

## Chapter 7

# Competitive and Cooperative Interactions in the Respiratory Microflora

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Rupture of the amniotic membranes marks the transition from a sterile prenatal environment to one of constant contact with microorganisms. The establishment of the complex ecosystem of the upper respiratory mucosa and its subsequent maintenance are rapid and dynamic processes (65). Over the course of a lifetime, people are exposed to a vast number of bacterial species that have the potential to colonize the upper respiratory tract, yet only a small number of these ever do so. Many of them are rapidly cleared, but some may persist for months or years by either joining or displacing existing organisms at a mucosal surface. A myriad of factors may influence changes in the upper respiratory flora, but the overriding principle is that of continuous interaction among the species present and the extensive host defense mechanisms of the respiratory mucosa. Some members of the bacterial flora have the ability to prevent subsequent colonization by other species ("bacterial interference"), and there have been attempts to harness this for therapeutic or prophylactic means. Conversely, there may be cooperation among species to maintain colonization through effects on the host immune system, the epithelial surface, or the ability of bacteria to withstand environmental challenges (including antibiotic therapy).

There are examples of both cooperative and competitive interactions among respiratory organisms in *in vitro* and *in vivo* models. Observation of clinical phenomena such as bacterial superinfection in the setting of respiratory viral infection has suggested the potential importance of these processes. In addition, alteration of the colonizing flora of humans as the result of medical interventions such as antibiotic therapy or vaccination provides both a means and a compelling justification for the study of interactions among the members of the upper respiratory flora. Hospitaliza-

tion (especially in intensive care units) and antibiotic use can predispose to colonization and overgrowth with gram-negative organisms and fungi that may go on to cause life-threatening disease (75). Artificial colonization with avirulent bacteria in the hope of excluding more harmful organisms has been tried in this setting, with some encouraging results (discussed below). In addition, the successes of vaccination against some upper respiratory organisms (including *Haemophilus influenzae* type b [Hib] and *Streptococcus pneumoniae*) has led to changes not only in the rates of invasive disease due to these organisms but also to a decline in their carriage (13, 16, 17, 38, 52, 54, 84). This has raised the question whether new niches are created by vaccination that might be filled by other potentially virulent organisms (41). One mechanism to explain this phenomenon is the removal of competitors via drug therapy or vaccination, which highlights the potential role of competition in determining the makeup of the indigenous flora of humans.

In this chapter, I review aspects of interaction among the members of the respiratory microflora by considering relevant laboratory models and examples of both cooperation and competition. In general, I focus on the anatomic area between the nasal mucosa and the epiglottis, where several bacterial species coexist and may cocolonize for extended periods. The lower airway, below the epiglottis, is a sterile environment under normal conditions. In contrast, another neighbor of the nasopharyngeal epithelium, the oral cavity, is home to literally hundreds of distinct species of bacteria (57). These exist in microenvironments such as the subgingival crevice, where cooperative interactions, including the formation of highly complex multispecies biofilms, are crucial elements of their pathogenesis (62). The species that colonize the dental surface are distinct from those that inhabit

the respiratory mucosal surface and are not considered here. Specific data regarding the anatomic localization of colonizing bacteria in the nasopharynx and the relative burdens of each species are limited; however, evolving concepts of interaction among the members of the commensal flora are furthering our understanding of carriage.

### EXPERIMENTAL MODELS

Questions regarding bacterial colonization of the respiratory system are best answered by *in vivo* studies of a natural host; much of what we know about carriage comes from studies of humans. As might be expected, these investigations have been largely observational, rather than experimental, in nature. Because respiratory pathogens often colonize prior to causing invasive disease, a good deal of attention has been paid to the natural history of carriage of these organisms (reviewed in reference 26). Children acquire potentially pathogenic respiratory organisms shortly after birth and may carry them for prolonged periods (3). They may harbor more than one of these species or more than one serotype of a particular species. Spread of colonizing bacteria from child to child takes place efficiently in the winter months and in crowded situations such as day care centers. However, our understanding of the nature of cooperative and/or competitive interactions within the microflora that influence carriage is limited. The few studies of human colonization with relevance to competitive or cooperative interactions have tended to involve attempts to use "bacterial interference"—instilling a nonpathogenic microbe in an attempt to prevent colonization or infection with more virulent organisms. In recent years, a model of experimental human carriage of *S. pneumoniae* has been established (49, 50), although experiments regarding cocolonization with distinct species have not been reported. In addition, some inferences regarding competition among nasopharyngeal colonizers may be drawn from vaccination studies. These sources of data are discussed in more detail below.

Mouse models of carriage of microorganisms that usually have tropism for human tissues are more convenient but may be problematic. Colonization of mice with members of the human flora tends to require high intranasal doses of bacteria for establishment, to be transient, and to necessarily involve alteration of some important interactions between the colonizing species and the host. For example, immunoglobulin A (IgA) protease expressed by both *S. pneumoniae* and *H. influenzae* is not active against murine IgA, making it difficult to assess the impor-

tance of that system in a mouse colonization model. However, short-term murine colonization has been used to assess some specific questions about the dynamics of pathogen interaction. One study assessed competition among serotypes of *S. pneumoniae* (42). Mice colonized with a streptomycin-resistant type 6B pneumococcus resisted challenge with either an optochin-resistant type 6B strain or an unrelated type 23F strain. However, animals that were first colonized with the optochin-resistant type 6B could still acquire the streptomycin-resistant variant, showing that inhibition was not always reciprocal. More subtle effects of competition or cooperation may require the use of genetically altered mice expressing human receptors or lacking immune system components responsible for clearance of organisms.

*In vitro* modeling of microbial interactions has been the most widely employed means of investigating competition and cooperation among species. Early studies of bacterial antagonism extended known microbiological techniques to the study of multiple organisms. Topley and Fielden (86) demonstrated an ordered progression of quantitatively dominant species in liquid culture of organisms from stool, and Colebrook (10) showed that when grown on solid media, a streak of pneumococcus could inhibit the growth of an intersecting streak of meningococcus. These techniques are still useful for the generation of novel data (58), but better-controlled systems such as continuous-culture chemostats (19) are becoming more widely used. The chemostat allows populations of bacteria to be kept in relatively static conditions for long periods. Nutrient levels, drug concentrations, and the presence of other species can each be altered, and the effects on the organisms and on the media can be measured. The concept of a chemostat has also been used as a starting point for mathematical modeling of competition and resistance to new colonizing strains among bacteria (77). The ability to incubate bacteria and/or viruses with cultured mammalian cells, epithelial and other types, has spawned a new discipline, cellular microbiology (11), and has facilitated investigations of the mechanisms of microbial interactions. For example, much of what is known about viral-bacterial synergy in the respiratory tract, discussed in the next section, has been defined in these *in vitro* systems.

### COOPERATIVE INTERACTIONS AMONG RESPIRATORY MICROORGANISMS

Cultures of the upper respiratory tract rarely reveal a single organism, and studies of colonization by potential bacterial pathogens show that simultaneous

carriage of more than one species is common (6). Colonization of the nasopharynx by one species may alter the dynamics of that niche, changing the probability that another species may succeed at entry. One possible result of this is bacterial interference, or exclusion of subsequent species from the niche. This is discussed in detail below. However, another possibility is that colonization by one species may change the micro-environment in a way that makes it more hospitable to another. I refer to this as bacterial cooperation.

The mere description of multiple species in a single anatomic site does not imply interaction. Smith (71) described cooperative interactions among bacterial and viral species in the pathogenesis of respiratory disease and laid out a model of synergy among several weakly pathogenic species in areas such as periodontal disease, but he did not address the question of the impact of these interactions on asymptomatic carriage. The first in vitro descriptions of cooperative interactions among bacterial species date to the late 19th century (cited in reference 64). More recently, enhancement of the growth of *Moraxella catarrhalis* by oral streptococci was noted by Rosebury et al. (64). In that study, various pairs of microorganisms were tested on solid media for either inhibitory or cooperative interactions. When changes in growth were noted, they were mostly inhibitory. The exception was that several species enhanced the growth of *M. catarrhalis* and one (*Candida albicans*) appeared to increase the growth of *Escherichia coli*.

Some clinical aspects of microbial synergism in both infection and, to a lesser extent, colonization have been reviewed (45, 46). Brogden (8) described a framework for consideration of potential mechanisms of polymicrobial infections, including those involving the respiratory tract. (Table 1). Despite the inherent differences between colonization and disease states, the concepts are useful in investigating the ecosystem of the upper respiratory flora. Alterations in the host immune system may be important in determining the composition of the respiratory flora. Even in the absence of "obliteration" of the immune system, subtle changes may be enough to affect colonization. For example, alteration of ciliary motility in the setting of viral infection can impair the clearance of bacterial pathogens, setting the stage for prolonged colonization or disease such as otitis media (4, 56). In addition, people with IgA deficiency are at increased risk of respiratory infections, possibly as a result of increased colonization.

Alteration in the mucosa by one organism may favor colonization by another. The best described examples of this involve the interplay among respiratory viruses and members of the bacterial flora. It has been known for decades that viral infections can in-

Table 1. Mechanisms of pathogenesis in polymicrobial disease<sup>a</sup>

Stress, physiologic abnormalities, or metabolic disease favors the colonization of multiple organisms
• Stress and acute respiratory infection (28)
Alterations in the mucosa by one organism favor the colonization of another
• Increased exposure of bacterial receptors during viral infection
■ Influenza virus/platelet-activating factor receptor (51)
■ Influenza virus RSV/CD14, CD18 (22, 60)
• Bacterial binding to viral proteins in the host membrane
■ RSV glycoprotein G/ <i>N. meningitidis</i> (59)
■ Influenza virus proteins/group B <i>Streptococcus</i> (67)
Synergistic triggering of proinflammatory cytokines increases severity of disease, reactivates latent infections, or favors the colonization of another organism
• Enhanced TNF- $\alpha$ response of influenza virus-infected macrophages to <i>H. influenzae</i> lipopolysaccharide (55)
• Synergistic epithelial cell response to muramyl peptide and lipopolysaccharide (24)
Sharing of determinants among organisms allows activities that neither organism possesses individually
• "Piracy of adhesins" <i>S. pneumoniae</i> , <i>S. aureus</i> , and <i>H. influenzae</i> bind to secreted proteins of <i>B. pertussis</i> (87)
• IgA protease-expressing <i>H. influenzae</i> enhances the adherence of IgA protease-insufficient <i>S. pneumoniae</i> by cleaving specific antibody (93)
Obliteration of the immune system by one organism allows colonization by others
• Overall immune suppression in the setting of viral illness
• Alteration of ciliary motility by viruses leading to increased bacterial colonization (4, 56)

<sup>a</sup>Modified from reference 8 with permission.

crease both colonization (29) and invasive disease such as pneumonia due to bacterial pathogens (31). Correspondingly, in vitro models demonstrate that infection with several different types of viruses (influenza virus, respiratory syncytial virus [RSV], and rhinovirus) can enhance the attachment of bacteria to respiratory epithelial cells. This may occur through damage to host cells and exposure of receptors for bacteria that are normally sequestered. For example, infection of respiratory epithelial cells with influenza virus (51) or rhinovirus (35) can increase interactions between the phosphorylcholine moiety on the surface of *S. pneumoniae* and the receptor for platelet-activating factor on the epithelial surface. A similar mechanism appears to exist for *Neisseria meningitidis* binding during RSV infection. RSV infection of epithelial cells in vitro leads to upregulation of several host cell molecules, including CD14 and CD18, both of which contribute to meningococcal adherence (60). Similar upregulation of CD14 and CD18 has been reported after epithelial cell infection with influenza virus (22). Adenovirus infection may also increase the epithelial attachment of

Table 1

*S. pneumoniae*, although the mechanism is unclear (30). In addition, viral proteins that are inserted into host cell membranes during viral replication can act as direct receptors for bacterial binding. This has been described for glycoprotein G of RSV, which, when present on host epithelial cells, enhances the adherence of meningococci (59). A similar mechanism may exist for influenza virus, since as infection of epithelial cells increases the adherence of group B streptococcus, an effect that can be blocked by antibodies to influenza A virus proteins (67).

Another potential mechanism for bacterial competition, the synergistic triggering of a cytokine response by the host, is of unclear importance in human upper respiratory colonization. However, expression of some bacterial receptors, such as the receptor for platelet-activating factor, is upregulated in the presence of proinflammatory cytokines including tumor necrosis factor alpha (TNF- $\alpha$ ) (12). Synergistic production of TNF- $\alpha$  from influenza virus-infected macrophages has been described following stimulation with *H. influenzae* lipopolysaccharide (55). In addition, exposure of epithelial cells to muramyl peptide (a component of peptidoglycan) and lipopolysaccharide together induces a synergistic cytokine response (24), raising the possibility that different species of bacteria acting in concert might alter the immune response of the respiratory epithelium in vivo.

Sharing of determinants among diverse species in the ecosystem of the upper respiratory tract is another means for the promotion of colonization. Cohabitation of an environmental niche suggests that the activities of one group of organisms, especially those that operate through secreted factors, might affect other residents of the niche. For example, one mechanism postulated to explain episodes of failure of penicillin therapy in the treatment of group A beta-hemolytic streptococcal pharyngitis is the presence of colonizing bacteria that elaborate  $\beta$ -lactamases (20); however, the clinical significance of that interaction has been questioned (27). The ability of many diverse species of bacteria to cleave human IgA in the hinge region is thought to facilitate colonization of the nasopharynx. Cleavage of type-specific IgA by *S. pneumoniae* facilitates the adherence to respiratory epithelial cells, and while an IgA protease-deficient pneumococcus does not manifest this increase in adherence, it can be complemented by coinoculation with an IgA protease-producing strain of *H. influenzae* (93). Thus, an enzyme produced by a distinct species of bacteria is able to cleave IgA specific for the pneumococcus and enhance its adherence, demonstrating a potential means for cooperation among species in colonization of the nasopharynx. A cooperative model involving shared determinants has also

been proposed to explain the increased rate of colonization and infection with other respiratory bacteria during infection with *Bordetella pertussis*. *B. pertussis* secretes both filamentous hemagglutinin and pertussis toxin into the environment. These then mediate bacterial binding to the cilia of respiratory epithelial cells. However, in an example of molecular cooperation (or "piracy"), other respiratory pathogens including *S. pneumoniae*, *Staphylococcus aureus*, and *H. influenzae* are also able to bind these proteins and thus enhance their own adherence manyfold during coinfection with *B. pertussis* (87).

It is likely that cooperative interactions that influence the initiation and maintenance of upper respiratory colonization are both more common and more diverse than we currently appreciate. Accumulating evidence suggests that cross-species quorum sensing and multispecies coaggregation and biofilm formation (62) may be common in other niches, and it is possible that these play a role in the respiratory tree as well. In addition, the role of anaerobic and difficult-to-culture pathogens in respiratory colonization is an area awaiting further study.

#### COMPETITION AND "BACTERIAL INTERFERENCE" IN THE RESPIRATORY SYSTEM

The study of bacterial competition or, as it is more commonly called, bacterial interference is nearly as old as bacteriology itself. It has been the subject of numerous review articles spanning decades and of at least one book (2, 9, 25, 61, 64, 71, 73). The first report of therapy using a microorganism involved an attempt to utilize yeast as a treatment for furunculosis (53). Pasteur and Joubert described inhibition of the growth of *Bacillus anthracis* in urine during coculture with the "common bacterium" (described in reference 25). They extended this result to an in vivo model, showing decreased disease in animals that received a mixture of the two bacteria compared to those inoculated with *B. anthracis* alone. The ensuing years saw other attempts at both in vivo therapy and in vitro models of bacterial antagonism, with variable results. Two particular studies merit mention here, since they involve alteration of the respiratory tract flora. In the early 1900s, a patient with a staphylococcal pharyngitis was mistakenly hospitalized in a ward for diphtheria patients but did not develop diphtheria despite prolonged contact with other patients on the ward. An attempt was then made to use staphylococci to replace *Corynebacterium diphtheriae* in the throats of carriers, with some success (cited in reference 25). Having de-

scribed in vitro inhibition of *N. meningitidis* by *S. pneumoniae*, Colebrook (10) attempted to use live pneumococci to displace meningococci in asymptomatic carriers. The effect, when noted, was short-lived.

Other epidemiologic observations have suggested that bacterial interference may be important in the establishment of the upper respiratory flora. Carriage of bacteria that cause in vitro inhibition of other respiratory organisms is common among both children and adults (36, 66). May noted an inverse relationship in the frequency of isolation of *S. pneumoniae* and *H. influenzae* from the sputa of patients with bronchitis (48). In a study of the bacteriology of middle ear fluid and nasal colonization in children with otitis media, *S. pneumoniae* and *H. influenzae* were found frequently (in 58 and 24% of nasal cultures, respectively) but were isolated simultaneously far less often than would be predicted mathematically (8% of nasal cultures) (43). Similar findings of inverse relationships among species of bacteria have been found in investigations of the carrier state (18, 39, 72). Bakir et al. studied nearly 1,400 healthy children and noted a positive correlation between carriage of either *S. pneumoniae* or *H. influenzae* and carriage of *N. meningitidis*. However, they also described a protective effect of colonization with the nonpathogenic *N. lactamica* against meningococcal carriage (5). Similarly, overgrowth of antibiotic-resistant bacteria or fungi may follow alteration of the upper respiratory flora by antibiotic therapy. Many such "overgrowers" are environmental, and people are constantly exposed to them. However, they are able to take up residence in the upper respiratory tract only following elimination of the normal flora, implying that the normal flora plays an inhibitory role.

More recently, the lessons of these early studies in bacterial interference have been applied in medical settings. Probiotics are frequently used to alter the intestinal flora and to treat gastrointestinal diseases (44), but experience of using bacterial interference as therapy in the respiratory tract has been more limited. In the early 1960s, the seminal work of Shinefield et al. on artificial colonization and bacterial interference using *S. aureus* demonstrated the feasibility of the clinical use of this phenomenon (70). Following an outbreak of staphylococcal disease among newborns in a nursery, an epidemiologic investigation implicated a nurse who was a nasal carrier of the virulent 80/81 *S. aureus* strain in the spread of this organism to the infants in her care. However, the investigators made the striking observation that while 22% of infants younger than 24 h old who were cared for by that nurse became colonized with the 80/81 strain, none of those infants who were older than 24 h of age

at the time that they were in her care did so. This raised the possibility that there was an age-related susceptibility to colonization with this virulent *S. aureus* strain or that prior colonization with other *S. aureus* strains inhibited colonization with the 80/81 strain. Evidence from colonization rates of children transferred from other nurseries suggested that the latter was the more likely possibility, so the investigators took the striking approach of directly testing the phenomenon of bacterial interference. After demonstrating that a relatively avirulent *S. aureus* strain (strain 502A) could colonize the nasopharynx of infants following deliberate inoculation, they effectively used this artificial colonization to prevent the acquisition of (and development of disease from) the more virulent 80/81. This approach was subsequently used in other outbreak settings (40, 69), as well as in treatment of adults with chronic furunculosis (47, 78). Unfortunately, reports of serious infections due to strain 502A have limited its further investigation (7, 34).

In another study, artificial colonization of the nasopharynx with diphtheroids protected infants against subsequent colonization with gram-negative bacilli but not pneumococci or streptococci (21). Sprunt and Redman examined the presence of alpha-hemolytic streptococci in the throats of children before and after antibiotic therapy prior to surgery. They found that elimination of these potentially inhibitory organisms from the nasopharynx predisposed patients to developing bacterial overgrowth with gram-negative organisms, a phenomenon that was not observed if the patients carried alpha-hemolytic streptococci that were resistant to the antibiotics used (76). Pretreatment of patients with oral penicillin for a period of days or weeks prior to surgery selected for colonization with resistant alpha-hemolytic streptococci and prevented overgrowth following subsequent antibiotic therapy (75). Artificial implantation of alpha-hemolytic streptococci into newborns with "abnormal" colonization (with gram-negative organisms or *S. aureus*) led to rapid replacement (74).

In some instances, one bacterial species or serotype may compete so effectively with another that it essentially excludes it from the nasopharynx. In this case, the interaction may become apparent only if the more effective organism is removed from its niche by vaccination or by antibiotic therapy. Vaccination against a bacterial pathogen can reduce both asymptomatic carriage and invasive disease due to that organism, as has been shown for both Hib (1, 83) and *S. pneumoniae* (15, 94). However, decreased carriage of one species may have effects on other members of the nasopharyngeal flora. A new niche may be created that allows the carriage of a species

or serotype not seen prior to vaccination, and competitive or cooperative systems may be disrupted, with consequences for other members of the ecosystem. The primary concern with vaccination against Hib and *S. pneumoniae* has been the potential for serotype replacement, where other, potentially more virulent serotypes of bacteria fill the niche left by those removed after immunization. This has not been a major problem with the Hib vaccine to date, but increases in the carriage of nonvaccine serotypes of *S. pneumoniae* have been documented in studies of pneumococcal vaccination (14, 15). In addition, at least one group has described an increase in otitis media due to *H. influenzae* in a cohort of children immunized with a pneumococcal conjugate vaccine (23). This 11% increase was not statistically significant but is suggestive that removal of certain members of the upper respiratory flora may predispose to increased carriage of and possibly invasive disease from other species.

There are at least two mechanisms of interaction that may be important in interspecies competition in the respiratory tract: direct interbacterial interactions and competition for nutrients or receptors in a particular niche. There are numerous examples of direct interactions among bacterial species, although there is a lack of *in vivo* data to assess the relative importance of these. *S. pneumoniae* produces a neuraminidase that is capable of desialylation of the lipooligosaccharide of *H. influenzae* or *N. meningitidis*, two species that inhabit the same environmental niche (68). Sialylation is important in the protection of these bacteria from the host immune system (33, 88) as well as in biofilm formation in *H. influenzae* (80); therefore, desialylation may represent a means for one species to expose another to potential harm, thereby potentially gaining a competitive advantage.

Inhibition of growth or direct killing among upper respiratory bacteria has been described *in vitro*. Early studies (10) showed antagonism of *N. meningitidis* and *S. pneumoniae* under laboratory conditions. Other groups have shown *in vitro* inhibition among various members of the nasopharyngeal flora (64). The best-described mechanism for this interspecies inhibition is the production of (and resistance to) high concentrations of hydrogen peroxide by *S. pneumoniae* (58). The pneumococcus generates concentrations of hydrogen peroxide sufficient to efficiently kill *H. influenzae* and *N. meningitidis* but not *M. catarrhalis* *in vitro*. This mechanism may also be active in other inhibitory interactions in the nasopharynx (90). Production of bacteriocins may represent another means by which bacteria compete with rivals in a particular niche. Bacteriocins are antimicrobial molecules which can be produced by a wide variety of bacterial species and which target related bacteria in

the environment (63). Bacteriocins are generally produced under conditions of stress and nutrient limitation. Important respiratory organisms, including group A *Streptococcus*, produce and are acted on by them (81). A bacteriocin produced by *S. salivarius* with action against group A *Streptococcus* may reduce the rate of streptococcal pharyngitis (82). In addition, a bacteriocin-like inhibitory substance produced by both *S. pneumoniae* and *S. pyogenes* may play a role in protection against otitis media in children (92). The relative importance of each of these mechanisms in determining the composition of the upper respiratory flora *in vivo* remains to be investigated.

Competition among bacterial species in the respiratory tract may also take place at the level of epithelial attachment. Organisms that fail to adhere to the mucosal surface risk removal by the mucociliary apparatus, and many distinct bacterial receptors have been described (89). However, there is overlap in receptor tropism among species that inhabit the nasopharynx, and competition for limited binding sites may occur. Both commensal and pathogenic neisseriae can adhere to the cell surface antigen CEACAM1 (CD66a) (85), and competition between these species and between *Neisseria* and *Haemophilus* species which also bind CEACAM1 has been detected *in vitro* (91). Krivan et al. described the ability of many respiratory pathogens to bind to a common carbohydrate sequence, Gal-NAc- $\beta$ (1-4)-Gal, which is expressed on epithelial cells (37). In addition, several inhabitants of the nasopharynx including *S. pneumoniae* and *H. influenzae* display the phosphorylcholine moiety that allows interaction with the eukaryotic receptor for platelet-activating factor (12, 79), but the presence of competition among any of these species has not been well documented *in vivo*. Competition for receptor availability among upper respiratory tract species is in contrast to the increased availability of bacterial receptors accounting for synergy in mixed bacterial-viral infections as described above.

In addition, many of the members of the upper respiratory flora are auxotrophs. Competition for nutrients among members of mixed bacterial populations has been proposed (32). Since the airway surface fluid is not a rich growth medium, differential access to limited resources may be an important determinant of the composition of the flora, although this area has not been investigated *in vivo*.

## FUTURE DIRECTIONS

There is ample evidence that competitive and cooperative interactions among species can play important roles in shaping the resident flora of the upper respiratory tract and in influencing the course of res-

piratory infections. Colonization is a dynamic process that involves a complex interplay among microbial species and host defense mechanisms. Numerous species coinhabit the human nasopharynx, and both in vitro and in vivo studies suggest that there is significant potential for interaction. Overlap in receptor tropism, competition for growth on solid or in liquid medium, and evidence of synergy in disease processes in humans all indicate that both cooperation and antagonism may be in constant play at the respiratory epithelial surface. There are significant technical challenges involved in accurately modeling this system, although progress in understanding the factors involved in the establishment and maintenance of carriage has been made. Artificial alteration of colonization through vaccination or antibiotic therapy may disrupt the ecological balance in this microenvironment and have unintended consequences. Further research in this area, especially if relevant in vivo models are employed, will contribute to our evolving understanding of the ecology of the upper respiratory tract.

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## Colonization of Mucosal Surfaces

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*Colonization of Mucosal Surfaces* is a state-of-the-art presentation of the opposing evolutionary forces that ultimately determine the health of host organisms and survival of pathogenic microorganisms. As mammalian defenses evolve to protect against infection, pathogens are simultaneously evolving to circumvent new barriers and gain access to valuable host nutrients and energy. Written by experts in the field, this new volume is an in-depth examination of the complex ecosystems of the mammalian mucosa and the successful adaptations of microorganisms that enable them to effectively colonize these surfaces.

First addressing general considerations, *Colonization of Mucosal Surfaces* then comprehensively covers colonization of the respiratory tract, the gastrointestinal tract, and the genitourinary tract and considers the various organisms present at these surfaces. Aspects of bacterial colonization revealed by the most recent research are also contemplated, including penetration of the mucous layer, innate immune effectors and their subversion, signaling of host cells by adherence factors, modulation of adherence, phase variation of colonization factors, and regulation of colonization effectors.

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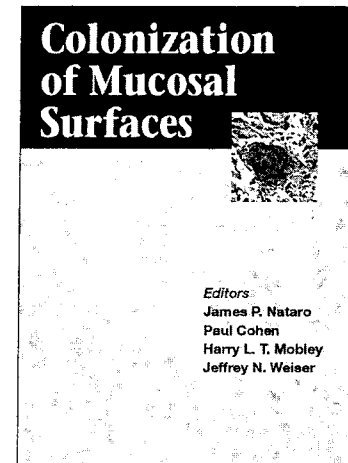
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### Key Features

- Presents a multi-disciplinary approach to colonization and considers microbiology, protein chemistry, cell biology, genetics, evolution, and biology of the host
- Addresses colonization of major mucosal systems
- Suggests principles that serve as hypotheses for investigators working on less-characterized organisms or models
- Contributes highly scientific research from recognized leaders in the field
- Emphasizes colonization events beyond adherence

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