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Coryneform Bacteria in Infectious Diseases: Clinical and Laboratory Aspects

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INTRODUCTION

In 1982, the literature on the clinical and microbiological aspects of infections caused by nondiphtheria *Corynebacterium* species was reviewed by Lipsky et al. (127). In the ensuing 8 years, recognition of infections with these organisms has increased and much new information has become available on many of them. This review provides an update on clinical presentations, microbiological features, and pathogenic mechanisms of infections with nondiphtheria *Corynebacterium* species and other pleomorphic gram-positive rods. The early literature is also reviewed for a few coryneforms, especially those whose roles as pathogens are controversial.

Recognition of infections caused by coryneform bacteria is highly dependent on the laboratorian's ability to identify these species. This has been dramatically demonstrated by the large number of publications that have followed the Centers for Disease Control (CDC) definition of coryneform groups JK and D-2, both of which are now recognized as important opportunistic pathogens. Clinical microbiologists in hospitals that care for severely compromised patients frequently encounter isolates of pleomorphic gram-positive rods that they are unable to identify after consulting all of the available identification schemes. It is not only the routine clinical laboratory that is confounded by identification of coryneform isolates. The reference laboratory for the National Collection of Type Cultures has reported that efforts to identify nondiphtheria coryneforms are much less successful than for other bacteria submitted for identification. Of 172 coryneform isolates received between 1965 and 1975, only 35% were identified to species level and 43% were identified to genus or possible species level; 22% could not be identified (85). Presumably other reference laboratories have similar experience with coryneforms submitted for identification.

One of the obstacles facing the microbiologist with a coryneform isolate is that >40% of them may belong to a genus other than *Corynebacterium* (162; J. E. Clarridge, Clin. Microbiol. Newsl. **8**:32–34, 1986). By cell wall analysis of 1,005 aerobic coryneform isolates obtained from the skin of hospitalized patients and normal volunteers, Pitcher

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found that only 59% were characteristic of the genus *Corynebacterium* and 20% were characteristic of the genus *Brevibacterium* (162). The remaining isolates could not be assigned to a genus. Jackman subsequently analyzed the whole-cell protein patterns of 40 axillary skin isolates that were presumed to be *Corynebacterium* species on the basis of Pitcher's cell wall analyses (91). Amazingly, none of the isolates could be grouped with any of the 40 reference strains representing 18 different *Corynebacterium* species! These studies indicate that many of the coryneforms recovered from clinical specimens belong to taxonomic groups that have yet to be characterized and named by taxonomic studies.

TAXONOMY

In the clinical laboratory, the term diphtheroid is used for any gram-positive rod that resembles *Corynebacterium diphtheriae* on Gram stain. Reliable identification of diphtheroids recovered from clinical specimens is ultimately dependent on the accuracy of the taxonomy of these organisms. Among taxonomists, the morphological term coryneform replaces the more familiar "diphtheroid." Coryneforms usually include both aerobic and anaerobic, non-acid-fast, pleomorphic, nonbranching, gram-positive rods that do not form spores. Because pleomorphic is such a vague term, the diverse genera that have been included within the coryneform groups include *Actinomyces*, *Arachnia*, *Arcanobacterium*, *Arthrobacter*, *Bacterionema*, *Bifidobacterium*, *Brevibacterium*, *Cellulomonas*, *Corynebacterium*, *Erysipelothrix*, *Eubacterium*, *Jensenia*, *Kurthia*, *Listeria*, *Mycobacterium*, *Nocardia*, *Oerskovia*, *Propionibacterium*, *Rhodococcus*, and *Rothia*. Excellent reviews of the history of the taxonomy of the coryneform bacteria have been written by Keddie (101) and Goodfellow and Minniken (71).

During the past 20 years, the advances in methods for classifying bacteria have been enormous. Identification of cell wall components, including amino acids, sugars, fatty acids, and mycolic acids, has been particularly useful for coryneform taxonomy. The isoprenoid quinones, the cytochromes, and the DNA base composition have also been useful for defining the genera. Nucleic acid hybridizations have been used to determine the degree of relatedness of many different organisms. An extreme example of the need for clarification in coryneform taxonomy has come from DNA-DNA hybridization values indicating that closely related strains, probably representing a single species, have been assigned to five different genera: *Oerskovia xanthineolytica*, *Cellulomonas cartae*, *Nocardia cellulans*, *Brevibacterium fermentens*, and *Corynebacterium manihot* (212). In contrast to DNA-DNA hybridizations, which are useful for analyzing the similarity between closely related organisms, hybridizations between DNA and rRNA provide estimates of the more distant relationships between genera because genes that specify rRNA sequences have evolved more slowly than the overall genome (72, 215).

Oligonucleotides from T_1 RNase digestion of rRNA have been sequenced and catalogued in a number of elegant taxonomic studies in E. Stackebrandt's laboratory (65, 173, 214, 216). This technique offers a major advantage over hybridization analyses, because once each organism is analyzed, the oligonucleotide data are stored in the computer and are available for comparisons in future analyses. The most recent approach to classification of coryneforms is the reverse transcriptase sequencing of 16S rRNA, which allows the sequencing of over 1,000 nucleotides (38, 39). These long stretches can then be compared between species, genera, or higher taxonomic groups. The levels of relatedness can be computed to provide an estimate of evolutionary relationships. Some examples of the recent changes in coryneform taxonomy that have resulted from the chemotaxonomy and nucleic acid analyses of coryneforms are listed in Table 1.

TABLE 1. Recent taxonomic changes for coryneform bacteria

New name	Previous name	Reference(s)
Actinomyces pyogenes	*Corynebacterium pyogenes*	168
Arcanobacterium haemolyticum	*C. haemolyticum*	37
C. ammoniagenes	*Brevibacterium ammoniagenes*	34
C. cystitidis	*C. renale* (in part)	245, 246
C. flavescens	*Microbacterium flavescens*	8
C. jeikeium	CDC group JK	93
C. matruchotii	*Bacterionema matruchotii*	32
C. pilosum	*C. renale* (in part)	245, 246
C. polymorphus	*Caseobacter polymorphous*	39
C. variabilis	*Arthrobacter variabilis*	33
Jonesia denitrificans	*Listeria denitrificans*	173
Rhodococcus equi	*C. equi*	70
Tsukamurella paurometabolum	*C. paurometabolum*	38
Oerskovia turbata	CDC groups A1 and A2 (in part)	205
O. xanthineolytica	CDC groups A1 and A2 (in part)	205

The recently published volume 2 of *Bergey's Manual of Systematic Bacteriology* (98) provides an overview of advances in the classification of the genus *Corynebacterium* as well as the wide variety of other genera that consist of nonsporing gram-positive rods with irregular shapes. Jones and Collins masterfully presented the advances in chemosystematics of the 21 diverse genera that were grouped together for practical purposes because they did not fit within any of the other suprageneric arrangements. Although *Bergey's Manual* includes the genus *Corynebacterium* with the irregular gram-positive rods, the authors did not intend to imply a close phylogenetic relationship. In fact, on the basis of cell wall and lipid composition, the genus *Corynebacterium* is most closely related to the genera *Mycobacterium*, *Nocardia*, *Rhodococcus*, and *Caseobacter*.

The genus *Corynebacterium* is now characterized by the presence of *meso*-diaminopimelic acid and arabinogalactan in the cell wall (cell wall type IV [119]); short-chain mycolic acids (22 to 36 carbon atoms) and dihydrogenated menaquinones with eight or nine isoprene units or both; and a DNA base composition within the approximate range of 51 to 63 mol% G+C. Other salient features of the genus *Corynebacterium* include morphology showing straight to slightly curved rods with tapered ends, and sometimes club-shaped forms; snapping division producing angular and palisade arrangements; gram-positive staining (although some cells stain unevenly); formation of metachromatic granules; lack of motility; facultatively anaerobic growth (although some organisms are aerobic); and catalase production (35).

Before clinical laboratories can identify coryneform isolates, many representative strains from this diverse group must be characterized by taxonomists, using current chemotaxonomic methods. Those not fitting into established taxa can be assigned to new groups with distinctive traits that can be determined with conventional tests. The proposed publication of the 9th edition of *Bergey's Manual of Determinative Bacteriology* will be a major resource for the clinical

microbiologist, but it too will be limited to only those organisms that have been defined by taxonomic studies.

INFECTIONS

Corynebacterium jeikeium (CDC group JK)

The definition of coryneform CDC group JK was recently refined, and the name *Corynebacterium jeikeium* is now validated by the International Committee on Systematic Bacteriology (93, 228). Infections caused by these organisms were fairly well characterized by the early 1980s (127), but new data have clarified the microbiology, epidemiology, and clinical features of *C. jeikeium* infections. Previously reported infections were exclusively from American hospitals, but recent publications have originated in Great Britain, Belgium, the Federal Republic of Germany, Denmark, Sweden, France, and Israel (2, 20, 29, 48, 54, 63, 79, 92, 104, 105, 129, 161, 165, 221, 238, 239, 242). The paucity of reports of *C. jeikeium* infections in Great Britain, compared with the United States, may be due to differences in identification procedures (106). Diphtheroids causing peritonitis in five Glasgow patients on chronic ambulatory peritoneal dialysis closely resembled *C. jeikeium*, although most were less resistant to antimicrobial agents than those described in earlier reports (121).

A recent prospective study, using a semiselective medium, found that, among 6,859 specimens from various sites submitted to the clinical microbiology laboratory of a large general hospital, 72 (1%) yielded *C. jeikeium* (239). Only 2 (2.7%) of these 72 specimens, however, were from patients who met strict criteria for infection rather than colonization. A different experience was reported in a retrospective study from a laboratory that used nonselective media, in which up to 20% of isolates were associated with serious nosocomial infections (170).

Infections continue to be reported mainly in patients who are immunocompromised (especially by malignancies) and those with medical devices (e.g., vascular or implanted access catheters), particularly when these patients have been hospitalized for prolonged periods, have breaks in their integument, or have previously received broad-spectrum antimicrobial therapy (48, 104, 141, 186). A new trend, however, has been the increasing recognition of *C. jeikeium* infections in patients who are immunocompetent and occasionally in those who are outpatients (2, 29, 142). A recent report of five cases of *C. jeikeium* endocarditis included two patients with infections of native heart valves (231). These were the first, among the 35 reported cases of *C. jeikeium* endocarditis, that did not affect a prosthetic valve.

New clinical manifestations of *C. jeikeium* infection have been observed. These include pulmonary infiltrates (235), skin rashes (48, 77), and septic cutaneous emboli and soft-tissue infections (48, 96). Pulmonary infections have now been described in 16 patients, all of whom were immunocompromised by bone marrow disorders (235). A recent review noted that 23 (26%) of 89 patients with *C. jeikeium* septicemia, all of whom were granulocytopenic, developed cutaneous or soft-tissue manifestations (48). *C. jeikeium* is also increasingly recognized as a cause of device-related nosocomial infections (2, 54, 63, 79, 161, 170).

Recent studies have shown that the prevalence of skin colonization with *C. jeikeium* is invariably highest in patients with malignancies or other severely immune compromising disorders. Rates in these patients range from 40 to 82%, compared with 13 to 73% in patients with nonmalignant diseases, and 12 to 36% in healthy hospital personnel (116, 239). Patients with malignancies also have a greater likelihood of developing infection after colonization, and antimicrobial resistance is much more prevalent in their *C. jeikeium* isolates. Skin colonization is most commonly found in the inguinal, axillary, and rectal areas (221). Since the perineum is the primary site of *C. jeikeium* colonization in most studies, it has been postulated that antibiotic-resistant strains may originate in the gastrointestinal tract and then spread to the skin (116). Once colonization occurs, it usually persists for long periods.

The means of transmission of *C. jeikeium* has been a subject of much debate. Some have suggested that the organism is spread within hospitals, presumably by the hand-to-hand route. Others postulate that nosocomial infections with multiresistant *C. jeikeium* occur by autoinfection with selected antibiotic-resistant subpopulations, or possibly mutants, from the normal skin diphtheroids. Recent epidemiological studies, however, suggest that this may not be the case. One illustrative case is that of an elderly man who died after a bacteremic infection involving his cardiac pacemaker (79). Two *C. jeikeium* strains were isolated, one of which was fully antibiotic susceptible and the other of which was multiresistant. The strains were shown to be clearly different, thus making it unlikely that a multiresistant clone emerged by simple mutation from a susceptible endogenous organism.

In a recent description of five *C. jeikeium* infections on a hematology ward, no cause for the outbreak was discovered (167). Environmental cultures showed that *C. jeikeium* was present on samples of various surfaces and in the air of most of the ward's rooms, suggesting the possibility of airborne or indirect spread. Alternatively, the presence of the organisms on the hands of 18% of ward staff suggested that breaks in aseptic practices might have been instrumental. A similar study from a Swedish hematology ward, on which three patients with leukemia developed *C. jeikeium* infections, revealed heavy environmental contamination of the ward's isolation rooms with this organism (221). Strains with the same antibiogram could be detected in the rooms for 4 months after the last colonized patients had left.

The discovery of plasmids and their profiling in strains of *C. jeikeium* have allowed this epidemiological tool to be applied to the issue of infection transmission. A study from Great Britain (105) reported that 23 of 39 *C. jeikeium* isolates possessed plasmids that were grouped according to restriction fragment patterns. The authors argued that the plasmid analyses provided strong evidence that the strains had a common origin, thus suggesting person-to-person transmission within the hospital. Since the patients infected with *C. jeikeium* strains with identical plasmids were rarely hospitalized simultaneously, it was postulated that colonization of staff or patients went undetected or the patients' environment was contaminated (105). An American study that also used plasmid profiling concluded, however, that patient-to-patient transmission of *C. jeikeium* did not occur (107). Among 27 isolates derived mostly from a single cancer ward, only 2 were found to harbor the same plasmid. Chromosomal DNA analysis showed that prolonged colonization with a single strand occurs, but strains from two clusters of infections all had distinctive patterns, making nosocomial transmission very unlikely. It is apparent that further work is needed before the epidemiology of *C. jeikeium* infections is defined.

In view of the potential for environmental contamination with *C. jeikeium* organisms, data on their susceptibility to

various antiseptics are of importance. A study of antibiotic-resistant coryneforms from patients undergoing chemotherapy found that, for chlorhexidine, cetrimide, and ethidium bromide, but not for hexachlorophane, the mean inhibitory concentrations for 14 *C. jeikeium* isolates were statistically significantly higher than those for the non-*C. jeikeium* strains (123). There was no evidence of plasmid-mediated antiseptic resistance for any of the strains.

Now that use of antibiotic-containing media is not essential for recognizing *C. jeikeium*, some strains have been isolated that are less antibiotic resistant than those in the original study by Riley et al. (172); some are fully susceptible to β-lactam antibiotics, while others are only moderately resistant to these agents, but can be successfully eradicated with combined penicillin and aminoglycoside therapy. Most reported strains, however, are still characterized by being resistant to all agents except vancomycin. Although vancomycin is effective in treatment of *C. jeikeium* infections, it does not eliminate skin colonization (116). The mechanism of the multiresistance to antibiotics remains unexplained, but, unlike resistance among gram-negative bacteria, it appears to be a stable trait (116). *C. jeikeium* strains have been observed, after serial subculture on antibiotic-containing agar media, to develop slightly increased resistance to β-lactam antibiotics (79). If antibiotic pressure plays a role in the development of resistance, it must be a complex one. One investigator has suggested that strain differences in the structure of the cell surface layer may affect their permeability to antibiotics (20). One new antibiotic group that has shown excellent in vitro activity against *C. jeikeium* is the quinolones, especially ciprofloxacin (129, 174, 233), but there is no report of their utility in treating infections.

CDC Coryneform Group D-2

CDC coryneform group D-2, occasionally referred to as "*C. urealyticum*," was first described by King at the CDC (237). It resembles *C. jeikeium* except for its urease activity and inability to acidify glucose. A case of "diphtheroid" pneumonia caused by group D-2 was described in 1979 (94), but it was not until 1985 that the major pathogenic role of this species was defined. In a series of studies from Madrid, Spain (1, 179, 200, 201), this microorganism was associated with urinary tract infections, particularly with alkaline-encrusted cystitis. This chronic inflammatory condition of the bladder is accompanied by localized ulcerations with deposits of ammonium magnesium phosphate (struvite). It has been associated with infections due to urea-spitting microorganisms, such as *Proteus* spp., in patients whose bladder was already affected by an inflammatory or neoplastic condition, i.e., providing "vesicular ground" (1).

The Madrid investigators first identified patients with this disorder from whom coryneform group D-2 was the sole pathogen isolated (200). All had had chronic or recurrent urinary tract infections following genitourinary surgery or instrumentation and had irritative voiding symptoms. Urine was alkaline (pH ≥ 8.0), and most had passed struvite stones. Each patient had at least two urine cultures yielding a pure growth of coryneform group D-2 at $\geq 10^5$ CFU/ml, and bladder stones also yielded the organism. Antimicrobial therapy directed at this organism, in combination with cystoscopic resection of stones, was curative in all. After treatment, the pH of the urine returned to the normal range and struvite crystals disappeared. Both clinical and experimental data (201) seem to confirm that group D-2, like *Proteus* spp., and some species of *Streptococcus*, *Staphylococcus*, and *Ureaplasma*, may cause alkaline-encrusted cystitis.

The Madrid group has reported a retrospective survey of 43 patients (1) and a prospective study of 82 patients (J. M. Aguado, F. Soriano, M. C. Ponte, R. Fernandez-Robles, and J. L. Rodriguez-Tudela, Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 929, 1989) with urinary tract infections caused by group D-2. This organism was isolated from 0.1 to 0.2% of all urine cultures submitted to their laboratory; the specimens were obtained by voiding and by bladder and perirenal catheterization, and all yielded $\geq 6 \times 10^4$ CFU/ml (1). Four patients had group D-2 isolated from the blood as well as the urine. The patients were predominantly men, and most were >65 years old. In most patients the urine had a pH of ≥7.13, and struvite crystals, erythrocytes (RBC), and leukocytes (≥5/high-power-field) were present. In the prospective study, only 51 (62%) of the bacteriuric patients were symptomatic. Of these, 20 had acute cystitis, 13 had chronic cystitis (including encrusted cystitis), and 18 had pyelonephritis. Risk factors significantly associated with symptomatic infection were preexisting immunosuppression, underlying genitourinary disorders, recent urological procedures, and urinary sediment abnormalities (Aguado et al., 29th ICAAC). Outcome was favorable in nearly all of those correctly treated, although several courses were often required. Vancomycin was found to be the antibiotic of choice. Other reports of infection with group D-2 have almost all been from Europe, and most have also involved patients with urinary tract infections (154, 185, 194). Two recent reports from France (64, 134) have confirmed the clinical and epidemiological characteristics of coryneform group D-2 bacteriuria, particularly its tendency to occur in patients who are elderly or immunocompromised or who have genitourinary disorders.

Coryneform group D-2 urinary tract infections may be hospital acquired (1, 64). This organism is found on healthy skin of 25 to 37% of hospitalized patients (204). One can speculate that group D-2 colonizes the skin, perhaps in the setting of recent antimicrobial treatment, and after urological instrumentation gains access from the skin to the urinary tract (154), where its urease activity causes alkalinization of the urine, leading to the formation of struvite stones in some patients (1). Since this organism may be missed by conventional urine culture techniques, it should be specifically sought by prolonged (24- to 48-h) incubation on blood or cysteine-lactose-electrolyte-deficient agars. Such an approach would be most appropriate in certain patients, particularly elderly men with underlying genitourinary disorders, who have clinical evidence of bacteriuria but negative standard urine cultures and who have alkaline urine, struvite stones, or gram-positive bacilli seen on a Gram-stained smear of urine.

Coryneform group D-2 may be isolated from many sites other than the urinary tract, but its role as a potential pathogen is difficult to establish (230). There have been a few reported nonurinary tract infections with this opportunistic organism, including peritonitis (230), endocarditis (114), pneumonia (94), and bacteremia (133, 134, 230). Many of these infections occurred in patients with underlying urinary tract disease.

Treatment of group D-2 urinary infections may be difficult. These organisms have been found to be highly resistant to antimicrobial agents, including nitrofurantoin, trimethoprim-sulfamethoxazole, ampicillin, cephalothin, and gentamicin, i.e., those agents commonly used to treat urinary tract infections (1, 179, 203, 226). They are, however, uniformly

susceptible to vancomycin and the quinolones (e.g., ciprofloxacin and ofloxcin) and often susceptible to erythromycin, rifampin, novobiocin, and tetracyclines (64, 134). Several courses of antimicrobial therapy are often necessary for organism eradication (Aguado et al., 29th ICAAC). Inhibitors of urease activity, e.g. acetohydroxamic acid or ammonium chloride, may augment the effect of antimicrobial agents (1, 202).

Arcanobacterium (*Corynebacterium*) *haemolyticum*

Arcanobacterium haemolyticum is a pleomorphic gram-positive rod that has evoked considerable controversy among taxonomists. On the basis of phenetic, peptidoglycan, fatty acid, menaquinone, and DNA data, it was recently removed from the genus *Corynebacterium* and assigned to a new genus, *Arcanobacterium*, composed of one species (35, 37). *A. haemolyticum* is a human pathogen occasionally isolated from throat cultures (7, 60, 75, 110, 130, 143, 144, 187, 240, 241), skin lesions (144, 146, 240), or (rarely) systemic infections such as endocarditis (28, 244) and meningitis (15, 40). Sepsis due to this organism was recently reported in a 15-year-old patient with infectious mononucleosis (73). The relative frequency of pharyngitis due to *A. haemolyticum* is between 5 and 13% of that due to *Streptococcus pyogenes* (7, 144). Over 90% of *A. haemolyticum* cases occur in patients between 10 and 30 years old (7, 60, 144, 187), whereas most group A streptococcal pharyngitis patients are <10 years old (7, 144). The severity of illness associated with pharyngitis due to *A. haemolyticum* seems to be as varied as that with streptococcal pharyngitis, and the two cannot be differentiated on clinical findings alone.

One striking feature of pharyngitis due to *A. haemolyticum* is the associated rash that occurs in 30 to 67% of the cases (7, 60, 144, 187). The rash has been described as erythematous, maculopapular, or, in some patients, scarlatiniform or rubelliform. It has also been mistaken for an allergic reaction to penicillin or other drugs (7, 130). Because the rash has been followed by desquamation in some patients, the infection has been misdiagnosed as toxic shock syndrome (L. S. Tompkins, Clin. Microbiol. Newsl. **5:** 29–30, 1983).

In their recent review of pharyngitis cases due to *A. haemolyticum*, Miller et al. raised the possibility that an unidentified toxin may be responsible for the rash in these patients (144). Early reports regarding the production of extracellular toxins by *A. haemolyticum* are contradictory. MacLean et al. concluded that the organism is only mildly invasive when tested by intracutaneous inoculation of human volunteers, rabbits, and guinea pigs (130). Although these authors could not detect a filterable dermotoxin, hemolysin, or toxin lethal for guinea pigs or rabbits (130), *A. haemolyticum* does produce at least two extracellular toxins, phospholipase D (PLD) and a hemolysin (207, 208). The PLD of *A. haemolyticum* is similar to that from *C. ulcerans* and *C. pseudotuberculosis* in its effects on experimental animals, producing hemorrhagic necrosis on intradermal injection in the rabbit and guinea pig and lethality for the rabbit (159). The PLD of *A. haemolyticum* is antigenically distinct from those of the other two species (210). Another potential toxin produced by *A. haemolyticum* is neuraminidase (152). DNA hybridization studies suggest that *A. haemolyticum* carries a gene related to the gene for the erythrogenic toxin of *Streptococcus pyogenes* (M. B. Coyle, N. B. Groman, J. Q. Russell, J. Nettles, and K. K. Holmes, Abstr. Annu. Meet. Am. Soc. Microbiol. 1988, B277, p. 76).

Actinomyces (*Corynebacterium*) *pyogenes*

A. pyogenes is a common cause of bovine mastitis and other pyogenic infections in various domestic animals. The mode of transmission in animals appears to be via flies (84, 220). Unlike the earlier reports of human infections with *A. pyogenes* which omitted definitive identification, two recent reports have documented human infections with this organism (11, 109). An epidemic of leg ulcers in school children in rural districts was reported from Thailand (108, 109). During the late spring to early fall between 1979 and 1984, there were yearly outbreaks, with 36 to 54% of school children affected. Antibiotic treatment eliminated the organism, but the leg ulcers remained unhealed. The authors hypothesized that, following accidental trauma to the legs, *A. pyogenes* was introduced to the lesion by Oriental eye flies. The resultant granulomatous ulcerative lesions may then have become secondarily infected by other common pyogenic bacteria, e.g., *Staphylococcus aureus* and beta-hemolytic streptococci. Ultimately these lesions were self-limited.

A. pyogenes infections have been observed in 11 patients in Denmark over a 20-year period (B. Gahrn-Hansen, personal communication). Pure cultures of *A. pyogenes* were isolated in all but four patients. The patients were adults and had a variety of infections, including abscesses, intraabdominal infections, cystitis, and one bacteremic case with mastoiditis. All but one of the patients recovered with antimicrobial or surgical treatment or both.

Epidemiological studies of bovine mastitis have demonstrated carriage of *A. pyogenes* by flies, and a recent preliminary report from England described transmission of mastitis via livestock flies (220). Transmission only occurred with two types of flies: a biting species; and *Hydrotaea irritans*, a species that feeds on punctures resulting from biting flies or abrasion of the udder. There is no evidence that *H. irritans* is a true vector of *A. pyogenes* because the organism is carried on the surface rather than in the internal organs of the fly (84).

The Special Bacteriology Section of the CDC (87) and the National Collection of Type Cultures (85) have received a number of *A. pyogenes* isolates from human sources, but to our knowledge descriptions of these cases have not yet been published. We urge that confirmed cases of *A. pyogenes* human infections be reported.

C. pseudodiphtheriticum (*C. hofmannii*)

C. pseudodiphtheriticum, a commensal of the human nasopharynx, is a rare human pathogen that primarily has been reported to cause endocarditis. Ten cases of *C. pseudodiphtheriticum* endocarditis, three with concomitant infection with other organisms, have been described (27, 126, 127, 175). However, the limited biochemical descriptions leaves the identification of at least one (27) of these isolates in doubt. Four cases involved prosthetic valves and the others occurred on previously damaged or congenitally abnormal valves. All cases affected left-sided cardiac valves, with an approximately equal split between the mitral and aortic valves. These infections presumably arise as a consequence of transient bacteremia from an upper respiratory source. Among the nine patients for whom information on outcome was provided, only four survived.

Lower respiratory tract infections with *C. pseudodiphtheriticum* have also been noted recently. Some cases have involved immunocompromised patients. One young man with systemic lupus erythematosus and glomerulonephritis,

who was receiving immunosuppressive therapy, developed pneumonia and had a pure growth of *C. pseudodiphtheriticum* isolated from bronchial washings (49). Another young man with human immunodeficiency virus infection developed a lung abscess that required lobectomy, from which only *C. pseudodiphtheriticum* was isolated (3). Other case reports have involved immunocompetent patients, but all had either sustained trauma (115, 145; B. M. Lockwood and J. Wilson, Clin. Microbiol. Newsl. **9**:5–6, 1987) or had underlying chronic bronchopulmonary disorders (171; N. Douat, M. Labbé, and G. Y. Glupczynski, Clin. Microbiol. Newsl. **11**:189–190, 1989). Of interest is that most of these infections were nosocomial, although evidence of an outbreak or a hypothetical means of transmission has not been shown. All of the reported patients survived while receiving various antibiotic regimens.

One case of urinary tract infection with *C. pseudodiphtheriticum* has been reported. A renal transplant recipient treated with prednisone and azathioprine developed a severe necrotizing infection of the entire urinary tract 3 months after her surgery (155). *C. pseudodiphtheriticum* was isolated in pure growth from the transplanted kidney. Interestingly, diphtheroids had been repeatedly isolated from her urine and nephrostomy site when her urinary symptoms began, but they were considered to be skin contaminants. Despite a nephrectomy and antibiotic treatment, the patient died. These cases illustrate the fact that *C. pseudodiphtheriticum* should be added to the list of low-virulence organisms that can become pathogens in immunocompromised hosts.

Rhodococcus (*Corynebacterium*) *equi*

There have been 21 reported cases of infections caused by *R. equi* to date (99). The more recent cases generally conform to those reported previously (127); i.e., most represent severe pulmonary infections in immunocompromised hosts. Van Etta and colleagues (232) described two immunocompromised patients with severe lung infections. Five patients with acquired immunodeficiency syndrome and *R. equi* infection have been reported, four of whom had pulmonary infections (19, 62, 128, 177, 178). The outcome of treatment in these patients was generally poor. Three *R. equi* infections were recently reported from New Zealand, two of which were pulmonary (99). Another case report described a nonimmunocompromised alcoholic woman with an empyema caused by *R. equi* (118).

These cases suggest that *R. equi* is emerging as an important opportunistic pathogen in patients with a variety of immunocompromising conditions. Among the reported cases, 18 (86%) were in patients with severe immunodeficiencies, especially of the cell-mediated type. Most infections developed insidiously, with fever and respiratory symptoms; >75% of patients had pulmonary involvement, usually manifesting as diffuse or nodular roentgenographic infiltrates, often associated with cavitation or a pleural effusion (99). Infections are often recurrent and refractory to treatment and may be associated with bacteremia and metastatic foci.

Antibiotics active against *R. equi* include penicillin G, doxycycline, and the aminoglyocosides, but erythromycin and rifampin are the most potent (99, 177, 232, 243). Used together, these last two agents act synergistically (166). Prolonged therapy appears necessary in most cases, especially when surgical drainage is not feasible (99). These characteristics may reflect the fact that *R. equi* is an intracellular pathogen (99, 118, 252).

The pathogenesis of *R. equi* infections in humans is not clear, but transmission from soil or animals may sometimes play a role. The organism is a common cause of pneumonia in foals, and recent studies in these animals have shed light on its role as an opportunistic pathogen for humans. In a mouse model, virulence of *R. equi*, which has a polysaccharide capsule and pili, was found to be related to resistance to phagocytosis and to decreased intracellular killing by macrophages (219). There were major differences in the virulence of *R. equi* strains when tested in the mouse model. Foal alveolar macrophages are capable of significant ingestion of *R. equi* only when the organism has been opsonized with specific antibody (251). Interestingly, opsonization of *R. equi* with specific antibody also increased its intracellular killing by macrophages. Apparently the ability of *R. equi* to survive and multiply within macrophages is related to the nonspecific degranulation of lysosomes which are thus unavailable for phagosome-lysosome fusion (83). The mechanism of lysosome destruction is under investigation. Presumably, cell-mediated immune responses are also involved in the normal host response to *R. equi* (83).

C. minutissimum

The name *C. minutissimum* was recently revived by Collins and Jones and is now recognized as a valid species (36). This organism is believed to be the causative agent of erythrasma, a relatively common and usually asymptomatic skin infection that generally occurs in the intertriginous and toeweb areas. Studies that cast doubt on the role of *C. minutissimum* in the pathogenesis of erythrasma are discussed in the next section.

Recently, several more serious infections caused by *C. minutissimum* have been described. A middle-aged woman developed recurrent breast abscesses 3 months after a biopsy at the affected site (16). Four drainage procedures and oral ampicillin and cloxacillin therapy failed to control the infection, which ultimately responded to treatment with intravenous vancomycin followed by oral erythromycin. Samples of pus from each of the operative procedures yielded heavy growth of only *C. minutissimum*, although the patient had no evidence of erythrasma. This was apparently the first reported case of deep-tissue invasion with this organism. The first known published report of *C. minutissimum* bacteremia involved an elderly man with chronic myeloid leukemia in blast crisis (76). The patient became febrile and, despite broad-spectrum antibiotic treatment, died. Three properly collected blood cultures, obtained after 3 weeks of hospitalization, yielded *C. minutissimum*. The source of the infection was not known, but the perineal skin was macerated, and previous sputum cultures grew diphtheroid organisms that were not identified. Finally, a case of infective endocarditis with embolic retinopathy due to *C. minutissimum* has been reported in a young woman with a history of rheumatic heart disease and a prolapsing mitral valve (82). The source of the infection was unknown, but penicillin treatment resulted in its rapid resolution. Although none of these patients with invasive *C. minutissimum* infection had clinical evidence of erythrasma, all had skin disruptions.

C. ulcerans

Human infections with *C. ulcerans*, a domestic animal-associated pathogen, have almost exclusively been cases of pharyngitis (78, 160). A recent letter described what was

believed to be the first reported human case of pneumonia caused by this organism (190). The elderly patient, who had previously undergone radiation therapy for metastatic lung cancer, developed a fatal pneumonia and only *C. ulcerans* grew from his sputum specimen. Two patients with ulcerated skin infections caused by *C. ulcerans* have also been reported (23).

In a comprehensive study of ten strains of *C. ulcerans* representing human, bovine, and equine sources, Carne and Onan (25) found only two toxins: the PLD of *C. pseudotuberculosis* and the diphtheria toxin of *C. diphtheriae*. Five of the ten strains had both toxins, three had only the diphtheria toxin, and two had the PLD alone.

C. pseudotuberculosis

C. pseudotuberculosis commonly causes suppurative lymphadenitis in domestic animals but only rarely infects humans, even those having close contact with infected animals (89, 169). There have been 12 human infections reported, 11 of which occurred in patients who had contact with animals on their products (23). All required prolonged antibiotic therapy and surgery for cure.

The importance of *C. pseudotuberculosis* as an animal pathogen has prompted studies of its toxins, particularly PLD, formerly called *C. ovis* exotoxin. The PLD of *C. pseudotuberculosis* hydrolyzes sphingomyelin in mammalian cell membranes and releases choline, leaving ceramide phosphate in the membrane (206). PLD does not lyse RBC membranes but does enhance RBC lysis by *R. equi*. The enhanced hemolysis may be due to the combined activity of two *R. equi* enzymes, phospholipase C and cholesterol oxidase; however, the latter enzyme alone can hemolyze RBCs in the presence of PLD (125). Conversely, the inhibition of the CAMP phenomenon by the PLD of *C. pseudotuberculosis* may be due to steric hindrance of the β-lysin of *Staphylococcus aureus* or to the fact that the β-lysin, which is a phospholipase C, is unable to act on ceramide phosphate (124).

The PLD of *C. pseudotuberculosis* may facilitate spread of the organism by attacking the sphingomyelin of endothelial cells of blood vessels (24). The PLD of *C. pseudotuberculosis* bears many similarities to the PLD of the brown recluse spider venom. They are similar in molecular weight, substrate specificity, and inhibition of staphylococcus β-lysin, but the two enzymes are immunologically distinguishable (17).

Although most of the early studies suggest that a single protein is responsible for PLD activity, inhibition of staphylococcus β-lysin, and dermonecrosis, the results from a recent study have raised some questions about this theory (151). The possibility that *C. pseudotuberculosis* produces additional exotoxins that are difficult to separate by routine purification procedures must be investigated with a variety of strains. Songer et al. have recently cloned the gene for PLD from *C. pseudotuberculosis* and shown that the expressed protein has both PLD activity and β-lysin inhibitory activity (199). The cell wall of *C. pseudotuberculosis* contains a lipid analogous to the cord factor of *Mycobacterium tuberculosis* which causes degeneration of phagocytic leukocytes after ingestion. This lipid causes hemorrhagic necrosis when injected intradermally but, unlike the cord factor, has no delayed systemic toxic effects in the guinea pig when injected intraperitoneally (26).

Both *C. pseudotuberculosis* and *C. ulcerans* can be lysogenized by bacteriophages of *C. diphtheriae* and thus can produce diphtheria toxin. One survey found that 2 of 16 (13%) *C. pseudotuberculosis* isolates produced diphtheria toxin (135). There have not, however, been any clinical cases of diphtheria attributed to *C. pseudotuberculosis* infection (23).

C. pseudotuberculosis is a relatively homogeneous taxonomic group that can be distinguished from all other *Corynebacterium* species by the production of PLD and urease and the inability to ferment starch. The PLD test (9) can be done on ordinary commercial sheep blood agar, rather than preparing media from washed sheep RBCs, provided that each test is quality controlled with a reference strain of *C. pseudotuberculosis* to confirm that the sheep blood agar does not contain antibodies against PLD. PLD can also be demonstrated by the reverse CAMP test (9). On the basis of host range, nitrate reduction, and DNA restriction fragment patterns, it has been proposed that *C. pseudotuberculosis* consists of two varieties: biovar *equi* that reduces nitrate and biovar *ovis* that fails to do so (18, 198).

C. xerosis

C. xerosis, a commensal of mucocutaneous sites, has been the cause of only a few reported human infections. Various infections in several immunocompromised patients have been described previously (127). A patient with a peritoneovenous shunt developed right-sided endocarditis with this organism (229). Two recent reports of *C. xerosis* endocarditis are apparently the first involving previously normal heart valves (52) (A. Goglio, C. P. Tosi, and F. Biroli, Clin. Microbiol. Newsl. **6**:83, 1984.). An isolate from the blood of a patient with subacute endocarditis was indistinguishable from *C. xerosis* by analysis of mycolic acid profiles (5). Septic arthritis (227) and vertebral osteomyelitis (111) due to *C. xerosis* have also been reported. Most of these patients were immunocompetent, but many had a history of previous surgery.

C. striatum

Reported to be a normal inhabitant of the anterior nares and skin, *C. striatum* has only rarely been recognized as a pathogen. Two cases of pleuropulmonary infection have been reported. One was a patient with chronic lymphatic leukemia (21), and the other was a young man on mechanical ventilation after a motor vehicle accident who had *C. striatum* repeatedly isolated in pure culture from his tracheal secretions and in mixed culture from an empyema (12). An organism resembling *C. striatum* caused severe destruction of the aortic valve of an elderly male with no history of heart disease (131).

CDC Coryneform Group G-2

The first reported infection with CDC coryneform group G-2 was a case of mitral and aortic valve endocarditis in a middle-aged man that occurred 6 weeks after he underwent replacement of porcine valves with Bjork-Shiley prosthetic valves (6). The CDC has reportedly received 75 isolates of this organism, but their pathological significance is unknown (6). A second reported case involved a man with disseminated intravascular coagulopathy who had many polymorphonuclear leukocytes containing these bacilli (117). In these patients blood cultures required 7 and 10 days of incubation, respectively, before becoming positive.

"C. aquaticum"

"*C. aquaticum*" is awaiting assignment to a different genus that accommodates its relatively high G+C content

and cell wall that contains diaminobutyric acid (50). This waterborne organism rarely causes human infections, but has been isolated from several different infected body sites. The first documented case of "*C. aquaticum*" meningitis has recently been reported in a neonate (14). Another neonate had a urinary tract infection with "*C. aquaticum*" 1 week after an uncomplicated vaginal delivery (222). An important feature of these cases was the initial confusion of the organism with *Listeria monocytogenes*, a much more frequent pathogen, which is also a motile gram-positive rod. *L. monocytogenes* differs from "*C. aquaticum*" primarily in its ability to hemolyze blood agar and in its metabolism of certain carbohydrates. "*C. aquaticum*" was also reported to be the cause of bacteremia in a child with chronic granulomatous disease (100) and relapsing peritonitis in two patients undergoing continuous ambulatory peritoneal dialysis (148; P. Casello, M. A. Basoni, and A. Tommasi, Clin. Microbiol. Newsl. **10**:62–63, 1988). Clinical isolates of "*C. aquaticum*" have shown greater antibiotic resistance than that seen with most other *Corynebacterium* species (148).

"*C. genitalium*" and "*C. pseudogenitalium*"

"*C. genitalium*" and "*C. pseudogenitalium*", described in the 1970s by Furness and Evangelista (67), were reported to be colonizers of the urogenital tract. While "*C. pseudogenitalium*" was considered part of the normal flora, "*C. genitalium*" appeared to cause various infections, including nongonococcal urethritis, epididymitis, and urinary tract infections. Reports of infections with these organisms have not been published by other investigators, but cell wall analyses of "*C. genitalium*" have confirmed that they are correctly placed in the genus *Corynebacterium* (56). Recent work has suggested that certain biovars of "*C. genitalium*" and "*C. pseudogenitalium*" have the same colonial morphology, biological reactions, and antimicrobial susceptibility patterns as strains of *C. jeikeium* (42, 55). However, DNA hybridization analyses, using a single strain of *C. jeikeium*, did not confirm identity of *C. jeikeium* with any of the tested biovars (90). Furthermore, DNA hybridizations have shown that "*C. genitalium*" consists of at least six unrelated groups, unlike "*C. pseudogenitalium*," which appears to be to a homogeneous group (90). The possible role of these species in urogenital infections must await further studies.

"*C. tenuis*"

Trichomycosis axillaris is a disease of the hairs of the axillary and, occasionally, pubic hairs. It is characterized by yellowish nodules and sheaths coating the hair shafts. Occasionally, the nodules are black or red. Electron microscopy has shown that only the cuticle of the hair (66, 137, 188) or the superficial cortex is affected (158). In 1952, Crissey et al. found that crushed and stained nodules revealed small, gram-positive bacillary and coccal forms (46). The authors selected only "characteristic colonies of Trichomycosis axillaris" for biochemical characterization. They found a number of very different colonial morphologies and biochemical reactions among the 31 coryneform isolates studied. Nevertheless, they suggested that these organisms represented a single species with the proposed name "*C. tenuis*." The characteristics shared by most members of *C. tenuis*" were: glucose fermentation, optimal growth in an alkaline medium (pH 7 to 9), and good growth without a lipid supplement. Subsequent studies of the etiology of trichomycosis axillaris have demonstrated that each nodule contains two or three kinds of coryneforms and that these fall into at least five different taxonomic groups (66, 136, 184, 188).

The origin of the yellow amorphous material that ensheaths the hair and embeds the nodules of trichomycosis axillaris is still unknown. The sheath substance may be produced by the embedded organisms (158, 188) or it may be derived from dried apocrine sweat. The latter explanation could account for the yellow color, the cementlike texture, and the gray-white fluorescence under Wood's light examination (122, 184). Levit has proposed that the nodules of trichomycosis axillaris are composed of corynebacterial colonies growing at the base of the hair shaft that have become coated with dried apocrine sweat and extend along the hair shaft as it grows (122). This theory is supported by the poor hygiene and lack of deodorant use that are highly associated with the presence of trichomycosis axillaris (189).

A recent proposal that erythrasma, trichomycosis axillaris, and pitted keratolysis are part of a "corynebacterial triad" was based on insufficient microbiological studies (189, 224, 249, 250). It is clear that clarification of the etiology of these superficial diseases awaits further study and that "*C. tenuis*" is an invalid name that has no place in the current literature.

IDENTIFICATION

Several investigators have used a variety of chemical techniques, including DNA hybridizations, to study coryneforms, and most agree that the type of peptidoglycan in the cell wall is one of the most important criteria for defining the genera (102, 119, 120, 218). Currently, determining the cell wall composition is beyond the scope of nearly all clinical laboratories. This problem is not unique to the *Corynebacterium* genus. The majority of the other 20 genera listed in *Bergey's Manual* (98) as irregular gram-positive rods are also defined in terms of their cell wall composition, including dibasic amino acids, sugars, and mycolic acids, when present. These include *Arachnia*, *Rothia*, and *Brevibacterium*, three genera encountered in a clinical setting.

We believe that the CDC system for identification of gram-positive rods is the most practical and reliable of those available (87). Table 2 presents the biochemical reactions reported by the CDC for former and current members of the genus *Corynebacterium* as well as species awaiting valid publication. (*C. bovis* and "*C. aquaticum*" are not members of the genus *Corynebacterium*, but they are included pending further taxonomic studies.)

The reactions shown in Table 2 are similar to those in Table 15.3 of Collins and Cummins (35) except for the biochemical reactions of *C. striatum* and *C. matruchotii*. Because we could not resolve these major discrepancies despite a detailed review of the early literature describing *C. striatum* (51, 150, 153) and *C. matruchotii* (69), we recommend using the CDC description of these two species as presented in Table 2. The major disagreements between *Bergey's* and the CDC for the biochemical reactions for *C. striatum* are difficult to understand because both authorities cite type strain ATCC 6940 as their reference strain.

The CDC maltose reactions differ from those listed in *Bergey's* for a number of species, but this probably reflects the purity of the compound, the method of sterilization, or differences in the broth base. Table 3 presents CDC's 12 coryneform groups, including the recently defined groups 1 and 2 (43, 156). Table 3 also lists species formerly in the genus *Corynebacterium*, or the CDC coryneform groups,

TABLE 2. Identification of medically significant corynebacteria and other coryneforms[a]

Species	Catalase	Beta hemolysis	Nitrate reduction	Pigment[b]	Urease	Gelatin hydrolysis	Motility	Esculin hydrolysis	Carbohydrate utilization[c]					Response to serum[d]
									Glucose	Maltose	Sucrose	Mannitol	Xylose	
C. diphtheriae[e,f]	+	+[e,g]	+[e]	N	−	−	−	−	+	+	−[e]	−	−	d[h]
C. ulcerans[f,i,j]	+	+[g]	−	N	+	−/+[k]	−	−	+	+	−	−	−	−
C. pseudotuberculosis[f,i,l]	+	+[g]	d[m]	y-w	+	−[n]	−	−	+	+	−	−	−	+[o]
C. xerosis[p]	+	−	+	N, y, T	−	−	−	−	+	+[q]	+	−	−	−
C. striatum	+	−	+	N, y-g	−	−	−	−	+	−	+	−	−	−
C. pseudodiphtheriticum	+	−	+	N	+	−	−	−	−	−	−	−	−	−
C. kutscheri	+	d	+	y-w, N	+	−	−	+	+	+	+	−	−	−
C. renale	+	−	−	Y	+	−	−	−	+	−	−	−	−	−
C. pilosum	+	−	+	Y	+	−	−	−	+	+	−	−	−	−
C. cystitidis	+	−	−	N	+	−	−	−	+	+	−	−	+	−
C. matruchotii	+	−	d	N	−	−	−	−	+	d	d	d	−	−
C. minutissimum	+	−	−	N	−	−	−	−	+	+	d	−	−	−
C. bovis	+	−	−	N	−	−	−	−	+	−	−	−	−	+
C. jeikeium (group JK)	+	−	−	N	−	−	−	−	+	d	−	−	−	+
"*C. genitalium*"[r]	+	−	−	N	−	−	−	−	+	wk	−	−	−	+
"*C. aquaticum*"[s]	+	−	−	Y	−	−	+	+	+	+	+	+	+	−

[a] +, 90% or more positive within 4 days; −, 90% or more negative; d, >10% or <90% positive; wk, weakly positive.
[b] N, White or gray; Y, yellow; y, pale yellow; y-g, yellowish green; y-w, yellowish white; T, tan. Pigmentation results are from references 35 and 87.
[c] Usually tested in peptone-water with Andrade indicator or in brain heart infusion broth.
[d] Two drops of sterile rabbit serum are required for good growth in peptone-water.
[e] Biotype *mitis* is weakly beta-hemolytic; it includes sucrose-positive strains that are rare in the United States and nitrate-negative strains that are subspecies *belfanti*. Biotype *gravis* attacks glycogen and starch and includes a few weakly hemolytic strains and rare isolates that are sucrose positive. Biotype *intermedius* is not beta-hemolytic.
[f] Produces halos on Tinsdale medium and does not hydrolyze pyrazinamide.
[g] Narrow zones of slight hemolysis at 18 to 24 h.
[h] Biotype *intermedius* is stimulated by serum.
[i] PLD is produced.
[j] Also ferments glycogen and usually starch and trehalose which should be read for 7 days.
[k] Negative or weak at 37°C; positive at 25°C.
[l] Does not attack glycogen or trehalose and usually not starch.
[m] Usually negative in strains from sheep or goats and positive in those from horses or cattle.
[n] Negative at 35 and 25°C but positive at 30°C after 14 days.
[o] Growth is stimulated by lipid but serum is not added for biochemical tests.
[p] Halos not produced on Tinsdale medium.
[q] In reference 35, this reaction is negative, with occasional strains positive.
[r] Reactions of biotypes 2 (ATCC 33031) and 4 (ATCC 33033).
[s] Glucose oxidizer. Reactions of reference strain ATCC 14655.

which are now assigned to other genera on the basis of chemotaxonomic studies. The response to serum has been included in Tables 2 and 3 because it is a useful trait for the identification of some species that are otherwise difficult to distinguish (87, 163). The absence of a standardized procedure for testing lipid stimulation is a longstanding concern that is discussed below.

Table 4 includes the genera of nonsporing gram-positive rods that might be encountered in aerobic cultures of clinical specimens. It was compiled from data available in reference 193 and includes only traits that can be readily recognized in a routine laboratory. Table 4 is designed to prompt the microbiologist to consider other genera to which an "unidentifiable" diphtheroid might belong. Other useful approaches to determine the correct coryneform genus are available (30, 31, 87; J. E. Clarridge, Clin. Microbiol. Newsl. 8:32–34, 1986).

Lipid-Requiring Coryneforms

On the basis of whole-cell fatty acids and mycolic acids, McGinley et al. have recently concluded that lipid-dependent skin coryneforms may represent a single species (139). Although they found diverse biochemical reactions, this group of investigators concluded that lipid-dependent coryneforms are identical to *C. jeikeium* in all parameters except antibiotic resistance. They proposed that *C. jeikeium* can be adequately identified on the basis of an absolute requirement for lipid, the production of catalase, and resistance of multiple antibiotics (140).

In early studies of skin coryneforms, lipid dependency was a major feature of identification schemes, but this trait has been omitted from most of the more recent publications prior to reference 139. The demonstration of lipid dependency is a relatively cumbersome procedure because it requires a lipid-free medium. McGinley et al. followed Ward's approach (234) and used a chemically defined broth medium that was supplemented with Tween 80 (0.05%). Both activated charcoal (53, 164) and chloroform (192, 197) have also been used to prepare lipid-depleted media. Estimates of the incidence of lipid dependency in skin coryneforms differ widely, presumably because of difference in technical details. Smith (192) and McGinley et al. (139) found that all of their lipid-stimulated coryneforms were lipid dependent, whereas Somerville (197) found that only 4 of 1,381 (0.29%) lipid-stimulated diphtheroids had an absolute lipid requirement for growth. In view of the diversity of methods used, it is not surprising that estimates of the prevalence of lipid-dependent coryneforms differ. In fact, in their original description of *C. jeikeium*, Riley et al. found that such coryneforms were not lipid dependent when tested by an undescribed method (172). Most other authors have noted that *C. jeikeium* is lipid dependent (53, 139, 140). The

TABLE 3. CDC coryneform groups and species that were formerly included with the corynebacteria[a]

Species	Catalase	Beta hemolysis	Nitrate reduction	Pigment[b]	Urease	Gelatin hydrolysis	Motility	Esculin hydrolysis	Carbohydrate utilization[c]					Response to serum[d]
									Glucose	Maltose	Sucrose	Mannitol	Xylose	
Group A-3	+	−	+	N, Y	−	−	+	+	+	+	+	−	+	−
Group A-4	+	−	d	Y, N	−	d	d	+	+	+	+	+	+	−
Group A-5	+	−	d	Y, N	−	d	d	d	+	+	+	+	−	−
B-1	+	−	d	T, N	−	d	−	−	+	d	d	−	−	−
B-3	+	−	−	T, N	−	+	−	−	−	−	−	−	−	−
Group F-1	+	−	d	N	+	−	−	−	+	d	+	−	−	d
Group F-2	+	−	d	N	+	−	−	−	+	+	−	−	−	−
Group G-1[e]	+	−	+	N	−	−	−	−	+ or (+)	d	+ or (+)	−	−	+
Group G-2[e]	+	−	−	N	−	−	−	−	+ or (+)	d	+ or (+)	−	−	+
Group I[f]	+	−	+	N	−	−	−	−	+	d[g]	−	−	−	−
Group E[h]	−	−	−	N	−	−	−	d	+	+	+	−	+	+
Group D-2	+	−	−	N	+	−	−	−	−	−	−	−	−	+
ANF-1	+	−	−	N	−	−	−	−	−	−	−	−	−	−
ANF-3	+	−	+	N	−	−	−	−	−	−	−	−	−	−
Group 1	+	−	+	N	−	−	−	−	+	+	+	+	+	−
Group 2	−	−	−	N	−	−	−	−	+	+	−	−	−	+
Actinomyces pyogenes	−	+	−	N	−	+	−	−	+	+	d	d	+	+
Arcanobacterium haemolyticum[i]	−	+[j]	−	N	−	−	−	−	+	+	d	−	−	+[k]
Oerskovia turbata	+	−	d	Y, N	d	+	+	+	+	+	+	−	+	−
Oerskovia xanthineolytica	+	−	+	Y	d	+	+	+	+	+	+	−	+	−
Rhodococcus equi	+	−	d	P	d	−	−	−	−[l]	−	−	−	−	−

[a] +, 90% or more positive within 4 days; −, 90% or more negative; + or (+), 90% or more positive, some strains positive after 4 or more days; d, >10% or <90% positive.
[b] N, White or gray; Y, yellow; P, pink (orange to red on glucose-yeast extract agar); T, tan. Pigmentation results are from references 35 and 87.
[c] Usually tested in peptone-water with Andrade indicator or in brain heart infusion broth.
[d] Two drops of sterile rabbit serum are required for good growth in peptone-water.
[e] Fastidious, but otherwise indistinguishable from *B. matruchotii* in these tests.
[f] Halos not produced on Tinsdale medium.
[g] Group I-2 produces acid from maltose but group I-1 does not.
[h] Fastidious. Major end products are succinic acid and acetic acid.
[i] PLD is produced.
[j] Narrow zones of slight hemolysis after 48 h on sheep blood.
[k] Growth is stimulated by lipid but serum is not added for biochemical tests due to false-positive xylose reactions.
[l] Weak reaction after 7 days.

Special Bacterial Pathogens Laboratory of CDC characterizes *C. jeikeium* as lipophilic (87).

Lipophilia is simpler to determine than lipid dependency because lipid stimulation of growth can be tested on almost any medium. Lipophilia is usually manifest as growth stimulation by Tween 80 (0.05 to 0.5%) or serum. Tween 80, one of a series of detergents, is a polyethoxysorbate oleate that contains a variety of fatty acids with 14 to 18 carbons (132, 192). The Special Pathogens Laboratory of the CDC tests lipid stimulation of growth by adding 2 drops of rabbit serum to 3 ml of peptone-water fermentation broth (45).

Before McGinley's simplified definition of *C. jeikeium* can be accepted, it is important to recognize that other lipid-dependent corynebacterial species or groups colonize the skin and mucous membranes. The early literature includes many reports of either lipid-dependent or lipid-stimulated coryneforms with biochemical patterns that clearly differentiate them from *C. jeikeium* (132, 164, 192). Most notable is the lipid-dependent *intermedius* variety of *C. diphtheriae* (234).

The advisability of assuming that all antibiotic-resistant corynebacteria are *C. jeikeium* has been questioned by Young et al. (247). In a patient culture survey using selective media supplemented with horse serum, they recovered 52 antibiotic-resistant clinical isolates of corynebacteria. Lipid dependency was not tested, but all isolates produced very small colonies that were morphologically consistent with *C. jeikeium*. Six (11.5%) of their isolates resembled the urease-producing CDC group D-2. These authors concluded that some of their antibiotic-resistant, urease-negative isolates did not belong to any of the currently recognized coryneform groups, including *C. jeikeium*. More recently, Bayston and Higgins (13) tested 38 antibiotic-resistant, lipid-stimulated coryneforms in two commercial systems and described three groups that are biochemically distinguishable from *C. jeikeium*. We believe that *C. jeikeium* cannot be identified solely on the basis of antibiotic resistance and lipophilia. The biochemical tests listed in Tables 2 and 3 are also needed to distinguish this species from other lipophilic coryneform groups.

Fluorescent Diphtheroids

The discovery by Sarkany et al. of fluorescent diphtheroids in erythrasma lesions provided a fascinating explanation for the coral-red fluorescence demonstrated by the affected skin when examined under a Wood's lamp (180). When material from erythrasma lesions was cultured on an agar medium containing 20% fetal calf serum in tissue culture medium 199 without phenol red or bicarbonate, the resulting colonies produced varying degrees of orange to coral-red fluorescence (182). Apparently only one colony type was characterized and sent to the National Collection of Type Cultures to become the type strain of *C. minutissimum*, NCTC 10288 (183).

Regrettably, Sarkany's study of experimental human

TABLE 4. Characteristics of nonsporing gram-positive rods, including aerobes and facultative anaerobes[a]

Genus[b]	Morphology			Pigmentation[f]	Catalase	Motility	Optimum temp (°C)	O_2 requirement[g]	Glucose metabolism[h]
	Branching mycelium[c]	Diphtheroid[d]	Coccoid[e]						
Actinomyces	T	+	−/+[occ]	N, R	−/+	−	35–37	Fac-an	O/F
Arachnia	T, N	+	+	N	−	−	35–37	Fac-an	O/F
Arcanobacterium	N	−/v's	+	N	−/+[wk]	−	37	Fac	O/F
Brevibacterium	N	−/v's	r-c	N, Y, O-R, V	+	−	20–37	Aer	O
Corynebacterium									
Animal pathogens	N	+	−	N, Y	+	−	30–37	Fac, Aer	O/F
Plant pathogens	N	+	+	Y, O, P, N	+	−	21–26	Aer	O
Erysipelothrix	N	−/v's	−	N	−	−	30–37	Fac	O/F
Gardnerella	N	−[i]	+	N	−	−	35–37	Fac	O/F
Kurthia	N	−	+	N	+	+	25–30	Aer	N
Lactobacillus	N	+	+	N, (Y, R)	−	−/+	35–40	Micro-an	F
Listeria	N	−/v's	+	N	+	+	30–37	Aer, Fac	O/F
Mycobacterium (rapid growers)	N, T	−	+	N, Y	+	−	30–45	Aer	O
Nocardia	P, T	−	+	N, Y, O, P, V	+	−	15–37	Aer	O
Oerskovia	P, T	+	−	Y, N	+[j]	+/−[k]	20–37	Fac	O/F
Propionibacterium	N	+	+	N, P, R, Y, O	+[l]	−	30–37	Ana, Aertl	F
Rhodococcus	P, T	−	r-c	N, Y, R, O	+	−	15–40	Aer	O
Rothia	N, T	+	+	N	+	−	35–37	Fac	O/F

[a] +, Positive reaction in 90 to 100% of strains; −, negative reaction in 90 to 100% of strains; wk, weakly positive. Where two symbols appear, the first indicates the more common property. Information compiled from reference 193.

[b] Includes genera that may be recovered from clinical specimens. The following genera have been omitted because recovery from animals or humans has not been reported *Arthrobacter*, *Caseobacter*, *Cellulomonas*, *Curtobacterium*, and *Microbacterium*. (Plant species of corynebacteria are unlikely in this setting.)

[c] N, None; P, persistent; T, transient.

[d] Genus description includes the term diphtheroid, coryneform, clubbed, or wedged shaped. v's indicate that V forms may be present.

[e] Genus description includes the term coccoid or coccobacillary. r-c indicates a marked rod-coccus cycle of growth.

[f] N, Nonpigmented; R, red; P, pink; Y, yellow; O, orange; O-R, orange-red; V, various other colors; ( ), pigments occur rarely.

[g] Fac, Facultative anaerobe; Fac-an, facultative but most strains prefer anaerobic atmosphere; Aer, strict aerobe; Ana, anaerobe; Micro-an, microaerophilic, some are anaerobes on isolation; Aertl, aerotolerant.

[h] O, Oxidative; F, facultative; N, glucose not utilized.

[i] *Gardnerella* forms small pleomorphic bacilli and coccobacilli that stain gram negative to gram variable.

[j] Catalase positive when grown aerobically.

[k] There are nonmotile *Oerskovia*-like strains.

[l] Usually catalase positive; some strains give negative reaction.

erythrasma infections did not include appropriate controls or microbiological studies of the induced lesions which fluoresced only briefly. When Somerville studied the pathogenesis of erythrasma (196), she found that scaling from maceration and chafing preceded colonization with fluorescent diphtheroids. It therefore seems unlikely that the etiology of erythrasma has been definitively established (181).

Following Sarkany's work, a number of investigators showed that fluorescent diphtheroids are commonly found in large numbers on normal skin. When Somerville cultured toe webs, axillae, and groins of 754 college students who were also examined by Wood's light, she recovered fluorescent diphtheroids from 42% of sites that fluoresced and from 13% of nonfluorescent sites (195). Hernandez (81) has recently cultured *C. minutissimum* from the skin of more than a third of men who had no evidence of infection. Marples (132) found that over 20% of the flora isolated from normal skin (axillae, foreheads, and toe webs) were fluorescent diphtheroids.

McBride et al. (138) used 35 biochemical tests in an attempt to classify 58 fluorescent diphtheroids that had been collected from normal skin, erythrasma lesions, and skin lesions other than erythrasma. Only 2 isolates from 25 erythrasma cases gave identical biochemical reactions, and less than half of the erythrasma isolates gave biochemical reactions consistent with *C. minutissimum*.

Somerville (195, 197) proposed a scheme to divide the fluorescent diphtheroids into eight different biochemical groups. She found that reference strains of other *Corynebacterium* species, including *C. bovis*, *C. ulcerans*, *C. xerosis*, *C. pseudotuberculosis*, and *C. renale*, also fluoresced (197). McBride et al. (138), however, did not find that any of the known species of coryneforms fluoresced in their medium 199 formulation, which was very similar to that used by Sarkany and Somerville. In view of the difficulty interpreting fluorescence on agar medium 199 supplemented with fetal calf serum, it is not surprising that conflicting results were obtained in different laboratories.

Microbial fluorescence has also been demonstrated on a blood agar medium containing δ-aminolevulinic acid, a precursor of protoporphyrin. Ghadially et al. (68) found that red fluorescence could be detected in *Staphylococcus* species and in many species in the family *Enterobacteriaceae*, as well as in *C. hofmannii*, *C. xerosis*, and *C. diphtheriae* biotypes gravis and mitis, but not biotype intermedius. Other *Corynebacterium* species were not tested. The δ-aminolevulinic acid test, which has proven to be reliable for rapid differentiation of *Haemophilus* species, might also have application in identification schemes for corynebacteria.

Distinguishing *C. jeikeium* from *C. minutissimum* and *C. bovis*

C. jeikeium, *C. minutissimum*, and *C. bovis* do not reduce nitrate, hydrolyze urea, or digest gelatin; production of acid from maltose is the only biochemical test in Table 2 that may help distinguish these species. The only characteristic in Table 2 that clearly distinguishes *C. minutissimum* from the

other two species is the lipid dependency of *C. jeikeium* and *C. bovis*. *C. minutissimum* grows well on ordinary media in the absence of lipid supplements. Unlike the other two species, which grow very lightly and cause no observable change on triple sugar iron agar slants, *C. minutissimum* grows well, producing an acid or alkaline reaction on the slant (D. Hollis, personal communication).

A negative *o*-nitrophenyl-β-D-galactopyranoside (ONPG) test can no longer be recommended for distinguishing *C. jeikeium* from *C. bovis*, as has been reported (45). McGinley et al. found that 4 of 20 (20%) *C. jeikeium* isolates produced a positive reaction in the ONPG produced by Sigma Chemical Co., St. Louis, Mo. (140). Using the ONPG product from Key Scientific Products Co. Inc., Los Angeles, Calif., Grasmick and Bruckner found that 16 of the 21 (76%) *C. jeikeium* isolates hydrolyzed ONPG (74), whereas all strains of *C. jeikeium* tested at the CDC with the same ONPG procedure have been negative. Why the CDC results do not agree with those of Grasmick and Bruckner is unknown.

A valuable description of the reference strains and clinical isolates of *C. jeikeium* from the United States and the United Kingdom was recently published by Jackman et al. (93). This work definitively established the group JK bacillus as a single species of *Corynebacterium* based on analyses of cell wall carbohydrates, amino acids, and mycolic acids as well as whole-cell protein patterns, G+C ratios, and DNA hybridization studies. Earlier analyses of mycolic acid profiles had also suggested that the *C. jeikeium* strains constituted a new species (5). Jackman and colleagues made a major contribution to clinical microbiology by going beyond molecular biology and examining members of the newly proposed species, *C. jeikeium*, for over 45 biochemical reactions that could be tested easily in a clinical laboratory. The only positive reactions given by the *C. jeikeium* were growth on 0.03% tellurite agar and on bile salt agar, hydrolysis of Tween 20 and 80, and acid production from glucose and galactose. Some strains also attacked maltose. Unfortunately, published descriptions of *C. bovis* and the various biovars of "*C. genitalium*" do not provide a battery of tests that might reliably distinguish them from the now clearly defined *C. jeikeium*.

The limitations of conventional methods for identification of corynebacteria were strikingly demonstrated by the Jackman study, which found that two of four strains believed to be *C. bovis* were actually *C. jeikeium* (93). One of the misidentified isolates of *C. jeikeium* was *C. bovis* NCTC 11914. As noted by Collins and Cummins (35), there seems to be much confusion regarding valid strains of *C. bovis*. Dopfer et al. (50) concluded from DNA studies and cell wall analyses that *C. bovis* ATCC 13722 is misclassified and probably belongs with the plant coryneforms. The reports that the *C. bovis* type strain ATCC 7715 is not lipophilic (50, 53) are inconsistent with many other descriptions of this strain (22, 35, 87, 95, 139, 140).

C. bovis, an Unlikely Human Pathogen

It appears unlikely that clinical microbiologists will encounter *C. bovis* from human sources. The CDC does not have a single human isolate in their collection (87). Furthermore, as already mentioned, Jackman et al. found that two of four human isolates received as *C. bovis* were, in fact, *C. jeikeium*; the other two were not further identified (93). Similarly, Brooks and Barnum (22) characterized 106 bovine strains and concluded that none of the six human isolates in the National Collection of Type Cultures was consistent with the *C. bovis* type strain ATCC 7715. On the other hand, Athalye et al. (5) found that mycolic acid patterns from 2 of 11 clinically significant human coryneforms closely resembled those of the *C. bovis* reference strains; definitive identifications were not attempted, however. It seems particularly ironic that *C. bovis* is so difficult to distinguish from other lipid-dependent coryneforms when chemotaxonomic studies indicate that it should be excluded from the genus *Corynebacterium* (35).

Distinguishing *A. haemolyticum* and *A. pyogenes*

Factors that have contributed to the earlier confusion surrounding both the taxonomy and the identification of *A. haemolyticum* include the following: (i) the designation *C. pyogenes* variety *hominis* by some investigators (207, 248); (ii) a report that it was a mutant of *C. pyogenes* (10); (iii) the description of a positive catalase test that is not observed with conventional testing methods (10); (iv) a major reference manual's statement (35) that most strains reduce nitrate to nitrite, which is not true of isolates from most regions of the world (45, 60, 80, 110, 176, 240); and (v) the lack of hemolysis after 24 h on sheep blood agar, the medium used by >95% of clinical laboratories in this country. Nevertheless, *A. haemolyticum* can now be distinguished reliably from other coryneform groups on the basis of colonial morphology and conventional biochemical tests (45). Most strains of *A. haemolyticum* have a unique colonial morphology that is helpful in recognizing this organism in mixed cultures on sheep blood agar. After 48 h of incubation, a narrow zone of beta-hemolysis usually surrounds the colony and transmitted light reveals a small dark dot at the center of each colony. After a colony is gently pushed aside, the dot is left behind as a tiny dark pit in the agar (60, 130, 240).

Although *A. haemolyticum* and *A. pyogenes* have been assigned to different genera, they have remarkably similar results on conventional biochemicals tests. It appears that the only reliable conventional test for distinguishing them is the ability of *A. pyogenes* to hydrolyze gelatin. A negative result after 48 h of incubation rules out *A. pyogenes*, which is rapidly proteolytic. Unfortunately, most of the reports of human infections with *A. pyogenes* did not include a test result for gelatin hydrolysis. Of those studies reporting the gelatinase reaction, only the organisms described in the most recent reports by Kotrajaras and Tagami (109) are consistent with *A. pyogenes*. The *A. pyogenes* reaction with antisera against group G streptococci has been suggested as a simple test for distinguishing this organism from *A. haemolyticum* (10, 112, 113); however, commercial streptococcal reagents have not yet been tested against *A. pyogenes*. The lack of PLD production by *A. pyogenes* can also distinguish it from *A. haemolyticum* (209), but this test has not been included in published identification schemes (35, 87). A reverse CAMP test for PLD has been reported for *A. haemolyticum* (248); the methods described for *C. pseudotuberculosis* are applicable (9).

Other Species of Corynebacteria

A number of authentic *Corynebacterium* species (35) have not been included in this review. *C. callunae*, *C. flavescens*, *C. glutamicum*, *C. variabilis*, and *C. vitarumen* have been omitted because there is no evidence that they occur in a clinical setting. *C. mycetoides* was isolated from a tropical ulcer in 1942 (35), but there has been no subsequent report and the CDC has not received any strains other than the original reference strain (87).

Brevibacterium ammoniagenes has also been validly published as a member of the genus *Corynebacterium* (34). *C. ammoniagenes* was originally isolated from infant feces and was believed to be responsible for diaper rash. Its wide distribution in putrefying materials (35) and its lack of virulence in animal studies (41) raise serious doubts regarding the possible role of *C. ammoniagenes* as a pathogen. There have been no subsequent publications on this organism and no isolates have been identified by the CDC. *C. ammoniagenes* produces catalase and urease, reduces nitrate, and does not hydrolyze gelatin. Its carbohydrate reactions are equivocal, but glucose was fermented when tested in a medium similar to that of Hugh and Leifson (35). Another organism omitted from this review is *C. renale*. Human infections due to this organism have not been reported since the 1982 review of corynebacterial infections (127). *C. pilosum* and *C. cystitidis*, originally described as serotypes of *C. renale* (245, 246), have not been reported from humans. The only report of infection with CDC group I1 involved the previously normal heart of an intravenous drug abuser with multivalve endocarditis (59).

The plant pathogens included in the genus *Corynebacterium* are not authentic members of the genus as it is now defined. The major peptidoglycan of their cell walls is diaminobutyric acid rather than *meso*-diaminopimelic acid, and the G+C content is 67 to 78 mol%, instead of 51 to 63 mol% as found in the true *Corynebacterium* species. This group of organisms will undoubtedly be reclassified in the near future.

Rapid Methods

The carbohydrate rapid fermentation tests used for identification of gonococci were evaluated for their utility in corynebacterial identifications by Hollis et al. (86). Data from 49 strains of gram-positive rods indicated that the 4-h reactions for corynebacteria probably are a great advantage over the peptone-water carbohydrates that frequently require serum supplementation and 2 to 7 days of incubation. Thompson et al. (223) evaluated a rapid (1- to 4-h) microbiochemical method that used a nutritionally rich broth for identification of corynebacterial strains. For 101 reference laboratory strains as well as 37 clinical isolates, the results from rapid and conventional methods were in agreement for 99.1% of the individual tests, and identifications were in complete agreement. Clarridge has found this method useful in her laboratory (Clin. Microbiol. Newsl. **8**:32–34, 1986).

Four commercial systems have been evaluated for identification of the corynebacteria, particularly for *C. jeikeium* that must be distinguished from other *Corynebacterium* species according to the College of American Pathologists requirements for extent-four laboratories. In an evaluation of the API 20S system (Analytab Products, Plainview, N.Y.), using very heavy inocula (equivalent to the turbidity of a no. 5.0 McFarland standard), all 56 isolates of *C. jeikeium* and 12 group D-2 isolates were accurately identified by unique profile numbers after overnight incubation (103). Pending results from a large number of strains representing other *Corynebacterium* species and CDC coryneform groups, the authors refrained from recommending this system for coryneforms other than *C. jeikeium* and the CDC group D-2. The API 20 Strep system, which is different from the API 20S system, has been evaluated for identification of *C. jeikeium* and group D-2 (225). This product requires a heavy inoculum (McFarland standard 4.0) and a 24-h incubation. When combined with tests for production of catalase, urease, and reduction of nitrate, the system provided reliable identifications. This system was also accurate in identifying *A. pyogenes* from bovine sources (149). The Minitek identification system (BBL Microbiology Systems, Cockeysville, Md.), using nine biochemical tests, was evaluated with 44 *C. jeikeium* isolates and 46 other isolates representing 13 *Corynebacterium* species and six different CDC groups (191). All organisms were correctly identified within 18 h of incubation. Grasmick and Bruckner (74) found that the 60-min Rapid Identification Method (Austin Biological Systems, Austin, Tex.) identified 16 of 21 (76%) *C. jeikeium* isolates on initial testing from blood cultures. On retesting, one false-positive sucrose and four false-negative reactions (including three glucose and one nitrate) were eliminated. The authors recommended using the Rapid Identification Method urea, nitrate, glucose, and sucrose for rapid identification of *C. jeikeium*. They concluded that these biochemical tests are sufficient for identification of *C. jeikeium* when used in conjunction with Gram stain, colony morphology, catalase production, and the failure of this lipid-requiring organism to grow on triple sugar iron medium.

Although rapid methods can be helpful for identifying well-defined *Corynebacterium* species and coryneform groups, their accuracy cannot exceed that of conventional methods.

Selecting Reference Strains

Microbiologists who are selecting reference strains for quality control or research projects should carefully review the literature to determine the most suitable strains. For example, three different reference strains of *C. xerosis*, ATCC 7094, ATCC 7711 (4), and NCTC 7243 (197), have been reported to be unable to reduce nitrate. Of even greater concern is the fact that the *C. xerosis* type strain ATCC 373 has a G+C content of approximately 67 mol%, which probably is too high for an authentic member of the genus *Corynebacterium* (35). Other strains of *C. xerosis* have a G+C content of 55%, well within the range (51 to 63 mol%) considered typical for the *Corynebacterium* species (35). As mentioned earlier, several reports suggest that reference strains of *C. bovis* that were originally isolated from human sources should not be considered authentic members of the species (5, 22, 93).

FUTURE DIRECTIONS

As the number of severely compromised patients increases, the incidence of opportunistic infections with unidentifiable skin coryneforms is rising. British microbiologists who have studied the flora of human skin have deplored the inadequacies of the existing coryneform taxonomy (57, 132, 157, 162, 197). Even when skin isolates do belong in the genus *Corynebacterium*, they usually are not members of any recognized species (91). Although the CDC identification scheme for gram-positive rods (87) is an invaluable resource, most clinical laboratories that serve immunocompromised patients continue to encounter difficulties with the identification of coryneform isolates.

One of the reasons for the difficulty with identifying coryneform species is the lack of DNA relatedness studies to confirm homogeneity within recognized taxa. This is due in part to the challenge of extracting sufficient quantities of DNA and RNA from these organisms that are relatively resistant to lysis. Nevertheless, considering the frequency

with which coryneforms are isolated, it is surprising that so few DNA or RNA hybridization or sequencing studies of authentic *Corynebacterium* species have been performed in the past 20 years (38, 39, 47, 88, 90, 93, 218). Nucleic acid techniques for analyzing the taxonomic relationships for other genera of coryneforms are also relatively few (50, 61, 97, 147, 173, 211–213, 217).

A taxonomically sound system for identification of coryneforms from humans cannot be developed until cell wall analyses (119, 120) and nucleic acid hybridization or sequencing or both (236) have definitively established the taxonomic groups. Once this is accomplished, biochemical tests that reliably distinguish the taxa can be selected. A multinational collection of reference strains and the CDC collection of coryneforms are likely sources of strains for these studies. Clinical laboratory collections of unidentified coryneform isolates from sterile body sites should also be included to provide a sufficiently broad data base. Application of the nucleic acid technology that has so greatly advanced the taxonomy of other medically important genera (44, 58) would provide the much-needed taxonomic foundation for development of a reliable coryneform identification scheme.

Meanwhile, all clinically significant, unidentifiable coryneforms should be submitted to the CDC via state laboratories. This practice will improve our ability to utilize the CDC tables (87) as well as document the magnitude of the problem presented by this diverse group of organisms.

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