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CHAPTER 3.3.12

The Genera *Proteus*, *Providencia*, and *Morganella*

JIM MANOS AND ROBERT BELAS

Introduction

The three genera *Proteus*, *Morganella* and *Providencia* presently comprise a total of ten species. All are motile, Gram-negative rods with peritrichous flagella, and are assigned to the *Enterobacteriaceae* family mainly on the basis of shared biochemical characteristics. Most significantly, they are characterized by their ability to oxidatively deaminate phenylalanine and, in most cases (except for some *Providencia* spp.), to hydrolyze urea (Farmer et al., 1977; Moltke, 1927; Wenner and Retger, 1919). Unusual features include the ability of *Proteus* sp. to differentiate into swarmer cells upon colonization of solid surfaces. This topic will be covered in more detail in ensuing sections.

Interest in the species comprising these genera has occurred mainly from a clinical perspective, as they include a number of significant human pathogens. In human disease, most infections are associated with prolonged hospitalization and in the case of *Proteus* and *Morganella* spp., colonization of indwelling catheters and associated urinary tract infections (UTIs).

Taxonomy and Phylogeny

Before the advent of phylogenetically based classification, an array of biochemical tests formed the basis for taxonomic classification of the genera *Proteus*, *Providencia*, and after its separation into a new genus, *Morganella*. Tables 1 and 2 list the major biochemical tests used to compare and differentiate between the genera. As shown in Table 1, the most significant shared characteristics are the (oxidative) deamination of phenylalanine and tryptophan; both are used to distinguish between these three genera and other *Enterobacteriaceae* that do not produce these deaminases. The tests for production of these deaminases were developed in the 1950s and still are widely used (Henriksen, 1950; Thibault and Le Minor, 1957). Table 2 shows the biochemical tests that are commonly used to distinguish between these genera. The only test that will distinguish *Morganella* from *Proteus* and *Providencia* is the lysine iron agar test. On the other hand, several tests will distinguish *Proteus* from *Providencia*. *Providencia* is characterized by the production of acid from a variety of sugars, whereas *Proteus* is distinguished from *Providencia* by the hydrolysis of gelatin and the production of lipase and hydrogen sulfide. The use of molecular phylogenetic methods of classification has resulted in several species being reassigned to separate genera based on relatedness at the DNA level. These changes include: the new genus *Morganella*, with transfer of the species *Proteus morganii* to it (Brenner et al., 1978); the classification of *Providencia alcalifaciens* biogroup 3 as the separate species (*Providencia rustigianii*; Higashitani et al., 1995); and the identification of a subgroup within the latter as a distinct species, *Providencia heimbachae* (Muller et al., 1986b).

Isolated in 1906 (Morgan, 1906), *Morganella morganii* was originally included in the genus *Proteus* as *Proteus morganii*. Brenner et al. (1978) showed that *P. morganii* had less than 20% homology to *Proteus* and *Providencia* spp., necessitating relocation into a new genus. The method employed by Brenner et al. in this reclassification compared the amount of single stranded ^{32}P-labeled DNA reassociating with DNA from the same source (homologous reaction), relative to the amount reassociating with DNA from other species in these genera. The resulting value was expressed as "percent DNA relatedness." *Morganella morganii* has subsequently been subdivided into two subspecies based on its ability to ferment trehalose and the results of DNA-DNA hybridization studies (Jensen et al., 1992). *Morganella morganii subsp. morganii* is composed of four biogroups (A, B, C and D), and it does not ferment trehalose, though *M. morganii* subsp. *sibonii* contains three biogroups (E, F and G) and does ferment trehalose.

Further subdivision of these species is likely with the application of more discriminatory molecular methods of characterization. As an example, the use of molecular typing by 16S ribosomal RNA (rRNA) gene fingerprints (ribotyping) has recently demonstrated that, though

Table 1. Biochemical characteristics common to the genera *Proteus*, *Morganella* and *Providencia*.

Biochemical test	*Proteus*	*Morganella*	*Providencia*
Arginine dihydrolase	–	–	–
Lysine decarboxylase	–	–	–
Ornithine deaminase	+	+	+
Phenylalanine deaminase	+	+	+
Growth on KCN	+	+	+
D-Glucose from acid	+	+	+
Acid from melibiose	–	–	–
Nitrite from nitrate	+	+	+
Oxidase production	–	–	–
ONPG production	–	–	–
Pectate utilization	–	–	–
Tartrate utilization	+	+	+

Symbols and Abbreviations: +, present; –, absent; KCN, potassium cyanide; and ONPG, *o*-nitrophenyl-β-D-galactopyranoside.

clinical isolates of *P. mirabilis*, *P. penneri*, *M. morganii* and *P. heimbachae* had identical ribotyping patterns to those of their respective type strains, those from the remaining species all exhibited heterogeneity, containing from two to four ribogroups each (Pignato et al., 1999). Thus it is possible that subdivision of members of these latter species into one or more subspecies may be considered appropriate in the future.

The genus *Proteus* presently contains four species: *P. mirabilis*, *P. vulgaris*, *P. penneri* and *P. myxofaciens*. *Morganella* has one species (*M. morganii*), whereas *Providencia* contains five species (*Providencia stuartii*, *Providencia rettgeri*, *P. rustigianii*, *P. heimbachae* and *P. alcalifaciens*; (Rozalski, 1997; Rustigian, R., and C. A. Stuart, 1945).

The 16S rRNA gene sequences of six representative species: *P. mirabilis*, *P. vulgaris*, *P. penneri*, *M. morganii*, *P. stuartii* and *P. rettgeri* were obtained and a phylogenetic tree constructed using the ClustalW alignment program (Thompson et al., 1994) and the tree-drawing program Phylodendron (Gilbert, D. G., 1989) to display the evolutionary relationships between the species in these genera. The tree (Fig. 1) indicates the close relationship between the two *Providencia* sp., as well as the similarity between two of the *Proteus* sp., *P. vulgaris* and *P. penneri*. The relationship between *P. mirabilis* and the *P. penneri–P. vulgaris* group is, however, more distant, a fact reflected in the horizontal distance between *P. mirabilis* and the other two *Proteus* sp. This greater distance at the 16S rRNA level between *P. mirabilis* and the other members of the genus *Proteus* may be a reflection of the phenotypic and physiological characteristics of *P. mirabilis*, which set it slightly apart from other members of the genus.

Electron micrographs of the six species, taken from overnight cultures grown in Luria-Bertani broth (LB; Ausubel et al., 1987), are shown in Fig. 2. Figure 2B is an electron micrograph of a *P. mirabilis* differentiated swarmer cell growing on Luria-Bertani agar (LBA). The cell elongation and hyperflagellation typical of this phenotype is clearly evident (see "Cell Differentiation and Swarming").

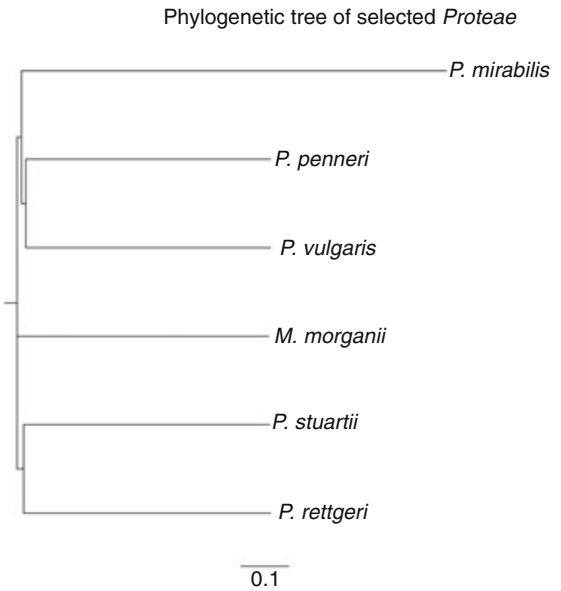

Fig. 1. Unrooted phylogenetic tree of the 16S rRNA sequences from selected *Proteus*, *Providencia* and *Morganella* sp. The tree was derived using the ClustalW alignment program (Warren, J. W., 1987a) and the tree-drawing program Phylodendron (Fletcher, M. et al., 1994). The scale bar represents the expected number of changes per sequence position.

The Genus *Proteus*

Habitat

Proteus mirabilis is the type species of the genus *Proteus* and by far the most extensively studied member of this genus. It was originally described and named by Hauser in 1885 for the Homer's *Odyssey* character who "has the power of assum-

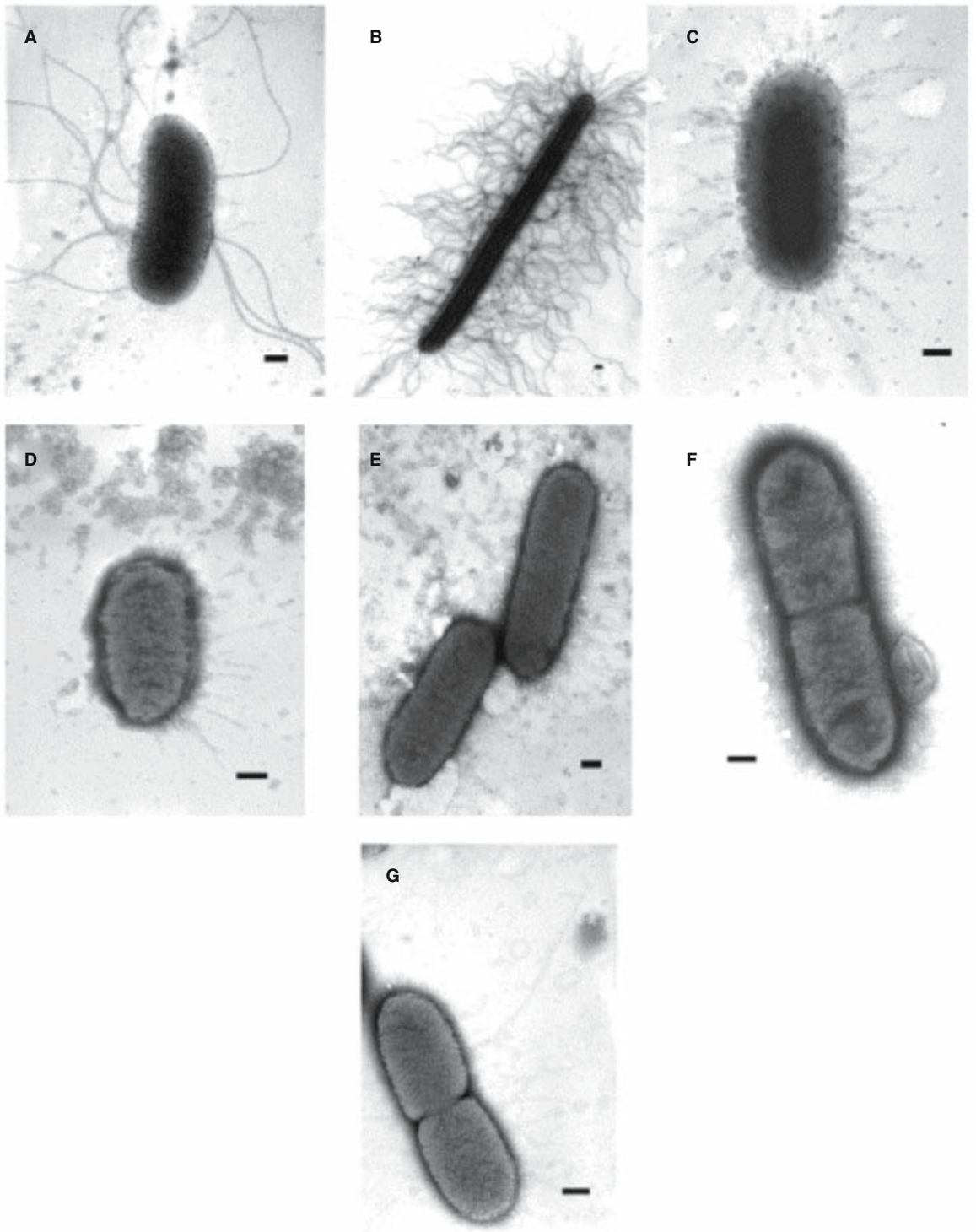

Fig. 2. Electron micrographs of selected species comprising the genera *Proteus*, *Morganella* and *Providencia*. (A) *Proteus mirabilis* swimmer cell; (B) *P. mirabilis* swarmer cell; (C) *P. vulgaris*; (D) *P. penneri*; (E) *M. morganii*; (F) *Providencia stuartii* and (G) *P. rettgeri*. The bar represents 200 nm.

ing different shapes in order to escape being questioned" (Hoeniger, 1964). Both *P. mirabilis* and *P. vulgaris* are widely distributed in the environment and have been isolated from the intestinal tract of mammals, birds and reptiles. *Proteus mirabilis*, and to a lesser extent *P. vulgaris*, are common inhabitants of the human gastrointestinal tract. *P. mirabilis*, in particular, also

may colonize the urinary tract under certain circumstances, where it is considered an opportunistic pathogen and one of the principal causes of UTIs in hospital patients with indwelling urinary catheters.

Proteus vulgaris is also a common inhabitant of the human gut and a urinary tract pathogen; however, it is associated much less commonly with UTIs than *P. mirabilis*. For example, in a study of *Proteus* species found in urine from 217 hospital patients, Senior identified 258 strains of *P. mirabilis* compared to four strains of *P. vulgaris* (Senior, B. W., 1979).

Proteus penneri was first described as a species distinct from *P. vulgaris* in 1982 (Hickman et al., 1982). It has since been isolated from a number of diverse clinical sites, including abdominal wounds, urine samples, bladder calculi, epidural ulcers and bronchoalveolar lavage fluid (Krajden et al., 1984; Krajden et al., 1987; Latuszynski et al., 1998; Li et al., 1992).

The species *P. myxofaciens* has been isolated from both living and dead gypsy moth larvae (*Porthetia dispar*; Costas, M., et al., 1993). DNA/DNA hybridization studies and phenotypic similarity have formed the basis of its inclusion in the genus *Proteus* (Brenner et al., 1978). No further investigations have been reported on its characterization or pathogenicity in the host.

Isolation and Identification

The species comprising the genus *Proteus* are distinguished biochemically from *Morganella* and *Providencia* spp. by their production of hydrogen sulfide and lipase, hydrolysis of gelatin and a lack of acid production from mannose (Table 2; Penner, J. L., and J. N. Hennessy, 1979b). Optimum growth conditions for these bacterial species are obtained at 37 C, which reflects the intestinal niche occupied by many of these bacteria. When grown in liquid media, *Proteus* sp. appears as short rods with six to ten peritrichous flagella (Fig. 2A). Most strains also can differentiate into elongated hyperflagellated cells during growth on solid surfaces such as LBA (Fig. 2B), leading to the surface translocation event known as "swarming" (see "Physiology"). Swarming behavior makes it difficult to isolate single colonies for further study; however, colony isolation on agar can be obtained through an increase in the agar concentration to 20 g/liter and the addition of 5 ml glycerol per liter of medium. This has the effect of slowing down or preventing the initiation of swarming, leading to the formation of discrete colonies (Belas, 1992).

The spot indole test has been evaluated by Bale et al. (1985) as a rapid method of distinguishing *P. mirabilis* from *P. vulgaris* (Bale et al., 1985). In this evaluation, the majority (95.7%) of *P. mirabilis* strains gave a negative spot indole result. The predictive value was greater than 99%, if only isolates representing single strains were used, whereas *P. vulgaris* isolates were 88.9% positive by this method. Differential culture media also has been developed for presumptive screening of *Enterobacteriaceae*, which in turn can distinguish between genera in this family, including *Proteus* sp. (Hawkey et al., 1986a; Houang, E. T., et al., 1999; Manafi and Rotter, 1991).

Physiology

CELL DIFFERENTIATION AND SWARMING. One significant phenotypic characteristic shared by members of the genus *Proteus* is the ability to transform into a distinctive "swarmer" cell when cultured on a solid agar-containing medium. Differentiation of *P. mirabilis* to the swarmer stage has been studied most extensively (Allison and Hughes, 1991; Belas, 1992; Williams and Schwarzhoff, 1978). When grown in liquid media, the cells exist as 1.5–2.0 m rods with 6–10 peritrichous flagella. These so-called "swimmer" cells exhibit characteristic swimming and

Table 2. Distinguishing biochemical characteristics of the genera *Proteus*, *Morganella* and *Providencia*.

Biochemical Test	*Proteus*	*Morganella*	*Providencia*
Acid from mannose	–	+	+
Color on LIA	Red	Colorless	Red
Acid from inositol	–	–	+
Acid from D-mannitol	–	–	+
Acid from D-arabitol	–	–	+[a]
Acid from adonitol	–	–	+[a]
Acid from erythritol	–		+[b]
Gelatin hydrolysis	+	–	–
Lipase production	+	–	–
H_2S production	+	–	–

Symbols and Abbreviations: +, present; –, absent; and LIA, lysine iron agar.
[a]Negative for *P. stuartii*.
[b]Negative for 10–89% of *P. stuartii* strains.

chemotactic behavior, moving away from repellents and towards attractants (Allison et al., 1993; Lominski and Lendrum, 1947). Transfer of swimmer cells onto a solid growth medium, such as that containing agar, results in a remarkable physiological and morphological transformation of the bacteria. Shortly after contact with the surface, the swimmer cells begin to differentiate into a morphologically and biochemically unique cell known as "the swarmer cell" (Fig. 2B).

Swarmer cell differentiation and swarming behavior may be broken down into discrete steps. The first step in swarmer cell morphogenesis is cellular elongation, resulting from inhibition of the septation mechanism (Armitage et al., 1974). The molecular basis that underlies the inhibition of proper septum formation is not known, but may involve SulA (also known as "SfiA") or other proteins known in *Escherichia coli* to adversely affect septum formation (Higashitani et al., 1995; Huisman and D'Ari, 1981; Huisman et al., 1984). Belas et al. (1995) analyzed several *P. mirabilis* mutants defective in swarming and many of these strains had defects in genes encoding proteins necessary for cell wall structure. Elongated swarmer cells are typically 60–80 m in length and are polyploid, with the number of chromosomes per cell being roughly proportional to the increase in length. Concurrent with this, overexpression of the flagellin protein leads to the synthesis of hundreds to thousands of new flagella required for movement across the solid surface (Armitage and Smith, 1978; Hoeniger, 1965; Hoeniger, 1966; Houwink and van Iterson, 1950; Leifson et al., 1955). Diagrammatic representations of typical swimmer and swarmer cells are shown in Fig. 3, together with a summary of the main distinguishing features of the two cell types. These flagella are composed of the same flagellin subunit as the swimmer cell flagella, and in both cases flagellin is transcribed from the *flaA* gene, indicating that the same flagellar species is produced upon surface induction (Belas, 1994a; Belas and Flaherty, 1994b; Murphy and Belas, 1999).

Studies in *P. mirabilis* and in the swarming bacteria *Vibrio parahaemolyticus* and *Serratia marcescens* have shown swarmer-cell-specific genes are expressed when swimmer cells are transferred to solid media, suspended in highly viscous broths or agglutinated with antibody to the cell surface (Alberti and Harshey, 1990; Allison et al., 1993; Belas et al., 1986; McCarter et al., 1988; Stewart et al., 1997). All of these conditions result in inhibition of flagellar rotation, leading to the conclusion that the flagella act as tactile sensors of the external environment.

Swarmer cell differentiation and swarming behavior are inextricably linked, but a differentiated swarmer cell by itself is unable to swarm

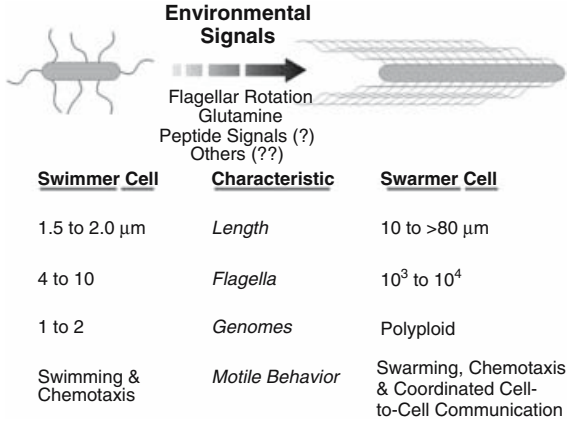

Fig. 3. The characteristics of *P. mirabilis* swarmer cell differentiation and swarming motility. Swarmer cell differentiation is controlled through a combination of sensing environmental conditions that reduce wild-type flagellar filament rotation and reacting to a specific chemical stimulus, the amino acid glutamine. The swarmer cell is characterized by an elongated polyploid cell that synthesizes numerous flagella in response to the aforementioned signals.

across a nutrient agar surface. Rather, swarming behavior is a cell-cell contact event that requires intimate contact and interaction between groups of swarmer cells to coordinate their movements (Bisset, 1973a; Bisset, 1973b; Bisset and Douglas, 1976; Brogan et al., 1971; Douglas and Bisset, 1976; Douglas, 1979). The arrangement of the coordinated swarmer cells during migration is illustrated in Fig. 4.

An important aspect of the *P. mirabilis* swarming colony pattern is its cyclic nature. As shown in Fig. 5, each cycle can be broken down into four parts, 1) swarmer cell differentiation, 2) the lag period prior to active movement, 3) swarming colony migration and 4) consolidation (where the cells stop moving and dedifferentiate back to swimmer cell morphology). During the migration phase, the fully differentiated swarmer cells move outward in unison in all directions from the original site of inoculation for a period of several hours. Movement then ceases and a process referred to as consolidation takes place (Bisset, 1973a; Bisset, 1973b; Hoeniger, 1964; Hoeniger, 1965; Hoeniger, 1966; Hoeniger and Cinits, 1969; Williams and Schwarzhoff, 1978), during which the swarmer cells dedifferentiate back into swimmer cells. After a period in this stage, the swarming phase recommences and proceeds until the next consolidation phase. The cycle of swarming and consolidation is then repeated several times, until concentric rings, formed by the swarming bacteria and delineating the phase changes, cover the agar surface (Fig. 7). The purpose of the consolidation phase has yet to be fully elucidated; however, recent work by Matsuyama et

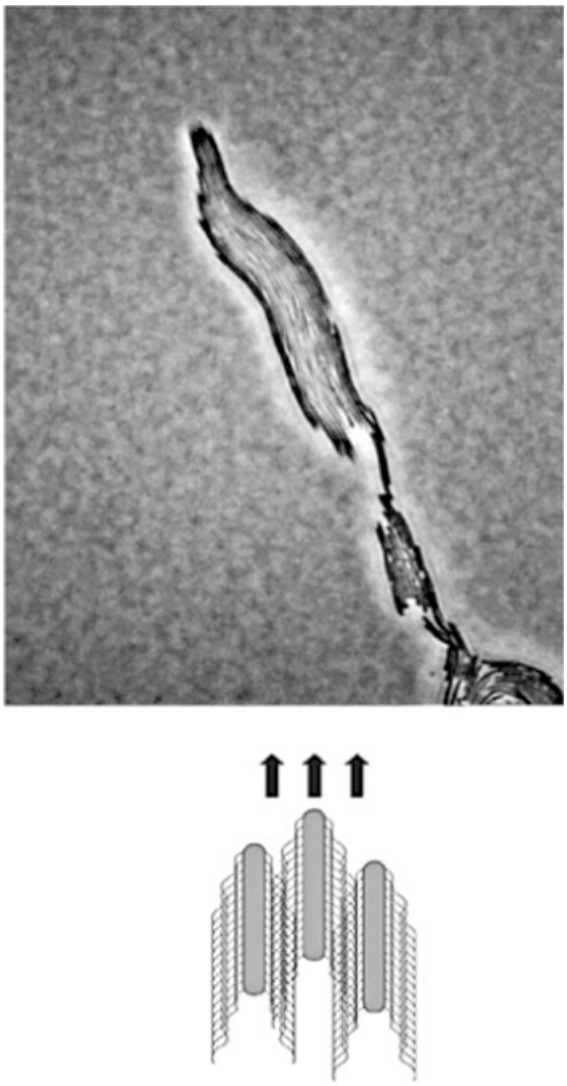

Fig. 4. The mechanics of swarming in *P. mirabilis* and the requirement for cell-cell contact. The micrograph (top) shows a finger-like projection of *P. mirabilis* swarmer cells migrating across a solid surface. The cartoon (bottom) demonstrates the arrangement of swarmer cells during coordinated motion across a solid surface. Individual cells are interlinked into groups and move en masse away from the point of inoculation, with the flagella from all cells in the group moving in unison. The arrows point in the direction of movement.

al. (2000) showed that the time course of this phase is unaffected by replica plating of the swarm edge. This indicates that consolidation is not a consequence of nutrient and metabolite changes in the medium. Figure 6 contains four video segments detailing the events associated with swarming at the microscopic level. Figure 7 shows swarming behavior during colony development and bulls-eye ring formation.

THE INFLUENCE OF SIGNAL TRANSDUCTION IN SWARMING. Swarming is, by its very nature, a surface-associated and cell-density-dependent phenomenon. Individual *P. mirabilis* cells rely on their ability to sense the surrounding environment and use these cues to trigger the development of the swarmer cell, as well as to coordinate movement of the swarm across the surface. One way this information is acquired is through monitoring the rotation of the flagella to initiate cellular differentiation (see "Cell Differentiation and Swarming"). Other methods include cell-to-cell contact with neighboring bacteria to aid in movement, the chemotactic sensing of nutrients and repellents in the external medium, and possibly through a density-dependent sensing of cell population density known as "quorum sensing." We will discuss each of these signal transduction mechanisms in turn in the next paragraphs.

Research into the relationship between chemotaxis and swarming in *P. mirabilis* (Belas et al., 1991a; Williams and Schwarzhoff, 1978) has preceded that into the relationship between chemotaxis and other swarming bacteria. Early work suggested that chemotaxis did not play a major role in the differentiation to the swarming phenotype (Williams et al., 1976). However, later studies demonstrated that nonswarming mutants of *P. mirabilis* produced by transposon insertion also exhibit deficiencies in chemotactic response (Belas et al., 1991b), suggesting that chemotactic signal transduction is important for swarming. Further work by Allison et al. (1993) has shown that the amino acid glutamine induces differentiation to the swarmer cell in *P. mirabilis* by acting as a chemoattractant. This effect may work at the level of transcription, because when glutamine is added to a defined, nonswarming medium, expression of the *flaA* (flagellin) and *hpmA* (hemolysin) genes in *P. mirabilis* increases 40-fold. The viscosity of the growth medium also affects swarming, with the addition of 3% v/v polyvinylpyrollidone (PVP) to liquid chemotaxis medium resulting in increased attraction to glutamine. Attempts to repeat these experiments in other laboratories using different strains of *P. mirabilis* have been unsuccessful, raising doubts as to whether all *P. mirabilis* strains respond to glutamine by swarming. In other swarming members of the *Enterobacteriaceae*, Harshey and Matsuyama (1994) reported a link between chemotaxis and the swarming of *E. coli* and *Salmonella typhimurium* on specific (Eiken) agar.

Quorum sensing is the ability of a bacterial population to monitor its density through expression of small extracellular signaling molecules referred to as "autoinducers." Quorum sensing was first identified and characterized in the luminescent marine bacterium *Vibrio fischeri* wherein bioluminescence is controlled by cell density and autoinducer signal transduction

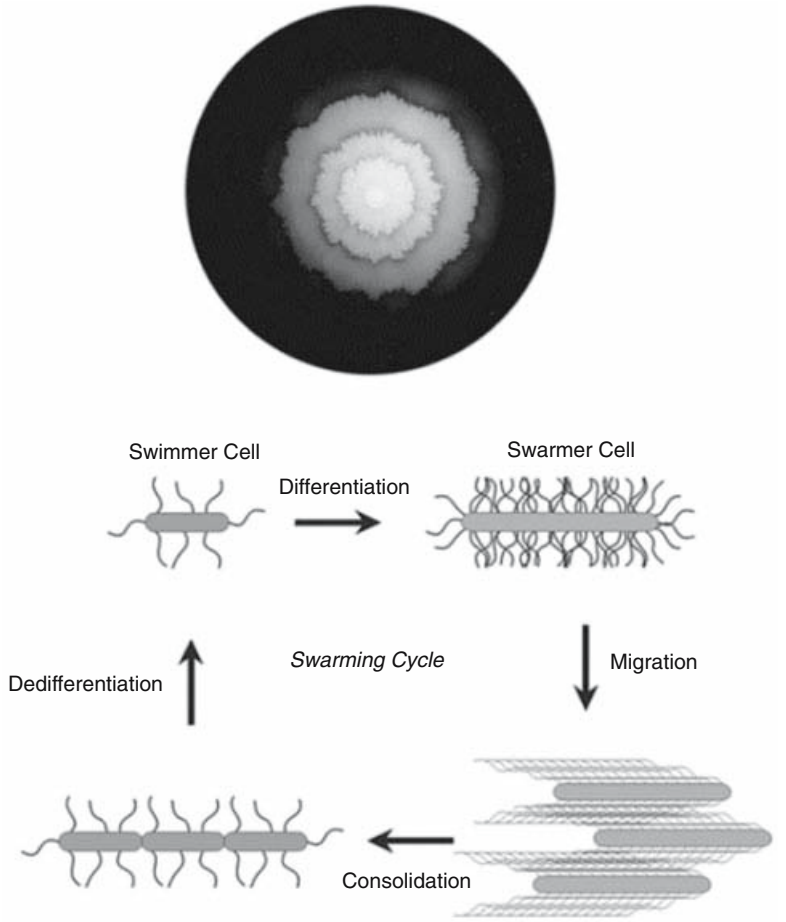

Fig. 5. The cyclic nature of *P. mirabilis* swarming behavior. Inoculation of *P. mirabilis* swimmer cells onto a solid nutrient surface such as Luria-agar induces the expression of swarmer-cell specific genes, leading to differentiation into the swarmer cell and migration away from the site of inoculation. This process is interspersed with periods of consolidation and dedifferentiation back into the swimmer cell morphology.

(A) Pm 1 colony rt.asf
(B) Pm 2 colony comp.asf
(C) Pm 3 colony comp.asf
(D) Pm 4 colony comp.asf

Fig. 6. Sequential events in the progress of the i) Cell Differentiation and Swarming phase of *P. mirabilis* differentiation. (A) A close up, in real time, of the periphery of a swarming colony. (B) Close up of colony development. (C) Swarming migration at the edges of a colony. (D) Close up of the periphery of the swarming edge in time lapse, showing cell-to-cell interaction. For the video, see the online version of *The Prokaryotes.*

(Eberhard, 1972; Eberhard et al., 1981; Nealson, 1977). The signal molecule, or autoinducer, is often a homoserine lactone with an *N*-acyl chain of variable length. In the case of *V. fischeri*, *N*-acylhomoserine lactone (AHL) can freely permeate the membrane and accumulate inside the cell until an optimum concentration is reached, whereupon it binds to a specific receptor and initiates activation of the bioluminescence genes (Kaplan and Greenberg, 1985). The specific receptors for the AHL signal are members of the LuxR family of transcription regulators. Two genes, *luxR* and *luxI*, were originally identified in *V. fischeri* as essential regulators of the AHL signaling system, and homologs of these have subsequently been identified in other Gram-negative bacteria (Stevens and Greenberg, 1998). In pathogenic bacteria such as *Pseudomonas aeruginosa*, AHL-mediated quorum sensing is involved in the regulation of multiple virulence determinants, including exoproteases, lipases and exotoxins, suggesting that a critical bacterial concentration must be attained for the deployment of its virulence factors (Parsek and Greenberg, 2000; Telford et al., 1998).

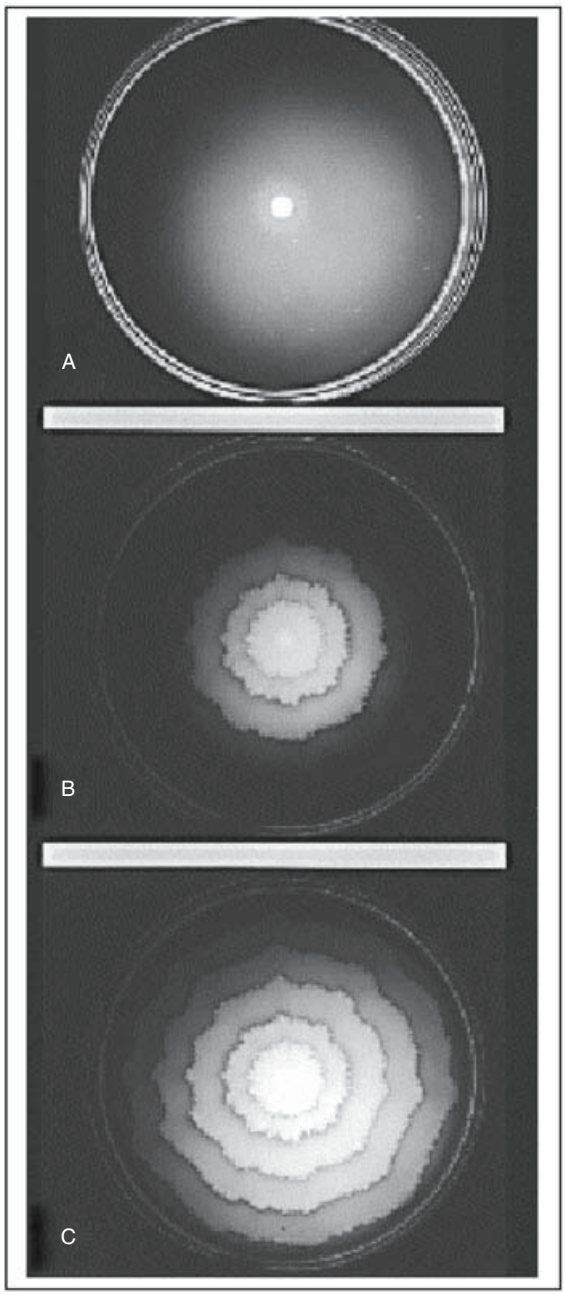

Fig. 7. Development of the bull's-eye rings of *P. mirabilis* colonies. (A–C) Sequential photographs of L-agar inoculated in the center with 5 ml of *P. mirabilis* swimmer cells and incubated at 30 C for 4 h (A), 24 h (B) and 48 h (C). (D) Video recording in time lapse showing swarming of *P. mirabilis* across the solid surface of an L-agar plate, taken over 24 hours of growth at 30 C and 80% humidity. For the video, see the online version of *The Prokaryotes.*

In *Serratia liquefaciens*, another swarming member of the *Enterobacteriaceae*, *S. liquefaciens*, Eberl et al. (1996) have demonstrated that initiation of swarmer-cell differentiation involves diffusible signal molecules that are released into the growth medium. In particular, the autoinducer *N*-acylhomoserine lactone (AHL) is required for swarming motility in this species (Givskov et al., 1998; Lindum et al., 1998). The AHL derivatives *N*-butanoyl-L-homoserine lactone (BHL) and *N*-hexanoyl-L-homoserine lactone (HHL) were identified by Eberl et al. (1996) in cell-free *S. liquefaciens* culture supernatants.

The *swrI* (swarmer initiation) gene, whose predicted translation product exhibits substantial homology to the LuxI family of putative AHL synthases, is responsible for directing synthesis of both BHL and HHL (Eberl et al., 1996). Further work by this group since has shown that the coordinate expression of *swrI* and the flagellar master operon *flhDC* is required to initiate swarming motility in *S. liquefaciens* (Eberl et al., 1999; Givskov et al., 1998; Lindum et al., 1998).

Attempts to prove the existence of an AHL-type autoinducer in *P. mirabilis* have been unsuccessful; however, evidence exists that this bacterium may utilize an alternate method of density-dependent quorum sensing. Belas et al. (1998) have characterized a gene that upon mutation decreases the length of the lag phase prior to swarming. This gene, referred to as "*rsbA*" (for regulator of swarming behavior) encodes a sensory protein displaying similarity to LuxQ and other bacterial histidine kinases of the two-component regulatory superfamily of bacterial response regulators that perform functions required for a second density-sensing system (Bassler et al., 1994; Freeman and Bassler, 1999; Lilley and Bassler, 2000). This finding suggests that RsbA may function as a sensor of environmental conditions required to initiate swarming.

Ecology

Both *P. mirabilis* and *P. vulgaris* are members of the normal flora of the mammalian intestinal tract and have been isolated from humans, dogs, monkeys, pigs, sheep, cattle, raccoons, cats, rats and other mammals. They also are distributed widely in the environment, with reservoirs in soil, water, sewage and feces (Guentzel, 1991). Other species of *Proteus* are less widely distributed. For example, *P. penneri* is absent from the intestines of livestock (Hawkey et al., 1986b), whereas *P. myxofaciens* is confined to the larvae of the gypsy moth (Cosenza and Podgwaite, 1966).

Epidemiology

Owing to their varied habitats, members of the genus *Proteus* and related genera have many possible routes of human infection. The modes of transmission may include nosocomial sources, such as hospital food and equipment, intravenous solutions and human contact through contaminated skin surfaces. Long-term indwelling catheters are a prime site of colonization and

infection for *P. mirabilis* and *P. vulgaris* (Kunin, 1989; Stickler and Hughes, 1999; Warren, 1987a).

Serological typing of *P. mirabilis* and *P. vulgaris* traditionally has been done using the slide agglutination test and the indirect hemagglutination test (Gmeiner et al., 1977; Schmidt et al., 1970). Previously, the Dienes test, in which swarming *Proteus* strains were inoculated on nutrient agar and allowed to swarm into one another, was used to distinguish between strains of these species. If a distinct line of demarcation (a Dienes line) occurred at the junction between the strains, they were considered different (Dienes, 1946). This method has fallen out of favor because of the difficulties associated with interpreting the results.

Other bacteriological typing methods also have been used, including biotyping, bacteriophage typing, and typing schemes using both bacteriocin production and bacteriocin sensitivity (Anderson and Engley, 1978; Hickman and Farmer, 1976; Kusek and Herman, 1980; Schmidt and Jeffries, 1974). In a comparative study by Kusek (1981), five bacteriological typing methods were assessed for their ability to differentiate 100 clinical isolates of *P. mirabilis*. The highest sensitivity and specificity was obtained using bacteriocin production typing, which yielded 29 distinct bacteriocin types among the 80% of strains that were typable (Kusek and Herman, 1981). Bacteriophage typing sets also have been tested as tools for differentiation of *Proteus* strains; however, a more diverse set of phages is needed to adequately differentiate between as many strains as possible (Sekaninova et al., 1994; Sekaninova et al., 1998).

Modern molecular methods employing the polymerase chain reaction (PCR) to produce DNA fingerprints and other 16S ribosomal RNA gene (ribotyping) methods of strain differentiation have been applied to distinguish *P. mirabilis*, *P. vulgaris* and *P. penneri* strains (Costas et al., 1993; Hoffmann et al., 1997; Hoffmann et al., 1998; Serwecinska et al., 1998). Hoffmann et al. (1998) compared four typing methods (including plasmid profiles, outer-membrane-protein profiles, randomly amplified polymorphic DNA PCR [RAPD-PCR], and restriction fragment length polymorphism [RFLP] on strains of *P. penneri* and found that RAPD-PCR alone, with one of two random primers, revealed 13 reproducible typeable patterns (Hoffmann et al., 1998). Thus, the RAPD method, essentially a DNA fingerprinting method using arbitrary primers (Akopyanz et al., 1992), revealed a significant DNA diversity among *P. penneri* strains that was not detected by other methods (Hoffmann et al., 1997; Hoffmann et al., 1998). The RAPD-PCR technique has the advantage of being quick and economical, with high reproducibility and typability; however, the choice of primers is critical to obtaining discriminating results (Madico et al., 1995).

Pathogenicity

The incidence of UTI involving *P. mirabilis* or *P. vulgaris* is lower than that for *E. coli*; however, *P. mirabilis* infections are more likely to be long-term and persistent, and to lead to greater complications threatening the patient's health than those involving *E. coli* (Mobley and Warren, 1987). The majority of *Proteus* infections are associated with prolonged hospitalization and the complications of long-term urinary catheterization. The complications that can result from *Proteus* UTI include catheter and urinary tract obstruction, kidney stone formation (urolithiasis), pyelonephritis, fevers and bacteremia (Mobley and Warren, 1987; Rubin et al., 1986; Senior, 1983; Story, 1954; Warren et al., 1987b). In serious cases of *Proteus* UTI, chronic renal inflammation, vasicoureteral reflux and renal failure are frequently observed (Cohen and Preminger, 1996; du Toit et al., 1995; Warren, 1987a). The sites of UTI and the respective complications resulting from infection at these sites are shown in Fig. 8, whereas Fig. 9 provides a breakdown of the causes of *P. mirabilis* UTI.

VIRULENCE FACTORS. At least ten virulence factors potentially contributing to the pathogenicity of *Proteus* sp. have been identified. The majority of these virulence factors, with the exception of the fimbriae, are expressed during swarmer cell differentiation and swarming behavior. These virulence factors can be divided into two groups: 1) proteins, enzymes and other secreted products, and 2) surface structures. In terms of their relevance to pathogenesis, the most significant virulence factors (in order of importance) are: urease, ZapA (a protease that specifically degrades immunoglobulins IgA and IgG), lipopolysaccharide, outer-membrane proteins, and hemolysin. The most significant surface structures, in order of importance to pathogenesis, are the flagella and associated swarming phenotype of *P. mirabilis* and *P. vulgaris*, and several types of fimbriae, including; mannose-resistant *Proteus*-like fimbriae (MR/P), mannose-resistant *Klebsiella*-like fimbriae (MR/K), *P. mirabilis* fimbriae (PMF), nonagglutinating fimbriae (NAF), and an uncharacterized fimbrial type with a 24-kDa major subunit (also referred to as "F24"). The potential of these virulence factors in *Proteus* to cause disease has been a prime area of study and the major conclusions in each case are presented here.

Urease. Urea is a by-product of nitrogen metabolism that is ubiquitous in a wide range of eukaryotes and prokaryotes. The enzyme urease breaks down urea to ammonia and carbon dioxide. These end products have the effect of

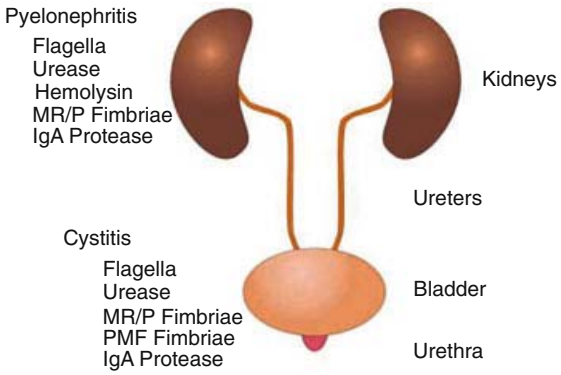

Fig. 8. The human urinary tract, showing the sites of *P. mirabilis* infections, hence the diseases resulting from infection, and the virulence factors associated with pathogenesis of disease at the respective sites (see "Pathogenicity").

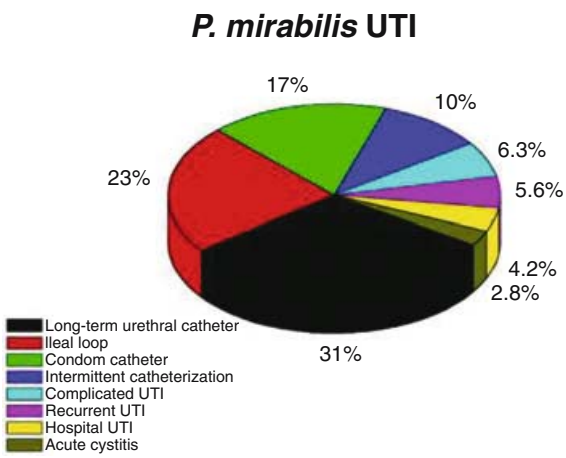

Fig. 9. The causes of *P. mirabilis* urinary tract infections (UTI) in humans, compiled using epidemiological data from hospitalized patients. Adapted from Mobley and Warren (1987).

increasing the pH, which in turn augments the survival of bacteria such as *Helicobacter pylori* to create a less acidic environment that may be more suited for colonization (Gomez-Duarte et al., 1998; Kuwahara et al., 2000; Lee et al., 1999). In other microbes, ureases play an important role in utilization of environmental nitrogenous compounds and urea-based fertilizers. At the same time, the production of urease by *P. mirabilis* and *P. vulgaris* may contribute to the development of urinary stones and pyelonephritis, as mentioned earlier. This is one possible reason why *Proteus* infections cause more cytological damage than *E. coli* infections (Cohen and Preminger, 1996; du Toit et al., 1995; Johnson et al., 1993; Mobley and Hausinger, 1989).

Early studies using *P. mirabilis* treated with urease inhibitors established a link between urease and colonization of rat urinary tracts. In these studies, the renal tissue of control-infected rats contained a far higher number of bacteria and had greater tissue damage than did those of rats infected with inhibitor-treated *P. mirabilis* (Musher et al., 1975). Further evidence of the role played by urease in *P. mirabilis* pathogenesis has been demonstrated by comparative histological examination of renal tissues postinfection by either the wild type, parental strain, or an isogenic urease-negative mutant using a mouse model of ascending UTI (Johnson et al., 1993; Jones et al., 1990). Mice challenged with the isogenic urease mutant developed significantly less bacteriuria and urinary stones compared to the parent strain. The parent strain also showed greater persistence in the bladder and kidney than did the strain lacking urease (for reference to sites of infection, see Fig. 8).

IgA and IgG Proteases. Secretory immunoglobulins of the IgA class are produced by mucous tissue and are particularly resistant to enzymatic breakdown by proteases. The ability to degrade a host's secretory IgA may provide a microorganism with an advantage by evading the host immune response, thus gaining valuable time for the bacterium to establish a foothold for colonization. Many pathogenic bacteria that invade mucosal tissues, such as the epithelial lining of the intestine and urogenital tract, have potent, extracellular IgA-degrading proteases, whereas nonpathogenic counterpart species in the same genus often do not. For example, pathogenic species of *Neisseria*, such as *N. gonorrhoeae* and *N. meningitidis*, possess IgA-degrading proteases, though nonpathogenic species (including *N. lactamica* and *N. sica*) do not (Kilian et al., 1983). The possession of IgA protease by certain members of this genus may thus be critical in providing these bacteria with an advantage to overcome the host humoral immune response during infection.

A protease capable of degrading two IgA subclasses (IgA1 and IgA2) as well as IgG has been identified in *P. mirabilis* (Loomes et al., 1990; Milazzo and Delisle, 1984; Senior et al., 1987b). Subsequent work by Wassif et al. (1995) has resulted in the characterization of this protease (referred to as "ZapA" and encoded by the *zapA* gene) as a metalloprotease of ca. 50 kDa. To investigate whether *zapA* expression correlates with another known virulence-enhancing phenomenon, swarmer-cell differentiation (see "Flagella and swarming"), Walker et al. (1999) measured the expression of *zapA* during swarmer-cell differentiation. The data obtained suggest that *zapA* expression is tightly coordinated not just with swarmer-cell differentiation, but with swarming behavior as well. Also, ZapA proteolysis is not essential for swarming, because ZapA$^-$ strains were shown to produce wild-type swarmer cells and swarming colonies.

Both *P. vulgaris* and *P. penneri* also have been reported to possess IgA proteases. In a survey of protease production amongst 24 *P. vulgaris* strains, Senior et al. (1988) found that half of them produced IgA protease. Each of five of the *P. penneri* strains surveyed in the same study also produced IgA protease. Subsequent purification and comparative analysis of IgA protease from *P. mirabilis*, *P. vulgaris* and *P. penneri* showed that they shared similar electrophoretic patterns on sodium-dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE) gels, with only slight differences in protein band mobility (Loomes et al., 1992).

Lipopolysaccharide and Outer-Membrane Proteins. During infection, bacterial lipopolysaccharide (LPS) is a primary target antigen (O-antigen) for host immunologic responses. Bacterial LPS activates macrophages to produce toxic oxygen radicals, interleukin-1 and tumor necrosis factor, leading to a wide range of effects in the host, including hypertension, fever and lethal shock (Hamilton and Adams, 1987; Rietschel et al., 1994). By way of example, the effect of *P. mirabilis* LPS on pig blood platelets is akin to that of thrombin (a strong platelet agonist), stimulating the enzymatic cascade leading to platelet aggregation (Wachowicz et al., 1998).

The outer membrane of Gram-negative bacteria contains several major proteins that are complexed with other membrane components such as LPS and phospholipid. The polysaccharide chains of the different species of *Proteus* LPS contain sufficient structural differences to result in an antigenically heterogeneous genus. These differences have been used to cluster *P. mirabilis*, *P. vulgaris*, and *P. penneri* strains into serogroups based on their agglutination when mixed with antibodies directed against specific species of LPS molecules (Kotelko, 1986; Penner and Hennessy, 1980a; Perch, 1948; Zych and Sidorczyk, 1989). Certain LPS epitopes have been investigated to determine their role in antigenic specificity. The particular groups on the oligosaccharides found to play a dominant role in the specificity of *P. mirabilis* and *P. penneri* LPS are the amide of D-galacturonic acid with L-lysine α-D-GalA-(L-Lys) (and the amide of D-galacturonic acid with L-threonine α-D-GalA-[L-Thr]), respectively (Radziejewska-Lebrecht et al., 1995; Sidorczyk et al., 1995).

Specific *P. mirabilis* outer-membrane proteins (OMPs) have been the targets of study with respect to their effects on the host immune response. One particular 39-kDa major OMP of *P. mirabilis* (subsequently identified as "OmpA") has been shown to greatly enhance the host IgG response for LPS in mice when complexed to LPS (Karch and Nixdorff, 1981; Karch and Nixdorff, 1983). Also, LPS is an activator of macrophages, another important component of the host immune response, through their production of toxic oxygen radicals, interleukin-1 and tumor necrosis factor (Guthrie et al., 1984). Weber et al. have shown that OmpA inhibits the LPS-induced oxidative response and interleukin-1 production of murine macrophages when complexed to LPS, thus acting as a modulator of the interaction of LPS with macrophages (Weber et al., 1992; Weber et al., 1993).

Hemolysin. Bacterial hemolysins are frequently involved in the destruction of erythrocytes during infection and have been shown to contribute to the invasiveness and pathogenicity of several bacterial species (Braun and Focareta, 1991; Braun et al., 1993; Goebel et al., 1988; Menestrina et al., 1995). The importance of hemolysin in the virulence of *E. coli* was demonstrated through the isolation, cloning and transfer of hemolysin genes from virulent strains to avirulent ones (Hacker et al., 1983; Welch et al., 1981).

The association between hemolysin and virulence in *Proteus* sp. has proved more difficult to establish. Hemolytic activity is the least significant virulence factor in strains of *P. mirabilis* recovered from the CBA mouse model of ascending UTI (Fig. 10). However, early work by Peerbooms et al. (1985) showed a correlation between the hemolytic activity of *P. mirabilis* and its virulence in mice (Peerbooms et al., 1983). Hemolytic strains of *P. mirabilis*, *P. vulgaris* and *P. penneri* demonstrated markedly greater invasiveness of human and sheep erythrocytes in

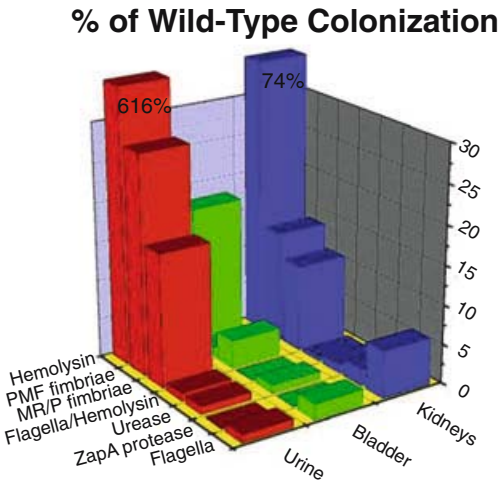

Fig. 10. The major virulence factors of *P. mirabilis* and their influence on urinary tract pathogenesis using the CBA mouse model of ascending UTI. Data are represented as percent survival of each isogenic mutant strain compare to the survival of wild-type parental strain postinfection in the CBA mouse model of UTI. Adapted from Mobley and Warren (1987).

vitro in work by Rozalski and colleagues (Rozalski et al., 1986; Rozalski and Kotelko, 1987).

At the molecular level, the hemolysin structural genes (*hlyA* and *hlyC*) and the principal secretion gene (*hlyB*) of *E. coli* can be functionally complemented by the homologous genes from *P. mirabilis*, *P. vulgaris* and *M. morganii*, suggesting a functional relatedness between the three components in the two species. A second *E. coli* secretory gene (*hlyD*) is present in *P. vulgaris* and *M. morganii*, but absent from *P. mirabilis* (Koronakis et al., 1987; Koronakis and Hughes, 1988a; Koronakis et al., 1988b). The *E. coli* hlyD gene is required for secretion of hemolysin (Pimenta et al., 1999). This finding may explain why the secreted hemolytic activity of *P. mirabilis* remains cell-associated rather than being released into the surrounding medium. This possibility has been supported by subsequent investigations showing that the secreted hemolysin (HpmA) of *P. mirabilis* and *P. vulgaris* is genetically distinct from that of *E. coli* (Swihart and Welch, 1990b; Welch, 1987). *Proteus mirabilis* HpmA is cytotoxic for a variety of cell lines, including cultured human renal proximal tubular epithelial cells (Mobley et al., 1991; Swihart and Welch, 1990a). As mentioned above, colonization by isolates showing hemolysin activity forms by far the greatest proportion of *P. mirabilis* isolates recovered from the urine, kidneys and bladder of CBA mice with UTI (Fig. 10; Mohr O'Hara, C., et al., 1999). However, HpmA activity in such clinical isolates does not appear to be crucial to the development of pathogenesis (Mobley and Chippendale, 1990). Thus, hemolysin is not considered as important a virulence factor in *P. mirabilis* pathogenesis as flagella or urease (Mobley and Belas, 1995). In the case of *P. vulgaris*, hemolysin production, measured as hemolytic titer (Peerbooms et al., 1983), was found by Peerbooms et al. (1985) to be significantly lower than that for *P. mirabili*, thus reducing the relevance of hemolysin in UTI for this species.

Structures Involved in the Virulence of *Proteus* sp. Flagella and Swarming. It is generally accepted that flagella and swarming behavior play some role in the pathogenicity of *P. mirabilis*, and several studies support this hypothesis. For example, in work by Allison et al. (1992) using two different human uroepithelial cell lines (EJ/28 and 5637) and *P. mirabilis* mutants lacking flagella (Fla$^-$), the loss of flagella resulted in a noninvasive bacterium when compared to the wild-type parent. In the same study, the ability to invade the EJ/28 and 5637 cell lines was closely identified with differentiated swarmer cells, which were 15-fold more invasive than undifferentiated swimmer cells. In in vivo studies using a mouse model of UTI, Mobley et al. (1996) reported a 100-fold lower recovery of a Fla$^-$ mutant defective in flagellar filament synthesis when compared to the parent strain. While nonflagellated strains are less invasive, flagella do not appear to be absolutely required for virulence. Zunino et al. (1994) have found that a naturally occurring nonmotile strain could infect mice and cause UTI, whereas Legnani-Fajardo et al. (1996) reported similar results with an isogenic mutant lacking flagella.

The differentiated swarmer cell (see "Physiology") probably provides *P. mirabilis* and other swarming species such as *V. parahaemolyticus* with the advantage of rapid colonization during pathogenesis. Apart from the benefits of motility and adherence due to hyperflagellation, swarmer cell differentiation in *P. mirabilis* coincides with increased expression of several virulence factors (see "Virulence Factors") and has been linked to the expression of extracellular (capsular) polysaccharide. Evidence for this has been provided in studies by Gygi et al. (1995) utilizing transposon mutagenesis of a gene coding for a cell surface (capsular) polysaccharide in *P. mirabilis*. The mutants clearly showed retardation in translocation velocity across solid media and were attenuated in their ability to establish UTI in mice (Allison et al., 1994; Gygi et al., 1995).

Fimbriae. Collectively, the different species of fimbriae, which can be distinguished from flagellae by their shorter "spiked" appearance (Fig. 2C) are important in the attachment of the bacteria to the epithelial cell surfaces and colonization of the surrounding tissues (Silverblatt, 1974). Fimbriae appear to be differentially expressed at particular stages of the swarming cycle (Fig. 5) and are absent on hyperflagellated swarmer cells (Hoeniger, 1965; Latta et al., 1999). *Proteus mirabilis* produces MR/P, MR/K, NAF and PMF fimbriae (Adegbola et al., 1983; Bahrani et al., 1993a; Bahrani et al., 1993b). Both MR/P and MR/K fimbriae also have been shown to function as hemagglutinins and are highly immunogenic.

Mutants defective in the synthesis of various fimbrial species have been used to assess the role of each fimbrial type during *P. mirabilis* UTI. In particular, MR/P mutants (MrpA$^-$) have been constructed by allelic exchange and are between 6 and 28–fold less efficient in colonizing mouse urinary tracts than the parental strain of *P. mirabilis* (see also Fig. 10). This result is supported by histopathology results showing less damage to the uroepithelium and no signs of pyelonephritis during colonization by Mrp– strains (Bahrani et al., 1994). In studies on PMF fimbriae, isogenic PmfA$^-$ mutants were found to colonize the bladder at lower levels than the wild-type parent, but bacterial colonization of the kidney was not affected by loss of this fimbrial type (Massad et al., 1994). The involvement of NAF fimbriae in bacterial adherence also has been demonstrated

in *P. mirabilis* strains that express NAF as their only fimbrial species. These studies have shown that NAF provide strong adherence to a number of mammalian cell lines in vitro, including uroepithelial cells (Latta et al., 1998; Tolson et al., 1995; Tolson et al., 1997). While it would appear that the production of fimbriae offers the bacterium a distinct advantage for survival in colonizing host tissues, one of the disadvantages of fimbriae to the potential colonizer is that they render the bacteria more susceptible to phagocytosis (Silverblatt and Ofek, 1978). Furthermore, the presence of fimbriae does not equally enhance adherence to all cell types. For example, the use of MR/P fimbrial mutants (*mrpA*$^-$) in the CBA mouse model of ascending UTI has shown that the loss of MR/P fimbrial expression does not completely prevent colonization of renal tissue in *P. mirabilis* (Bahrani et al., 1994).

The Genus *Morganella*

Habitat

The sole species in this genus, *Morganella morganii*, is a commensal organism that can rapidly colonize the host gut with an accompanying hypertrophy of Peyer's patches and development of specific IgA responses in the lamina propria cells (Shroff et al., 1995). Strains of *M. morganii* also are known to infect the human urinary tract, respiratory system and blood, though they have only been recovered occasionally from these sources (Braunstein and Tomasulo, 1978).

Isolation and Identification

Isolation of *M. morganii* is accomplished using media for the routine isolation of *Enterobacteriaceae*. Enrichment media for culturing *M. morganii* from fecal specimens frequently include tetrathionate and selenite, which are added to nutrient broth (Rustigian and Stuart, 1945). The biochemical tests used to identify and distinguish *M. morganii* are shown in Table 2. It should be noted that although *M. morganii* is urease and indole positive, it does not swarm and is negative for most of the biochemical reactions characteristic of the *Proteus* spp.

The isolation of atypical *M. morganii* strains whose characteristics differ from those listed in Table 2 has resulted in the creation of a number of distinct biogroups that subdivide the species. Hickman et al. (1980) described 19 strains that were lysine positive and fermented glycerol within 24 h, in contrast to the type strain of *M. morganii*, which is lysine negative and ferments glycerol slowly or not at all. Another group of 14 *M. morganii* strains was found to be ornithine negative, whereas the type strain is ornithine positive. Because both groups were closely related to *M. morganii* by DNA-DNA hybridization, they were considered distinct biogroups. There are currently seven recognized biogroups, based on ornithine and lysine decarboxylase reactions; however, some strains may carry plasmid-borne genes that code for these enzymes (Cornelis et al., 1981). Other phenotypes also have been used to distinguish the various biotypes. Janda et al. (1996) found resistance to the antibiotic tetracycline to be a useful distinguishing characteristic in their classification of 73 strains of *M. morganii* principally recovered from routine clinical specimens. The future subdivision of *M. morganii* into two or more species based on differences between biotypes remains a distinct possibility as more characteristics are used to distinguish between the biotypes.

Ecology

Morganella morganii occurs in low numbers in the feces of healthy humans and animals, including dogs, cattle and chickens (Hawkey et al., 1986b; Phillips, 1955; Prasad and Pandey, 1966; Tanaka et al., 1995). Its habitat may be more far-reaching, as *M. morganii* strains have been isolated from snakes, chickens suffering from respiratory disease, and ocular lesions of harbor seals and elephant seals (Lin et al., 1993; Muller, 1972; Thornton et al., 1998). It is unclear whether *M. morganii* was the causative agent in these diseases or an opportunistic colonizer of the previously diseased tissue.

Epidemiology

The incidence of *M. morganii* in diarrhea has been studied by Muller (1986a). In this study of fecal specimens from diarrheal and non-diarrheal patients, Muller isolated *P. mirabilis* and *M. morganii* more frequently from human diarrheal cases than from the stools of healthy individuals. These results agree with the data from earlier studies that showed a similar pattern of *M. morganii* recovery from diarrheal patients (Ahren, 1990; Das, 1996).

Epidemiological typing schemes have been developed for *M. morganii* based on the bacterial somatic and flagellar (O and H, respectively) antigens (Penner and Hennessy, 1979b; 1979d; Rauss and Voros, 1959; Rauss and Voros, 1967a; Rauss and Voros, 1967b; Rauss et al., 1975). The typing of *M. morganii* strains using the lytic activity of bacteriophages has been investigated in detail by Schmidt and Jeffries (1974). Seven phages were isolated from three *M. morganii* strains and these phages were successfully used to differentiate 13 of the 19 *M. morganii* strains in the study. Furthermore, lytic patterns remained stable in randomly selected *M. morganii* isolates retested several weeks later. While

phage typing is no longer widely used in the United States, these methods are still in favor in many East European countries.

A bacteriocin (referred to as "morganocin") typing scheme for *M. morganii* based on production of and sensitivity to the protein has been described by Senior (Senior, 1987a). A total of 160 *M. morganii* strains were tested for sensitivity to morganocin and classified according to morganocin production and sensitivity. Most strains (97.5%) were sensitive to several different types of morganocins. Subsequent typing studies found that a combination of three distinct methods (bacteriocin typing, O-antigen serotyping and protein profiling) could be used to achieve a much greater degree of strain discrimination, especially inasmuch as protein profiling appears to be independent of O-serotype and bacteriocin type (Senior and Voros, 1989; Senior and Voros, 1990).

Pathogenicity

While the etiological role of *M. morganii* in diarrhea has not yet been firmly established, it is consistently recovered from the feces of diarrheal patients suggesting an involvement in the disease. Furthermore, some researchers have found *M. morganii* to be the sole potentially pathogenic bacterial species in the feces of diarrheal patients, thus strengthening its claim to being the cause of the disease in these cases (Rauss, 1936; Senior and Leslie, 1986).

In spite of the involvement of *M. morganii* in diarrheal disease, this species is less likely to be the causative agent of human UTI than *P. mirabilis*. This is mainly due to the slower growth rate of *M. morganii* in urine compared to that of *P. mirabilis* and the noninducible nature of its urease (Senior, 1983). Although not a major contributor to human UTI, *M. morganii* has been implicated in outbreaks of septicemia and bacteremia in humans and animals (Bagel and Grossman, 1985; Barragan Casas et al., 1999; Heard et al., 1988; McDermott and Mylotte, 1984; Novak and Seigel, 1986; Rowen and Lopez, 1998). *Morganella morganii* bacteremia most commonly occurs in postoperative patients who receive β-lactam antibiotics. McDermott and Mylotte (1984) investigated the case histories of 19 documented episodes of *M. morganii* bacteremia in 18 hospital patients and showed that the majority of infections were either postoperative or had associated wound injuries. They concluded that *M. morganii* is an infrequent cause of bacteremia and its presence in blood cultures may be an indicator of an environment, such as surgery, that is conducive for an outbreak of nosocomial infection.

VIRULENCE FACTORS. There is very little known about the virulence factors involved in *M. morganii* pathogenesis. Despite the paucity of reports, the most significant of these virulence factors are described below, though it should be noted that the data supporting the efficacy of each virulence factor may be minimal or not as substantial as those for the virulence factors of *P. mirabilis*, for example.

Hemolysin. The synthesis of active intracellular hemolysin (Hly) by *M. morganii* follows a pattern similar to that seen with the hemolysins from *E. coli*, *P. mirabilis* and *P. vulgaris*. Emody et al. (1980) measured the virulence of *M. morganii* strains due to hemolysin. Hemolysin (Hly^+) wild-type strains and Hly^+ transconjugants were found to be more virulent than Hly^- in mice and chick embryos. This enhanced virulence seems to be connected with the production of a diffusible α-hemolysin. There is an important difference between the hemolysins of *M. morganii* and those of *P. mirabilis* and *P. vulgaris*. Koronakis et al. (1987) found that hemolytic activity in all *M. morganii* strains tested was cell free (extracellular), whereas in all *P. mirabilis* and 60% of *P. vulgaris* strains, hemolysin was only found associated with intact cells. The presence of the secretory gene *hlyD* in *M. morganii*, may explain the difference in secretion patterns observed in these two genera.

Urease. While both *P. mirabilis* and *M. morganii* possess urease activity with some similarities, there are also significant differences between the enzymes that may play a role in choice of habitat and pathogenicity. possess ureases, there are distinct differences between the enzymes in the two species that may play a role in habitat and pathogenicity. For example, *M. morganii* urease possesses a higher affinity for urea than *P. mirabilis* urease, but the latter hydrolyzes urea at a rate 6- to 25-fold faster (Jones and Mobley, 1987). *Morganella morganii* survives in acidic conditions and its ureases have been shown to be activated in vitro by low pH, with an unusually low activity optimum of pH 5.5 (Young et al., 1996). In this respect, the urease from *M. morganii* is similar to the urease of *Y. enterocolitica* and *H. pylori*, both of which can hydrolyze urea at significantly higher rates under acidic conditions when compared with other pathogenic bacteria. A critical assessment of whether the *M. morganii* urease is a significant factor in the pathogenesis of this species will ultimately require in vivo studies with urease-negative mutants.

The Genus *Providencia*

Habitat

The members of the genus *Providencia* are all facultative anaerobes and motile by peritrichous flagella (Figs. 2F, G); however, they do not

exhibit cellular differentiation and swarming behavior. Urease production is not characteristic of all *Providencia* species, with only *P. rettgeri* strains producing urease (Brenner et al., 1978).

Providencia stuartii is found most frequently in hospital patients with urinary tract infections. Less frequently, it is found in respiratory and skin infections (Stickler et al., 1985; Warren, 1986). *Providencia alcalifaciens* is generally isolated from stool samples along with other enteric pathogens. A similar species (*P. rustigianii*), was originally isolated from human feces as *P. alcalifaciens* biogroup 3 (Ewing et al., 1972) and subsequently redesignated as a separate species (Hickman-Brenner et al., 1983). It has since been isolated from a range of human and animal sources, including (oddly enough) penguin feces (Costas et al., 1987; Muller, 1983). While this species can colonize the human gastrointestinal tract and some of the sources included diarrheal patients, no direct link with diarrhea has been established.

The third, taxonomically defined species of *Providencia*, *Providencia heimbachae*, was first described by Muller 1986 (Muller et al., 1986b) who isolated it from penguin feces and from an aborted bovine fetus. A strain of this species recently has been isolated from humans, specifically, the stool of a patient with idiopathic diarrhea (Mohr O'Hara et al., 1999). It should be noted, however, that this strain possesses important biochemical and physiological differences compared to the type strain of Muller (Muller et al., 1986b). While the type strain is positive for phenylalanine deaminase, gas production from glucose and fermentation of maltose and D-mannitol, the human isolate is negative for these tests. Furthermore, motility is only observed after 6 days for the human isolate, compared with 4 days for the type strain.

Isolation and Identification

Isolation of *Providencia* sp. is routinely performed using bacteriological nutrient media for the general identification of *Enterobacteriaceae*, and, together with the biochemical tests shown in Table 2, to descriminate this species from other enteric forms. Machtiger et al. (1971) found that *P. stuartii* and *P. alcalifaciens* required five amino acids (isoleucine, leucine, valine, glutamic acid and cystine), as well as niacin, for growth on minimal medium containing glucose as a carbon source (Machtiger and O'Leary, 1971). Hawkey et al. (1982b) used a selective and differential enrichment medium to isolate low numbers of *P. stuartii*. Thaller et al. (1992) used a modified MacConkey containing methyl green phosphatase (MGP) to successfully identify 100% of *P. stuartii* isolates from 1,278 seeded urine samples. By comparison, standard MacConkey medium and the API20E (API System, Bio Merieux Vitec, Inc. Hazelwood, MO.) were only able to identify 82.5% of the same isolates. *Providencia stuartii* and *M. morganii* are the only phosphatase-positive members of the *Enterobacteriaceae*, and MGP distinguishes phosphatase producing colonies on Luria-Bertani-agar by their green pigmentation or halo (Pompei et al., 1990; Satta et al., 1979), while on MacConkey medium the same colonies appear red. Thaller et al. (1992) also added methyl blue to MCP to distinguish lactose-positive colonies (violet) from the phosphatase producers.

A simplified method for the identification of *P. alcalifaciens* has been described by Senior (1997). This method relies on the probability that *P. alcalifaciens* is the only oxidase-negative organism likely to be present in fecal cultures enriched in tetrathionate broth, which also is unable to ferment the mannitol, xylose and galactose present in the medium. When grown on this agar-solidified medium, colonies of *P. alcalifaciens* appear red, in contrast to the colorless colonies of non-*P. alcalifaciens* bacteria that ferment the three sugars. Extensive tests by Senior showed the medium to be both highly specific and sensitive in detecting *P. alcalifaciens* (Senior, 1997). A number of commercial kits have become available for identification purposes and have been utilized, with varying success, for identification of *P. rustigianii* (Kitch et al., 1994; Piccolomini et al., 1991).

Ecology

The emergence of *P. stuartii* as a significant hospital pathogen since the 1970s has led to efforts to uncover the natural sources and reservoirs of this species. Early work had discounted the gastrointestinal tract as a potential site owing to the lack of isolates obtained using traditional fecal culture methods; however, Hawkey et al. (1982a) demonstrated fecal colonization by *P. stuartii* using a combination of pre-enrichment and selective media. Moreover, the long-term-catheterized human urinary tract appears to offer an attractive niche to this species. Results from studies of patients catheterized for long periods indicate that *P. stuartii* can often be found on catheter surfaces as frequently as more familiar uropathogens such as *E. coli*, *P. mirabilis*, *Enterococcus* sp., and *P. aeruginosa* (Warren, 1986). It also has been isolated from burn and wound infections and bacteremias, which further emphasizes the pathogenicity of this species (Penner, 1984).

Providencia rettgeri similarly has emerged in recent years as a nosocomial pathogen of clinical importance. This species has been isolated with

regularity from the urinary tract of catheterized or immunocompromised patients and less frequently from human feces, bile and sputum (Bauernfeind and Wiersma, 1977; Cipriani et al., 1988; Gunalp, 1979; Mino et al., 1997). Of the remaining species, *P. alcalifaciens* is an intestinal colonizer and a recognized cause of gastroenteritis (Janda et al., 1998). *Providencia rustigianii* also has been confirmed as a gastrointestinal tract inhabitant and often is found in the intestinal tract of mammals, such as humans and pigs, and even in arctic birds, e.g., penguins. The true ecological niche inhabited by *P. heimbachae* has yet to be determined, but the evidence at hand suggests that it may inhabit the gastrointestinal tract, as is common for other *Providencia* species (Costas et al., 1987; Higashitani et al., 1995; Mohr O'Hara et al., 1999).

Epidemiology

Both the indirect hemagglutination test and the indirect hemagglutination inhibition test have been used to type *Providencia* sp (Levina et al., 1980). These tests are frequently useful in distinguishing between individual *Providencia* serogroups (Levina et al., 1980). Antigenic serotyping methods based on the flagellar (H), LPS (O) and capsular (K) antigens also have been applied to *P. stuartii* strains. Such serotyping may be particularly useful in identifying specific strains endemic in different hospitals. Penner and colleagues have used O serotyping successfully (Penner and Hennessy, 1979a; Penner and Hennessy, 1979b; Penner et al., 1979c) to type strains from *P. stuartii*, *P. rettgeri* and *P. alcalifaciens* (Penner and Hennessy, 1979a; Penner and Hennessy, 1979b). In the O serotyping of *P. stuartii* isolates, Penner and his colleagues found that 97% of 829 isolates tested fell into one of 14 O-antigen serotypes. However, the somatic (O) antigen serotyping scheme for 54 isolates of *P. rettgeri* based upon a set of 93 O-antigens, also developed by Penner and Hennessy (1979b), failed to detect a single predominant serotype. While the small size of the strain pool may have influenced this latter result, it is possible that infection by *P. rettgeri* is not due to a few serotypes, as has been found in is much less strain specific than that by *P. stuartii*. Similarly, in the serotyping of *P. alcalifaciens*, Penner (1979c) detected 29 serotypes among 82 typeable isolates. Serotyping schemes for the remaining species of *Providencia* have yet to be developed but will undoubtedly employ similar approaches to those used for other *Providencia* species.

Bacteriophage and bacteriocin typing methods for *Providencia* sp. have yet to be developed, though a number of studies have looked for and isolated bacteriophages from both *P. stuartii* and *P. rettgeri* (Coetzee, 1967; Gabrilovich et al., 1998; McHale et al., 1981a). A bacteriocin typing scheme has been tested on >300 *Providencia* sp. isolates, though no follow-up confirmation of its reliability has been published (Al-Jumaili and Fenwick, 1978).

Molecular methods of epidemiological typing, such as restriction fragment length polymorphism (RFLP) and ribotyping, have been used with *P. stuartii* and *P. alcalifaciens*. Owen et al. (1988) noted that the DNA restriction fingerprints for *P. stuartii* were quite distinct from species of the allied genera of *Providencia* and *Proteus*, and provided a more sensitive measure of minor genomic differences than total DNA digests. Rahav et al. (1994) used RFLP to demonstrate that a single strain of *P. stuartii* persisted in the same patient during a nursing home outbreak of *P. stuartii* bacteriuria, and that several different strains were responsible for the outbreak. In comparison, neither biochemical tests nor antibiotic sensitivity were able to distinguish separate strains during this outbreak. Guth et al. (1999) used clonal analysis based on ribotyping to show that diarrheal isolates of *P. alcalifaciens* were clustered into two main groups.

The application of genetic methods to the identification of bacteria has become routine in the past decade and this is reflected in the current methods being applied to identification of *Providencia* sp. Apart from classical ribotyping, other methods that potentially could be used to distinguish strains of *Providencia* include automated ribotyping, RAPD-PCR (Akopyanz et al., 1992), amplification and restriction analysis of the 16S rRNA gene (ARDRA; Andrighetto, 1998; Dijkshoorn, 1998) and multilocus sequence typing (MLST), which exploits the electronic portability of nucleotide sequence data (Maiden et al., 1998).

Pathogenicity

The *Providencia* species that have been clearly identified as pathogens are *P. stuartii*, *P. rettgeri* and *P. alcalifaciens*. In human pathogenicity, the most significant member of the genus is *P. stuartii*, whereas the virulence of *P. rettgeri* and *P. alcalifaciens* is less clear. *Providencia stuartii* is particularly effective in colonizing urinary catheters and is a leading risk factor for bacteremia (Muder et al., 1992; Rahav et al., 1994; Rudman et al., 1988; Woods and Watanakunakorn, 1996). It has been proposed that *P. stuartii*, as well as *P. mirabilis* and *M. morganii*, probably establish a niche within the urinary catheter, thus increasing their ability to cause subsequent bladder bacteriuria (Warren, 1987a). *Providencia stuartii* is not particularly invasive; however, certain circumstances tend to increase the probability of infection, including prolonged catheterization and urinary surgery. This species also is resistant

to many common antibiotics, including most penicillins, aminoglycosides, tetracyclines, older cephalosporins, sulfamethoxazole and fosfomycin (Gomez-Lus et al., 1977; Paradise et al., 1998; Rather et al., 1997; Stock and Wiedemann, 1998; Swiatlo and Kocka, 1987). Such antibiotic resistance gives *P. stuartii* an opportunistic advantage in nosocomial patients. Furthermore, *P. stuartii* also has been implicated in septicemia (bacteremia), with symptoms typical of other septicemias, except that vascular collapse is not a prominent feature (McHale et al., 1981b; Prentice and Robinson, 1979).

While cases of *P. stuartii* septicemia usually prove fatal due to antibiotic resistance, patient survival in response to medical therapy has been reported in individual case studies (Keren and Tyrrel, 1987) and more recently, in long-term epidemiological surveys (Muder et al., 1992; Woods and Watanakunakorn, 1996). In the latter case, Woods and Watanakunakorn (1996) found a mortality rate of 25% in a review of 49 cases of *P. stuartii* bacteremia. Considering that 51% of patients in this survey were infected by more than one bacterial species (polymicrobial bacteremia), the mortality rate for *P. stuartii* bacteremia alone is probably lower. The main differences between *P. stuartii* and *P. rettgeri* are at the biochemical level. *Providencia rettgeri* can metabolize the sugars D-arabitol, adonitol and erythritol (Table 2). Otherwise, most *P. rettgeri* strains exhibit pathogenic properties similar to those of *P. stuartii*. *Providencia rettgeri* UTIs in catheterized and otherwise compromised patients are also difficult to treat owing to multiple antibiotic resistance. Overall resistance is, however, less marked in this species than in *P. stuartii*. By way of example, *P. rettgeri* is particularly susceptible to the aminoglycosides gentamycin and tobramycin, whereas *P. stuartii* is highly resistant to both (Penner and Preston, 1980b; Penner et al., 1982; Piccolomini et al., 1987).

In contrast to *P. stuartii* and *P. rettgeri*, *P. alcalifaciens* is an invasive enteric pathogen and implicated as a cause of diarrheal disease (Albert et al., 1992; Albert et al., 1998; Guth and Perrella, 1996; Haynes and Hawkey, 1989; Sen, 1962). In studies using pure cultures derived from stool specimens that were inoculated into the ilea of adult rabbits with removable ileal ties (RITARD model; Davis, 1991; Spira, 1981), it has been shown that the development of diarrhea is accompanied by an intestinal histopathology typical of other invasive bacterial species, such as *Shigella flexneri* (Albert et al., 1992). Mathan et al. (1993) have added more evidence to the *P. alcalifaciens* virulence model, invasiveness model by demonstrating two modes of bacterial entry into epithelial cells. The first mode of entry is by direct endocytosis associated with polymerization of cytoskeletal components, and the second mode by which the bacteria enter is through disruption of tight junctions, with the bacteria entering into and proliferating in intercellular spaces. The invasive abilities of *P. alcalifaciens* have been tested in HEp-2 cells (an epithelioid cell line from a human laryngeal carcinoma) by two independent scientific groups (Albert et al., 1992; Janda et al., 1998). Both groups were able to confirm penetration by *P. alcalifaciens* isolates, whereas no strain of *P. stuartii* or *P. rettgeri* tested invaded the HEp-2 cells.

VIRULENCE FACTORS. Those contributing to the pathogenicity of *Providencia* sp. that have been investigated include cellular adherence, the production of fimbriae and of urease. *Providencia stuartii* has been the focus of the majority of research.

Adherence and fimbriae. Urinary tract infections (UTIs) due to *P. stuartii* persist longer than those due to other Gram-negative bacteria. It has been suggested that a possible reason for this increased persistence may be due to the ability of *P. stuartii* to adhere to uroepithelial cells (Mobley et al., 1986). Adherence to uroepithelial cells can be enhanced by the expression of MR/K (hemagglutinin)-type fimbriae (see "Fimbriae"). Mobley et al. (1988) found that a significant proportion of *P. stuartii* isolated from patients experiencing bacteriuria of long duration expressed MR/K fimbriae. These data implicate the MR/K hemagglutinin in an important role in UTI persistence of *P. stuartii*.

Urease. While *Providencia rettgeri* is urease positive, as are some strains of *P. stuartii*. In fact, *P. rettgeri* and *P. stuartii* were originally subdivided based on urease production (Penner et al., 1976). There is some evidence that urease-producing strains of *P. stuartii* are more likely to be involved in long-term colonization of urinary catheters with subsequent development of blockages due to stone formation (Kunin, 1989; Stickler et al., 1998). Urease-producing *P. stuartii* strains also have been found to inhibit the in vitro growth of *E. coli* on catheter surfaces and in urine (Fletcher et al., 1994). This adaptive advantage in growth may explain why *P. stuartii* are the dominant species isolated in these mixed infections. The construction of isogenic urease-negative mutants may help to better define the role of urease in *P. stuartii* pathogenesis.

Conclusion

The genera *Proteus*, *Morganella* and *Providencia* contain a number of important human pathogens that often cause serious infections in hospitalized and immunocompromised patients. Other species are normal intestinal flora in animals or animal pathogens. One of the most conspicuous features of members of the genus *Proteus* is their

ability to differentiate into elongated, multinucleated swarmer cells upon contact with a solid surface. Methods of isolation and identification have been developed for most species and these now include several DNA-based methods of detection; however, treatment of infected patients is often problematic owing to the development of antibiotic resistance and the immunocompromised state of the patient.

The information contained in this chapter gives the reader a broad understanding of the current state of knowledge concerning these related genera. There are a number of areas where this knowledge base needs strengthening in the future. For example, our understanding of the ecological and/or pathogenic role of several species, including *P. myxofaciens*, *P. rustigianii* and *P. heimbachae*, has advanced very little since their initial identification, and much work remains to be done in this regard.

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