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Chapter 25

Respiratory Tract Viruses

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INTRODUCTION

Virus infections of the respiratory tract affect all people in all places at all times throughout life. Over 140 viruses are involved: the average child under the age of five years or adult in the developed countries will experience four to five and two
to four infections each year, respectively; and although many infections are relatively mild, some are life-threatening. Douglas and Edelstein (1988) have said that, "About three hundred million cases of acute respiratory disease occur in the United States each year, accounting for about one hundred and fifty million visits to physicians. The cost of these illnesses exceeds one billion dollars exclusive of time lost for work": this statistic, adjusted for population, can be directed at any country. The size of the problem demands much of a general physician's time, while the importance has focused the attention of epidemiologists, microbiologists, pharmaceutical companies and many others.

**THE VIRUSES**

The viruses which cause respiratory tract infections in man include both RNA and DNA viruses in six families: this does not include many viruses which can cause respiratory symptoms, but where the principal tissue or organ of infection is other than the respiratory tract. These families are listed in Table 1, together with data on the finer classification into sub-families, genera, or sub-genera, the number of distinct types of virus in each group and the number of these that cause human respiratory infections. Thus, there are six families encapsulating 21 sub-divisions and over 240 viruses, of which over 140 cause respiratory tract infections in man, while the remainder cause other types of infection or infections in other species. The exact numbers are complicated by the rhinoviruses where more than 100

**Table 1. Viruses Causing Respiratory Tract Infections (RTI) In Man**

| Family          | Sub-Divisions of Sub-family; Genera; Subgenera (No. Types) | No. Distinct Infective Agents Causing RTI (Common Name) |
|-----------------|------------------------------------------------------------|-------------------------------------------------------|
| Orthomyxoviridae| Orthomyxovirus (3)                                         | 3 (Influenza A, B and C)                              |
| Paramyxoviridae | Morbillivirus (3)                                           | 1 (Measles virus)                                     |
|                 | Paramyxovirus (8)                                           | 4 (Paramyxoviruses)                                   |
|                 | Pneumovirus (2)                                             | 1 (Respiratory syncytial virus)                        |
| Adenoviridae    | Mastadenvirus (6 subgenera; 47)                             | 8 (Adenoviruses in 3 subgenera)                        |
| Picornaviridae  | Rhinovirus (>100)                                          | >100 (Common Cold virus)                              |
|                 | Enterovirus:                                               |                                                       |
|                 | Coxsackie virus A (23)                                     | 4 (Coxsackie A viruses)                               |
|                 | Coxsackie virus B (6)                                      | 4 (Coxsackie B viruses)                               |
|                 | Echovirus (31)                                              | 14 (Echoviruses)                                      |
| Coronaviridae   | 4 antigenic groups (13)                                     | 2 (Coronaviruses)                                     |
| Herpetoviridae  | α Herpesvirinae (3)                                         | 1 (Varicella-zoster virus)                             |
|                 | β Herpesvirinae (1)                                         | 1 (Cytomegalovirus)                                   |
|                 | γ Herpesvirinae (1)                                         | 1 (Epstein-Barr virus)                                |
| 6 Families      | 21 Sub-divisions (>241)                                     | >144 Serotypes                                        |
serotypes are known, but many more probably exist, and by influenza A and B virus which exhibit continuing genetic change producing new antigenic variants in most years.

**THE INFECTIONS**

The respiratory tract can be considered to be stratified horizontally into levels, beginning with the nasal passages and descending sequentially to the throat, trachea, bronchi, bronchioles, and the alveoli: it is convenient to divide the respiratory tract in this manner, since many viruses have a predilection for infection of a particular level, and these associations are shown in Table 2. Thus, the common cold, limited to the nasal passages, is caused commonly by rhinoviruses and

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**Table 2.** Viruses and Respiratory Infections of Man

| Syndrome                      | Common Infections          | Other Infections                          |
|-------------------------------|-----------------------------|------------------------------------------|
| Common cold                   | Rhinoviruses, Coronaviruses | Coxsackie Viruses, Echoviruses, Parainfluenza viruses, Respiratory Syncytial Virus (RSV), Influenza C |
| Upper Respiratory Tract       |                             |                                          |
| Febrile sore throat           | Adenoviruses, Epstein-Barr Virus | Influenza A B C, Coxsackie Viruses, Echoviruses, Parainfluenza viruses |
| Influenza                     |                             |                                          |
| Lower Respiratory Tract       |                             |                                          |
| Laryngotracheitis/croup (< 3 yrs) | Parainfluenza viruses | Influenza A and B, RSV, Coxsackie Viruses, Echoviruses |
| Acute Bronchitis              | Adenoviruses                | Rhinoviruses, RSV (children), Measles virus, Influenza A and B |
| Chronic Bronchitis            | RSV, Rhinoviruses, Parainfluenza viruses |                                          |
| Bronchiolitis (<2 yrs)        | RSV                         | Parainfluenza viruses, Adenoviruses     |
| Pneumonia                     |                             | Adenovirus, Influenza A and B, Measles Virus, Varicella/Zoster Virus, Cytomegalovirus |
coronaviruses, whilst sore throats are the primary site of infection by the ade­noviruses and Epstein-Barr virus. The data shown are not completely secure: viruses can have different associations according to age, immune status, and patient history; and infections of one level commonly extend to contiguous ones. Despite these limitations, the Table is a convenient tool for classifying the various viruses causing respiratory infection, and will be used as a format for the present chapter.

Common Colds

**Rhinoviruses**

**Virology.** Rhinoviruses belong to the family Picornaviridae and are distin­guished from other members of this family by a higher particle density, acid lability which limits intestinal infection, relative heat stability, resistance to a variety of detergents and survival for several hours or even days outside the body. Virus particles contain an internal RNA which is single-stranded with positive polarity surrounded by a capsid of 60 capsomeres arranged in icosahedral symmetry: particles are approximately 30 nm in diameter. Rhinoviruses replicate in human cells and less well in the cells of other primates: the conditions for growth are a relatively low pH of 7.0 to 7.2, a low temperature of 33 °C and aeration of cell cultures; and under these conditions cytopathic effects can be observed. The growth cycle takes some 11 to 17 hours; and each infected cell yields 10–200 virus particles. Cross-neutralization tests indicate over 100 distinct serological types, but some sharing of epitopes does exist (Hamparian et al., 1987).

**Epidemiology.** The frequency of respiratory infections is 2 to 4 each year for adults, with a higher incidence in children: most are common colds of which some 30% are due to the rhinoviruses, and a number of serotypes can circulate concurrently with no evidence of cross-immunity. Infections tend to be most common in spring and autumn, and are spread by large and small droplets of nasal secretions from infected persons, by direct spread from nasal secretions via hand to hand contact and auto-inoculation of nasal or conjunctival mucosa or via inanimate objects: infection can be initiated by very little virus, and the viruses can survive for long periods outside the body. Peak titers appear in nasal secretions 1 to 3 days after the onset of symptoms, and virus persists for 5 to 7 days; however, virus secretion can continue for 2 to 3 weeks. A serum antibody response is seen in 30 to 90% of affected patients and a local IgA response in 70 to 100%; immunity lasts 2 to 4 years, but the multiplicity of circulating serotypes gives little or no protection against clinical disease (Gwaltney, 1982).

**Pathogenesis.** The pathogenesis of rhinovirus infection is not understood: viruses grow to high titer in the nasal epithelium, but biopsies of antigen-positive nasal mucosa cells show little pathological change. Infection causes progressive loss of ciliated epithelial cells, an inflammatory cell infiltrate, edema, hyperemia
Respiratory Tract Viruses

and a seromucinous exudation (Hendley, 1983). Virus replication is predominantly in the nasal mucosa: other cell types such as in the nares and throat are relatively resistant.

Clinical features. After an incubation period of 1 to 4 days during which virus titers increase, symptoms of nasal obstruction and discharge, sneezing and coughing occur; a sore throat with erythema and headache may be experienced, but fever and systemic symptoms are usually absent. The symptoms usually improve after 2 to 3 days; but symptoms may last for 7 days, and in 25% of cases for 14 days. Complications include sinusitis and otitis media; rhinoviruses have been isolated from the middle ear, but more often a bacterium has been found in conjunction with virus. Small particle infection can cause tracheobronchitis and bronchiolitis, and exacerbations of asthma and chronic bronchitis are commonly precipitated by rhinovirus infection.

Diagnosis. Rhinoviruses can be recovered from infected persons by inoculating nasal secretions onto monkey or human cells and incubating these in a roller drum at 33 °C to maximize the cytopathic effects; this appears 2 to 6 days after infection (Al-Nakib and Tyrrell, 1988). Isolates are serotyped using a battery of neutralizing antisera in various combinations, but this is seldom carried out except for research purposes; and the lack of any specific treatment means that laboratory diagnosis is seldom attempted.

Treatment. There is no specific treatment for rhinovirus infections, and the treatments recommended are to relieve symptoms: nasal decongestants can be used to relieve obstruction; gargles will relieve the sore throat; and analgesics can be used if necessary. If the cough is severe, suppressants such as codeine or dextromethorphan can be given. The multiplicity of antigenic types makes vaccine development impractical, and volunteer studies have shown that inactivated vaccines have little protective effect. Locally applied interferon α suppresses virus replication, but long-term use is cytotoxic causing irritation, bleeding, and ulceration in some patients.

Coronaviruses

Virology. Coronaviruses, within the family Coronaviridae are divided into four antigenic groups containing a total of 13 serotypes of which two are infectious agents of man. The singular structure and method of replication distinguish these viruses. Virus particles are 80 to 160 nm in diameter, and contain a large single-stranded RNA with positive polarity and a nuclear protein coiled internally to form the nucleocapsid. This core is surrounded by a lipid bilayer into which are inserted three distinct glycoproteins which radiate from the surface: these are a receptor binding glycoprotein which initiates cell fusion and induces neutralizing antibody production; a glycoprotein with combined neuraminidase and hemagglutinating
activity; and a glycoprotein which binds to the internal nucleocapsid and effects virus budding. Coronaviruses can be cultivated in organ cultures of human embryonic trachea or less successfully in tissue cultures of human cells. The serotypes are distinguished by neutralization tests, or more commonly by immunofluorescence or ELISA tests.

**Epidemiology.** Coronavirus infections usually occur in the winter and early spring months, with epidemics every 2 to 3 years: the two serotypes causing human infection tend to be exclusive, and 5 to 30% of common colds are due to these viruses. Infection is spread by small particle aerosols; many infections are asymptomatic, and may not induce an immune response, but clinical infections invariably induce detectable antibody; however, antibody titers may not be sustained, and reinfection with the same serotype can occur within months (Isaacs et al., 1983). Almost 100% of adults have detectable antibody to both serotypes.

**Pathogenesis and clinical disease.** These features are similar to those described for rhinoviruses; however, the incubation period is usually longer at 2 to 5 days, the illness persists for 2 to 18 days, some 25% of patients exhibit a mild fever but throat infection and cough is less frequent. Complications of infection are unusual, but isolated cases of pneumonia are recorded; and these viruses cause exacerbations of asthma and chronic bronchitis. The pathogenesis of infection is little understood, but the evidence suggests a slow and progressive destruction to the ciliated epithelium.

**Diagnosis and treatment.** Diagnosis of coronavirus infection is both difficult and unsatisfactory: organ cultures are the most sensitive for virus isolation but are rarely available, and tissue culture systems are relatively insensitive. Direct demonstration of virus in cells in respiratory secretions by immunofluorescence or ELISA are used in some laboratories, but most diagnoses are made retrospectively by demonstrating a significant rise of antibody following infection (Schieble and Kapikian, 1979).

As for rhinovirus infection, treatment is symptomatic: no antiviral drugs have been developed and no vaccine is available for coronavirus infections. Experimentally, α-interferon has been shown to ameliorate symptoms and reduce virus replication.

**Other Viruses**

Some 50% of common colds, characterized as an afebrile illness localized to the nasal epithelium and presenting with nasal obstruction and discharge, sneezing and coughing are caused by rhinoviruses and coronaviruses; the remainder are caused by a number of other viruses including Echoviruses, Coxsackie A and B viruses, Respiratory Syncytial Virus, influenza C and parainfluenza viruses (Table 2). As these infections are relatively mild and a large number of agents are involved, exact
laboratory diagnosis is seldom undertaken except for research purposes, and there are no specific treatments.

Febrile Sore Throats

Adenoviruses

Virology. There are 47 serotypes of human adenoviruses in six subgenera in the genus Mastadenovirus in the family Adenoviridae: eight serotypes in three subgenera cause respiratory infection in man (Table 2). Virus particles contain single-stranded DNA surrounded by at least 11 polypeptides. The outer capsid is made up of 252 capsomeres arranged in an isicosahedral of 20 triangles with 12 vortices giving a particle diameter of 60 to 80 nm: 240 capsomeres are hexons with six neighbors and are composed of a single protein with common epitopes for all serotypes; and the remaining 12 capsomeres are pentons with five neighbors, each composed of a base with a fiber-like projection radiating outwards and are serotype specific. Human adenoviruses only replicate sequentially in human cells. Virus particles attach to cell receptors via the penton fiber and then to other cell receptors by the hexons: following entry, cellular DNA and protein synthesis are inhibited; replication takes place in the cell nucleus; newly-formed pentons are toxic to cells; and virus is released after cell death.

The division of human adenoviruses into six subgenera is based on the sequence homology of the DNA genome, DNA fragment analysis following restriction enzyme treatment, oncogenicity for newborn hamsters, the molecular mass of the internal proteins, length of fibers and percent G + C in the viral DNA. The division into serotypes is based on neutralization tests which show no cross-reactivity. This classification is important, since it is consistent with the association of the viruses with various human infections (Wadell, 1984).

Epidemiology. Adenoviruses cause both sporadic and epidemic infections: five per cent of acute respiratory infections and ten per cent of febrile infections of children, together with 3 and 7% of these infections in adults, are caused by these viruses; and some 10% of all pneumonias in children are due to adenovirus infection. Transmission is by respiratory droplets, whilst in children fecal/oral transmission is important: fecal excretion can continue for weeks and months after acute infection. By the age of 10 years, 50% of children have antibody to serotypes 1, 2, and 5; antibody to other serotypes is less common, but in total the results reflect the importance of these viruses in human infection.

Pathogenesis. Adenoviruses, spread by droplet infection, impinge on epithelial cells in the pharynx or in the lower respiratory tract to enter and kill cells by a combination of inhibition of cellular metabolism, virus replication and the toxic effects of the penton: the results are extensive desquamation of affected areas, causing sore throat, necrotizing bronchitis, bronchiolitis and interstitial pneumonia.
In lymphoid cells, infection causes hypertrophy: affected cells can harbor latent virus for months, years or throughout life; and although 50% of excised tonsils and adenoids contain latent virus, there is no evidence that this can exacerbate, except possibly in pertussis syndrome.

**Clinical disease.** Adenoviruses cause some 5% of all acute respiratory disease (ARD) seen in children aged five years or less (Brandt et al., 1969). These are predominantly due to serotypes 1, 2 and 5 (subgenera B); and the frequency of these infections in children means adult infections are unusual. Spread is by droplet infection: after an incubation period of 2 to 4 days, symptoms begin with pharyngitis, cough, nasal congestion and coryza, whilst fever, exudative tonsillitis, malaise, headache and myalgia are often seen. Infection tends to progress over a 2 to 3 day period, and resolves in 5 to 8 days. Infection may extend to cause laryngotracheobronchitis, bronchitis and pneumonia, the last being particularly important in young children and the cause of some deaths.

Sporadic infections of both children and adults are also caused by adenovirus types 3 and 7 (subgenera C): these present as above, but laryngotracheobronchitis and pneumonia are more commonly seen, with 40 to 50% showing radiological evidence of pneumonia; and with conjunctivitis, when the infection is known as pharyngo-conjunctival fever, and that occasionally is seen as epidemics among children and in families. The respiratory tract complications are particularly severe in immunocompromised patients. Probably due to overcrowding and fatigue, adenovirus types 3, 4 and 7 cause epidemic ARD in military recruits: some 80% of recruits can become infected, 20 to 40% require hospitalization for lower respiratory tract infection and pneumonia, and deaths are recorded.

Adenoviruses have been frequently isolated from patients with whooping cough syndrome in conjunction with *Bordetella pertussis*; this is usually reported as adenovirus type 5. However, there is little evidence that adenoviruses can produce this syndrome alone: the presence of adenovirus may be due to reactivation from tonsillar tissue by *Bordetella pertussis* to complicate the infective process.

**Diagnosis.** Adenoviruses are present in throat swabs, throat or nasal washings or feces of infected persons. Virus growth is best in tissue culture of human embryonic kidney, but HeLa and KB cells are a more available alternative. Growth is recognized by a characteristic cytopathic effect; however, this may take days or weeks to develop, but virus can be demonstrated early in infected cells by immunofluorescence with specific antibody. Isolates can be identified as adenoviruses with antisera to the common epitopes of the hexon using complement fixation, immunofluorescence or ELISA tests; and specific serotypes identified by neutralization tests.

**Control and treatment.** There are no effective antiviral agents for the treatment of adenovirus infection, and treatment is limited to the relief of symptoms. In
addition, there is no adenovirus vaccine; however, the problem of ARD in military recruits is of such importance that a vaccine has been developed: live adenovirus types 4 and 7, the main viruses responsible for ARD, are given orally as a coated enteric preparation; this establishes an intestinal infection, induces an immune reaction and, in bypassing the respiratory tract, does not cause symptoms (Tarafuji et al., 1979).

**Epstein-Barr Virus**

_Virology._ Epstein-Barr virus (EBV) is a member of the family Herpetoviridae, and the only member of the sub-family gammaherpesvirinae to cause infection in humans: the virus is distinguished from other Herpetoviridae in replicating or establishing a latent infection in β-lymphocytes, and the potential for promoting tumorigenicity of these cells. The virus is relatively large at 150 to 200 nm diameter: particles are composed sequentially of linear double-stranded DNA and an internal core of proteins; a capsid of 162 capsomeres arranged in an icosahedral form; a protein tegument; and a trilaminar envelope derived from the cellular membrane into which are inserted spikes of several virus-specific glycoproteins. Infection is primarily of the epithelial cells of the oropharynx, and via the complement receptor CD21: virus infection from these cells spreads to β-lymphocytes where a few cells undergo lytic infection while the majority support a latent infection that leads to cell proliferation. The mechanism for this latency is not fully understood, but is believed to be due to the absence or low-level of host cell transcriptional factors that are essential for virus replication: the result is a persistent, life-long β-lymphocyte infection.

_Epidemiology._ Serological studies from most developed countries have indicated that EBV infection is common, and 80 to 90% of adults have been infected: in developing countries, infection occurs earlier and is more common. Once infected, a subject will remain a virus excretor for months, years and probably life, with continuous virus production from a variable number of β-lymphocytes in the oral cavity. Infection is accompanied by an intense immune response; and it is the balance between virus production and immune status which determines the extent of virus secretion at any one time. The immune response is not sufficient to resolve the illness, as infected lymphocytes appear to be resistant to cytotoxic T cells and there is a down-regulation of HLA antigen expression. The immortalization of β-lymphocytes is polyclonal and leads to cell proliferation; this can be further exaggerated in immunosuppressed patients, such as HIV or malaria infected persons, which in turn can lead to a chromosome translocation where the c-myc oncogene comes adjacent to a strong promoter: the outcome is a malignant cell transformation giving rise to Burkitt’s lymphoma (Lenair and Bornkamm, 1987).

_Pathogenesis._ Infection is from saliva of previously infected subjects: since virus production is low, transmission requires close contact, and peaks of infection
are seen at ages 1-6 and 14-20 years corresponding to the ages of early and adolescent intimacy. The exact site of infection remains unknown, but Waldeyer's ring, rich in lymphocytes, epithelial cells or the salivary glands are suggested by various authors. Virus-infected β-lymphocytes are disseminated throughout the body via the bloodstream, and antigen-positive cells can be detected in most organs and tissues. Infection is accompanied by an intense immune reaction to virus and to the proliferating β cells which includes virus-specific antibody, heterophile antibody, autoantibodies and rheumatoid factor (Robinson and Stevens, 1984); indeed, the clinical disease is due to the nature and the intensity of the immune responses. The changing pattern of the immune state regulates virus secretion, and the infectivity of the patient for others.

Clinical features. Following contact with infected saliva, there is an incubation period of 30-45 days followed by a short prodromal illness of headache, malaise and fatigue: after this, the definitive symptoms of glandular fever occur. Most patients complain of a sore throat with hyperemia and hyperplasia of the lymphoid tissue; exhibit an exudate over the pharynx; have a fever which lasts for some 10 days; and have cervical or general lymphadenopathy: fever and malaise can persist for weeks or months; secondary infections are common; blood dyscrasias occur; splenic enlargement is common, but rarely leads to rupture; and a mild hepatomegaly is seen in 5 to 10% of patients associated with a transient jaundice. Mild rubelliform skin rashes can occur; however, ampicillin causes a maculopapular rash and is not used in patients with sore throats. Oral cavity obstruction due to massive enlargement of tonsils, adenoids and epiglottis may require emergency treatment. Fatalities are recorded, but are usually associated with immunocompromised patients.

Diagnosis. The symptoms of glandular fever usually alert the physician who can confirm his suspicions by a number of laboratory tests. The virus is difficult to cultivate: in vitro growth is only seen in lymphocytes, but only a few cells support virus replication; however, virus protein or DNA can be demonstrated in infected cells by Western blotting or DNA hybridization tests, respectively. Serological tests include the demonstration of serum IgM antibody to virus capsid proteins using an ELISA test, or the detection of the heterophile antibody response using the Paul Bunnell test. Atypical monocytes can form up to 20% of the peripheral blood leucocytes.

Treatment and control. Both interferon and acyclovir have been shown to diminish virus secretion during treatment, but relapses occur when treatment is stopped: more importantly, neither treatment significantly ameliorates symptoms, and are therefore not recommended. In the absence of specific therapy, treatment is supportive: the sore throat can be treated with analgesics; and some suggest corticosteroids limit the duration of illness, possibly by the effect on the immune
response. The importance of EBV in initiating Burkitt’s lymphoma in African children where the incidence is 1:5000, has focused attention on developing an EBV vaccine; such vaccines are undergoing clinical trials at the present time.

Other Viruses

Although febrile sore throats are caused by adenovirus and EBV infection, a large number of other viruses can produce the same clinical symptoms; these include influenza A, B, and C, numerous serotypes of Coxsackie and Echoviruses and Parainfluenza viruses. Collectively, these latter viruses are responsible for more than half the febrile sore throats which occur; and collectively, viruses are responsible for over 90% of the febrile sore throats caused by infectious agents.

Influenza

Virology. Influenza viruses are the only viruses of the genus Orthomyxovirus in the family Orthomyxoviridae, affecting man, birds, horses, pigs, and other species. The viruses are approximately spherical with a diameter of 80 to 120 nm. Each virus particle consists of single-stranded RNA of negative polarity segmented into eight fragments of varying size. The RNA is closely associated with a nuclear protein (NP) and the polymerase enzyme complex to form a helical structure: the NP takes one of three antigenic forms which allows influenza viruses to be classified into types A, B, and C. Surrounding a nuclear protein is the matrix or membrane protein, and this in turn is surrounded by a lipid bilayer. Inserted into the bilayer, and radiating from the surface, are two virus glycoproteins. The most numerous glycoprotein is the hemagglutinin (HA) which is the receptor binding component; the classification of influenza types into subtypes is based principally on the different antigenic forms of the HA (H1, H2, H3) molecule. The second glycoprotein is the neuraminidase (NA) which is important in both cell infection and in facilitating the release of newly formed virus from the surface of infected cells; the NA is antigenically variable (N1, N2) and this variation is used in the subtype classification of the viruses.

Influenza viruses grow in human and monkey cells and in the amniotic and allantoic cavity of embryonated hens’ eggs. Absorbed virus is uncoated and the virus RNA together with the polymerase enzyme complex pass to the cell nucleus. Replication, which is dependent on cell RNA synthesis, produces virus components which pass to the cell membrane for assembly, and are then budded from the cell surface: the complete cycle takes 8 to 10 hours.

Epidemiology. Influenza holds a unique position among the viruses causing respiratory tract infection, since it commonly and dramatically causes local outbreaks or widespread epidemics, and these occur in most parts of the world and in some countries in most years. Epidemics occur suddenly and without warning, and the number of people infected range from few hundreds to hundreds of thousands:
although short-lived, epidemics can infect up to 70% of a population, with clinical disease occurring in 50% of infected subjects, and deaths due directly or indirectly to influenza number from 1000 to 25,000 per 50 million persons per year in developed countries. The importance of this infection in causing morbidity and mortality is reflected in the enormous scientific effort made to understand the virus, the nature of the disease and to devise methods for control.

When influenza virus isolates are cross-referenced to patients, time and place, several patterns are seen. Firstly, most pandemics and widespread epidemics are caused by influenza A viruses; influenza B viruses are associated with self-limiting epidemics which occur in families or small communities; and influenza C virus is associated with sporadic infections, mainly among young children. Influenza A exhibits the greatest antigenic diversity; influenza B exhibits some variation; and influenza C is relatively stable. Secondly, the recorded patterns of influenza A epidemics during the past century exhibit two phenomena. Every 10 to 15 years since records began in 1890, influenza virus has undergone major antigenic changes in the HA molecule, termed antigenic shift: the emergence of these new subtypes has resulted in the pandemics seen in the years 1933 (H1), 1947(H1), 1957(H2) and 1968(H3); and caused the epidemics which followed until the next new subtype emerged. These subtypes are distinct, and immunity to one provides no protection against infection by others. The origin of new subtypes cannot be by simple mutation from previously existing strains, since many genetic changes occur and intermediary strains are not found. Two theories for the origin of new subtypes are advanced. Firstly, two influenza viruses, one of human origin and the other probably of avian origin, infect the same cell: due to the segmental nature of the virus genomes, reassortant virus is easily produced combining the properties to infect man and the HA glycoprotein of the non-human strain. The new subtypes can now cause pandemic infection in populations with no previous immunity. An alternative theory is that the various subtypes circulate sequentially over a period of 70 to 80 years, since on two occasions antibody to new serotypes has been detected in sera from elderly people years prior to the emergence of that new subtype to cause pandemic infection: where the viruses survive between times is unknown.

Between the times of antigenic shift, epidemics occur in most years and the strains which cause them exhibit antigenic drift; these strains belong to the same subtype, but do not cross-react completely, and infection by one strain does not induce solid immunity to later emerging strains. This sequential accumulation of mutations arises naturally, and is selected by antigenic pressure in the immune and partially-immune population. In addition to antigenic drift and shift, viruses isolated from different places at the same time, and even viruses from different individuals in the same epidemic, can exhibit antigenic differences; this is known as inter- and intra-epidemic variation, and both underline the difficulty in matching vaccine virus to epidemic strains, and contributes to the disappointing low levels of immunity induced by inactivated influenza vaccines. The degree of cross-protection is directly related to the degree of cross-reaction of the virus HA, and
this is shown in Table 3. Influenza B viruses exhibit antigenic drift but not antigenic shift.

Pathogenesis. The pathogenesis of influenza has not been agreed among researchers, and many features are not understood. Virological investigations indicate that infection is from virus inhaled as droplets on to the epithelial cells of both the upper and lower respiratory airway. Histological studies of nasal exudate and tracheal biopsies indicate that the major site of infection is the ciliated columnar epithelial cells which become progressively rounded and swollen, and exhibit vacuolation with loss of ciliation; the progression usually begins in the tracheal bronchial epithelium and then ascends. The result is the widespread destruction of the ciliated epithelium down to the basement membrane which itself is not affected; the lesions become increasingly permeable with polymorphonuclear infiltration and edema. Because of the generalized symptoms of uncomplicated influenza, viremic spread has been suspected; however, there is no conclusive evidence that viremia occurs. In contrast, virus infections have been associated with ECG and EEG changes; some unconfirmed observations of virus antigen in brain and heart tissue have been published; and infection can be associated with viral encephalitis, particularly among children. These findings suggest dissemination of either virus

Table 3. Antigenic Changes in the Hemagglutinin of Influenza A Viruses

| Antigenic Shift | Serum HI Antibody Titer to Influenza Virus* |
|----------------|-------------------------------------------|
| Virus Strain  | A/PR/8/34 | A/FM/1/47 | A/Sing/1/57 | A/HK/1/68 |
| H1N1          | 1280      | <10       | <10        | <10       |
| H2N2          | <10       | 640       | <10        | <10       |
| H3N2          | <10       | <10       | 1280       | 1280      |

Antigenic Drift

| Virus Strain  | A/HK/1/68 | A/Eng/42/72 | A/PC/1/73 | A/Vic/3/75 | A/Bang/1/79 |
|---------------|-----------|-------------|-----------|------------|-------------|
| H1N1          | 1280      | 320         | 40        | 40         | <10         |
| H2N2          | 240       | 2560        | 80        | 120        | 40          |
| H3N2          | 40        | 1280        | 320       | 320        | 160         |

Note: *Influenza A viruses grown in eggs were tested in HI tests with antisera from ferrets infected intranasally with live virus and bled 3–4 weeks later. The serum HI antibody titers against 8 HA units virus are listed. Potter, C.W. (1990) Influenza. In: Principles and Practice of Clinical Virology (Zuckerman, A.J., Banatvala, J.E., & Pattison, J.R., eds.). Reprinted with permission from Wiley, New York.
or virus products from the respiratory tract; virus is known to grow in leucocytes and the release of pyrogens or cytokines offers an explanation for some systemic symptoms.

**Clinical disease.** The symptoms of influenza tend to be constant regardless of the subtype or strain of virus; however, the clinical features of influenza in young children may vary from that of adults, with croup a more common symptom in children and sore throats more common in adults. Droplet infection is followed by an incubation period of approximately 24 to 96 hours: the onset of illness is usually abrupt. Symptoms include fever, headache, photophobia, shivering, dry cough, malaise, aching of muscles and a dry, ticking throat which can lead to the voice becoming husky or lost. The eyes are often watery, burning and painful on movement. Fever is usually continuous, and typically lasts some 3 days: in a percentage of patients, a second rise in temperature may occur, usually smaller than the first, which gives the infection a biphasic fever curve. The cough may persist for several days; the nose can be blocked or show a purulent discharge; and myalgia is most severe in leg muscles, but also may involve the other extremities. Acute illness usually resolves within 7 days, but patients frequently complain of feeling listless for weeks, and depression is a common residual complaint. Infections caused by influenza B resemble closely those caused by influenza A; in contrast, influenza C is usually a mild upper respiratory tract infection.

The complications of infection include tracheobronchitis and bronchiolitis: these patients exhibit a productive cough and chest tightness, and crepitations are commonly heard but the lungs are usually radiologically clear. These complications are most commonly seen in patients with obstructive bronchitis and in older people, and death from influenza can result in such patients. Pneumonia in patients with influenza virus infection can be primary or secondary. In viral pneumonia, patients developed a persistent fever and leucocytosis, dyspnea, hypoxia, and cyanosis; this follows the acute symptoms described above. Sputum specimens show no bacterial cause, and a proportion of these patients die of diffuse hemorrhagic pneumonia. More commonly, pneumonia following influenza is due to secondary bacterial infection, principally with *Staphylococcus aureus*, but also with *Streptococcus pneumoniae, Hemophilus influenzae* and other bacterial species: this complication is a major cause of death among elderly people and those with underlying disease such as congestive heart failure and chronic bronchitis. In addition, patients with diabetes, renal disease, alcoholism and those who are pregnant also have an increased susceptibility to secondary bronchopneumonia. Influenza is also associated with myalgia, a common feature of acute disease, but clinical myositis and myoglobinuria can occur: the symptoms develop after the onset of respiratory infection, when muscles become painful and tender, but without neurological symptoms. An important complication of influenza infection is the syndrome known as Reye's syndrome characterized by encephalopathy and fatty liver degeneration; this is chiefly seen at age 8 to 15 years, and among those hospitalized the
mortality can be as high as 50%. The association of Reye's syndrome following infection by influenza A or B or other viruses has been fully demonstrated, but the pathogenesis remains obscure (Carey et al., 1976); researchers have highlighted the association of virus infection with treatment of fever with high concentrations of aspirin, and for this reason aspirin should not be given to patients in this age group. More conjectural is the association of influenza infection in pregnancy with congenital abnormality; this is not justified with our current knowledge. Further complications reported are ketoacidosis in diabetic patients, acute viral encephalitis in children, Guillain-Barré syndrome, sudden infant death syndrome and toxic shock syndrome resulting from the dual association of *Staphylococcus aureus* and influenza infection.

**Diagnosis.** Influenza viruses can be recovered from throat washings or swabs by inoculating tissue cultures of kidney tissue from Rhesus monkeys, chicks, and a variety of other species. After incubation, newly produced virus can be detected in supernatant fluids by the ability to agglutinate erythrocytes (hemagglutination), or the adherence of erythrocytes to virus particles assembled on the cell surface (hemadsorption). Influenza virus can also be cultured in the amniotic cavity of embyronated eggs: after incubation, high titers of virus are found in the amniotic fluid, and are detected by hemagglutination. The viruses are recognized as influenza A, B, or C by complement fixation tests using extracts of infected cells containing high concentrations of NP antigen, and type-specific antisera. Further identification of influenza isolates into sub-types and strains is dependent upon antigenic differences in the HA. This is determined by hemagglutination inhibition (HI) tests against antisera raised in experimental animals against a range of virus subtypes and strains: the titer of each antisera against homologous virus is known prior to testing, and the pattern of HI titers found against an unknown influenza virus determines the strain and type. However, this is a highly specialized typing system which is the responsibility of WHO reference laboratories who constantly type new isolated viruses in a worldwide endeavor to detect new virus variants as they arise. Proof of influenza infection can also be obtained by demonstrating a rise in specific complement fixing or HI antibodies in sera collected early after the onset of symptoms and 14 to 21 days later.

**Control and treatment.** The constant, almost annual antigenic changes seen in influenza virus A and to a lesser extent influenza B means that vaccines need to be developed for each new epidemic strain. At present, vaccines are produced by inoculating virus into embryonated eggs, purifying and inactivating the resultant virus growth to give a whole virus, disrupted virus or virus subunit (HA and NA) vaccines (Potter, 1982). To date, no live attenuated virus vaccines are available. Inactivated vaccines produce few reactions, but most are mild and ephemeral; induce serum antibody in the majority of subjects, but immunity in only 60 to 90% of vaccinees. Due to the severity and fatalities from influenza, vaccine is offered
annually to at-risk patients: these include persons aged 65 yrs of age, patients with a history of chronic chest or heart disease, and patients with asthma, renal dysfunction and metabolic disorders. In some years, such as when a new subtype is recognized, key personnel in industry and social services should be offered vaccine.

At present, the treatment of influenza is symptomatic: patients are advised to remain in bed for 2 to 3 days until the acute symptoms subside; symptoms of headache and fever are treated with paracetamol; codeine linctus can relieve the cough; insomnia may be treated by barbiturates or promethazine; and antibiotics are indicated when chest complications are present or suspected. The use of prophylactic antibiotics in patients with chronic chest disease is common, but not recommended. The compound amantadine, and the analog rimantidine, are active against influenza: an oral dose of 100 mg per day given to people in contact with influenza decreases the chance of infection by some 70%, and given to patients with clinical disease can reduce both the length and severity of disease (Dolin et al., 1976).

Laryngotracheitis and Croup

Parainfluenza Viruses

Virology. Parainfluenza viruses of the genus Paramyxovirus in the family Paramyxoviridae are distinguished by the size and shape of the nucleocapsid, biochemical similarity, antigenic cross-reactivity and the presence of a surface glycoprotein with combined hemagglutination and neuraminidase activity. Virus particles consist of single, non-segmented, negative-strand RNA, and three internal proteins surrounded by a lipid bilayer with a fourth protein, into which are inserted the hemagglutinin/neuraminidase molecule and a fusion protein which both radiate from the surface of the virion particle. The complete virion has a diameter of 150–200 nm. The viruses replicate in primary human and monkey cells with assembly of new virus particles taking place in the cytoplasm and release by budding: the effect on the cells is lytic with cytopathic effect and occasionally syncytia formation. Viruses can be detected by hemadsorption of guinea-pig erythrocytes to infected cells through virion particles budding through the cell membrane. Four serotypes cause respiratory infection in man, and are individually recognized by various tests including hemagglutination inhibition, hemadsorption inhibition and neutralization tests.

Epidemiology. Parainfluenza viruses types 1, 2, and 3 are the major cause of tracheobronchitis and croup in young children; type 3 is frequently associated with pneumonia; and type 4 causes mild upper respiratory tract infections. Infection is by droplets and requires only a small dose of virus; virus from infected persons is shed for 3 to 10 days, but in some cases can continue for 3 to 4 weeks. Infection by all types is worldwide with peak numbers occurring in the winter months: epidemics are frequently recorded, and reinfection common (Chapman et al., 1981). Over
50% have antibodies to one or more of these viruses by age 2 years, and over 75% by age 4 years.

Pathogenesis. Mild infections are mostly of the nose and throat with minimal involvement of the lower respiratory tract; more extensive infection by types 1 and 2 involves the larynx, trachea, and bronchi with pneumonia occurring in some 15 to 20% of patients; and type 3 infection causing a higher incidence of bronchiolitis and pneumonia. Virus replication has a lytic effect on the epithelial cells, whilst in the trachea and bronchi infection causes excess mucus production leading to atelectasis and pneumonia. Infection induces an IgE antibody response in serious cases which in turn initiates histamine release: it is thought that these responses are important in the pathogenesis of infection.

Clinical features. Following an incubation period of 2 to 4 days, primary infection in children is seen as a rhinitis and pharyngitis with erythema: some evidence of bronchitis is commonly seen with hoarseness, cough with croup and bronchitis with rhonchi. Fever is recorded and lasts 2–3 days. In more severe cases, infection extends to produce a heightened fever, a laryngotraceobronchitis with a barking cough and croup which lasts for 48 to 72 hours; symptoms may worsen to cause air hunger and cyanosis, sternal and intercostal retractions, airway obstruction and glottic and subglottic narrowing (Parrott et al., 1962): if pneumonia develops, the cough is productive, and radiological examination may show interstitial and perihylar infiltration.

Diagnosis. Viruses present in throat washings can be cultivated on monkey kidney cells: after replication, virus particles can be demonstrated on the surface of infected cells by hemadsorption. Alternatively, virus can be detected directly by immunofluorescence tests on respiratory secretions (Ray and Minnich, 1987). Diagnosis based on serological tests is less satisfactory: primary infection induces a type-specific antibody response detectable by hemagglutination inhibition, complement fixation, or neutralization tests, but subsequent infections induce a heterotypic response.

Control and treatment. Much research has been carried out on the development of a parainfluenza virus vaccine but none is available at the present time: inactivated vaccines induce serum antibodies, but only partial immunity. Treatment is symptomatic: children may be nursed in plastic tents supplied with cool moistened oxygen for 2 or 3 days to relieve respiratory symptoms; severe obstruction may require endotracheal intubation or tracheostomy; and accumulative and excessive tracheobronchial secretion may require bronchoscopy aspiration. Antibiotics are used where investigations indicate secondary bacterial infection. The use of corticosteroids is contentious, but aerosolized preparations of the antiviral compound ribavirin may be valuable.
Other Viruses

Some 50% of cases of laryngotracheitis and croup in children under age three years are due to parainfluenza virus infection; the remaining cases are due to influenza A and B, respiratory syncytial virus (RSV) and various serotypes of Coxsackie and Echoviruses. The severity of infection indicates laboratory investigation; thus, the contribution of these latter agents to the syndrome is well-documented.

Bronchitis

Acute bronchitis, or more commonly tracheo-bronchitis since contiguous respiratory compartments are usually involved, has been associated with adenovirus type 3, 4 and 7 infection in both children and adults, but other serotypes have been identified. Among the other infections causing bronchitis are rhinoviruses and RSV virus in children, and measles and influenza A virus infections in children and adults: these infections may precede secondary bacterial infection. Exacerbation of chronic bronchitis is frequently associated with virus infections; these include a wide range of viruses, but are most commonly caused by RSV, rhinoviruses, and parainfluenza viruses.

Bronchiolitis

Respiratory Syncytial Virus

Virology. Respiratory syncytial virus (RSV) belongs to the genus Pneumovirus within the family Paramyxoviridae; and is distinguished by the form of a nucleocapsid, replication entirely in the cell cytoplasm and the absence of hemagglutinin and neuraminidase glycoproteins. The virus particle is structurally similar to that of other members of the family consisting of a single, non-segmented, negative strand of RNA and three internal proteins surrounded by a lipid bilayer with two associated proteins: inserted into the outer aspect of the lipid bilayer are spikes of an attachment protein and a fusion protein. The diameter of the virion is 120 to 300 nm. RSV replicates in the cytoplasm of a range of human and animal cells: cell death is principally the result of cell fusion, and the formation of multinucleate syncytia indicates the presence of virus and gives the virus its name. Antigenic variants are known, and this has resulted in recognition of two subgroups.

Epidemiology. RSV causes annual epidemics in the winter months in most countries which are indicated by an abrupt rise in the number of pediatric admissions to hospital (Glezen and Denny, 1973). Infection is spread by large droplets and therefore require close contact; by hand from nasal and conjunctival secretions; or via inanimate objects and self-inoculation: the virus is highly infectious, and 50% of children are infected by 1 year of life, and all children by age 2 years, with
Respiratory Tract Viruses

recurrent infection common. The virus causes 75% of all bronchiolitis and 25% of all pneumonia cases seen in children under 1 year of age: the mortality rate is 0.5 to 2.5% with most in children with underlying heart or respiratory disease. Infection is essentially an upper respiratory tract infection in children aged less than 6 weeks or over 6 months; however, between these age limits 30% of infections involve the lower respiratory tract. Recovery is accompanied by serum antibody and a cell-mediated immune response which protects against subsequent lower respiratory tract infection; the local IgA antibody response is ephemeral, allowing further upper respiratory tract infections in later life.

Pathogenesis. After an incubation period of 3 to 6 days, infection begins in the nasopharynx with virus titers reaching a maximum at 2 to 3 days, declining between 3 to 6 days but can be detected in some patients for 3 weeks. Spread to the lower respiratory tract is by cell-to-cell interaction in the respiratory epithelium and via aspirates. Cell infection is cytopathic following cell fusion, causing inflammation and necrosis with associated plugging of the airways; but other factors are involved in the disease which are not fully defined: these include immunopathology due to antibody production, the formation of antigen-antibody complexes, delayed hypersensitivity reactions, an exaggerated cytotoxic T-cell response and an IgE response as described for parainfluenza virus infection (Welliver et al., 1984).

Clinical disease. In children aged less than 6 weeks or greater than 6 months infection is usually seen as an upper respiratory tract (URT) infection with rhinitis, a mild fever, sneezing, and wheezing; some 40% of children exhibit a lower respiratory tract involvement with tachypnea, rales, and rhonchi. More severe lower respiratory tract (LRT) infection may occur, but this is more common at age 6 to 24 weeks: following the mainly URT infection, patients develop a bronchiolitis with dyspnea, severe tachypnea, and intercostal and subternal retraction; and in most severe cases an added pneumonia occurs with hypoxia and cyanosis. Radiological appearances vary from normal to that of a bacterial pneumonia, but clinical severity is not mirrored by the radiological changes. The infection lasts 6 to 12 days with patients showing improvement after 3 to 4 days, but in severe cases symptoms may persist for several weeks.

Diagnosis. Aspirates or nasal secretions contain virus that can be detected by inoculating tissue cultures which show syncytia formation following virus replication, or by direct tests for virus antigen using immunofluorescence tests. Infection induces a rise in serum antibody detected by complement fixation or neutralization tests.

Treatment. Patients with LRT infection commonly require hospitalization for supportive therapy: reduction of fever and hydration is commonly adequate, but in more severe cases oxygen may be required to assist breathing; mechanical removal of respiratory secretions may be necessary, and blood gases should be monitored.
The infection responds to treatment with the antiviral compound ribovirin, and administration of this compound as a small particle aerosol has proven effective (Hall et al., 1983). No effective vaccine has been developed despite 20 years of dedicated research.

**Other Viruses**

Studies have shown that 50 to 90% of bronchiolitis cases are caused by RSV; and characterized by necrosis and sloughing of the bronchiolar epithelial leading to the plugging of small airways, obstruction and atelectasis (Hall et al., 1986). However, other viruses more appropriately associated with other compartments of the respiratory tract, can produce the same pathological changes and clinical symptoms. Thus, bronchiolitis has been associated with infections by influenza viruses A and B, and adenoviruses; and in young children with parainfluenza virus infection: these virus infections are described under separate headings.

**Pneumonia**

Pneumonia, characterized by radiological changes, physical signs and pathology, is uncommonly related to infection by any virus; however, three reservations should be admitted. Firstly, cases of acute pneumonia due to adenovirus and influenza viruses, although unusual, are well-documented, and fatalities have been recorded following these infections. Secondly, severe infection by viruses in higher compartments of the respiratory tract, can extend to cause pneumonia: these include adenovirus and influenza viruses again, and RSV and parainfluenza viruses in young children. Thirdly, primary pneumonia is a rare presentation by measles, chicken pox (varicella/zoster) and cytomegalovirus (CMV) infection: although unusual in normal subjects these are more commonly seen in immunocompromised persons, where the infection can be devastating.

Pneumonia in the immunocompromised by measles, chicken pox or CMV is usually an extension of typical infection to involve the lungs, but can present without a rash or with an atypical rash in patients with no history of infection. Patients develop cough and chest pains, and more seriously dyspnea and cyanosis; X-rays may show evidence of viral pneumonia with atypical, patchy consolidation; and deaths are recorded in 40% or more of immunocompromised patients. Pathologically, the alveoli contain edema fluid with macrophages, but few polymorphonuclear cells; and typically and diagnostically, giant multinuclear cells. The viruses can be grown from the bronchial secretions; however, since these are rapidly progressing infections and suggested treatments are available for two of these viruses, quicker methods such as the direct demonstration of virus by immunofluorescence or ELISA tests on cells in secretions are needed. There is no treatment for measles virus pneumonia; acyclovir or ganciclovir are reported to be of value in the treatment of CMV; and acyclovir will prevent pneumonia in chicken pox patients, but has no proven value in treating established pneumonia.
SUMMARY

Respiratory tract infections are among the commonest of illnesses, and most individuals will experience two to five infections during each year of their lives. The illnesses vary from relatively mild common colds caused by rhinoviruses and coronaviruses, to severe bronchiolitis and pneumonia caused by adenoviruses and influenza viruses and respiratory syncytial virus (RSV) in infants: the former is associated with little morbidity and no mortality, while influenza is responsible annually for between 1 and 25 thousand deaths per 50 million population. Over 140 viruses cause respiratory tract infections, with the added complications of influenza viruses where new antigenic variants are recognized almost annually; and immunity to infection by one virus strain offers little or no protection to infection by others. Knowledge of the mechanisms of spread of respiratory viruses is largely understood and has helped in infection control; however, the clinical signs and symptoms of infection tend not to be diagnostic of the causative agent; and although vaccines have been developed for the more serious infections such as influenza and some adenovirus infection, none are available for other important infections. Treatment is largely symptomatic, but the compounds ribovirin for RSV infection and amantadine for influenza virus infection have been shown to be effective. Much remains to be discovered before more effective measures can be implemented to limit the enormous costs incurred by these infections. The number of viruses involved is large, and the spectrum of illness complex; in the present chapter, the viruses are described, together with the features of the epidemiology, pathogenesis, clinical disease, and treatment.

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