Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
The skin and mucous membranes are the principal barriers to invasion of the body by microorganisms. Besides functioning as a mechanical barrier, the mucosae are endowed with an array of still poorly characterized specific and nonspecific host defense capabilities. These include the production of mucus, secretory immunoglobulin (IgA), lysozyme, lactoferrin, and alpha-antitrypsin, in conjunction with a low-grade exudation of leukocytes. In addition, the mucosal surfaces of the upper respiratory, gastrointestinal, and lower vaginal and urinary tracts support a large number of "nonpathogenic" microorganisms that comprise the so-called "normal flora." This commensal flora plays an important and complex role in protecting the host from microbial invasion. Mechanisms for this protection likely include the following: (1) competition for the same nutrients (interference); (2) competition for the same receptors on host cells (tropism); (3) production of bacteriocins, that is, bacterial products that are toxic to other organisms, usually of the same species; and (4) stimulation of cross-protective immune factors such as the "natural antibodies." The "normal" flora is inconstant and may be altered by dietary factors, debilitation, hormonal events (such as menstruation, pregnancy, and possibly use of oral contraceptives), personal hygiene, medications, intercurrent infection, and probably many others. Antibiotic therapy and menstruation can have a profound effect on the composition of this group of microorganisms. Disturbance of the delicate host-commensal relationship may cause a clinically significant infection due to these "nonpathogens." This may occur in response to the aforementioned factors (e.g., pregnancy predisposing to vaginal candidiasis) or because of disruption of the anatomic barrier (e.g., local mucosal infection at a site of trauma, or injury from cytotoxic drugs) or in association with exogenous infection (e.g., rhinoviral infection leading to secondary bacterial otitis media). Invasion by "normal flora" may result in serious systemic illness. A clear example of the latter is the development of infective endocarditis caused by viridans streptococci following a dental procedure.
The majority of all human pathogens enter the body through a mucosal surface, at which point they may or may not cause local disease. Whether or not local mucosal infection is established on entry, the mucosae may still be affected secondarily as part of the systemic disease process. Consequently, it is far too ambitious a task to describe in detail every infection known to involve the mucosae, even excluding the sexually transmitted ones.

What must be considered an incomplete tabulation of those non-sexually transmitted infectious diseases with manifestations in the oral, nasal, or vaginal mucous membranes is given in Tables 1, 2, and 3. Instead, the focus of this chapter is to review the clinical features of an important and common syndrome, pharyngitis, with particular reference to newer concepts regarding the relationship of this entity to that of the "normal flora."

**Pharyngitis**

Respiratory infections are the leading cause of acute illness in the United States, and sore throat is the third most common symptom seen in medical practice. Despite years of experience with this condition, its management is far from settled or secure issue, and questions being raised today are not the same as those in prior years. The most important bacterial cause of sore throat is the Group A streptococcus, also known...
TABLE 2. Non-sexually Transmitted Infectious Diseases that May Involve the Nasal Mucosa

| Viral               | Bacterial                           | Fungal                | Parasitic           |
|---------------------|-------------------------------------|-----------------------|---------------------|
| Adenovirus          | Klebsiella ozaeae (Ozaena)          | Aspergillus species   | Leishmania species  |
| Coronavirus         | Klebsiella rhinoscleromatis (Rhinoscleroma) | Mucormycosis         |                     |
| Enteroviruses       | Mycobacterium leprae                | Rhinosporidium seeberi|                     |
| Influenza viruses   | Mycobacterium tuberculosis          |                       |                     |
| Parainfluenza viruses | Streptococcus pyogenes              |                       |                     |
| Respiratory syncytial virus | Staphylococcus aureus |                       |                     |
| Rhinoviruses        |                                     |                       |                     |
| Rubella             |                                     |                       |                     |
| Rubeola             |                                     |                       |                     |
| Varicella-zoster    |                                     |                       |                     |

as Streptococcus pyogenes. Other strains of beta-hemolytic streptococci, such as Groups C and G, occasionally produce an identical clinical picture but without the risk of such serious sequelae as rheumatic fever or glomerulonephritis. Other bacterial pathogens that may on occasion mimic streptococcal pharyngitis, such as Corynebacterium diphtheriae, C. hemolyticum, C. ulcerans, Franciscella tularensis, Hemophilus influenzae, Brucella species, Listeria monocytogenes, Coxiella burnetii, and Yersinia enterocolitica, are much less common and usually occur in special epidemiologic settings; they are rarely important considerations in the usual patient with sore throat. The same can be said of pharyngeal involvement with such sexually transmitted pathogens as Treponema pallidum, Neisseria gonorrhoeae, and Chlamydia trachomatis.

Group A streptococci cause only 15-30% of all sore throats and about half of those with tonsillar exudates. Somewhat higher figures are reported during epidemic periods, and somewhat lower percentages are found in young infants with pharyngitis.

Streptococcal sore throat occurs most often in patients between the ages of 5 and 15 years, and in temperate climates the highest incidence of illness occurs in the colder months. Transmission of disease is usually by person-to-person spread of respiratory droplets, although epidemics of streptococcal pharyngitis (both Groups A and G) have been traced to contaminated food or water.

The usual incubation period is 2-5 days with a range of 1-10 days. Illness typically begins abruptly, with fever, chills, headache, and sore throat. Clinical manifestations, however, may vary greatly in severity from patient to patient. The most severe forms of tonsillopharyngitis are seen in epidemics occurring in closed institutional settings (eg, military barracks).

Abdominal pain, nausea, vomiting, and coryzal symptoms are more often present in

TABLE 3. Non-sexually Transmitted Infectious Diseases of the Vagina

| Viral               | Bacterial                          | Fungal               | Parasitic       |
|---------------------|------------------------------------|----------------------|-----------------|
| Herpes simplex I    | Actinomyces                         | Candida species      | Enterobius vermicularis |
| (Autoinoculation from oral lesion in children) | ? Hemophilus influenzae | (Pinworm)           |                 |
|                     | Gardnerella vaginalis ("Bacterial vaginosis"; "Nonspecific vaginitis") | Schistosoma species |                 |
|                     | Mycobacterium tuberculosis          |                      |                 |
|                     | Shigella species                    |                      |                 |
|                     | Salmonella species                  |                      |                 |
|                     | Streptococcus pyogenes              |                      |                 |
|                     | Staphylococcus aureus               |                      |                 |
children than adults. Cough or hoarseness is not typically seen in streptococcal pharyngitis and suggests a viral etiology.

About 15-20% of asymptomatic school children carry Group A streptococci in their throats in winter months, as do 20-60% of asymptomatic family contacts of index cases. Thus, the majority of individuals who harbor this organism have no complaints whatsoever. Many of these individuals appear to be carriers; that is, this streptococcal species behaves as a commensal, does not elicit an antibody response, and at least for a time blends into the "normal flora." A study in the past with intramuscular penicillin (benzathine penicillin G) had shown nearly uniform success in clearing *S. pyogenes* from the oral mucosa. Slightly lower cure rates were reported for oral penicillin preparations, probably because of poor compliance with the full 10-day course of therapy. Even a 7-day treatment course with oral penicillin has been shown to be significantly less effective than the 10-day regimen.

Of concern, therefore, is the unfavorable bacteriologic response to penicillin therapy found in almost all recent studies. Regardless of the penicillin preparation, 20-40% of symptomatic patients have had positive post-treatment cultures. Furthermore, retreatment was unsuccessful in 30-62% of patients. Resistance of the organism did not appear to explain this outcome, since the streptococcal organisms were extremely sensitive to the inhibitory effects of penicillin. On occasion, apparent failures are actually reinfections from close personal contacts or possibly even from pets who may harbor the organism. However, this explanation was evaluated but considered unlikely in at least one study that involved a semiclosed population.

Whether or not the use of antibiotics hastens clinical recovery, once a highly controversial issue, has now been resolved on the basis of several new studies as well as re-analysis of an older one. Use of appropriate antibiotics shortens the duration of illness by 24-48 hours if begun early. In fact, it is so unlikely for fever to persist beyond the first 24 hours of treatment that another diagnosis or a suppurative complication should be considered when this occurs. Antibiotic therapy also prevents rheumatic fever, provided that the streptococcal organism can be eradicated from the pharynx. It is doubtful, however, that antibiotics prevent or attenuate acute glomerulonephritis, a complication that occurs more frequently after cutaneous streptococcal infection.

Studies in the past with intramuscular penicillin (benzathine penicillin G) had shown nearly uniform success in clearing *S. pyogenes* from the oral mucosa. Slightly lower cure rates were reported for oral penicillin preparations, probably because of poor compliance with the full 10-day course of therapy. Even a 7-day treatment course with oral penicillin has been shown to be significantly less effective than the 10-day regimen.

Of concern, therefore, is the unfavorable bacteriologic response to penicillin therapy found in almost all recent studies. Regardless of the penicillin preparation, 20-40% of symptomatic patients have had positive post-treatment cultures. Furthermore, retreatment was unsuccessful in 30-62% of patients. Resistance of the organism did not appear to explain this outcome, since the streptococcal organisms were extremely sensitive to the inhibitory effects of penicillin. On occasion, apparent failures are actually reinfections from close personal contacts or possibly even from pets who may harbor the organism. However, this explanation was evaluated but considered unlikely in at least one study that involved a semiclosed population.

A bacteriologic cure rate with penicillin of 80% or less is low in absolute terms. This figure is even more striking, however, when it is compared with the 71% spontaneous cure rate of streptococcal pharyngitis, observed in a study published in 1961, of symptomatic children in Chicago who were not treated with an antimicrobial.

Role of the Normal Flora in Streptococcal Treatment Failures

Itzhak Brook has made an increasingly persuasive argument that the growing number of penicillin failures is due to the recent emergence of penicillin-resistant β-lactamase-producing microorganisms (ie, penicillin-destroying) in the "normal" mouth flora. According
to this theory, \( \beta \)-lactamase producing organisms, by inactivating penicillin, protect Group A streptococci from the antibiotic. In addition to \textit{Staphylococcus aureus}, the oropharyngeal cavity may normally harbor a number of other aerobic and anaerobic organisms that have the potential to produce \( \beta \)-lactamase. These organisms include various \textit{Bacteroides} and \textit{Hemophilus} species and \textit{Branhamella catarrhalis}. In studies of children with recurrent tonsillitis who underwent tonsillectomy, Brook and Yocum were able to correlate the presence of \( \beta \)-lactamase activity measured directly in tonsillar tissue with recovery of \( \beta \)-lactamase-producing flora from culture of the tonsils.\textsuperscript{44} In a subsequent clinical trial, 100 children with acute Group A streptococcal tonsillitis were treated with a 10-day course of an oral penicillin.\textsuperscript{41} Sixty-three of the children were bacteriologically cured, and 37 were considered treatment failures. Prior to therapy, \( \beta \)-lactamase-producing organisms were recovered from oral cultures of 25\% of the 63 children who were cured compared with 68\% of the 37 children for whom treatment failed. Also \( \beta \)-lactamase producing organisms were present in significantly larger numbers in the nonresponders than in the responders. Other data suggest that penicillin treatment itself promotes the emergence of a penicillin-destroying flora\textsuperscript{45,46} and that these resistant strains may be transferred to household contacts.\textsuperscript{46} Further evidence to support the role of \( \beta \)-lactamase-producing bacteria in streptococcal treatment failures comes from an experimental model in which a mixed subcutaneous abscess containing both a penicillin-susceptible Group A streptococcus and a \( \beta \)-lactamase-positive strain of \textit{Bacteroides} species is produced in mice. In these studies, mice treated with either clindamycin (active \textit{in vitro} against both isolates and not susceptible to \( \beta \)-lactamase) or penicillin in combination with a \( \beta \)-lactamase inhibitor (clavulanic acid) had a greater reduction in abscess size and in total number of streptococci recoverable on culture than did untreated control animals or those receiving penicillin alone.\textsuperscript{46} Thus, it is reasonable to suggest that greater cure rates in patients with streptococcal pharyngitis might be achieved by one of several therapeutic strategies:  

1. Use of an antimicrobial (with or without penicillin) which is not susceptible to \( \beta \)-lactamase.  
2. Use of combined therapy with penicillin and a second drug that either inhibits \( \beta \)-lactamase directly, such as clavulanic acid, or which inhibits the bacteria that are responsible for \( \beta \)-lactamase production.  

Consistent with this hypothesis, in comparative studies using regimens similar to these such as clindamycin alone,\textsuperscript{48-49} an oral cephalosporin alone,\textsuperscript{50-51} dicloxacillin alone,\textsuperscript{52} or penicillin plus rifampin,\textsuperscript{53,54} cure rates were superior to those with penicillin alone.  

It is quite fortunate that despite documentation of increasing difficulties in eradicating streptococci, and little convincing evidence for a decrease in the frequency of streptococcal pharyngitis, that the incidence of rheumatic fever has not increased. On the contrary, rheumatic fever has all but vanished from suburban America. One county in California reported 430,000 cases of streptococcal illness over an 11-year interval but only three cases of rheumatic fever.\textsuperscript{55} Similarly, the incidence of acute rheumatic fever among whites in suburban and rural parts of Shelby County (Tennessee) was only one case per 200,000 school children annually over the 5-year period from 1977 through 1981.\textsuperscript{56} Rheumatic fever rates are somewhat higher in inner city areas of major United States metropolitan centers and higher yet among large segments of the developing world in Asia, Africa, or South America.  

It is difficult to define precisely the contribution of penicillin to the downward trend in rheumatic fever incidence. Considerable evidence exists, however, that antibiotic use may not be the primary factor and that the principal reason for the decline is actually a change in the "rheumatogenicity" of prevalent streptococcal strains.\textsuperscript{57} In fact, the decrease in incidence of rheumatic fever antedated the discovery of penicillin and began even before the causative relationship to Group A streptococci was known. Older studies, done when rheumatic fever was more common, indicate that about one third of patients with rheumatic fever do not recall a
preceding respiratory tract infection and thus would not have received treatment for a streptococcal infection. If penicillin therapy were the only reason for the decline in incidence of rheumatic fever, one might anticipate that among newly diagnosed cases, the proportion who had an asymptomatic streptococcal pharyngitis and consequently did not receive penicillin would be higher. Instead, Land and Bisno recently reported that of 41 patients with rheumatic fever diagnosed between 1977 and 1982, 31.7% denied a preceding upper respiratory infection or sore throat—a figure nearly identical to the 34% figure cited in a study published 13 years earlier.

How important then is the lessened efficacy of penicillin preparations for streptococcal pharyngitis noted in recent studies? Clearly, inadequate bacteriologic responses have not been associated with a resurgence in rheumatic fever cases in this country, nor apparently with a rise in suppurative complications or a poorer clinical response during acute infection. Vigilance for such changes, rather than abandonment of penicillin as first-line therapy, seems the appropriate course of action at present.

Another concern in the management of patients with possible streptococcal pharyngitis is when to begin antibiotic treatment. Endemic cases cannot be diagnosed reliably on clinical grounds alone unless the characteristic rash of scarlet fever is present. A properly performed throat culture has been the diagnostic method of choice. Results can be available in as short a time as 15 minutes. The specificity of these systems is excellent, often over 98%, whereas the sensitivity is somewhat lower, 80–95%, when compared with standard culture. Use of Rayon throat swabs appears to give better results than do cotton ones. Therefore, a practical approach to management is to base the decision to give or withhold treatment on the result of such an immediate diagnostic test, and to confirm the negative reactions by culture.

Other Causes of Pharyngitis

Members of the mouth flora, usually what appears to be a mixture of anaerobic bacteria and spirochetes, are an uncommon cause of acute pharyngitis (Vincent's angina), sometimes complicated by tonsillar abscess formation. With this infection, a purulent exudate and a foul odor to the breath may be present. The lesion typically begins unilaterally but may spread to the other side of the pharynx or to the larynx. Regional lymphadenopathy and leukocytosis are common. Septicemia, specifically with the penicillin-sensitive anaerobe Fusobacterium necrophorum, can be a disastrous complication of this condition (Lemierre's disease), which may be associated with jugular vein septic thrombophlebitis and metastatic infection of the lung, joints, and other sites. Peritonsillar abscess formation also occurs unilaterally and is associated with severe pain and dysphagia.

In one retrospective review of 12 patients who presented with peritonsillar abscess or cellulitis, throat cultures were negative for Group A streptococci in 11 (92%) prior to any treatment. Cultures of the tonsillar pus obtained by needle aspiration also failed to grow Group A streptococci in seven of eight patients, and the one patient with a positive culture had had a prior negative throat culture. Thus, this unusual group of patients is liable to go un-
treated initially because of a negative throat culture. One can only speculate as to the number of such patients who may have been benefited inadvertently by the liberal and perhaps excessive use of penicillin for patients with exudative pharyngitis. The existence of such cases certainly argues against overly dogmatic recommendations on the "necessity" of withholding antibiotics, at least early on, in sick patients without streptococcal disease. More information is still needed on diagnosis and pathogenesis of this infection.

A related infection known as acute necrotizing ulcerative gingivitis (Vincent's disease, Vincent's stomatitis, or trench mouth) is caused by the same or similar microorganisms indigenous to the oral cavity. The typical patient experiences the sudden onset of gingival pain and has tender, bleeding gums, fetid breath, and a bad taste. The gingival mucosa, especially the papillae between the teeth, becomes ulcerated and may be covered by a gray exudate, which is removable with gentle pressure. Involvement of the gingiva is usually patchy but may be more extensive or spread to the posterior pharynx (Vincent's angina—see above). If the ulceration is extensive, fever, cervical lymphadenopathy, and leukocytosis occur. Most patients are young adults with poor oral hygiene. Treatment includes local debridement and lavage with oxidizing agents, which usually brings prompt relief. Antibiotic therapy with penicillin or metronidazole is highly effective.

Mycoplasma pneumoniae is another treatable cause of pharyngitis that has been incriminated etiologically in varying frequencies up to approximately 10% of cases. The illness is relatively mild, although an exudate is sometimes seen. In the absence of concomitant myringitis or pneumonitis, however, it would likely go undiagnosed since mycoplasmal cultures are generally unavailable and routine antibody testing would be impractical. Erythromycin or tetracycline, not penicillin, is the drug of choice.

Viruses cause the majority of cases of pharyngitis in which some pathogen is identified, and may well be responsible for most of the other approximately 40% of cases without a known cause. Usually, the sore throat is mild and merely part of the overall symptom complex of the common cold. Rhinoviruses are the most frequently isolated viruses, but several other viruses can cause an identical clinical picture (Tables 1 and 2). Sore throat is often a major complaint in patients with influenza but is rarely the only manifestation of the disease. The clinical presentation of pharyngitis due to adenovirus may be quite severe with pharyngeal erythema and exudate, more closely mimicking streptococcal infections. Distinguishing features of adenoviral infections include their occurrence in the summer and the presence of conjunctivitis, which occurs in one third to one half of patients. Conjunctivitis is unilateral in 75% of patients.

Pharyngitis associated with primary herpes simplex infection or that due to strains of coxsackievirus may be recognizable clinically. Both are characterized by the presence of vesicles and shallow ulcers. Primary herpes infection varies from asymptomatic to agonizingly severe. Vesicles and ulcers are often numerous and may occur anywhere in the mouth, sometimes with a concomitant gingivitis. Tender cervical adenopathy and fever are seen in the more ill patients. Herpangina primarily affects children between the ages of 3 and 10 years, is usually caused by coxsackievirus A (types 1-10, 16, and 22) and less commonly by coxsackievirus B (types 1-5) or echoviruses (types 3, 6, 9, 16, 17, 25, and 30), and is characterized by two to six small vesicles typically confined to the posterior pharynx (soft palate, uvula, anterior tonsillar pillars). In some cases, the presence of anorexia and abdominal pain mimic acute appendicitis. Gingivitis, prominent systemic toxicity, and cervical lymph node enlargement are not seen in herpangina. Hand-foot-and-mouth disease is also caused by coxsackievirus (usually type A-16 and less commonly A-5, A-7, A-9, A-10, B-2, and B-5). This illness occurs predominantly in children under 10 years of age and is associated with vesicles in the oral cavity. Unlike herpangina, however, in hand-foot-and-mouth disease, the oral lesions characteristically occur in the front of the mouth, especially on the inner aspects of the lip, the anterior buccal mucosa, and the tongue,
and in most cases, lesions are also found on the extremities. The skin lesions are tender and consist of papules and clear vesicles with a surrounding zone of erythema.\(^{6,7}\)

Pharyngitis with tonsillar exudate persisting for 4 or more days with a negative throat culture for group A streptococci, or occurring in association with diffuse lymphadenopathy, splenomegaly or with many atypical lymphocytes on blood smear suggests the possibility of infectious mononucleosis (IM) (Epstein-Barr virus). Pharyngeal involvement occurs in over 80% of patients with IM, and tonsillar exudate and a palatal cantharidarc each found in approximately one quarter of patients.\(^{24}\) In most cases, the severity of the pharyngitis increases over several days, peaks around 5 days, and then slowly improves.\(^{24,68}\) Inflammation of the pharynx may be severe and may pose one of the infrequent life-threatening complications of the disease. Both pharyngeal and laryngeal edema can occur along with massive tonsillar enlargement (anginose mononucleosis, see Fig. 1). Inspiratory stridor with significant airway obstruction secondary to lymphoid tissue hypertrophy is a medical emergency.

In the past, concurrent streptococcal pharyngitis was reported to occur in 30% of patients with IM.\(^{69}\) More recent studies, however, have failed to confirm this association.\(^{70-72}\) Prior studies also emphasized that the use of ampicillin is associated with the development of a macular-papular skin rash in up to 95% of patients with IM.\(^{73,74}\) The pathogenesis of this phenomenon is unknown, but evidence exists that discounts an allergic basis.\(^{75}\) Interestingly, patients appear to tolerate penicillin normally. In a more recent study from three community hospitals of 80 patients with IM who received ampicillin, only 10 (28%) developed a rash.\(^{76}\) The reason for the discrepancy between this and prior studies is unknown.

Diagnosis of IM is established either by documentation of the presence of heterophile antibody, which is present in 90% of patients, or by demonstration of the characteristic antibody responses to specific Epstein-Barr viral antigens.

Management of patients with anginose mononucleosis is controversial. Various therapies have been promoted only to be later discarded. These include neoarsphenamine, gamma globulins, bismuth, chloroquine, and metronidazole. Differing opinions exist concerning the role of therapeutic or symptomatic intervention with corticosteroids. Seven prospective controlled studies with a total of 349 patients have been done to evaluate the effect of corticosteroids on the duration of sore throat and/or resolution of tonsillar enlargement.\(^{77-82}\) Findings are conflicting. Further, anecdotal cases of patients with anginose IM have been reported for whom tracheostomy, placement of a temporary airway or emergency tonsillectomy was required despite the use of corticosteroid therapy. Therefore, the value of these medications in preventing airway obstruction in anginose IM has not been established by objective data in the published literature. Whether or not the immunosuppressive properties of corticosteroids may enhance the potential oncogenicity of the Epstein-Barr virus is unknown, but this consideration does warrant caution in their use.

Epstein-Barr virus has been shown to be susceptible in vitro to several antiviral agents including acyclovir,\(^{83,84}\) adenine arabinoside,\(^{85}\) leukocyte interferon,\(^{86}\) and phosphonacetic acid,\(^{87}\) and use of one or more of these drugs might seem a more logical and specific therapeutic approach. Andersson and colleagues randomized 31 patients with IM who had symptoms for 7 or fewer days to treatment with intravenous acyclovir (30 mg/kg per day) or placebo for 7 days in a double-blind trial. Acyclovir significantly inhibited oropharyngeal viral shedding compared with placebo (\(P < 0.001\);
however, there was no significant improvement in rate of recovery of sore throat or tonsillar swelling, and one patient in the acyclovir group required tracheotomy because of respiratory obstruction due to tonsillar enlargement. Therefore, to date, no therapy has been proved to be of clinical benefit to patients with anginose IM. Further studies are needed to determine if certain patients might benefit from the use of corticosteroids and/or specific antiviral drugs.

Recently, several investigators have reported a syndrome of prolonged atypical illness thought to be an Epstein-Barr-associated chronic mononucleosis syndrome. Patients with this illness have had pharyngitis, chronic fatigue, low-grade fevers, lymphadenopathy, and other nonspecific symptoms in association with elevated antibody titers to certain Epstein-Barr viral antigens. The pathogenesis and treatment of this condition have not been elucidated.

**Conclusion**

Mucosal infections are common and extremely varied. As illustrated by the preceding discussion of non-sexually transmitted infections of the oral mucosa, it is clear that the pathogenesis of many of these infections is directly related to phenomena that affect the background ("normal") microbial flora. Depending on conditions, this flora may assume divergent roles for the host, ranging from protector, to commensal, to pathogen. Interactions between these organisms and those exogenous microbial species encountered by the host are undoubtedly complex but of immense interest to students of infectious diseases, and of potential practical importance in the day-to-day management of patients. Emerging evidence has also suggested that the normal flora may influence the success of antibiotic therapy for streptococcal pharyngitis, adding still another dimension to the complicated interrelationship between these organisms and mucosal disease.

**References**

1. Tramont EC. General or non-specific host defense mechanisms. In: Mandell GL, Douglas RG Jr, Bennett JE. Principles and Practice of Infectious Disease. 2nd ed. New York: John Wiley & Sons, 1985:25-31.
2. Larsen B, Galask R. Vaginal microbial flora: composition and influences of host physiology. Ann Intern Med. 1982;96(Part 2):926-930.
3. Sobel J, Aronson B, Aronson S, et al. Pharyngeal conjunctival fever. Am J Dis Child. 1968;92:596-612.
4. MacNaughton MR, Madge MH, Reed SE. Two antigenic groups of human coronaviruses detected by using enzyme-linked immunosorbent assay. Infect Immun. 1981:33:734-737.
5. Cherry JD, Jahn CL. Herpangina: the etiologic spectrum. Pediatrics. 1965:36:52-534.
6. Robinson GR, Doane FW, Rhodes AJ. Report of an outbreak of febrile illness with pharyngeal lesions and exanthem. Can Med Assoc J. 1958;79:615-621.
7. Alsop J, Flewett T, Foster JR. "Hand-foot-and-mouth disease" in Birmingham in 1969. Br Med J. 1960:2:1708-1711.
8. Glezen WP, Fernald GW, Lohr JA. Acute respiratory disease of university students with special reference to the etiologic role of Herpesvirus hominis. Am J Epidemiol. 1975:101:111-121.
9. Jordan WS, Denny FW, Badger GF, et al. A study of illness in a group of Cleveland families. XVII. The occurrence of Asian influenza. Am J Hyg. 1968:68:190-212.
10. Smith CB, Purcell RH, Bellanti JA, et al. Protective effect of antibody to parainfluenza type 1 virus. N Engl J Med. 1966:276:1145-1152.
11. Hall CB, Geiman JM, Biggar R, et al. Respiratory syncytial virus infections within families. N Engl J Med. 1976:294:414-419.
12. Gwaltney JM Jr, Hendley JO, Simon G, et al. Rhinovirus infections in an industrial population. I. The occurrence of illness. N Engl J Med. 1966;275:1261-1268.
13. Gwaltney JM Jr. Rhinoviruses. In: Evans AS, ed. Viral Infections of Humans: Epidemiology and Control, 2nd ed. New York: Plenum, 1982:491-517.
14. Seidenfeld SM, Sutker WL, Luby JP. Fusobacterium necrophorum septicemia following oropharyngeal infection. JAMA. 1982:248:1348-1350.
15. McCluskey BV, Eiler JJ, Green M, et al. The 1970 epidemic of diphtheria in San Antonio. Ann Intern Med. 1971:75:495-503.
16. Lipsky BA, Goldberger ACC, Tompkins LS, et al. Infections caused by non-diphtheria Corynebacteria. Rev Infect Dis. 1982:4:1220-1235.
17. Meers PD. A case of classical diphtheria, and other infections due to Corynebacterium ulcerans. J Infect. 1979:1:139.
18. Caruso VG, Caruso AP, Panebianco RJ. Oropharyngeal tularemia. NY State J Med. 1985:83:226-227.
19. Van Asperen PP, Donohue J. Empyema due to beta-lactamase-producing H. influenzae type B complicating severe laryngopharyngitis and cervical cellulitis. Aust NZ J Med. 1984:14:280.
20. Komaroff AL, Aronson MD, Pass TM, et al. Serologic evidence of chlamydial and mycoplasmal pharyngitis in adults. Science. 1985:222:297-299.
21. Wormser GP, Hewlett D. Strategy for streptococcal pharyngitis. Hospital Medicine. May 1984;20:13-34.

22. Stryker WS, Fraser DW, Facklam RR. Foodborne outbreak of Group G streptococcal pharyngitis. Am J Epidemiol 1982;116:533-540.

23. Tacket CO, Davis BR, Carter BP, et al. Yersinia enterocolitica pharyngitis. Ann Intern Med. 1988;99:40 42.

24. Hoagland RJ. The clinical manifestations of infectious mononucleosis, a report of two hundred cases. Am J Med Sci. 1960;240:21-28.

25. Bothwell PW. Brucellosis in children. Arch Dis Child. 1962;37:628-639.

26. Buchner LH, Schneierson SS. Clinical and laboratory aspects of Listeria monocyotosis infections. Am J Med. 1968;45:904-921.

27. Eshchar J, Waren M, Alkan WJ. Syndromes of Q fever. JAMA 1966;195:390-393.

28. Rice DP, Feldman JJ, White KL. The current burden of illness in the United States. Occasional Papers of the Institute of Medicine. Washington DC: National Academy of Sciences. 1976:1.

29. Dingle JH, Badger GF, Jordan WS Jr. Illness in the home; study of 25,000 illnesses in a group of Cleveland families. Cleveland: The Press of Western Reserve University, 1964.

30. Huss H, Jungkind D, Amadio P, Rubenfeld I. Frequency of Chlamydia trachomatis as the cause of pharyngitis. J Clin Microbiol. 1985;22:858-860.

31. Kaplan EL. The group A streptococcal upper respiratory tract carrier state: an enigma. J Pediatr. 1980;97:246:1790-1795.

32. Denny FW. Effect of treatment on streptococcal pharyngitis: is the issue really settled? Pediatr Infect Dis. 1985;4:352-354.

33. Lowe R. Early treatment of streptococcal pharyngitis. Ann Emerg Med. 1985;14:440-448.

34. Hall CB, Breeze BB. Does penicillin make Johnny's strep throat better? Pediatr Infect Dis. 1984;3:7-9.

35. Nelson JD. The effect of penicillin therapy on the symptoms and signs of streptococcal pharyngitis. Pediatr Infect Dis. 1984;3:10-13.

36. Krober MS, Bass JW, Michels GN. Streptococcal pharyngitis. Placebo-controlled double-blind evaluation of clinical response to penicillin therapy. JAMA. 1985;253:1271-1274.

37. Randolph MF, Gerber MA, DeMeeo KK, et al. Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. J Pediatr. 1985;106:870-875.

38. Schwartz RH, Wientzen R, Pedreira F, et al. Penicillin V for Group A streptococcal pharyngotonsillitis: a randomized trial of seven vs ten days' therapy. JAMA. 1981;246:1790-1795.

39. Gastanaduy AS, Kaplan EL, Huwe BB, et al. Failure of penicillin to eradicate Group A streptococci during an outbreak of pharyngitis. Lancet. 1980;2:498-501.

40. Kaplan EL, Gastanaduy AS, Huwe BB. The role of the carrier in treatment failures after antibiotic therapy for Group A streptococci in the upper respiratory tract. J Lab Clin Med. 1981;98:326-335.

41. Brook I. The role of beta-lactamase-producing bacteria in the persistence of streptococcal tonsillar infection. Rev Infect Dis. 1984;6:601-607.

42. Cooperman SM. Cherez le chien. Household pets as reservoirs of persistent or recurrent streptococcal sore throats in children. NY State J Med. 1982;82:1855-1857.

43. Siegel AC, Johnson EE, Stollerman GH. Controlled studies of streptococcal pharyngitis in a pediatric population: I. Factors related to the attack rate of rheumatic fever. N Engl J Med. 1961;265:559-566.

44. Brook I, Yocum P. Quantitative measurement of beta lactamase in tonsils of children with recurrent tonsillitis. Acta Otolaryngol (Stockh). 1984;98:556-559.

45. Bernstein SH, Stollerman M, Allerhand J. Demonstration of penicillin inhibition by pharyngeal micro-flora in patients treated for streptococcal pharyngitis. J Lab Clin Med. 1964;63:14-22.

46. Brook I, Gober AF. Emergence of beta-lactamase-producing aerobic and anaerobic bacteria in the oropharynx of children following penicillin. Clin Pediatr (Phila). 1984;23:338-339.

47. Brook I, Pazzaglia G, Coolbaugh JC, et al. In vitro protection of Group A beta-hemolytic streptococci by beta lactamase producing Bacteroides species. J Antimicrobial Chemother. 1988;12:599-606.

48. Randolph MF, Redys JJ, Hibbard EW. Streptococcal pharyngitis. III. Streptococcal recurrence rates following therapy with penicillin or with clindamycin (7-chlorolincyclomycin). Del Med J. 1970;42:87-92.

49. Brook I, Hierkawa R. Treatment of patients with recurrent tonsillitis due to Group A beta-hemolytic streptococci: prospective randomized study comparing penicillin, erythromycin, and clindamycin. Pediatr Res. 1984;18:270A.

50. Ginsburg CM, McCracken GH Jr, Gibson P. The role of beta lactamase producing bacteria in treatment failures of Group A streptococcal pharyngitis. International Conference on Antimicrobial Agents Chemotherapy. Minneapolis, MN, 1985: Abstract #603.

51. Gooch WM III, Swenson E, Higbee MD, et al. Comparison of cefoxime axetil and penicillin V as therapy for Group A beta-hemolytic streptococcal pharyngitis. International Conference on Antimicrobial Agents Chemotherapy. Minneapolis, MN, 1985: Abstract #604.

52. Smith TD, Huskins WC, Kim KS, et al. Eradication by dicycloxacinil of Group A streptococci from penicillin treatment failures. International Conference on Antimicrobial Agents Chemotherapy. Minneapolis, MN, 1985: Abstract #606.

53. Tanz RR, Shulman ST, Barthel MJ, et al. Penicillin plus rifampin eradicates pharyngeal carriage of Group A streptococci. J Pediatr. 1985;106:876-880.

54. Chaudhary S, Bilinsky SA, Hennessy JL, et al. Penicillin V and rifampin for the treatment of Group A streptococcal pharyngitis: a randomized trial of 10 days of penicillin vs 10 days penicillin with rifampin during the final 4 days of therapy. J Pediatr. 1986;106:481-486.

55. Pantel RH. Cost effectiveness of pharyngitis management and prevention of rheumatic fever. Ann Intern Med. 1977;86:497-499.

56. Land MA, Bano AL. Acute rheumatic fever: a vanishing...
disease in suburbia. JAMA. 1983;249:895–898.

57. Stollerman GH. Global changes in Group A streptococcal diseases and strategies for their prevention. Adv Intern Med. 1981;27:375–406.

58. Gordin L, Lilienfeld A, Rodriguez R. An evaluation of the Maryland rheumatic fever registry. Public Health Rep. 1969;84:335–339.

59. Brien JH, Bass JW. Streptococcal pharyngitis: optimal site for throat culture. J Pediatr. 1985;106:781–785.

60. Kaplan EL, Couser R, Huwe BB, et al. Significance of quantitative salivary cultures for Group A and non-Group A β-hemolytic streptococci in patients with pharyngitis and in their family contacts. Pediatrics. 1979;64:904–912.

61. Rapid detection of beta haemolytic streptococci. Lancet. 1986;1:247–248.

62. Schwartz RH, Hayden GF, McCoy P, et al. Rapid diagnosis of streptococcal pharyngitis in two pediatric offices using a latex agglutination. Pediatr Infect Dis. 1985;6:647–650.

63. Berkowitz CD, Anthony BF, Kaplan EL, et al. Cooperative study of latex agglutination to identify Group A streptococcal antigen on throat swabs in patients with acute pharyngitis. J Pediatr. 1985;107:89–92.

64. Gerber MA. Culturing of throat swabs: end of an era. J Pediatr. 1985;107:85–88.

65. Gray WC. Throat culture in impeding peritonsillar abscess. South Med J. 1984;77:1545–1547.

66. Stephen KW, McLatchie MF, Mason DK, et al. Treatment of acute ulcerative gingivitis (Vincent's type). Br Dent J. 1966;121:313–322.

67. Gwaltney JM Jr. Pharyngitis. In: Mandell GL, Douglas RG Jr, Bennett JE. Principles and Practice of Infectious Disease. 2nd ed. New York: John Wiley & Sons. 1985:355–359.

68. Lassari AD, Bapat VR. Syndromes of infectious mononucleosis. Clin Pediatr. 1979:300–305.

69. Henke CF, Kurland LT, Elueback LR. Infectious mononucleosis in Rochester, Minnesota, 1950 through 1969. Am J Epidemiol. 1973:98:483–490.

70. Collins M, Fleisher GR, Fager SS. Incidence of beta-hemolytic streptococcal pharyngitis in adolescents with infectious mononucleosis. Journal of Adolescent Health Care. 1984:5:96–100.

71. Merrimac SC, Keeling RP. Beta-hemolytic streptococcal pharyngitis: Uncommon in infectious mononucleosis. South Med J. 1983;76:575–576.

72. Chretien JH, Esswein JG. How frequent is bacterial superinfection of the pharynx in infectious mononucleosis? Clin Pediatr. 1976;15:424–427.

73. Pullen H, Wright N, Murdoch JM. Hypersensitivity reactions to antibacterial drugs in infectious mononucleosis. Lancet. 1967;2:1176–1178.

74. Patel BM. Skin rash with infectious mononucleosis and ampicillin. J Pediatr. 1967;40:910–911.

75. Geyman JP, Erickson S. The ampicillin rash as a diagnostic and management problem: case reports and literature review. J Fam Pract. 1978;1:498–496.

76. Crespin FH Jr, Gordon RC. Infectious mononucleosis in the community hospital. J Fam Pract. 1983;16:703–708.

77. Collings M, Fleisher G, Kreisberg J, et al. Role of steroids in the treatment of infectious mononucleosis in the ambulatory college student. J Am Coll Health. 1984;33:101–105.

78. Cronk GA, Naumann DE, ACTH, tetracycline, and tetracycline combined with cortisone in the treatment of infectious mononucleosis. Lancet. 1966;76:77–78.

79. Evans AS. Infectious mononucleosis in University of Wisconsin students. Am J Hyg. 1960;71:342–362.

80. Antilla V, Makela TE, Kiemola E. Corticotropin in the treatment of infectious mononucleosis. Acta Med Scand. 1962:171:345–348.

81. Prout C, Dalrymple W. A double-blind study of eighty-two cases of infectious mononucleosis treated with corticosteroids. J Am Coll Health. 1960;15:02–66.

82. Klein E, Cochran JF, Buck RL. The effects of short-term corticosteroid therapy on the symptoms of infectious mononucleosis. Acta Pediatr Scand. 1969;17:446–452.

83. Colby BM, Shaw JE, Elion GB, et al. Effect of acyclovir [9-(2′-hydroxyethoxymethyl) guanine] on Epstein-Barr virus DNA replication. J Virol. 1980;34:560–568.

84. Hirsch MS, Schooley RT. Drug therapy: treatment of herpesvirus infections. N Engl J Med. 1983;309:963–970.

85. Coker-Vann M, Dolin R. Effect of adenine arabinoside on Epstein-Barr virus in vitro. J Infect Dis. 1977:135:447–453.

86. Thorley-Lawson D. The transformation of adult but not newborn human lymphocytes by Epstein-Barr virus and phytohemagglutinin is inhibited by interferon: the early suppression by T cells of Epstein-Barr infection is mediated by interferon. J Immunol. 1981;126:829–833.

87. Thorley-Lawson D, Strominger JL. Transformation of human lymphocytes by Epstein-Barr virus is inhibited by phosphonoacetic acid. Nature 1970;283:332–334.

88. Andersson J, Britton S, Ernberg I, et al. Effect of acyclovir on infectious mononucleosis: a double-blind, placebo-controlled study. J Infect Dis. 1986;153:283–290.

89. Horowitz CA, Henle W, Henle G, et al. Clinical evaluation of patients with infectious mononucleosis and development of antibodies to the R component of the Epstein-Barr virus-induced early antigen complex. Am J Med. 1975;58:330–338.

90. Toth M, Strauss SE. Chronic Epstein-Barr virus disease: a workshop held by the National Institute of Allergy and Infectious Diseases. Ann Intern Med. 1985;103:951–953.

91. Strauss SE, Tosato G, Armstrong G, et al. Persisting illness and fatigue in adults with evidence of Epstein-Barr virus infection. Ann Intern Med. 1985;102:7–16.