rods without branching. Colonies appear glassy on sheep blood agar and achieve diameters of 0.2 to 0.5 mm only after 48 h of incubation in the presence of 5% CO_2. However, in contrast to lipophilic *Corynebacterium* spp., growth of *A. bernardiae* cannot be stimulated by addition of Tween 80 to the medium. Na'was et al. reported that *A. bernardiae* needs serum for optimal growth in fermentation broth (306). In addition to the basic biochemical reactions given in Table 8, it should be noted that *A. bernardiae* ferments maltose more rapidly and strongly than it ferments glucose, a very unusual feature for coryneform bacteria. Most strains of *A. bernardiae* also ferment glycogen, which also is observed only rarely in other coryneform bacteria.

A. pyogenes is phylogenetically the closest relative of *A. bernardiae* (152). Both *Actinomyces* species have the unusual L-alanine–L-lysine–D-glutamic acid (ratio, 3:2:2) interpeptide bridge (152). However, *A. pyogenes* is readily distinguished from *A. bernardiae* by its larger colonies (0.5 to 1 mm in diameter), its stronger beta-hemolysis on SBA, and its ability to ferment sucrose, mannitol, and xylose. The CFA patterns of *A. bernardiae* strains are similar to those of other *Actinomyces* species, with $C_{16:0}$, $C_{18:1\omega9cis}$, and $C_{18:0}$ predominating but significant amounts of $C_{10:0}$, $C_{12:0}$, and $C_{14:0}$ also detected (30, 152).

All *A. bernardiae* strains were susceptible to clindamycin, erythromycin, β-lactams, rifampin, tetracycline, and vancomycin, whereas ciprofloxacin and gentamicin showed only limited activity (141).

Ieven et al. described a case of a severe *A. bernardiae* infection in a compromised patient (212).

A. radingae-A. turicensis complex. *A. radingae* and *A. turicensis* were previously designated "*Actinomyces pyogenes*-like" bacteria (462) but were recently shown to comprise parts of the former CDC coryneform group E bacteria (253, 463). The authors of this review preferred to refer to the two species as *A. radingae-A. turicensis* (ART) complex for reasons stated below. Strains belonging to the ART complex were isolated at the Department of Medical Microbiology, University of Zürich, with increasing frequency beginning in 1990 (462); this was followed by yearly increases from 1991 to 1994. As outlined above, during that period, strains belonging to the ART complex represented about 60% of all strains belonging to the genus *Actinomyces* isolated in this institution (158). In 1995, however, we observed a decrease in the number of isolates of strains belonging to the ART complex from clinical samples. The reasons for the detection of the large number of ART bacteria in the early 1990s are not known, but we would not attribute this to an increased awareness. Another striking feature of ART bacteria is that they were never isolated in pure culture, and therefore their pathogenic potential by themselves has been considered low (462). ART bacteria were frequently cultured with mixed anaerobic flora as well as with gram-negative rods (462). Pilonidal cysts, perianal abscesses, superficial and deep abdominal infections, and genitourinary infections were the most frequent sources of ART bacteria. Although the natural habitat of ART bacteria is not known at present, it is not unlikely that these bacteria belong to the human intestinal flora. *A. turicensis*(-like) strains have been isolated from patients with bacterial vaginosis (435).

ART bacteria are catalase-negative, facultative anaerobes which grow equally well under aerobic and strict anaerobic conditions. Colonies are whitish to grayish, slightly dull, circular, and low convex and measure 0.2 to 0.5 mm in diameter after 48 h of incubation on SBA plates. Alpha- or rarely beta-hemolysis of sheep erythrocytes is only weak or even absent when cells are grown aerobically, and hemolysis is always undetectable when cells are grown anaerobically (462). Gram stains show straight and slightly curved gram-positive rods with some branching.

By using phenotypic criteria only, it was initially difficult to distinguish strains belonging to the ART complex. The most consistent differentiating feature is the ability of *A. radingae* to weakly ferment prereduced anaerobically sterilized (PRAS) glycogen whereas *A. turicensis* is negative for this reaction. ART bacteria can also be differentiated by means of peptidoglycan analysis: the peptidoglycan of *A. radingae* is of a unique type, as the L-lysine in position 3 of the peptide subunit is partly replaced by L-ornithine and the interpeptide bridge consists of a D-glutamyl–L-lysine dipeptide (463). In contrast, the peptidoglycan of *A. turicensis* is of the L-ornithine–L-lysine–D-glutamic acid type and is identical to that described for *A. israelii* (463). As the fastidious technique of peptidoglycan analysis is available only in reference laboratories, we preferred to report strains being either *A. radingae* or *A. turicensis* as ART complex. However, very recent investigations reexamining ART strains from the initial study (462) showed that *A. radingae* strains are consistently positive for pyrazinamidase, β-galactosidase, and β-N-acetylglucosaminidase activity whereas *A. turicensis* strains are negative (141). Therefore, *A. radingae* and *A. turicensis* might be differentiated by using, e.g., the API Coryne system.

CFA profiles of ART bacteria are qualitatively consistent with those of other *Actinomyces* spp. Incubation of ART bacteria in PRAS PYG-T medium may be necessary to obtain an acceptable cell mass (462). Qualitative differences in CFA patterns of ART bacteria will result from the use of different media (e.g., solid Columbia agar base medium versus PRAS-PYG-T) (253, 462). Phylogenetically, *A. odontolyticus* is the closest genealogical relative of *A. turicensis*, whereas *A. radingae* is more closely related to *A. hyovaginalis* than to *A. turicensis* (463).

It has been demonstrated that the majority of strains previously designated CDC coryneform group E bacteria actually belong to the ART complex (463). However, there has been one report on the identification of *Bifidobacterium adolescentis* as being similar to CDC group E bacteria (187). *Bifidobacterium* spp. and *Actinomyces* spp. are readily differentiated by their end products of glucose metabolism, which are mainly acetate for *Bifidobacterium* spp. and succinate for *Actinomyces* spp. Initially, Wüst et al. named their isolates "*Actinomyces pyogenes*-like" bacteria due to similar basic biochemical screening reactions (Table 8), but they emphasized that *A. pyogenes* colonies are larger than the colonies of ART bacteria and that *A. pyogenes* consistently produces beta-hemolysis and has a positive gelatinase reaction (462).

No single case report regarding disease association of ART bacteria can be found in the literature at present. Like *A. neuii*, ART bacteria do not seem to cause typical actinomycosis.

MINIMAL MICROBIOLOGICAL REQUIREMENTS FOR PUBLICATIONS ON DISEASE ASSOCIATIONS OF CORYNEFORM BACTERIA

As outlined above, many case reports on disease associations of coryneform bacteria were inappropriately documented, which has led to misidentifications and consequently to miscitations in the literature. It is simply not sufficient to state "identification was made by the API Coryne system" or "identification was performed in the State Laboratory" without giving any further information on the identification. Therefore, the following guidelines are proposed to avoid these problems in future publications. In addition, the guidelines will facilitate establishing true disease associations of coryneform bacteria.

(i) (a) List the results of Gram stain of the clinical material as well as of the coryneform bacteria cultured.

(b) List the size, pigment, odor, and hemolysis of colonies.

(c) Include a minimal set of biochemical reactions: catalase; fermentative or oxidative metabolism; motility; nitrate reduction; urea hydrolysis; esculin hydrolysis, acid production from glucose, maltose, sucrose, mannitol, and xylose; CAMP reaction; and lipophilism of strains.

(ii) Chemotaxonomic investigations (e.g., CFA patterns, presence of mycolic acids, peptidoglycan analysis, G+C content) and/or molecular genetic analysis (e.g., 16S rRNA gene sequence analysis, DNA-DNA hybridizations) should accompany the identification in cases where phenotypic characteristics by themselves do not differentiate between coryneform bacteria.

(iii) (a) A positive direct Gram stain and a strong leukocyte reaction strengthen a possible disease association.

(b) Pure cultures also strengthen a possible disease association. The predominance of coryneform bacteria in material from normally sterile sites should also be considered an indicator for a possible disease association.

FUTURE CONSIDERATIONS

Coyle and Lipsky suggested in their 1990 review that the taxonomy of coryneform bacteria should be studied more intensely (91). By now, a taxonomic framework for coryneform bacteria which may facilitate further investigations in this field has been established. It is our own experience that a certain percentage of coryneform bacteria isolated from clinical specimens still represent undescribed taxa. We believe that, apart from the well-characterized genus *Corynebacterium*, the presently defined taxa of coryneform bacteria represent only the "tip of the iceberg" regarding the heterogeneity of these bacteria, although the most frequently encountered taxa are probably characterized by now. Therefore, we strongly believe that further new taxa will be proposed in the near future. On the other hand, improvements in the databases of the commercially available identification systems will facilitate the daily routine work of the clinical microbiologist. Finally, a lot of work still needs to be invested to clarify the associations of particular coryneform bacteria with diseases.

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