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I. Introduction

Humans and animals are constantly being inoculated with various microorganisms resident in the upper respiratory tract and by inhaled aerosols, yet pneumonia is a relatively rare event. This implies the existence of very efficient defense mechanisms which are capable of eliminating the vast majority of microorganisms before they colonize and multiply to sufficient levels to result in clinical disease. In order to overcome this continuous barrage of microorganisms, there is a complex array of defense mechanisms present in the upper and lower respiratory tract capable of clearing these organisms. However, in individuals suffering from a variety of diseases, including virus infections, colonization occurs rapidly with subsequent development of pneumonia. Thus, it is estimated that 90% of bacterial pneumonias
develop after a viral infection. Furthermore, individuals suffering from a viral pneumonia have a 40% chance of developing bacterial pneumonia (Jakab, 1982). The reasons for the increased colonization of the lung by bacteria following virus infections has been shown to be related to the surface properties of epithelial cells lining the respiratory tract, the physiological environment of the respiratory tract, as well as the alteration of the specific and nonspecific defense mechanisms of the lung which occurs as a result of virus infection. These conditions allow greater numbers of bacteria to adhere to the surface of cells, possibly to replicate at a faster rate and overcome some of the nonspecific defense mechanisms present in the respiratory tract. In the present review, we will attempt to indicate how viruses enhance bacterial colonization and adherence to respiratory epithelial tissue, how viruses alter the specific and nonspecific defense mechanisms of the respiratory tract, which allow the newly adhered bacteria to replicate and further overcome some of these compromised defense mechanisms. In addition, we will discuss how the host defense mechanisms, in attempting to clear the viruses or bacteria, can themselves lead to immunopathology and further increase the replicative rate of the bacteria and aid in the development of pneumonia. Finally, we will discuss potential ways of reducing viral bacterial respiratory infections by immunization or the use of various chemotherapeutic and immunomodulators presently being developed. Although examples will be used from a variety of different human and animal respiratory infections, the major emphasis will be on attempting to provide a unifying hypothesis of how viruses modify the environmental conditions of the lung and alter host defense mechanisms to allow bacteria to replicate faster and produce pneumonia. Examples will be used to demonstrate specific events, but it should not be construed that every event occurs in every situation.

II. Virus Infections

During the past 15–20 years, considerable advances have been made in understanding the events which occur at the molecular level during initiation of respiratory disease (Fields, 1985). The sequence of events in respiratory infections, whether they are caused by rhinoviruses, orthomyxoviruses, paramyxoviruses, or adenoviruses, or coronaviruses, etc., is rather similar in that in order to initiate infection and produce illness the viruses must enter their host and come in contact with susceptible tissues and cells. This initial infection generally occurs in one of two ways: direct contact with droplets or secretions
containing virus or with aerosolized virus. The small aerosolized virus particles can enter various sections of the respiratory tract, including the lower respiratory tract. However, in general, the majority of the initial infections occur in the upper respiratory tract. Immediately upon contact with the respiratory epithelium the virus can encounter a variety of nonspecific defense mechanisms including mucus and nonspecific compounds inhibiting virus attachment to the host cell epithelium. If a specific interaction between the virus and host cell receptors occurs, the virus initiates its replication cycle and generally induces lytic infection of the respiratory epithelium. Since most viruses which infect the upper respiratory tract cause local infections and cytopathology, the incubation time is generally short.

One of the initial defense mechanisms in the respiratory tract is mucus, which may contain either glycoproteins similar to the receptor molecules on respiratory epithelial cells, or, indeed, secreted receptors. These glycoproteins may interfere with the initial attachment of the viruses to epithelial cells. Some viruses possess specific enzymes (neuraminidase) which may destroy some of these mucous glycoproteins to allow attachment and infection of epithelial cells. Furthermore, some proteases present within the mucus may result in cleavage of specific virus glycoproteins which are required for infectivity (Choppin and Scheid, 1980).

Once infection of the epithelial cells of the respiratory tract occurs, virus replication ensues with the production of a large number of progeny viruses, which can either bud from the plasma membrane of the epithelial cell or, in the case of naked viruses, result in lysis of the virus-infected cells. Upon release of virus from infected cells, they can spread throughout the respiratory tract either by cell-to-cell spread (slow), aerosolization into the lower tract during breathing, or spread in the mucus due to ciliary action. As a result of this spread, virus infection of the sinuses, bronchi, lower trachea, and lung occurs (Chanock et al., 1963; Parrott et al., 1959). The result may be rapid vascular reactions and accumulation of transudates and exudates, cell debris, and inflammatory cells. As a result of cellular degeneration, environmental conditions are established which are conducive to bacterial cell attachment and growth (see Section III). In some cases, even if death of virus-infected cells does not occur, some of the host epithelial cells "luxury functions" may be reduced. These may include secretion of various glycoproteins, mucus, or bactericidal factors.

As a consequence of virus infection, interferon (IFN) is produced and released into the extracellular environment of the respiratory tract as well as systemically (Green et al., 1982; Babiuk et al., 1985). This family of antiviral molecules can limit the rate of virus replication and
modulate the host's defenses to both the virus and superinfecting bacteria (Babiuk et al., 1985). In addition to the release of IFN, infected cells also release other viral components which can be detrimental to epithelial and leukocyte functions (see Sections V and VI).

III. BACTERIAL ADHERENCE

The binding or attachment of bacteria to various substrates within their environment is an important prerequisite in the process of colonization. Attachment of bacteria to the surface of cells is mediated through adhesins present on the bacterial cell wall. These adhesin proteins bind to specific glycolipid or glycoprotein receptors expressed on the surface of cells (Normark et al., 1986). Not only is this attachment of bacteria to the mucosal surface an important initial step in colonization, it also forms the basis of infection and production of disease by pathogenic bacteria (Costerton et al., 1981; Beachey, 1981; Sparling, 1983). The adherence of bacteria to the mucosal surface is a complex phenomenon involving virulence factors (including adhesins) of the pathogenic bacteria, as well as by the mucosal surface itself (local immunity, epithelial cell turnover, and the mucous lining or layer) (Babiuk, 1984; Reid and Sobel, 1986). The expression of these adhesin proteins can be modulated by the environmental conditions of the lung and are subject to both phase and antigenic variation. A single bacterial cell can give rise to progeny cells that express adhesin proteins that are different in structure, number, serology, and function depending on the environment. This variation in expression of adhesins is thought to be an important factor in the ability of the bacteria to adapt to its microenvironment and to evade the primary host defense mechanisms (Haas et al., 1986). Although the type of adhesins varies with each bacteria, fimbriae, pilus, and lipoteichoic acid have been shown to be primarily involved in mediating adhesion (Ofek, 1984). Other factors have also been shown to be important adhesins, for example, the filamentous hemagglutinin and toxin of Bordetella pertussis (Twomanen and Weiss, 1985). In fact, these two adhesins have been reported to work in concert during the process of colonization (Twomanen and Weiss, 1985). The agglutinogens of B. pertussis have also been shown, in vitro, to be capable of acting as adhesins (Redhead, 1985).

The ability of bacteria to produce more than one adhesin-type protein is an added advantage for the bacteria during initial infection, since it is at this time that it is crucial for the bacteria to be able to become established and colonize (Ofek, 1984). As stated above, the
regulation of these factors is influenced by the phase variation and growth cycle of the bacteria. The microenvironment of the lung will therefore add selective pressure in determining whether or not the bacteria expresses one or more of the adhesins (Ofek, 1984). If virus infection favors bacterial growth and phase variation, the probability is high that colonization and subsequent pneumonia will ensue.

Structural variation, or phenotype, of bacteria also plays a role in bacterial adherence. Capsule production affects not only the hydrophobicity of the organism but alters its ability to interact with epithelial and phagocytic cells (Whitnack et al., 1981; Beachey, 1981; Ofek et al., 1982; Ofek, 1984). It has been suggested that the production of hyaluronic capsules interferes with adhesion. Thus, variation in phenotype, may be very important in pathogenesis in that noncapsulated bacteria can initiate the infection, as a result of their adherence capabilities, and, once established, they can become capsulated and thereby have a better chance of survival by preventing attachment to phagocytic cells (Ofek, 1984; Babiuk, 1984). Capsules composed of polysaccharide also have the ability to interfere with adhesion (Craven et al., 1980; Selinger and Reed, 1979; Glorioso et al., 1982). Ofek (1984) points out that the functional ability of bacteria to adhere to host cells is not always beneficial to the bacteria; that is, attachment of bacteria to the mucosal epithelium is essential for the initial survival of the pathogen, whereas attachment of bacteria to phagocytic cell does not, in most cases, benefit the bacteria but increases the survival of the host. The ability of the bacteria to change the expression of type and number of adhesin proteins and the production of substances capable of interfering with attachment may be of fundamental importance not only in the establishment of colonization and subsequent infection, but also as a means of circumventing the host's defense mechanisms.

Alteration of adherence of bacteria may also come about by extrinsic factors such as the presence or absence of divalent cations. It has been shown that zinc levels are altered during bacterial infections and that zinc reduces the surface charges so that adhesion is enhanced (Sugarman et al., 1982). Viral infections appear to influence adherence and colonization of bacteria (Davison and Sandford, 1981; Fainstein et al., 1980; Sanford et al., 1978; Nugent and Pesanti, 1982). The mechanisms by which viruses alter bacterial adherence are many and include alteration of host cell surface membrane receptors and alteration of the microenvironment in which bacterial attachment occurs (Babiuk, 1984). Viral infections alter the levels of fibronectin production. Since colonization by bacteria has been correlated with low fibronectin levels (Hynes and Bye, 1974; Woods, 1987), this may be a very
important factor in bacterial colonization. Cell death caused by viruses also increases the release of proteases, which may be responsible for degrading fibronectin on the surface of innocent-bystander cells, thus favoring adherence. Bacteria themselves produce proteases which would be capable of further decreasing fibronectin levels and increasing colonization (Woods et al., 1981; Yamada and Weston, 1974). Many medically important bacterial pathogens produce IgA proteases (Miluzzo and Delisle, 1984; Mulks and Plaut, 1978). Furthermore, many of these proteases are dependent on divalent cations for their activity (Labib et al., 1978). If during a viral infection extensive hemorrhage and tissue damage occurs, an increase in levels of divalent cations will result. One other ion that has been shown to be very important in bacterial growth and pathogenesis is iron (Hatch et al., 1981; Miles and Khimji, 1975). Certain bacteria produce iron chelators or iron-binding proteins capable of trapping the iron required for their growth. Furthermore, in some cases iron does increase the levels of adhesins or pilus formation on bacteria (Babiuk, 1984). If a virus infects the respiratory tract and induces extensive cell damage and hemorrhages, this would increase the levels of iron and other divalent cations, which would favor both bacterial adhesion and growth. Furthermore, the amount of iron bound to transferrin has been shown to be critical in immune regulation (Matzner et al., 1979). Thus, the level of iron can affect not only bacterial adhesion and growth, but also the host's ability to respond to the infection.

Viral infections have been implicated in alteration of epithelial cell secretion (Pijoan et al., 1980). Some of these secretions have bactericidal activity. Therefore, their absence allows bacteria to gain a hold and initiate colonization. During infection of the upper respiratory tract, microcolonies are formed which can enter the lower respiratory tract either by aspiration (Johanson et al., 1979) or by reduced mucociliary clearance (Jakab, 1982). Large microcolonies are difficult to phagocytize and may in fact cause phagocytic cells to discharge their enzymes; these contain granules which cause surrounding tissue damage (Slauson, 1982), thereby creating a better environment for bacterial replication and further adhesion. In addition, these bacteria can release cytotoxins which have an adverse effect on phagocytic cells (see Section VII), induce more cell death, and further improve the environment for bacterial growth.

IV. PULMONARY DEFENSE MECHANISMS

Defense of the normal lung against various microorganisms is mediated by a plethora of inflammatory and immune effector cells acting
in concert with various soluble factors. In the majority of cases, more than 90% of the cells obtained by bronchoalveolar lavage are macrophages and less than 1% are neutrophils (Hunninghake et al., 1985). Based on these findings, it has often been considered that macrophages are the major cell type involved in maintaining sterility in the normal lung. However, it must be emphasized that part of the defenses begin in the upper respiratory tract where the initial interaction of the host and pathogen occurs, and the outcome of these interactions will determine whether the organism will ever enter the lung. The first defenses include anatomical barriers, mucociliary clearance mechanisms, reflex mechanisms, local secretory IgA, iron-containing proteins such as transferrin, and surfactant—even before alveolar macrophages become involved. These early surveillance mechanisms do not depend on the immunological status of the host, with the exception of immunoglobulin. When some of these mechanisms either individually or in concert fail to eliminate the microorganisms, then other more specific defense mechanisms must come into play to clear the organism. These include both humoral and cellular immune responses, as well as inflammatory responses best characterized by the influx of polymorphonuclear granulocytes (PMN; see Table I). In this review we will not discuss in detail all of the individual defense mechanisms that are functioning in the respiratory tract to prevent infection, but we will summarize the important defense mechanisms which can be altered as a result of virus infection and thereby increase the opportunity for bacteria to colonize the lower respiratory tract and cause pneumonia.

The advent of the bronchioalveolar lavage procedure has rapidly expanded our knowledge during the past 10 years of understanding the various secretory and cellular components of the lung. In normal individuals, a variety of secretory products are present at various levels in the respiratory tract. In many cases, these secretions contain complement components, transferrin, surfactant, fibronectin, and immunoglobulins. Mostly, these various humoral factors act in concert with specific immunoglobulin and cells to help destroy or reduce the replication of viruses and bacteria. Fibronectin, transferrin, and surfactant are three substances which, in addition to being able to potentiate nonimmune opsonic activity in host defense mechanisms, also are important in altering the rate of adherence and bacterial replication. For example, fibronectin or fragments thereof have been shown to be functionally important in enhancing macrophage—monocyte phagocytosis of particles, not only as a conventional opsonin, but also by stimulating the macrophages to ingest opsonized particles (Czop et al., 1982; Pommier et al., 1983). Transferrin has been demonstrated to have bacteriostatic effects on some bacteria which are strongly depen-
TABLE I

SOME IMPORTANT COMPONENTS OF LUNG DEFENSE

| Defense component       | Function                                                                 |
|-------------------------|--------------------------------------------------------------------------|
| Surveillance mechanisms |                                                                         |
| Ciliated epithelium     | Removal of foreign pathogens; reduces probability of infection           |
| Mechanical barriers     |                                                                         |
| Mucus                   |                                                                         |
| Epithelium              |                                                                         |
| Humoral                 |                                                                         |
| Surfactant              | Alter surface charges; reducing macrophage surface tension; facilitate killing of bacteria by macrophages; direct antibacterial activity |
| Fibronectin             | Enhance phagocytosis by macrophage–monocytes; alter bacterial attachment |
| Transferrin             | Iron binding                                                             |
| Lysozyme                | Bacterial activity                                                       |
| Immunoglobulin          | Prevent adherence; opsonization                                           |
| Cellular                |                                                                         |
| Macrophage/monocyte     | Phagocytosis, killing of bacteria; release of chemotactic factors; release of soluble mediator (fibronectin, complement); antigen presentation |
| Lymphocytes             |                                                                         |
| T, B, NK, etc.          | CELLULAR AND HUMORAL RESPONSES                                            |
| Granulocytes            |                                                                         |
| Neutrophils, eosinophils, basophils | Phagocytosis and killing of bacteria; immunopathology, superoxide free radicals |

dent on the presence of iron for their growth (Rankin and Reynolds, 1985). Although many studies have been conducted in vitro, very little information is available regarding the role of transferrin in lower respiratory tract infections and their effects there. Also lacking is information on whether the synergistic interaction between transferrin and secretory IgA has an effect similar to that of lactoferrin in breast milk (Stephens et al., 1980). The action of surfactant in reducing alveolar surface tension has long been appreciated. Moreover, some evidence suggests that surfactant can also facilitate the killing of bacteria by alveolar macrophages (Laforce, 1976). In addition to enhancing alveolar macrophage killing of bacteria, surfactant has also been shown to have antibacterial activity against gram-positive bacteria (Conrod and Yoneda, 1983). Thus, surfactant appears to be able to reduce bacterial growth by two mechanisms: by direct killing and by activation of cells with antibacterial activity.
In summary, the respiratory tract is endowed with many different components, all playing a crucial role in clearing various foreign organisms from the respiratory tract (Table I). In some cases, one factor is more important than another, both in relationship to the kinetics of the infection as well as to the specific organism involved. However, in many cases, these specific factors act in concert to eliminate the organism quickly, or if indeed the organism is not eliminated they may play an important role in immunopathology and enhancement of replication of the bacteria. Evidence for the interplay between these various factors is forthcoming from studies wherein a deficiency in one single component may predispose individuals to recurrent respiratory tract infections. More specifically, following virus infections not all of the specific and nonspecific defenses are compromised, yet superinfection with bacteria frequently occurs. The probability of bacterial superinfection will depend on the capacity of the lung to eliminate bacteria, which is determined by a large number of humoral or cellular factors (Table I), on the dose of virus or bacteria and the virulence of the organisms, and on the adequacy of the specific and nonspecific host defense mechanisms. In the following section, we will discuss how viruses alter various aspects of the host's defense mechanisms, which may then lead to a reduced threshold level of susceptibility to the bacteria.

V. Viral Effects on Nonspecific Host Defense Mechanisms

As stated above, pulmonary virus infections predispose animals and humans to secondary bacterial pneumonia (Jakab, 1981, 1982a; Loosli, 1973; Barber et al., 1985), and it is assumed that this is, at least in part, a result of virus-induced impairment of alveolar macrophage (AM) functions (Jakab, 1982a). In the lungs, distal to the ciliated airway epithelium (i.e., bronchioles and alveoli), the resident AM and monocytes, migrating into the alveolar interstitium and lumen from the blood, offer the first line of defense against invading microorganisms, partly by production and secretion of antimicrobial factors such as IFN (Bielefeldt Ohmann et al., 1984), reactive oxygen species (ROS), and enzymes, and, partly, by direct cytotoxic effector mechanisms, including phagocytosis and degradation of the microbial agents. In addition, the AM may have a proinflammatory function by producing factors that form part of or can activate other parts of the defense system, thereby inhibiting microbial spread or leading to pathological lesions (see below), or both (Slauson, 1982).

In experimental animal models using various respiratory viruses, it
has been demonstrated that the severity and duration of illness depends on the amount of virus reaching the lower respiratory tract (Yates et al., 1983a; Jakab, 1982b). In the acute stages of the infection the epithelial cells of the airways appear to be the principal sites of viral replication (Yates, 1982; Jakab, 1982b), leading to direct destruction of the epithelium or at least obstruction of the "luxury functions" of cells (Oldstone et al., 1982), such as production of pulmonary surface-active lipoproteins called surfactant. AM functions may thus be indirectly inhibited (1984, 1986). In addition, viral infection may have a direct suppressive (Schwartz and Christman, 1979) or its opsonizing effect (Juers et al., 1976, 1976), which is important especially in AM phagocytosis of invading bacteria. The immediate tissue reaction to virus infection is the production of IFN, which can modulate various macrophage activities both in vivo and in vitro (Bielefeldt Ohmann and Babiuk, 1984; Bielefeldt Ohmann et al., 1984, 1986). In addition, viral infection may have a direct suppressive effect on the AM population, affecting such functions as their immunological (Fc and complement (C')) and nonimmunological membrane receptor-binding activities and receptor-mediated phagocytosis, phagosome–lysosome fusion, intracellular killing, and bacterial degradation (reviewed by Jakab, 1982b), as well as production of neutrophil chemotactic factors (McGuire and Babiuk, 1983; Gadek and Hunninghake, 1980). Although these effects are clearly evident following in vitro infection of AM by viruses, there often appear to be discrepancies between in vitro and in vivo observations. This has been amply demonstrated in the bovine herpesvirus 1 (BHV-1) infection model. Bovine AM are susceptible to infection with BHV-1 in vitro, resulting in impairment of immune receptor functions and antibody-dependent cell-mediated cytotoxicity (ADCC) (Forman and Babiuk, 1982). In contrast, less than 0.1% of AM retrieved from experimentally infected calves are productively infected with BVH-1, and neither ADCC nor receptor functions appear to be altered or at least only transiently so (Forman et al., 1982; Bielefeldt Ohmann and Babiuk, 1986). In fact it appears that selected stimulation of AM occurs after BHV-1 infection, rather than compromising functional activity (Bielefeldt Ohmann and Babiuk, 1986), as well as selective inhibition of some functions such as ADCC, chemotaxin production, and IL-1 generation (Bielefeldt Ohmann and Babiuk, 1986; McGuire and Babiuk, 1983). Whether this disparity in viral effect, directly or indirectly induced, is caused by selective effects on the activities of the AM population as a whole, or can be ascribed to a differential effect on subpopulations of AM (Bielefeldt Ohmann et al., 1986b) varying in functional activities, remains to be investigated. Whatever the explanation might be, the functionally altered AM pop-
ulation may play both a beneficial role, as well as contribute to lung injury via its proinflammatory activities. AM and monocytes are avid producers of IL-1, complement components, tissue factor (McGee and Rothenberger, 1985), platelet-aggregating factor (Roubin et al., 1983), arachidonic acid derivatives (Larson and Henson, 1983), and neutral proteases (Unanue, 1976). These factors may contribute to increased vascular permeability, coagulation, fibrinolysis, and tissue damage (Bevilacqua et al., 1984; Till and Ward, 1986; Till et al., 1982; Slauson, 1982) (see below), thereby creating an environment which promotes secondary bacterial invasion and growth, and at the same time interferes with normal clearance mechanisms (Newhouse et al., 1976).

In some virus-host systems a temporal relationship between virus replication in the lungs, development of specific immunity, and suppression of pulmonary bactericidal activity has been noted. This has led to the suggestion that the depression of AM function during viral infection may be due to an immunopathological mechanism (Jakab, 1982a; Jakab and Warr, 1983; Astry and Jakab, 1984). That this is the case in some viral infections (e.g., influenza virus pneumonia) will not be challenged here, but it certainly is not applicable to all virus–lung defense relationships (Yates et al., 1983a).

PMN may play a crucial role in the clearance of bacteria from the lower respiratory airways. PMN recruitment is induced within hours after bacterial invasion, probably mediated by the combined effect of AM-, epithelial-, and endothelial-derived chemotactic factors; including complement fragments, thromboxanes, and leukotrienes (Davies et al., 1984; Larsen and Henson, 1983). However, prior lung infection with virus can delay this recruitment (McGuire and Babiuk, 1983), and thus, perhaps, give the bacteria enough time to multiply to numbers which eventually will overwhelm the various defense mechanism and/or cause severe inflammation which will progress into a circulus vitiosus. This delay in PMN immigration may be caused either by suppressed production of AM-derived chemotactic factors (McGuire and Babiuk, 1983), by a direct suppressive effect of the virus on the migratory activity of the PMN (Ruutu et al., 1977; Bultman and Gruler, 1983; Bultman et al., 1982), or, indirectly, via the induction and production of IFN or arachidonic acid derivatives by the various cell types in the lung (Bielefeldt Ohmann and Babiuk, 1984; Davies et al., 1984). Finally, it should be taken into consideration that the circulating PMN pool may already have been depleted of the readily migrating cells due to the virus-induced PMN migration into the alveoli (McGuire and Babiuk, 1983; Yourtee et al., 1982), by the time the secondary bacterial invasion occurs. This scenario seems conceivable
in light of the neutropenia that often occurs following virus infection of the respiratory tract (Yates, 1982; Bale et al., 1982).

Whether other functions of the PMN are affected by virus infection seems to vary among various virus–host systems. Influenza virus infection has been reported to cause depression of chemiluminescence, a measure of the respiratory burst, and bactericidal activities of PMN, whereas phagocytosis remained unaffected (Abramson et al., 1981, 1982a,b). In contrast, superoxide anion production by peripheral blood PMN is significantly increased during infection of cattle with BHV-1 (Bielefeldt Ohmann and Babiuk, 1985). Bovine viral diarrhea virus (BVDV) also is reported to suppress PMN-mediated bacterial defense (Roth et al., 1981; Reggiardo and Kaeberle, 1981; Roth and Kaeberle, 1983). In humans, except for delayed impairment of chemotaxis, no consistent abnormality in PMN function has been found during mild influenza (Martin et al., 1981). Whether more severe influenza infection in humans has similar suppressive effects as in other species remains to be determined. Furthermore, it cannot be excluded that once migrated into the lung, the antibacterial functions of the PMN may be suppressed by locally produced factors, such as IFN and prostaglandins (Bielefeldt Ohmann and Babiuk, 1984, 1985; Davies et al., 1984), or by partial autoinactivation by myeloperoxidase or ROS released from the PMN itself (Weber et al., 1983; Stendahl et al., 1984; Baehner et al., 1977; Mills et al., 1981; Kobayashi et al., 1982; Voetman et al., 1981).

VI. Viral Effects on Specific Host Defense Mechanisms

In addition to affecting nonspecific defenses, many viral infections also cause suppression of specific immune defense mechanisms. Although many of the mechanisms by which viruses suppress the immune response are not fully understood, attempts will be made in this section to discuss some alterations of the immune system which clearly are modified following virus infection. What is known is that in many cases suppression of the immune response is due to alteration in functional activity of the effector cell and that this impairment is caused either by a direct virus–effector cell interaction or indirectly by the release of suppressor molecules by a variety of cells in response to virus infection (Friedman et al., 1984). Although the exact role of lymphocytes in prevention or recovery from a primary viral bacterial infection in the lung is not clearly known, there is a considerable amount of evidence that viral infection does adversely affect lymphocyte functions. In studies using mitogen-driven lymphocyte prolifera-
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of T-cell function may also be induced by virus-specific glycoproteins that are released during viral replication (Isfort et al., 1986; Rea et al., 1985). Thus, during viral infection the presence of viral products released from virus-infected cells can alter lymphocyte functions even if the virus does not replicate in the lymphocytes.

Indirect effects such as toxic soluble factors, induced by viruses that affect the functional integrity of lymphocytes, have been recorded (Wainwright et al., 1979). Furthermore, viral infections also induce the production of IFN, which is known to have immunomodulatory activity (Bielefeldt Ohmann et al., 1987b; Babiuk et al., 1987a). IFN production in nasal passages is evident within 1–3 days after viral infection. Although very little free IFN is detectable in plasma following virus infection of the respiratory tract, it is possible that it is rapidly cell associated and thereby alters lymphocyte reactivity. Studies involving the pharmacokinetics of clearance of IFN clearly demonstrate that exogenous IFN is rapidly cleared (half-life approximately 2 hours). Coupled with the observation that IFN can dramatically alter lymphocyte function, it suggests that this possibility is highly likely (Bielefeldt Ohmann and Babiuk, 1985). IFN has been shown to inhibit lymphocyte proliferation in vitro and reduce the cells' responsiveness to IL-2 and PMA (Griebel et al., unpublished observation). The observation that bovine IFN activity is enhanced at elevated temperatures (Letchworth and Carmichael, 1984) and that maximal immunosuppression correlates with peak temperature responses and IFN in nasal secretions, suggests that even low levels of serum IFN may play an important role in reduction of lymphocyte reactivity.

VII. BACTERIAL EFFECTS ON HOST DEFENSE MECHANISMS

Bacteria, like viruses, can reduce the effectiveness of the immune response by a number of direct and indirect suppressive mechanisms. The indirect mechanisms include expression of virulence factors with reduced antigenicity, antigenic shift, production of IgA proteases, resistance to degradation by phagocytic cells, and the formation of cell wall-deficient L forms (Smith, 1984).

In respiratory bacterial infections, virulence factors with poor immunogenicity include the production of capsular material which interferes with the process of phagocytosis and opsonization by antibody and complement. This is evident for capsular polysaccharides of pneumococcal bacteria and M protein of streptococci (Smith, 1977; Densen and Mandell, 1980). Bacteria can inhibit the bactericidal activity of macrophages or granulocytes by blocking both the oxygen-dependent
and oxygen-independent killing mechanisms, by resisting the toxic effects of the ROS or enzymatic action of lysosomal enzymes and proteases, or by escaping from the phagocytic vacuole into the cytoplasm. *Mycobacterium tuberculosis* is a good example of a bacterium capable of surviving in phagocytic cells. Its mechanism of survival has been related to prevention of phagosome–lysosome fusion (Lowrie *et al.*, 1979), or, if fusion occurs, to the resistance to lysosomal enzymes (Armstrong and Hart, 1975) and resistance to killing by H$_2$O$_2$ (Jackett *et al.*, 1981). The mechanisms by which *M. tuberculosis* resists intracellular killing have been related to the presence of sulfated glycolipids in the bacterium's cell walls (Draper, 1981). Other correlations have been found with increased levels of cyclic AMP (Lowrie *et al.*, 1979), presence of polyglutamic acids (Draper, 1981), and production of ammonia (Gordon *et al.*, 1980) or bacterial catalases (Walker and Lowrie, 1981).

*Pasteurella haemolytica* species are also able to circumvent the phagocytic effect of macrophages and neutrophils and to survive in an intracellular environment (Lawman *et al.*, unpublished observations). The reason for their survival is unclear; however, *Pasteurella* strains are capable of producing a cytotoxin during the log phase of growth that is detrimental to bovine leukocytes (Shewan and Wilkie, 1982). In *in vitro* bactericidal studies it is evident that phagocytes with ingested bacteria undergo morphological changes (i.e., cytoplasmic swelling with extrusion of the cytoplasm and nuclear swelling). The majority of these phagocytic cells are nonviable as assessed by trypan blue dye exclusion. Survival of bacteria in bovine phagocytes (neutrophils) has also been shown with *Haemophilus somnus* (Czuprynski and Hamilton, 1985).

Some bacteria that are pathogens of mucosal surfaces, including the respiratory tract (*Haemophilus influenzae, Streptococcus pneumoniae*) are able to produce and excrete IgA proteases (Kornfeld and Plaut, 1981). The ability of the bacterial IgA protease to cleave the immunoglobulin molecule into Fab and Fc fragments may be important in reducing the biological activity of the antibody (i.e., opsonization). In addition, the effectiveness (affinity) of antigen binding may be affected (Kornfeld and Plaut, 1981).

The generation of the immune response is a complex phenomenon involving cell–cell interaction and soluble factors. Therefore, in the generation of a specific immune response, there are many stages at which pathogenic bacteria may be able to induce suppression (Campa, 1984). The direct effects on the immune response involve the induction of specific suppressor cells (T lymphocytes) and activation of macrophages (Klimpell and Henney, 1979; Wadee *et al.*, 1980). Antiisotype
antibody responses have also been induced in response to antigen. Furthermore, this antiidiotypic response may be important in either binding to antigen receptors or activating suppressor cells (Siskind et al., 1982; Eichman, 1975). Although we have provided some examples of how bacteria may evade the immune system and even cause immunosuppression, the mechanism of inducing specific immune suppression at the respiratory tract mucosal surface is not fully understood.

In addition to altering immune responses, bacteria can also aid in the replication of viruses. Thus, one of the prerequisites for infection by some of the myxoviruses and paramyxoviruses is cleavage of the surface glycoproteins (Lazarowitz et al., 1973; Scheid and Choppin, 1974). Recent evidence suggests that colonization with *Haemophilus influenzae* results in enhanced virus infectivity due to the release of proteolytic enzymes by the bacteria which can cleave the viral hemagglutinin protein (Tashiro et al., 1987). Once this occurs, the virus and bacteria benefit each other in that the virus allows better adherence of the bacteria, due to cell surface changes (Ramphal et al., 1980) and the bacteria in turn release proteases to enhance virus infection of cells.

VIII. OTHER PREDISPOSING FACTORS IN RESPIRATORY DISEASE

Clinical observations in both humans and animals, as well as experimental studies in animals, have suggested that stress is associated with increased susceptibility to viral and bacterial pneumonia (Stephens, 1980; Pennington, 1977; Nugent and Pesanti, 1982; Filion et al., 1984). Even though the exact mechanisms whereby increased susceptibility occurs have not been completely elucidated, stress does alter endocrine gland functions. An important response of the body to stress is the secretion of adenocorticotropic hormone (ACTH), which in turn stimulates the synthesis and secretion of cortisol (Stephens, 1980). High cortisol levels may have a deleterious effect on both the non-specific and the antigen-specific defense mechanisms (Keller et al., 1981; Hirschberg et al., 1982; Forslid and Hed, 1982; Fauci, 1976; Crabtree et al., 1980; Chretien and Garagusi, 1972; Zor et al., 1982; Taylor et al., 1981; Roth et al., 1982; Pennington, 1977; Nugent and Pesanti, 1982; Nair and Schwartz, 1984; Bielefeldt Ohmann et al., 1987b), thereby increasing the individual's susceptibility to invading microorganisms (Stephens, 1980; Filion et al., 1984). In many cases, stress can be associated with crowding of individuals, exposure to new environments including new microorganisms, and increased infection rates. This occurs most frequently in army recruits and feedlot situations. Moreover, high cortisol levels may cause reactivation of latent
infections (Pastoret et al., 1980; Davies and Duncan, 1974), either by a
direct alteration of viral replication (Nutter and Doeherty, 1978; Costa
et al., 1974) or by suppression of immune functions controlling the
state of latency (Wildy et al., 1982; Babiuk and Rouse, 1979). Such
reactivation of viral infection may in itself lower resistance to second-
ary bacterial infections by mechanisms dealt with in other sections of
this review.

There is evidence to suggest that the peripheral nervous system can
modulate immunological responses at mucosal surfaces (Payan and
Goetzl, 1985). At present, it is not known how stress can modulate
these responses, but the combination of stress with viral infections,
and production of endorphins (Johnson et al., 1982) can all play an
important role in reducing resistance.

Pneumonia in aging individuals represents a clinical problem of
increasing magnitude as the population ages. Thus, although the prev-
alence of viral bacterial infections in persons over 65 years of age is
not much greater than in the normal population, a large percentage of
these individuals require hospitalization once infection occurs, and
despite extensive care, pulmonary infections are the leading cause of
depth in persons 65 years of age and older (Kovar, 1977). Furthermore,
the average duration of hospitalization is much longer in the elderly
with pneumonia than in younger individuals. At present very little is
known about the differences in the immunobiology of the elderly as
compared to middle-aged or younger individuals. Thus, very little in-
formation is available on the quantity and quality of the secretions in
the respiratory tract of aged individuals versus younger people. Fur-
thermore, it was not possible to correlate directly deficiencies of im-
mune function or inadequacies of the inflammatory response with the
occurrence of either colonization or pneumonia in the elderly (Phair
et al., 1971). Thus a considerable amount of investigation is required to
elucidate why the elderly are more susceptible to life-threatening
pneumonias following even mild virus infections than are other indi-
viduals. Suggestions have been made that some of this increased sus-
ceptibility is due to a decline in mucociliary transport and abnor-
malities of the ciliated epithelial cells lining the tracheobronchial tree,
as well as the quantity, distribution, and viscoelasticity of the secre-
tions coating the airways. However, these remain to be further investi-
gated. One of the major factors which may be involved and enhance
the severity of pneumonia is the patterns of respiration in elderly
versus younger populations. Thus, it is suggested that the elderly are
at a much greater risk of nocturnal aspiration. As a result, a much
larger number of bacteria can enter the lower lung, and specific bacte-
rial colonies may end up being aspirated into the lung where they
cause pneumonia. If this occurs, then even a minor viral infection, which causes minimal depression of specific and nonspecific defenses, may be sufficient to prevent elimination of the bacterial microcolonies aspirated into the lungs.

IX. IMMUNOPATHOLOGY

In the present context, the definition of immunopathology will be restricted to lung injury caused by immunological mechanisms induced by the invading microorganism(s), as the immunological defense per se has already been dealt with in preceding sections. The role of leukocytes in inflamed lungs, the contribution of the coagulation and fibrinolytic systems, as well as that of other mediators to inflammatory events in the lung, have been comprehensively reviewed by Slauson (1982), Ward (1986), and Malik and Staub (1982). On a more general basis, Larsen and Henson (1983) have reviewed the mediators of inflammation, Davies et al., (1984) the role of arachidonic acid derivatives in inflammation, and Roubin et al. (1983) the pathobiological effects of macrophage-derived platelet-activating factor. It is beyond our scope here to do more than highlight a few aspects of the pathogenesis of pulmonary immunopathology. Thus, for more comprehensive overviews the reader is referred to the above-cited reviews.

In viewing leukocyte functions in pulmonary defense, it must be taken into account that these cells not only have an obvious value in defending the lung against the microbial invaders, they are also one of the major mediators of tissue injury because they produce and release potent inflammatory mediators, such as complement factors, prostaglandins, IL-1 (Larsen and Henson, 1984; Unanue, 1976), lysosomal products, including acid hydrolases and neutral proteases (Klepner et al., 1978; Lonki and McCarren, 1983), and ROS (Ward, 1986; Gerberick et al., 1986). Such products may have an injurious effect in their own right through specific substrate cleavage, direct cytotoxicity, or cell activation/suppression (Holt, 1986), but can also have an amplifying effect in the developing pulmonary inflammatory response via their diverse effects on kinin generation, complement cleavage, controls over leukotoxins, and the generation of plasminogen-independent systems for intracellular and extracellular fibrinolysis (reviewed by Slauson, 1982).

The involvement of arachidonic acid derivatives in lung inflammation represents a very complicated picture, as various products with agonistic and antagonistic effects may be produced by the same cell types (AM, endothelial, or epithelial cells), and the resulting effect
may therefore reflect the degree of imbalance between the various agents (Davies et al., 1984; Slauson, 1982). In addition, there appear to be considerable species variations in the effect of the thromboxanes, prostacyclins, and other arachidonic acid products, as well as variations in the amounts produced in response to any particular stimulus or virus (Higgs et al., 1979; Davies et al., 1984).

Complement factors derived via the alternative pathway of C’ activation have been shown to produce selective enzyme (lysosomal acid hydrolases) secretion from macrophages (Schorlemmer et al., 1977a,b). This may have considerable importance in relation to lung infections, as many microorganisms can activate the alternative complement pathway locally or systemically (Fearon and Austen, 1980; Cooper and Oldstone, 1983; Bielefeldt Ohmann and Babiuk, 1985) and thereby indirectly cause selective enzyme release from AM, and, subsequently, tissue injury. In addition, systemic C’ activation has been shown to promote acute lung injury by inducing sequestration of PMN in lung interstitial capillaries, perhaps via involvement of arachidonic acid derivatives (Imasawa and Osifchine, 1983; Golditz and Movat, 1984). The activated PMN subsequently produce ROS which mediate acute lung microvascular injury (Martin, 1984; Till and Ward, 1986; Bass et al., 1986; Fox et al., 1981; English and Lukens, 1983), immediately followed by tissue reactions to the insult (Harlan and Callahan, 1984; Hoover et al., 1984; Slauson, 1982). There is also growing evidence that macrophage-derived tumor necrosis factor (TNF-α) may be intimately involved in inflammatory and immunoregulatory reactions, either directly or indirectly by inducing IL-1 and other cytokines (Ruddle, 1987). It remains to be determined whether such mechanisms are operational during viral–bacterial infections of the lung and what their possible implications might be.

Although much still remains to be done to complete the very complex picture of the immunopathological scenario in the lungs, it is obvious that the possibilities for circumventing such events are limited once the complex processes are initiated. Thus, the best strategem seems to be to avoid infection in the first place, by induction of specific immunity and/or by modulating the nonspecific and specific immune defense mechanisms (Babiuk et al., 1985).

X. Control

As stated above, it is important to avoid initiation of pneumonia because once it is initiated, the host itself may contribute to the immunopathology and severity of the disease. With this in mind, control can
be directed at a number of areas, such as immunization against the viral or bacterial pathogens, use of antiviral or antibacterial therapeutic agents, or use of immunomodulators which enhance either non-specific or specific defense mechanisms. This is especially important in those viral infections where immunosuppression is one of the major underlying causes of increased susceptibility to secondary bacterial infections. In each of these strategies it is important to consider the timing of administration and delivery of the specific agents so as to ensure their efficacy. Thus, treatment with antibiotics after extensive lung damage and bacterial microcolony formation has occurred will be of little value, since the antibiotics cannot penetrate the microcolonies and the host's response to the infection will only lead to further immunopathology. If antibiotics are used, they should be selected for defined infections in a manner which results in cure, with reasonable cost and minimal damage to the environment. It is not recommended to use subclinical doses in animal feeds to prevent respiratory infections in animals. Unfortunately, this practice is often used.

A. Virus Vaccines

Since most of the viruses involved in respiratory infections enter via the respiratory tract and replicate in the respiratory epithelium, it is crucial to ensure local immunity at the site of entry. Thus, early intervention will greatly reduce the environmental alterations of the respiratory tract caused by the viruses, as well as the subsequent immunosuppression associated with some virus infections. Although immunity can be induced by intramuscular immunization with live or killed viral vaccines, it is often accepted that local immunization with attenuated vaccines is potentially more efficacious. Thus, currently inactivated vaccines given intramuscularly are between 60 and 90% effective against influenza viruses of the same antigenic type (Meyer et al., 1978). The potential advantages of a live attenuated vaccine include stimulation of both mucosal and systemic immunity. Recent advances in this area have included the production of deletion mutants, and temperature-sensitive or cold-adapted mutants (Johnson et al., 1986). In the case of segmented viruses such as influenza, it is possible to develop cold-adapted, temperature-sensitive mutants with temperature-sensitive lesions in a number of different segments of the virus. Cocultivation of the cold-adapted, temperature-sensitive mutant with wild-type virus of vaccine interest will result in a variety of different reassortants containing the hemagglutinin and neuraminidase of the virus of interest, but the temperature-sensitive segments from the attenuated virus vaccine. Thus, it is possible to isolate master strains containing
six RNA genes from the attenuated cold-adapted virus and two of the genes encoding the surface glycoproteins from the wild-type virus. These attenuated reassortant vaccines are infectious, immunogenic, relatively stable genetically, and often nonreactogenic when administered intranasally into humans (LaMontagne et al., 1983).

Other examples of live attenuated vaccines against respiratory viral infections include those of bovine herpesvirus. BHV1 infection of cattle is one of the major initiators of secondary bacterial infections. It is possible with BHV-1, as with other herpesviruses, to induce deletions in the BHV-1 genome corresponding to the TK gene of the virus (Kit et al., 1986). As a result of this deletion, the virus can still replicate in the respiratory epithelium of the animal; however, the degree of replication and systemic spread and latency is dramatically reduced (Stanberry et al., 1985). Experiments need to be conducted in order to determine whether indeed there is minimal immunosuppression by this TK deletion mutant, or whether it can still predispose the animal to secondary bacterial infections, especially when it is stressed and vaccinated on entry into the feedlot.

The recent advances in recombinant DNA technology have great potential for the production of a wide variety of different subunit vaccines against respiratory infections. This approach appears to be especially relevant to producing vaccines against viruses which do not replicate well in culture or cannot be attenuated with ease. Furthermore, it is important for those viruses which may be genetically unstable and where reversion to virulence may be a problem with live attenuated vaccines. At present a large number of the important antigens or epitopes present on respiratory viruses have been identified and either synthesized using synthetic peptide technology or cloned into various expression systems (Bennink et al., 1984; Norrby, 1987). Although most of these subunit vaccines will be injected intramuscularly, and therefore have the potential for inducing high levels of circulating antibody, they generally do not produce very good local immunity. In order to overcome this impediment, there is a considerable amount of effort being focused on delivering subunit vaccines to mucosal surfaces to be able not only to stimulate systemic immunity, but also to induce local immunity. It is our contention that within the next few years intramuscular vaccines will be administered in such a way that they will be able to induce local immunity as well as systemic immunity.

B. Antiviral Chemotherapy

At present a large number of compounds have been identified with potential antiviral activity in vitro against a number of the viruses
involved in initiating respiratory disease (Streissle et al., 1985). Although few of these compounds have been either tested or proved to be effective in vivo against viruses of the respiratory tract (Gangemi et al., 1987), the important advances made in this area over the last decade warrant serious consideration for the potential application of some of these drugs in the control of viral infections of the respiratory tract. In this section we will discuss the potential sites of activity of a selected number of drugs and speculate as to their application in respiratory tract infections. In addition, the limitations of using antiviral drugs in these infections will be addressed. The problems of delivery and maintenance of drugs at the site of infection so as to prevent initiation of infection rather than therapy will be emphasized.

In respiratory infections, as in other virus infections, the targets of antiviral drugs must be at sites that are unique to the virus and not have any physiological effects on the specific cells of the respiratory tract. As is the case in other virus infections, the antiviral drug must be directed at various stages of the virus replication cycle such as virus attachment, penetration, uncoating, macromolecular synthesis, and viral maturation and assembly. Regardless of the stage of virus replication to which the antiviral drug is targeted, the major problems with using antiviral drugs in controlling viral-induced respiratory infections is the rapidity with which respiratory diseases occur following local infection. Thus, prevention of viral activity at the early stages of infection appears to be the most promising approach, but also creates the most problems regarding delivery and maintenance of the antiviral drug for considerable periods of time within the respiratory tract environment during a pending epidemic.

In addition to the various chemicals that are used as antiviral drugs, the application of IFN as a broad-spectrum antiviral has continued to generate interest since Isaacs and Lindenmann first described this antiviral compound in 1957. The advent of recombinant DNA technology and production of recombinant forms of IFN has made it economical to use them as direct antiviral agents in the respiratory tract. These agents, as with many antiviral compounds, need to be present prior to challenge (Monto et al., 1986; Turner et al., 1986). It was initially felt that the economic production of IFN by recombinant DNA technology would greatly facilitate their use in respiratory infections. However, at the doses required for inhibition of some viruses in humans, symptoms of nasal irritation were observed following prolonged administration. Thus, there appear to be some unacceptable side effects in humans following administration of IFN-α. Since there are a variety of different types of IFN, it is possible that some of them may be less of a problem in inducing adverse clinical effects than others.
Thus, one should not discount the value of using IFN as an antiviral for local administration against respiratory infections. Certain host species are much more susceptible to the adverse side effects of local administration of IFN than are others. For example, cattle do not experience any intolerance to extremely high doses of IFN-α-administered intranasally. In addition to having direct antiviral effects, IFNs appear to have a very important role in reducing respiratory virus replication indirectly by stimulating the immune system (Babiuk et al., 1985, 1987a).

C. Immunomodulators

Before effective manipulation of the immune system with various lymphokines can be achieved, some comprehension of the complexity of the interactions between lymphokines and the immune system is required. Thus, it is important to understand which specific arm of the immune system is required to be stimulated and which specific lymphokine or lymphokine combinations would best meet this need. Once this knowledge is available, it should be possible to regulate the immune system in such a way that they would be more resistant both to the viral infection and to secondary bacterial superinfection. However, before IFN or other lymphokines can be administered and used judiciously, more information regarding the types of IFN, dose, route of administration, and the mechanisms responsible for either the antiviral state or immunomodulation needs to be determined. Primary interest of the clinical investigations conducted with both bovine and human IFN-α have been concerned with the antiviral affects of compounds. However, it was found that the preventive treatment of calves with bovine IFN-α had a beneficial effect on clinical performance in experimental viral/bacterial pneumonia ("shipping fever") without significantly reducing virus replication in nasal passages (Babiuk et al., 1985, 1987a). Therefore, it was assumed that IFN had an overall effect on the disease situation by modulating immune responses.

While the overall effect of recombinant bovine IFN-α and IFN-γ on bovine macrophages and PMN might be characterized as activation, it appears that the influence of any particular function of these cell types is selection—that is, either enhancement, inhibition, or no detectable affects (Bielefeldt Ohmann et al., 1987b). Similar effects are being observed with lymphokines from other species including humans. Thus, using the appropriate delivery systems and combinations of lymphokines, it should be possible to modulate selectively the arm of the immune system required to combat the infection, but not activate it in such a way as to result in immunopathology.
XI. SUMMARY

In the present review we have identified how viruses can alter the host's susceptibility to bacterial infections by altering both environmental conditions in the lung which favor bacterial replication as well as by suppressing the host's defense mechanisms which prevent clearance of the bacteria. In many instances, these interactions are extremely complex but similar for many viruses. If the virus can overcome the initial host defense mechanisms, which include local antibody and mucus, the virus initiates tissue damage as a result of direct replication within the epithelial cells lining the mucosal surfaces of the respiratory tract. As a result of virus infection, the host cells respond by producing a variety of mediators including various types of interferons, which can alter both virus replication and host response. Replication also produces by-products of virus infection capable of initiating an inflammatory process, which in turn, through release of other mediators, can further modify lung defense mechanisms and
encourage bacterial adherence and growth. The bacterium, in turn, releases chemotactic factors which encourage infiltration of specific effector cells into the lung. These effector cells can cause tissue damage and immunopathology, which encourage rapid bacterial growth and may result in death of the animal. In order to be able to control this complicated scenario, it is important either to prevent the initial infection with viruses or to reduce the degree of immunosuppression, so that bacterial clearance can occur rapidly before microcolony formation and extensive lung damage occur. Once a large amount of bacterial replication and lung damage is present, the use of antibiotics is generally of limited value. A schematic illustration of the complexity of the various interactions and counteractions occurring during virus-bacterial synergistic interactions is presented in Fig. 1.

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