CHAPTER 11

Adenovirus Infections in Humans

STEPHEN E. STRAUS

I. INTRODUCTION

Adenoviruses are ubiquitous agents that infect humans of all ages. The discovery of the first adenovirus types three decades ago paved the way for countless studies that continue to uncover additional viral strains and ever expand our comprehension of their significance to man. Whereas some human adenoviruses are being examined at the increasingly sophisticated molecular and cellular levels, the means by which they infect man, provoke illness, or are handled by the body's immune system remain very poorly understood.

This chapter represents an attempt to catalogue the known human adenovirus agents, to summarize the data pertaining to their acquisition and transmission, to review the range of illness with which they are associated, and to highlight those aspects of adenovirus infection that are in need of further investigation.

II. ADENOVIRUSES RECOVERED FROM HUMANS

The 41 distinct adenovirus types that have been recovered from humans thus far are listed in Table I. Most of these agents were isolated during an extremely fruitful decade of studies that followed the initial discovery of adenoviruses. A wide range of illnesses has been associated with the better-defined, lower-numbered virus types, but the predilection

STEPHEN E. STRAUS • Medical Virology Section, Laboratory of Clinical Investigation, National Institutes of Health, Bethesda, Maryland 20205.

H. S. Ginsberg (ed.), *The Adenoviruses*

TABLE I. Adenovirus Immunotypes[a]

Type	Prototype strain	Source	Patient diagnosis	Major associated diseases[b]
1	Ad71	Adenoid	Hypertrophied tonsils and adenoids	Respiratory
2	Ad6	Adenoid	Hypertrophied tonsils and adenoids	Respiratory
3	G.B.	Nasal washing	Common cold	Respiratory
4	RI67	Throat washing	Influenzalike or viral (atypical) pneumonia	Respiratory
5	Ad75	Adenoid	Hypertrophied tonsils and adenoids	Respiratory
6	Ton99	Tonsil	Hypertrophied tonsils and adenoids	Respiratory
7	Gomen	Throat washing	Pharyngitis	Respiratory
8	Trim.	Eye swab	Epidemic keratoconjunctivitis	Ocular
9	Hicks	Stool	Rheumatoid arthritis	—[c]
10	J.J.	Eye swab	Conjunctivitis	—
11	Slobitski	Stool	Polio	Cystitis
12	Huie	Stool	Polio?	—
13	A.A.	Stool	Healthy	—
14	DeWit	Throat swab	Acute respiratory illness	Respiratory
15	Ch38	Eye swab	Conjunctivitis	—
16	Ch79	Eye swab	Conjunctivitis	—
17	Ch22	Eye swab	Conjunctivitis	—
18	D.C.	Rectal swab	Niemann–Pick disease	—
19	587	Conjunctival scraping	Trachoma	Ocular
20	931	Conjunctival scraping	Trachoma	—
21	1645	Conjunctival scraping	Trachoma	Respiratory
22	2711	Conjunctival scraping	Trachoma	—
23	2732	Conjunctival scraping	Trachoma	—
24	3153	Conjunctival scraping	Trachoma	—
25	BP-1	Rectal swab	Healthy	—
26	BP-2	Rectal swab	Healthy	—
27	BP-4	Rectal swab	Healthy	—
28	BP-5	Rectal swab	Healthy	—
29	BP-6	Rectal swab	Healthy	—
30	BP-7	Rectal swab	Healthy	—
31	1315163	Stool	Healthy	—
32	H.H.	Rectal swab	Healthy	—
33	D.J.	Rectal swab	Healthy	—
34	Compton	Urine	Renal transplant	—
35	Holden	Lung, kidney	Renal transplant	—
36	275	Stool	Gastroenteritis	—
37	G.W.	Conjunctival scraping	Keratoconjunctivitis	Ocular, genital?

(*Continued*)

TABLE I. (*Continued*)

Type	Prototype strain	Source	Patient diagnosis	Major associated diseases[b]
38	No assignment	—	—	—
39	D335	Stool	Acute respiratory illness	—
40	Dugan	Stool	Gastroenteritis	Enteric
41	Tak	Stool	Gastroenteritis	Enteric

[a] Modified from Kasel (1979) with permission. The type status of recently identified adenoviruses is according to the current (October 1982) American Type Culture Collection nomenclature.
[b] Major infectious syndrome associated with each immunotype.
[c] Human disease not proved to be associated with the immunotype.

of these human strains for ocular and respiratory tissues is most prominent. The nature of the few more recently recognized adenoviruses remains uncertain, and it is possible that these strains represent variants or hybrids of previously known virus types, though some of the newer agents have been linked to illnesses with which other adenoviruses were never associated. Adenovirus type 37 (Ad37), for example, has been associated with urethritis and cervicitis and represents the first adenovirus for which the suggestion of sexual transmission has been seriously entertained (de Jong *et al.*, 1981). In addition, a number of unusually fastidious adenoviruses have been associated with diarrheal disease and perhaps respiratory disease as well in infants and immune-compromised patients (Retter *et al.*, 1979; Gary *et al.*, 1979; Yolken *et al.*, 1982). These recent observations challenge our complacency about adenoviruses and suggest that we have yet to complete the list of all medically important types and the diseases with which they are associated.

III. CLASSIFICATION OF HUMAN ADENOVIRUSES

A. General

All human adenoviruses are members of the genus *Mastadenovirus* of the family Adenoviridae to indicate their similarity to other vertebrate (but nonavian) adenoviruses (Norrby *et al.*, 1976). Human adenoviruses have been classified into types and subgroups in many different ways according to biological, chemical, immunological, or structural properties (Table II) (Rosen, 1960; Piña and Green, 1965; Norrby, 1969; Green, 1970; Green *et al.*, 1979a; Kasel, 1979; Wadell *et al.*, 1980a). The most widely employed subgrouping scheme is based on the ability of specific immunotypes to partially or completely hemagglutinate rat or rhesus erythrocytes (Rosen, 1960). Other subgroupings have been defined by percentage of guanine plus cytosine (GC) content (Piña and Green, 1965),

TABLE II. Some Subgroup Classifications for Human Adenoviruses[a]

Type	HA	GC	ONCO	PROT	*Sma*I
1	III	H	C	C	M
2	III	H	C	C	M
3	I	M	B	B	M
4	III	H	C	E	H
5	III	H	C	C	M
6	III	H	C	C	M
7	I	M	B	B	M
8	II	H	C	D	H
9	II	H	C	D	H
10	II	H	C	D	H
11	I	M	B	B	M
12	III	L	A	A	L
13	II	H	C	D	H
14	I	M	B	B	M
15	II	H	C	D	H
16	I	M	B	B	M
17	II	H	C	D	H
18	IV	L	A	A	L
19	II	H	C	D	H
20	II	H	C	D	H
21	I	M	B	B	M
22	II	H	C	D	H
23	II	H	C	D	H
24	II	H	C	D	H
25	II	H	C	D	H
26	II	H	C	D	H
27	II	H	C	D	H
28	II	H	C	D	H
29	II	H	C	D	H
30	II	H	C	D	H
31	IV	L	A	A	L
32	II	—	C	D	H
33	II	—	C	D	H
34	II[b]	—	B	B	M
35	I[c]	—	B	B	M
36	II[d]	—	—	—	H[d]
37	II[e]	—	—	D	—
38	—	—	—	—	—
39	II[f]	—	—	—	H[f]
40	—	—	C	F	H[g]
41	—	—	C[g]	G	H[g]

[a] (HA) Hemagglutination grouping (data from Kasel, 1979): (I) absent rat erythrocyte (RBC) HA, complete rhesus RBC HA; (II) complete rat RBC HA, complete or absent rhesus RBC HA; (III) partial rat RBC HA, absent rhesus RBC HA; (IV) absent rat RBC HA, absent rhesus RBC HA. (GC) Percentage guanine plus cytosine content (data from Piña and Green, 1965): (L) low (48–49%); (M) medium (50–52%); (H) high (57–60%). (ONCO) Oncogenicity (grouping data adapted from Green, 1970; Wadell *et al.*, 1980a). (PROT) Protein analyses (grouping adapted from Wadell, 1979; Wadell *et al.*, personal communication). (*Sma*I) Number of DNA fragments induced by cleavage with restriction endonuclease *Sma* I (data adapted from Wadell *et al.*, 1980a): (H) high number (≧14); (M) medium number (8–12); (L) low number (4–5).

[b] Hierholzer *et al.* (1975). [c] Myerowitz *et al.* (1975). [d] Wigand *et al.* (1980).

[e] De Jong *et al.* (1981). [f] Hierholzer *et al.* (1982).

[g] H. E. Takiff and S. E. Straus (unpublished observations).

morphology (Norrby, 1969), oncogenicity (Green, 1970), electrophoretic mobility of virion proteins (Wadell *et al.*, 1980a), genome homology (Green *et al.*, 1979a), and restriction endonuclease cleavage profiles (Wadell *et al.*, 1980a). A complete review of all classification schemes is beyond the scope of this chapter. In general, however, the various classification schemes are highly concordant and merely reflect different facets of relatively few biochemical properties shared by adenoviruses. There is also a limited tendency for virus types within the same subgroups to be associated with similar host-tissue tropisms and pathogenicity. Sections III. B–E summarize briefly the data regarding four of the more interesting or recent approaches to adenovirus subgrouping (Table II).

B. Oncogenicity

A number of human adenoviruses have been subgrouped according to their ability to induce tumors in newborn hamsters or to transform rodent cells *in vitro* (Huebner, 1967) (see Table II and Chapter 9). Subgroup A includes highly tumorigenic strains (serotypes 12, 18, and 31) and subgroup B includes weakly tumorigenic strains (serotypes 3, 7, 11, 14, 16, 21, 34, and 35), while the members of subgroup C (serotypes 1, 2, 5, 6, and others) are nontumorigenic strains capable of transformation only *in vitro*. Some have proposed dividing subgroup C into two distinct groups that differ in the antigenicity of some early proteins [tumor (T) antigens] that are expressed in the transformed cells (McAllister *et al.*, 1969). Since adenoviruses have not been implicated in the development of human neoplasms (see Sections VI, VII. I, and XI), and there are no general differences in the clinical expression of members of each subgroup, this scheme of classification has no current relevance to human disease.

C. Electrophoretic Mobility of Virion Polypeptides

The hemagglutinating, serological, and oncogenic properties of adenoviruses probably reflect features of relatively few of the viral proteins. Analyses of virion polypeptides by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) allow one to assess simultaneously the similarities or differences among many of the proteins of various adenovirus strains. Wadell has classified all known adenovirus immunotypes into seven subgroups [A–G (see Table II)] based on the apparent molecular weights of virion polypeptides as assessed by SDS-PAGE (Wadell *et al.*, 1980a; Wadell, 1979 and personal communication). Interestingly, the composition of these groups closely parallels that defined by oncogenicity. For example, Ad12, 18, and 31 are all highly oncogenic, and their polypeptides display similar electrophoretic patterns. Moreover, there appears to be some clinical relevance to this classification scheme.

Three members of subgroup D (Ad8, 19 and 37) are most associated with severe ocular infection and the members of subgroup C (Ad1, 2, 5, and 6) with commonly occurring mild respiratory illnesses of children, while strains assigned to (the tentatively defined) subgroups F (Ad40) and G (Ad41) are fastidious in cell culture and linked to diarrheal disease.

D. Genome Homologies

Most of the human adenovirus immunotypes have been grouped by methods that can detect significant differences or similarities in base sequences throughout the genome. By heteroduplex mapping and liquid-phase DNA–DNA hybridizations, 31 adenovirus types were placed in five subgroups (A–E) that correlate highly with their classifications by polypeptide analysis and oncogenicity (Garon *et al.*, 1973; Green *et al.*, 1979a). Similarly, the homology of enteric adenoviruses to other human adenoviruses has recently been examined (H. Takiff and S. Straus, unpublished observations). Strains of Ad40 and 41, which possess restriction patterns similar to those of (Wadell's) F and G subgroups, exhibit partial to high levels of DNA homology throughout the genome, but little homology (and that largely limited to the left half of the genomes) to other lower-numbered adenovirus types.

E. Restriction Endonuclease Analysis

A highly sensitive probe of adenovirus genome sequences involves agarose-gel electrophoresis of viral DNA digested by restriction endonucleases. Mutations in one DNA base will alter the cleavage profile of the genome if the change occurs within the recognition site for the enzyme. This technique has allowed the rather artificial grouping of adenoviruses according to the number of restriction endonuclease *Sma*I-generated cleavage segments, a reflection of GC content (Wadell *et al.*, 1980a). More important, restriction endonuclease analysis has become the definitive method for typing strains and for studying the molecular epidemiology of adenovirus outbreaks (Wadell and Varsanyi, 1978; Wadell and de Jong, 1980; Wadell *et al.*, 1980a, 1981). Endonuclease analysis has been most fruitfully applied to resolving problems pertaining to the latency, transmission, and reactivation of herpes simplex viruses (Buchanan *et al.*, 1978). Restriction endonuclease analysis has yet to be utilized to determine whether adenoviruses can undergo cycles of latency and reactivation.

IV. EPIDEMIOLOGY AND TRANSMISSION

Our current comprehension of the epidemiology and modes of transmission of adenoviruses derives largely from two major groups of studies.

The first group involved careful observations of naturally occurring or experimentally induced outbreaks of specific adenovirus-induced clinical syndromes such as pharyngoconjunctival fever (PCF), epidemic keratoconjunctivitis (EKC), and acute respiratory disease (ARD) of military recruits. The epidemiological features of these syndromes are discussed in Section VII together with the clinical description of the illnesses themselves. The second group of studies entailed a series of longitudinal community and institutional studies (Jordan, 1957; J. A. Bell *et al.*, 1961; Sterner, 1962; Hamre *et al.*, 1966; Fox *et al.*, 1969; Hall *et al.*, 1971; Cooney *et al.*, 1972; Brandt *et al.*, 1972; Foy and Grayston, 1976). These two groups of seroepidemiological and viroepidemiological studies established that adenoviruses are ubiquitous. These viruses can infect humans of all ages, races, and nationalities, and, other than for ARD of military recruits (who are primarily males), there is no apparent difference in attack rate according to sex. In addition, the combined data from these studies suggests that adenovirus types can be divided for clinical purposes into three overlapping groups: those types that are endemic particularly in early childhood, those that are epidemic, and those that are predominantly sporadic. All the known human adenoviruses have been recovered on one or more occasions from patients with a wide range of sporadically appearing illnesses.

The lower-numbered adenoviruses, Ad1, 2, 5, and 6, appear to be endemic in many areas of the world. In western Europe and the United States, between one third and one half of children have acquired antibodies to one or more of these adenovirus types by the age of 1 year (Fig. 1). (Huebner *et al.*, 1954; Sterner, 1962; Hall *et al.*, 1971; Foy and Grayston, 1976). The prevalence of adenovirus-specific neutralizing antibodies by age 3 has been estimated to be about 37% in Sweden, and about 80% in the United States, and close to 100% in Taiwan (Sterner, 1962; Hall *et al.*, 1971; Cooney *et al.*, 1972; Foy and Grayston, 1976). Institutionalized children tend to acquire adenoviruses at an even earlier age than children living at home (J. A. Bell *et al.*, 1961; Sterner, 1962). In general, conditions of crowding and poor hygiene lead to earlier acquisition of adenovirus-specific antibodies. Few individuals enter adult life lacking immunological experience with these endemic adenovirus types.

Ad3, 4, 7, 8, and occasionally other types, such as Ad11, 14, 19, and 21, tend to be associated with epidemic infections. Ad3, 4, and 7 are commonly associated with epidemics of PCF (J. A. Bell *et al.*, 1955, 1956; D'Angelo *et al.*, 1979). Ad4 and 7, and less often Ad11, 14, and 21 are associated with epidemic ARD of recruits (Hilleman *et al.*, 1954; Van der Veen and Kok, 1957; Tai *et al.*, 1960; Van der Veen *et al.*, 1969), while Ad8 and 19 are associated with EKC (Sprague *et al.*, 1973; O'Day *et al.*, 1976; D'Angelo *et al.*, 1981). More recently, outbreaks of gastroenteritis have been attributed to fastidious enteric adenoviruses (Gary *et al.*, 1979; Retter *et al.*, 1979; Yolken *et al.*, 1982).

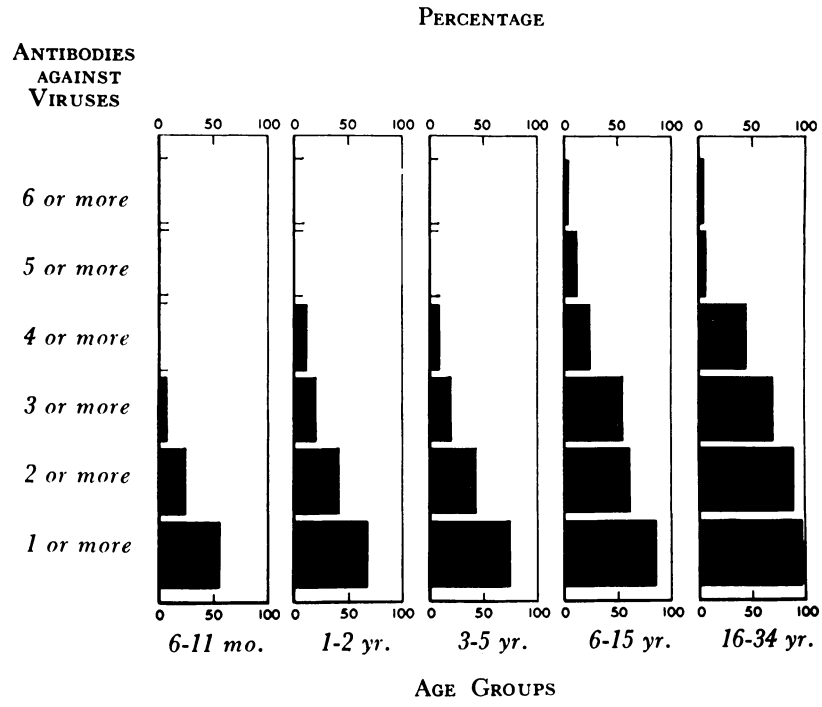

FIGURE 1. Percentage of Washington, D.C., area residents possessing antibodies to one or more of Ad1–6, by age. These data were acquired using a rather insensitive neutralization assay and are now thought to considerably underestimate the prevalance of seropositivity (R. Chanock, personal communication). Reprinted from Huebner *et al.* (1954) with permission.

Adenovirus infections have been documented in tropical (S. D. Bell, Jr., *et al.*, 1960; Kurian *et al.*, 1966) and temperate climates and occur throughout the year. Seasonal differences in infection rates are not as marked in the tropical settings as they are in temperate zones. Brandt *et al.* (1972) studied inpatient and outpatient children in Washington, D.C., over a 10-year period. Their data (Fig. 2) revealed two annual peaks in adenovirus-associated respiratory illness: midwinter and midsummer. Whereas there were more children from whom adenoviruses were recovered in the winter, the percentage of isolates that were believed to reflect respiratory illness was greater in the summer. Hilleman (1957) showed that adenovirus-induced ARD in military recruits is largely confined to one broad peak in the cooler months of the year [see Fig. 7 (Section VII. C.4)].

The fecal–oral route is thought to be the major means by which adenoviruses are transmitted, at least during childhood (Fox *et al.*, 1969). This belief is based on the observation that adenoviruses continue to be excreted for months or years following the initial infection (Table III). Chronic respiratory shedding occurs, but fecal shedding appears to be more intense and prolonged. Longitudinal studies of families in the New

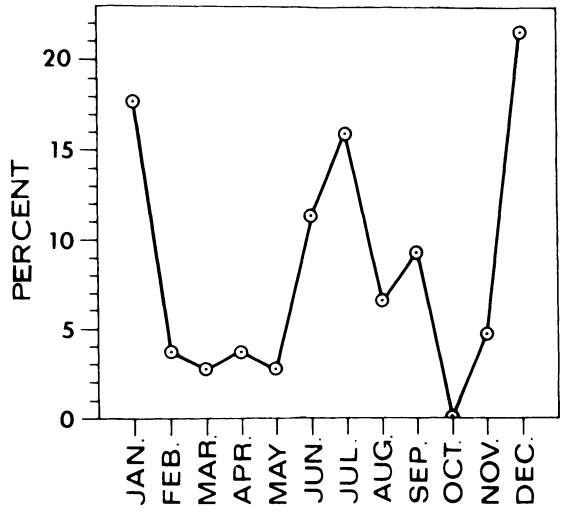

FIGURE 2. Percentage distribution of adenovirus-associated respiratory illness in inpatients, by month (12 months = 100%). Data reprinted from Brandt *et al.* (1972) with permission.

York Virus Watch documented a number of infants who became infected shortly after birth into families in which there were older siblings who chronically excreted the same virus type in their stools (Fig. 3).

ARD can be transmitted by oral instillation of infected respiratory secretions (Commission on Acute Respiratory Diseases, 1947a,b). PCF is thought to be transmissible by instillation of contaminated swimming pool water or other infected materials into the nose or eyes (J. A. Bell *et al.*, 1956; D'Angelo *et al.*, 1979). Direct conjunctival inoculation is im-

TABLE III. Percentage of Persons Who Excreted Adenoviruses for at Least the Numbers of Days Indicated following an Initial Infection[a]

Days	%
1	100
2	52
16	44
31	36
61	32
91	26
181	20
361	9
721	2

[a] Modified from Fox *et al.* (1969) with permission. Percentages are those of 133 patients from whom stool specimens remained positive.

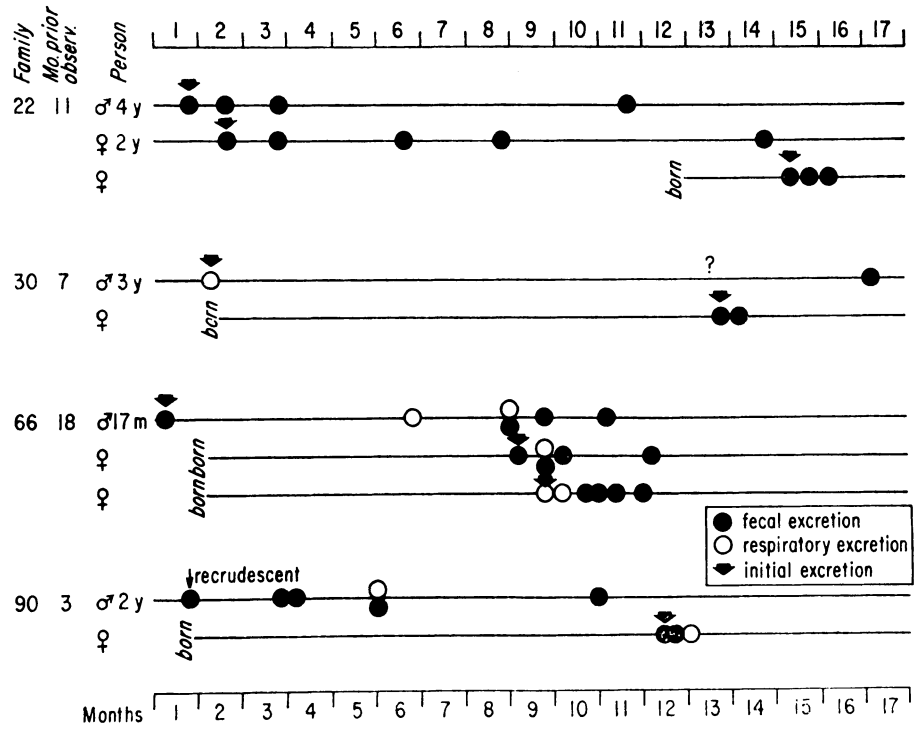

FIGURE 3. Spread of Ad2 infection to infants born into families in which older siblings were previously infected. Reprinted from Fox *et al.* (1969) with permission.

portant for transmission of Ad8 in cases of EKC (Dawson *et al.*, 1970; D'Angelo *et al.*, 1981).

The incubation period of adenovirus infections has been defined best in volunteer trials. In studies of PCF, J. A. Bell *et al.* (1955) estimated an incubation period of 5–10 days with a mean of about 7 days. Military studies of ARD suggest an incubation period of about 4–10 days with a mean of 5–6 days for that syndrome (Commission on Acute Respiratory Diseases, 1947a,b). Careful observations of natural outbreaks of ARD and of EKC indicated mean incubation periods of 7–10 days (Hilleman, 1957; Sprague *et al.*, 1973).

V. PATHOLOGY

The pathological alterations that attend typical adenovirus infections are not very well defined. Only the more severe infections have generally justified acquisition of tissue specimens. Most of the reported pathological studies have described the results of postmortem examinations of patients who succumbed to pulmonary, hepatic, or disseminated adenovirus infections. Becroft (1967), in a study of fatal adenovirus respiratory tract infection of infants, observed extensive destruction of bronchial ep-

ithelium and bronchial glands. Alveoli were distended with an eosinophilic exudate. All involved tissues displayed a cellular, predominantly mononuclear infiltration. Two types of nuclear changes were described: The first involved a diffuse accumulation of strongly Feulgen-positive basophilic or amphophilic material. The second entailed more discrete Feulgen-negative, amphophilic, or eosinophilic intranuclear inclusions. Similar patterns of tissue necrosis, mononuclear infiltration, and irregular amphophilic or basophilic inclusions were observed in an acutely infected liver (Aterman *et al.*, 1973). Myerowitz *et al.* (1975) reported similar pathological alterations in several organs in a patient with a fatal disseminated infection (Fig. 4). Electron-microscopic (EM) studies of involved tissues from fatal infections demonstrate typical paracrystalline arrays of adenovirus particles (Fig. 5).

Thus, much of the pathological alteration observed in adenovirus infections is mediated by direct tissue damage from productive virus replication in susceptible tissues (Becroft, 1971; Henson and Mufson, 1971; Aterman *et al.*, 1973). The results of studies in which animals were inoculated with large numbers of human adenoviruses have suggested that abortive infectious cycles may also participate in tissue injury, but there are no data to support this in the proper (human) host (Duncan *et al.*, 1978). There is also some evidence for cellular injury via immunopathological mechanisms. Chronic inflammatory sequelae of adenovirus-induced keratitis appear to evolve in the absence of cultivable virus and respond to corticosteroid therapy (Laibson *et al.*, 1970). It has been postulated that persistent viral antigen–antibody complexes incite an inflammatory response that is capable of injury to the cornea (Boniuk *et al.*, 1965).

VI. PATHOPHYSIOLOGY AND IMMUNE RESPONSES

Since there are no satisfactory animal models of human adenovirus infection, our understanding of what occurs following initial infection is sketchy and derives largely from speculation or extrapolation from better-defined virus–host systems. It is presumed that adenoviruses establish productive infections in gastrointestinal, respiratory, or ocular epithelial cells (Fishaut *et al.*, 1980). The lower-numbered adenovirus types are commonly recovered from ocular and respiratory tissues. The higher-numbered types (Ad25–41) have almost always been recovered from stools (see Table I). For these latter types, the major and primary site of infection may be in the gastrointestinal tract. From the primary sites of infection, the newly replicated virus may then enter the bloodstream and spread to other body tissues, where the ultimate events will depend on a complex interplay of host and viral factors (Andiman *et al.*, 1977). It is clear that different adenoviruses possess unique tissue tropisms. Most cases of severe lower respiratory or disseminated infections have involved

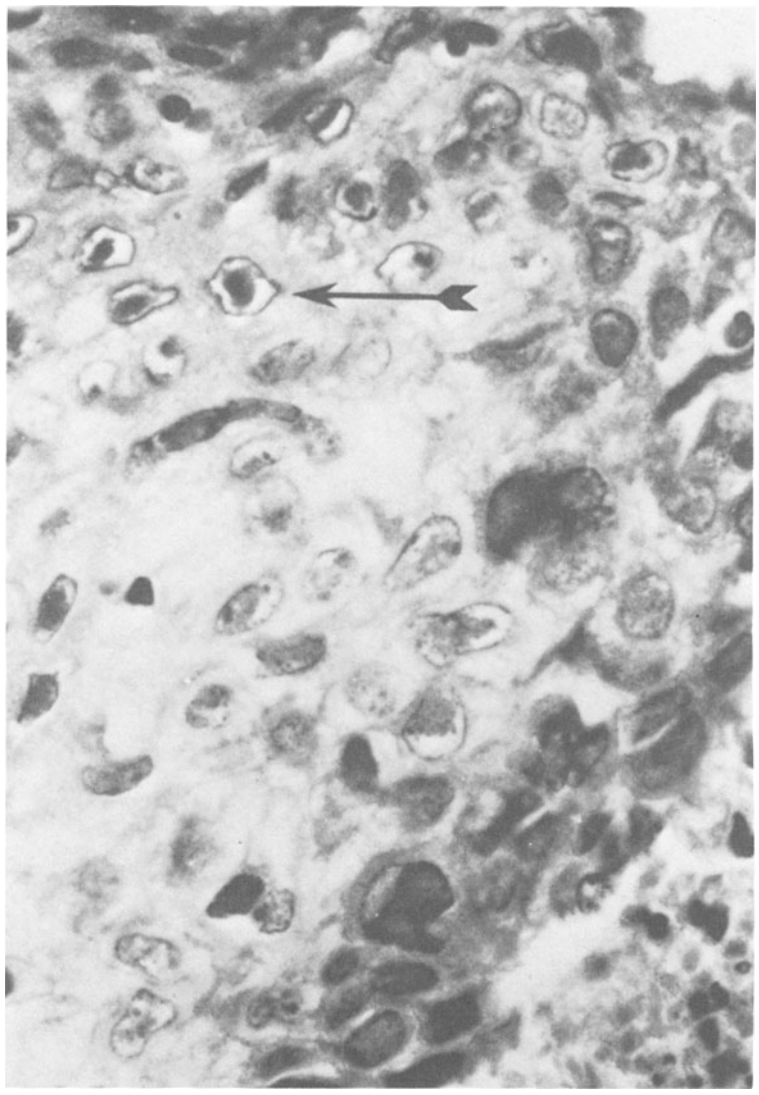

FIGURE 4. Photomicrograph of esophageal epithelium of a patient with disseminated Ad34 infection demonstrating cytoplasmic swelling and haloed intranuclear inclusions (←). Original magnification: ×400. Reprinted from Myerowitz *et al.* (1975) with permission.

Ad1–5, 7, and 21 (Lang *et al.*, 1969; Henson and Mufson, 1971; Dudding *et al.*, 1972; Aterman *et al.*, 1973; Field *et al.*, 1978; Carmichael *et al.*, 1979; Zahradnik *et al.*, 1980). Ocular infections are common with Ad3, 4, 7, 11, and 37 and are likely to be severe with Ad8 and 19 (Dawson *et al.*, 1970; O'Day *et al.*, 1976). Some Ad7 strains may be particularly neurotropic (Gabrielson *et al.*, 1966; Huttunen, 1970; Simulä *et al.*, 1970).

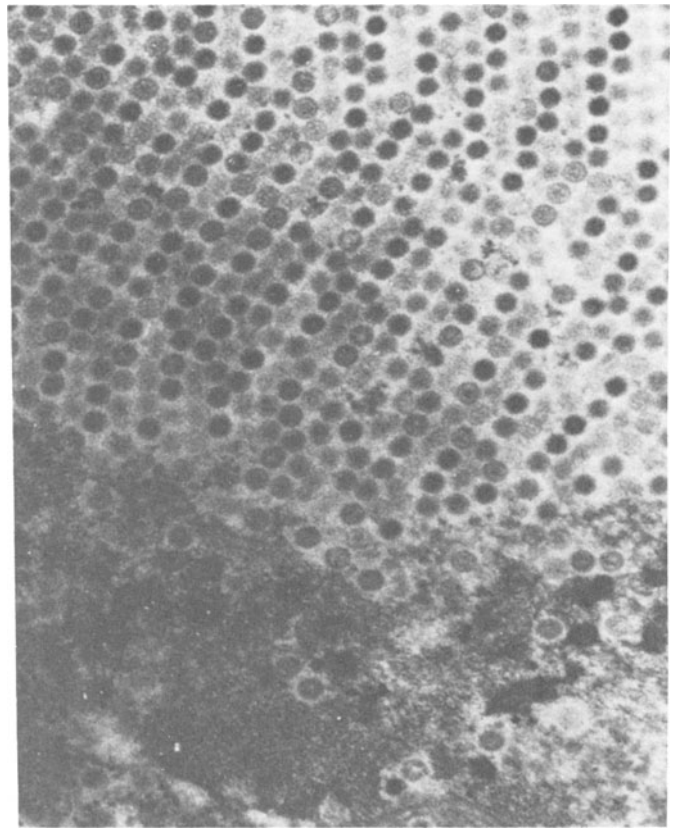

FIGURE 5. Electron micrograph of a pulmonary alveolar cell from the patient in Fig. 4 demonstrating 80-nm particles in a paracrystalline array. Original magnification: ×46,500. Reprinted from Myerowitz *et al.* (1975) with permission.

Immune clearance of infecting virus presumably requires successful interactions among macrophages, lymphocytes, natural killer cells, and humoral factors including antibody, complement, interferon, and other lymphokines (Fishaut *et al.*, 1980). Although there is some evidence that humoral responses modify the course of adenovirus infections (McCormick *et al.*, 1972; Siegal *et al.*, 1981), it is obvious that cell-mediated immune mechanisms are of paramount importance for the containment and resolution of these infections. Most cases of devastating adenovirus infections have been documented in individuals devoid of adequate cellular immunity, including neonates, immune-depressed cancer or transplant patients, or children with congenital thymic aplasia or other T-cell disorders (Henson and Mufson, 1971; Aterman *et al.*, 1973; Hierholzer *et al.*, 1975a; Myerowitz *et al.*, 1975; Andiman *et al.*, 1977; Carmichael *et al.*, 1979; Zahradnik *et al.*, 1980).

Infections with adenoviruses are analogous to infections with herpesviruses, which are better understood in terms of host–virus interactions. The ultimate outcome of infection with either virus is dependent on cellular immunity. Importantly, members of both virus families induce persistent or latent infections of human tissues. Herpesviruses and adenoviruses can be shed chronically and asymptomatically, indicating a failure of immune clearance. Unlike the case with the herpesvirus, however, it is not known whether adenoviruses can reactivate from a latent infectious state and induce recurrent disease. In addition, the results of *in vitro* and animal studies of viral transformation have led to speculation regarding the potential of both kinds of viruses for human oncogenesis, but the evidence has been far less supportive for such an association with adenoviruses than for an association with herpesviruses (Huebner, 1967; McAllister *et al.*, 1969; Green, 1970).

VII. INFECTIOUS SYNDROMES ASSOCIATED WITH ADENOVIRUSES

A. General

Among the many adenovirus serotypes, only about a dozen (including Ad1–8, 11, 14, 19, 21, and 37) have been proved to produce defined clinical syndromes (Chanock, 1974). This is not to say that the remaining serotypes are devoid of pathogenic potential. Rather, proving causality for those serotypes has been difficult for two reasons: First, many adenovirus-associated infections are subclinical (Hilleman, 1957; J. A. Bell *et al.*, 1961; Forsyth *et al.*, 1964; Fox *et al.*, 1969). Second, it is not uncommon for adenoviruses, especially the lower-numbered serotypes, to be persistently shed for months or years following an initial infection (see Table III) (Fox *et al.*, 1969). Thus, recovery of an adenovirus from an individual with a particular clinical syndrome does not imply a causal relationship between the syndrome and that virus. It must be demonstrated that individuals with a specific illness are statistically more likely to be shedding a specific virus type than are well controls. This has been feasible only in challenge studies, in very large population studies, and with epidemics of certain infectious syndromes.

B. Asymptomatic Infections

The proportion of adenovirus infections that result in clinical illness has been estimated in a number of studies involving continuing surveillance for infection and illness in defined populations (J. A. Bell *et al.*, 1961; Fox *et al.*, 1969). The onset of illness in close temporal relationship to the first detection of excretion of virus has been considered to be one

measure of viral pathogenicity. In the Junior Village study, 53% of children who showed a rise in homologous neutralizing-antibody titer in association with shedding of virus had a febrile illness (J. A. Bell *et al.*, 1961). In a study of Marine Corps recruits at Camp Lejeune, North Carolina, who were commonly infected with Ad4, first recovery of virus within the week of onset of illness was assumed to be evidence for pathogenicity. Forsyth *et al.* (1964) estimated that about 48% of infected recruits experienced a compatible clinical illness. In another study, Hilleman (1957) showed that as many as 80% of military recruits acquired adenovirus infections (particularly Ad4 and 7) during basic training. About half these infections were asymptomatic. In the Virus Watch Program in New York City, in which surveillance cultures were taken every other week, first recovery of virus between 14 days before and 7 days after onset of an illness was considered evidence of pathogenicity. By comparison with the incidence of first recovery of virus in the absence of clinical illness, it was estimated that a maximum of 45% of adenovirus infections were associated with symptoms (Fox *et al.*, 1969). This estimate may be further reduced by additional data generated in the Virus Watch Study. Other agents, predominantly rhinoviruses, were also recovered from many of the subjects in close temporal relationship to illnesses. Assuming that these other agents were primarily responsible for the symptoms observed, it was estimated that as few as 15% of all adenovirus infections were symptomatic.

The differences in the aforecited estimates of the proportion of asymptomatic infections may be attributed, in part, to the system employed in each study to define illness. In the Junior Village Study, temperatures were recorded for all subjects twice daily and brief physical examinations were performed daily. Minor illness could be readily detected. In the New York Virus Watch Program, only those children whose parents recognized a problem and documented a fever were followed. For this reason, the rate of symptomatic illness may be underestimated in this latter study (15–45%).

The proportion of asymptomatic adenovirus infections is also dependent on serotype. In a controlled study in Washington, D.C., involving over 900 pediatric respiratory patients with adenovirus infections, it was estimated that among those with throat or anal swab isolates or both, adenoviruses were causally related to respiratory illness in 32% overall, including 47% with Ad1, 20% with Ad2, 61% with Ad3, 30% with Ad5, 93% with Ad6, and 43% with Ad7 infection (Brandt *et al.*, 1969).

C. Respiratory Infections

1. Spectrum

Data on the relationship between adenoviruses and symptomatic illness give one measure of the pathogenic potential of these agents. An-

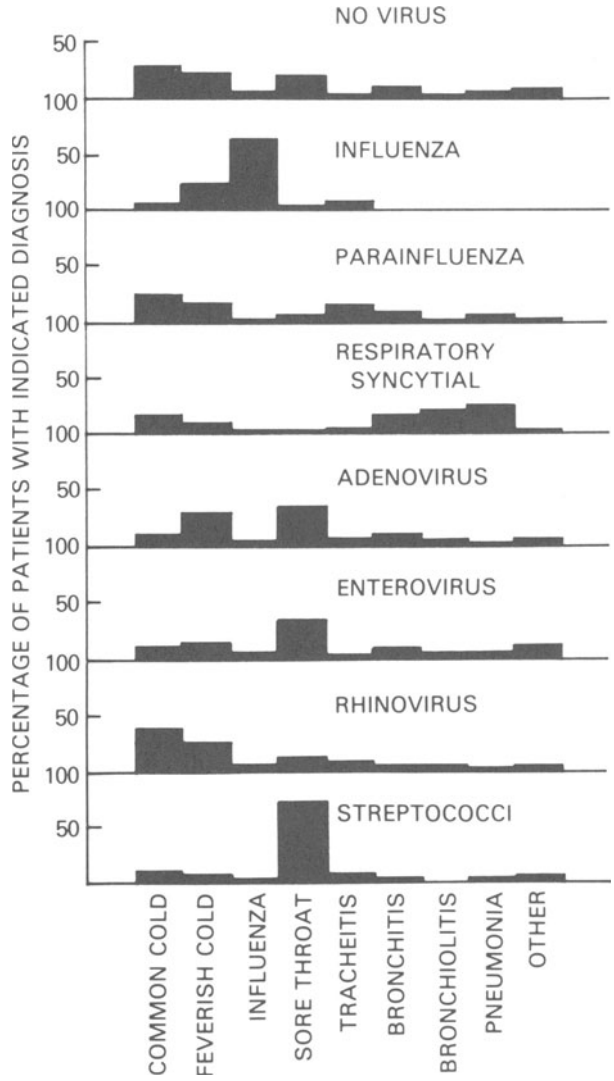

FIGURE 6. Relative frequency of various clinical syndromes among patients infected with respiratory pathogens. Redrawn from the Medical Research Council Working Party on Acute Respiratory Virus Infections (1965) report with permission.

other way of examining this problem is to assess the proportions of various clinical syndromes that are associated with adenovirus infection.

Adenoviruses have been clearly shown to contribute significantly to the total community morbidity, especially from respiratory infections. A Medical Research Council (1965) study in Britain demonstrated that in the general community, adenoviruses are associated with the entire spectrum of respiratory illness, but are important causes of relatively mild illnesses such as febrile colds and sore throats (Fig. 6). In Tecumseh, Mich-

igan, adenoviruses accounted for about 4.5% of pathogens recovered from patients of all ages with respiratory infections (Monto and Ullman, 1974). During a decade of study of infants and children at D.C. Children's Hospital, adenovirus was recovered from throat or anal swab specimens or both from 12.4% of 6700 respiratory outpatients and 10.2% of 4700 respiratory inpatients (Brandt *et al.*, 1969). On the whole, the adenovirus group ranked third behind respiratory syncytial virus and parainfluenza viruses as a cause of pediatric respiratory disease (Kim *et al.*, 1979).

2. Coryzal Syndromes

Monto and Ullman (1974) reported that the average number of upper respiratory illnesses experienced each year decreases with age. Averages of 6, 4, 2, and 1 infection/year were recorded for individuals aged 0–2, 3–9, 10–39, and 40 or more, respectively. Coryzal syndromes consisting of rhinorrhea, nasal congestion, and sneezing accounted for most of the illnesses at all ages. Hamre *et al.* (1966) showed that medical students experience almost 2 upper respiratory infections per year, of which 83% are coryzal. Only a few (2–4%) of all coryzal illnesses are associated with adenoviruses; the rhinoviruses, coronaviruses, parainfluenza viruses, and respiratory syncytial virus being more prevalent.

3. Pharyngoconjunctival Fever

Parrott *et al.* (1954) reported that a syndrome characterized by fever, sore throat, and conjunctivitis, was commonly associated with adenoviruses. The illness is a relatively mild one that follows a 5- to 7-day incubation period. Fever, lasting 4–5 days, seldom exceeds 102–103°F. Headache, malaise, anorexia, and sore throat dominate the early phase of the illness. Hoarseness, nonproductive cough, and dull chest pain become evident later in the illness. Unilateral or bilateral follicular conjunctivitis may be present. Examination of the pharynx reveals mild erythema, tonsillar enlargement, and a modest exudate. The syndrome is distinguished from streptococcal pharyngitis in several regards. Adenovirus infection is more likely to result in constitutional symptoms, coryza, a mild tracheobronchitis, conjunctivitis, and preauricular adenopathy. The β-hemolytic streptococci tend to produce a more severe pharyngitis, more intense erythema, and more extensive exudates and do not cause conjunctivitis. An elevated leukocyte count with a shift toward immature forms is more characteristic of streptococcal disease. One unique and characteristic epidemiological feature of pharyngoconjunctival fever (PCF) has been its appearance in common-source outbreaks of individuals exposed by bathing in inadequately chlorinated swimming pools (D'Angelo *et al.*, 1979). The illness observed in the swimming-pool outbreaks is very similar to that observed in non-water-related PCF cases (Table IV). In one recent epidemic involving 72 individuals with PCF,

TABLE IV. Pharyngoconjunctival Fever: Swimming-Pool Outbreak[a]

Signs and symptoms	*N* (%)
Fever	50 (69)
Conjunctivitis	49 (68)
Sore throat	31 (43)
Headache	31 (43)
Runny nose	13 (18)
Chills	12 (17)
Myalgias	8 (11)
Vomiting	7 (10)
Earache	7 (10)
Nausea	6 (8)
Arthralgia	6 (8)
Cough	5 (7)
Swollen lymph nodes	5 (7)
Diarrhea	5 (7)
Rash	0 (0)
Sputum	0 (0)

[a] Modified from D'Angelo *et al.* (1979) with permission.

D'Angelo *et al.* (1979) reported that acquisition of adenovirus infection correlated with the amount of time spent in the water and that the virus could be recovered from the inadequately chlorinated pool water. The viral infection apparently can be acquired by nasal or oral aspiration of contaminated pool water or by direct conjunctival inoculation (J. A. Bell *et al.*, 1956).

4. Acute Respiratory Disease of Recruits

Among the first clinical syndromes attributed to adenoviruses was that of an epidemic respiratory infection occurring in closed populations, most notably among new military recruits. The history of this entity is a fascinating one that has been reviewed extensively (Dingle and Langmuir, 1968).

Briefly, it was recognized for many years that epidemics of respiratory illness befall companies of new recruits, but not of seasoned troops, and that similar problems occur in schools. Stuart-Harris *et al.* (1938) termed the illness "febrile catarrh," postulating it to be distinct from influenza. In the winter of 1941–1942, an epidemic of an illness labeled "primary atypical pneumonia" was described in Camp Claiborne, Louisiana. To further define this entity and to better understand the nature of the illness that produced such extensive morbidity in new recruits, the Surgeon General of the U.S. Army created the Commission on Acute Respiratory Diseases (ARDs). The studies of ARD by the commission during and following World War II formed the basis of our current comprehension of this

entity. The commission's studies defined an epidemic illness of recruits that was most prevalent in the winter months, resulted in sustained immunity, and could be transmitted to volunteers by bacteria-free filtered respiratory secretions (Commission on Acute Respiratory Diseases, 1947a,b).

Studies in the early 1960s showed that *Mycoplasma pneumoniae* was one cause of the primary atypical pneumonia syndrome recognized during World War II (Chanock *et al.*, 1962). Hilleman and Werner (1954) reported that Ad4 was a major cause of the other respiratory problem of recruits (ARD). Analysis of paired sera saved from World War II studies documented that most of the ARD was associated with agents serologically related to Ad4. It is now known that AD3, 4, 7, 14, and 21 are the major causes of ARD in military recruits around the world (Van der Veen and Kok, 1957; Tai *et al.*, 1960; Van der Veen *et al.*, 1969). The predictability and impact of ARD in military troops led to the development of an effective live enteric vaccine that is now widely utilized (see Section X.C).

ARD is usually a mild illness. Hilleman (1957) showed that up to 80% of susceptible new recruits became infected, with most cases occurring during the cooler months (Fig. 7). About half the infected recruits were asymptomatic. Most of the remainder experienced a mild illness that interfered with training. About 20% of all recruits were admitted for ARD because on American military bases a fever higher than 100°F necessitated hospitalization.

The incubation period of ARD is 5–7 days, with a gradual onset of fever and chills over 2–3 days (Fig. 8). The symptoms are commonly accompanied by headache, malaise, and anorexia. Many individuals manifest upper respiratory signs of nasal discharge, mild sore throat, and a nonproductive cough. Some patients possess pharyngeal injection and tonsillar and cervical adenopathy. Fever is generally of a low grade and lasts for 2–4 days. Constitutional symptoms are similarly of a mild nature, but a postviral "neurasthenia" and troublesome cough may persist for 1–2 weeks or longer. Most laboratory tests are within normal limits except in rare, severely ill patients.

5. Pneumonia

As indicated, adenovirus infections most commonly involve the upper respiratory tract. However, lower respiratory tract infection with frank pneumonia is observed with some frequency in special settings. Infants, military recruits, and immune-deficient patients account for most documented cases of adenovirus pneumonia. Ad3, 4, 7, and 21 have been most prevalent in adults. There are no pathognomonic features of adenovirus pneumonias that permit them to be distinguished from other viral pneumonitides on purely clinical grounds.

The natural history of adenovirus pneumonia has been best defined in military personnel (see Section VII.C.4). Because mild fever and ina-

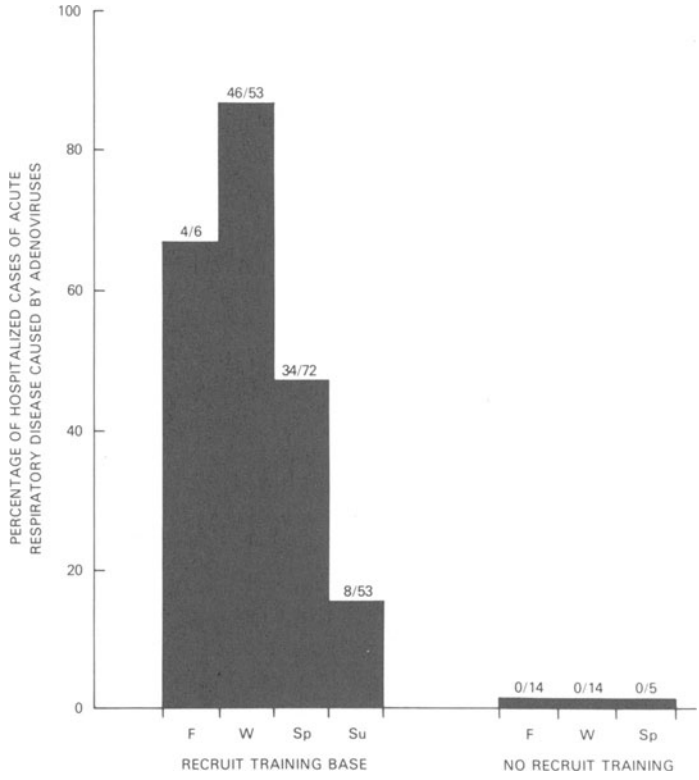

FIGURE 7. Percentage of hospitalized cases with ARD caused by adenoviruses at recruit training bases or other bases, by season. Redrawn from Hilleman (1957) with permission.

bility to perform assigned duties necessitate hospitalization of American military personnel, the entire spectrum of adenovirus pneumonias has been observed. Dascomb and Hilleman (1956) showed that as many as 20% of all hospitalized adenovirus-infected recruits develop objective clinical and radiological features of adenovirus pneumonia (Fig. 8). The signs and symptoms associated with adenovirus pneumonia in 12 recruits are shown graphically in Figs. 9 and 10 (Bryant and Rhoades, 1967). Pneumonic infiltrates are usually limited to one or a few lower pulmonary segments. Excellent recovery is expected without significant chronic pulmonary sequelae (Klocke *et al.*, 1966). In some individuals, the pneumonias have been more aggressive, and rare fatalities have been observed (Dudding *et al.*, 1972).

The appearance of adenovirus pneumonia in the general medical community is in striking contrast to the military experience. The cases tend to be sporadic rather than epidemic and involve infants more often than adults (Lang *et al.*, 1969; Henson and Mufson, 1971; Field *et al.*, 1978). Because hospitalization of patients in the general community is usually dictated by significant illness, the clinical features of adenovirus

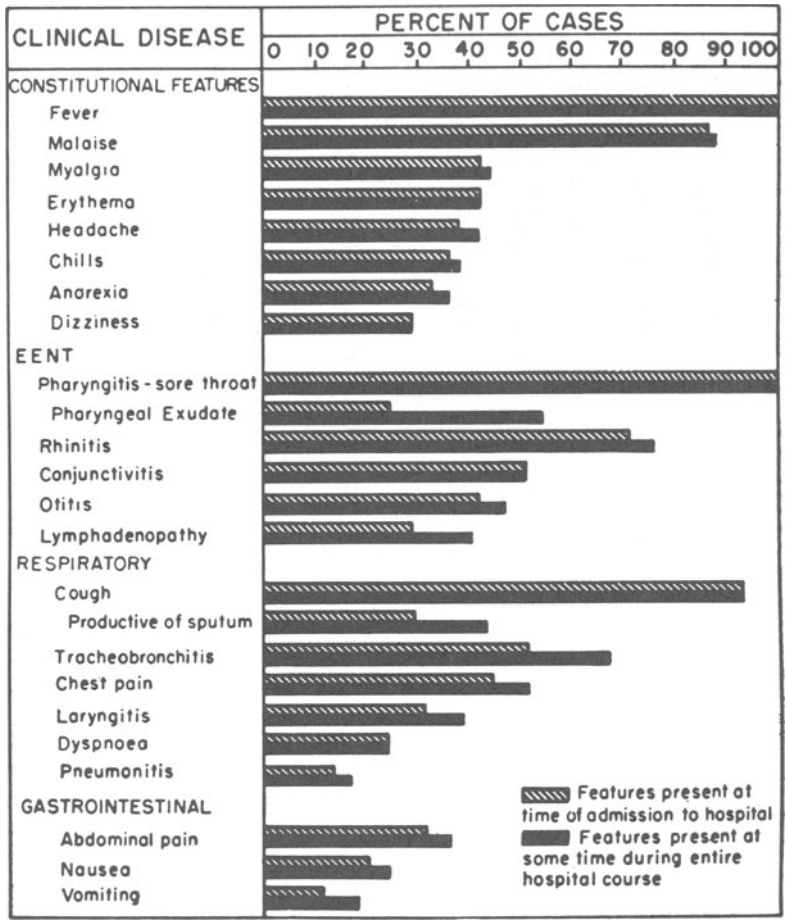

FIGURE 8. Clinical features of 45 military recruits hospitalized with acute respiratory disease. Reprinted from Dascomb and Hilleman (1956) with permission.

pneumonias in that population are rather more dramatic. Lang *et al.* (1969) reviewed the histories of 25 infants with Ad21 pneumonia. Most patients demonstrated moderate to severe dyspnea at the time of admission. Some of the more severely ill patients experienced a protracted illness lasting several weeks with exacerbations attributable to secondary bacterial infections. The acute radiological abnormalities were quite variable, including diffuse or patchy bronchial, peribronchial, or interstitial infiltrates. Significant pleural effusions were not observed. Ultimately, 2 (8%) of these 25 children died, while 8 (32%) showed full recovery. Importantly, 15 (60%) developed bronchiectasis or other chronic pulmonary sequelae.

Becroft (1971) reported histological findings in five children who died of acute Ad7 pneumonia. Their lungs displayed varying degrees of necrotizing bronchitis, bronchiolitis, and pneumonia. As in the adult and

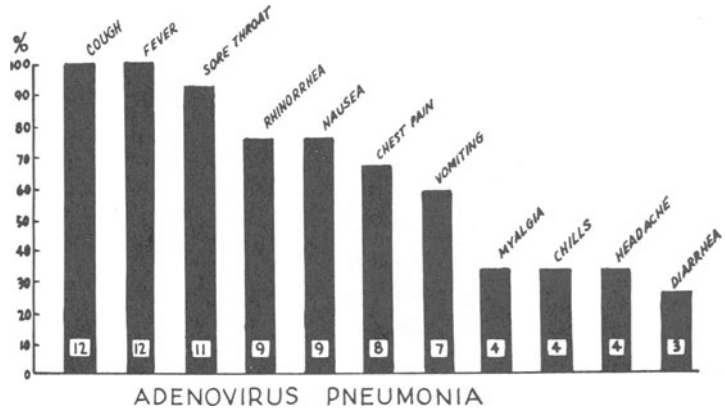

FIGURE 9. Frequency of symptoms in 12 recruits with adenovirus pneumonia. Reprinted from Bryant and Rhoades (1967) with permission.

military patients who succumbed to adenovirus pneumonia, the lungs of these infants also showed characteristic basophilic or amphophilic intranuclear inclusions [see Fig. 4 (Section V)]. The prominent feature of adenovirus pneumonia is ulceration and scarring of bronchial epithelium with destruction of bronchial glands. Becroft (1971) postulated that these changes contribute directly to the high incidence of chronic pulmonary sequelae observed in the children who survived infantile adenovirus pneumonia. Bronchiolar obliteration and bronchiectasis were demonstrated histologically in 5 of 25 survivors of Ad21 pneumonia (Lang *et al.*, 1969).

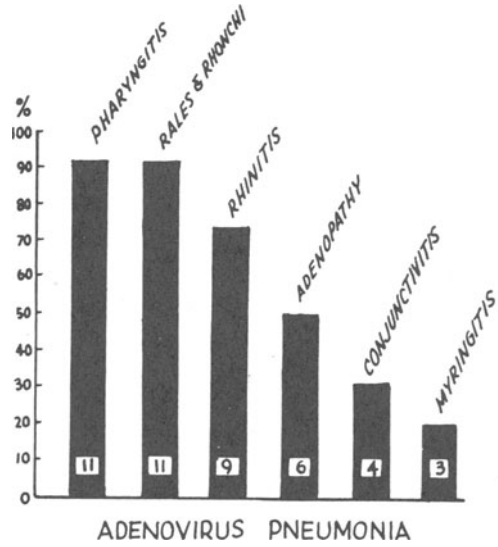

FIGURE 10. Frequency of physical findings in 12 recruits with adenovirus pneumonia. Reprinted from Bryant and Rhoades (1967) with permission.

Thus, adenovirus pneumonia may be a major cause of postinfectious bronchiectasis of childhood. Presumably, the unique vulnerability of developing airways of infants permits expression of chronic pulmonary sequelae that are not readily apparent in adults who have recovered from adenovirus pneumonia.

6. Pertussis Syndrome

Pertussis represents a classic syndrome that begins rather inauspiciously as a minor upper respiratory illness (Wilkins and Wehrle, 1979) After about 1–2 weeks, bronchial involvement becomes apparent with the onset of paroxysmal bouts of coughing that are terminated by vigorous inspirations resulting in a characteristic whooping sound. This syndrome is primarily caused by *Bordetella pertussis*, with occasional cases caused by the related bacteria *B. parapertussis* and *B. bronchiseptica*. A common laboratory observation in this syndrome is a profound lymphocytosis. Despite good immunization practices, pertussis has not been totally eradicated, suggesting that the immunization is of inadequate efficacy or that other organisms also cause pertussis. In the context of this latter hypothesis, adenoviruses have been implicated in some patients with a pertussislike syndrome. Connor (1970) reported 13 infants and children with pertussis, most of whom lacked microbiological or serological evidence for *Bordetella* infection. Of these 13 children, 11 shed Ad1, 2, 3, or 5. Sera from 7 of the children also showed rising titers of adenovirus antibodies. Klenk *et al.* (1972) reported 19 children with the pertussis syndrome. *Bordetella* species were recovered from 14 patients, 7 of whom had virological or serological evidence of concomitant adenovirus infections. Nelson *et al.* (1975) studied 134 patients with the pertussis syndrome. Adenoviruses were recovered from 22 patients, while 8 additional patients exhibited at least 4-fold rise in antibody titers to adenoviruses (Table V). Adenovirus infections were more common in patients from whom *Bordetella* species were also recovered.

The role of adenoviruses in the pertussis syndrome remains uncertain. The syndrome is not reproduced in volunteer studies. As indicated earlier, and as was correctly concluded by Nelson *et al.* (1975) and Baraff *et al.* (1978), the adenoviruses that are isolated may have been reactivated endogenously, or chronically shed, and may have played no part in the etiopathogenesis of pertussis. Alternatively, adenoviruses may be capable of provoking a pertussislike syndrome when acting alone or in combination with *Bordetella* species or other agents.

D. Adenovirus Infections in the Immune-Suppressed Patient

Life-threatening localized or disseminated adenovirus infections are uncommon and involve primarily the lower-numbered adenovirus ser-

TABLE V. Numbers of Patients with the Pertussis Syndrome and of Healthy Controls from Whom Various Viruses Were Isolated[a]

Virus	Pertussis (N = 134)	Control (N = 101)
Adenovirus	22	5
Coxsackie A	2	1
Coxsackie B	2	0
Poliovirus	8	1
Parainfluenza	5	0
Herpes simplex	3	4
ECHO	6	14
No viruses	90	76
TOTAL:	138[b]	101

[a] Modified from Nelson *et al.* (1975) with permission.
[b] More than one virus was isolated from 4 patients.

otypes. The progression of an adenovirus infection to the point at which life is endangered is most likely to take place in the setting of immune deficiency. Many of the fatal adenovirus infections have occurred in infants and young children with an immature or congenitally deficient immune system or with coexisting malnutrition (Aterman *et al.*, 1973; Andiman *et al.*, 1977; Zahradnik *et al.*, 1980). Additional fatal adenovirus infections have developed in adults or older children who are immune-compromised by virtue of either underlying diseases or immunosuppressive treatments involving steroids, cytotoxic drugs, or radiation (Zahradnik *et al.*, 1980; Carmichael *et al.*, 1979).

The lung is the most frequent target of severe adenovirus infections in the immune-compromised host, but disseminated infection involving multiple organ systems, particularly the liver, occurs as well. It is presumed that involvement of other organs follows a viremic event (Andiman *et al.*, 1977). In the largest series of immune-deficient patients with adenovirus infection, Zahradnik *et al.* (1980) described 15 individuals ranging in age from 2 days (premature infant) to 65 years. In this series, 7 patients had underlying malignancies, 3 were recipients of bone marrow or kidney transplants, and 4 were treated with steroids or cytotoxic drugs for other reasons. Eighty percent of the patients had severe systemic symptoms and pneumonia, while moderate to severe hepatitis occurred in nearly half. Nine patients died. At autopsy, adenovirus involvement was most commonly demonstrated in the lung and liver. One feature shared by 5 of these patients and many other immune-deficient individuals with viral infections is the presence of simultaneous infection with multiple organisms. Coexisting infections with fungi, bacteria, pneumocystis, and even cytomegalovirus make it difficult to determine how much the adenoviruses contributed to the total morbidity and mortality.

An understanding of the role of adenovirus in the immune-deficient host is confounded because recovery of the virus from respiratory secretions and even from lung tissue is not sufficient evidence for active infection. Recovery of virus from other viscera or demonstration of viral inclusions in the tissues, or both, are more indicative of active infection.

E. Keratoconjunctivitis

1. General

Ocular involvement during respiratory infection with adenovirus is common. Thus, conjunctivitis is a defining feature of classic PCF (see Section VII.C.3). Other patterns of adenovirus-induced eye infection are also recognized. Inflammation of the cornea (keratitis) accompanies conjunctivitis in sporadic cases of infection with certain adenoviruses including Ad3, 11, and 37 (Tai *et al.*, 1974; Yin-Murphy *et al.*, 1974; Schaap *et al.*, 1979).

2. Epidemic Keratoconjunctivitis

The keratitis that occasionally accompanies the aforementioned sporadic infections must be distinguished from that which occurs in a more virulent form of ocular adenovirus infection, termed "epidemic keratoconjunctivitis" (EKC). Typical epidemics of severe keratoconjunctivitis were first described nearly a century ago (Fuchs, 1889) and in 1955 were shown to be associated with Ad8 (Javetz *et al.*, 1955). This syndrome is distinguished by its greater ocular morbidity, its potential for chronicity and permanent visual impairment, its unique epidemiological setting, and its association with Ad8, 19, and rarely others (Dawson *et al.*, 1970; Sprague *et al.*, 1973; O'Day *et al.*, 1976).

Direct inoculation of virus into the eye and ocular trauma appear to predispose to EKC. The prevalence of antibodies to Ad8 or 19 in the general community is low, so that most individuals are considered susceptible (Sprague *et al.*, 1973; O'Day *et al.*, 1976). Proven outbreaks, each involving as many as 200 individuals, have been associated with industrial settings in which an eye injury is common and with eye-care facilities. A typical case would involve an industrial worker who presents to the plant nurse with the complaint that a foreign particle has lodged in his eye. The nurse removes the particle, but 2 weeks later the typical features of EKC appear. Careful investigation would reveal that the eyewash solution or the nurse's hands or medical instruments were contaminated with adenoviruses.

The clinical features of the illness that this worker may expect to endure have been well defined (Dawson *et al.*, 1970; Sprague *et al.*, 1973; O'Day *et al.*, 1976; D'Angelo *et al.*, 1982) (Table VI). Following an in-

TABLE VI. Signs and Symptoms of Epidemic Keratoconjunctivitis[a]

Signs and Symptoms	Patients (%)
Redness	98.4
Discharge	90.6
Eye pain	70.3
Visual change	70.3
Light sensitivity	68.2
Swollen lymph nodes	38.5
Headache	26.0
Fever	14.1
Sore throat	12.0
Cough	7.3
Nausea or vomiting	5.7
Diarrhea	3.1

[a] Modified from D'Angelo *et al.* (1981) with permission.

cubation period of 3–21 days, unilateral or bilateral conjunctival infection develops, and the patient senses ocular discomfort similar to that caused by an irritating foreign body. The pattern of conjunctival and corneal inflammation is often sufficiently characteristic to suggest a diagnosis. On an average, the illness lasts about 2 weeks, but permanent visual impairment may result. Moreover, prolonged viral shedding and even chronic or relapsing ocular pathology have been described (Boniuk *et al.*, 1965). Pettit and Holland (1979) reported recovery of virus from the conjunctiva for up to 25 months after the onset of EKC. Most individuals with chronic infection do not shed virus, but display a papillary conjunctivitis that is quite distinct from the original keratoconjunctivitis. These later manifestations may be the result of immunopathological rather than infectious mechanisms.

F. Meningoencephalitis

Adenoviruses have occasionally been associated with aseptic meningitis, meningoencephalitis, and encephalitis. The distinction in each case rests on the presence or absence of stiff neck and headache, of other signs of meningeal irritation, or of altered mental status and other signs of brain dysfunction. Most patients have some encephalitic component in their illness, rather than a pure aseptic meningitis (LeLong *et al.*, 1956; Faulkner and van Rooyen, 1962; Gabrielson *et al.*, 1966; Huttunen, 1970; Simulä *et al.*, 1970; Kelsey, 1978). In addition, most have been children or immune-compromised individuals in whom central nervous system involvement was but part of a generalized infection. The mortality and prospects for neurological sequelae are substantial (Similä *et al.*, 1970).

Ad3 and 7 are most commonly implicated, and virus has been recovered from the brain or spinal fluid (LeLong *et al.*, 1956; Faulkner and van Rooyen, 1962; Similä *et al.*, 1970). Whereas nearly all cases have involved an acute illness, Roos *et al.* (1972) reported a single, unconvincing case of a subacute encephalitis associated with Ad32.

The medical literature records the histories of but a few sporadic cases or small epidemics in which neurological symptoms accompanied adenovirus infection. Unfortunately, our understanding of this syndrome is clouded by a lack of rigorous documentation in many of these cases. Altered mental status is not necessarily a sign of encephalitis in febrile children with severe systemic illness. Brain tissue obtained at the time of postmortem examination of patients with putative adenovirus encephalitis has in some instances been surprisingly normal (Similä *et al.*, 1970). Moreover, several patients reported as having adenovirus encephalitis had recent bouts of varicella or zoster, each of which is well recognized to cause a postinfectious encephalitis. Thus, it would appear that adenovirus meningoencephalitis can occur, but it is rare, difficult to document, and of inadequately defined pathophysiology and prognosis.

G. Gastrointestinal Infections

1. Gastroenteritis

Adenoviruses are commonly recovered from stools of patients with recent respiratory illness even when symptoms of gastroenteritis are absent, indicating that the detection of fecal virus does not necessarily imply intestinal illness (Brandt *et al.*, 1969; Fox *et al.*, 1969). This observation has confounded our understanding of the significance of adenoviruses that are recovered from stools of patients with acute nonbacterial gastroenteritis (Joncas and Pavilanis, 1960; Dunkin and Hutchinson, 1961). In one pediatric study, about as many individuals with gastroenteritis shed cultivable adenoviruses in their stool as did control patients with respiratory disease (Brandt *et al.*, 1980). Thus, an etiological relationship between adenoviruses and gastroenteritis had not been as apparent as with the rotaviruses and Norwalk-like agents (Flewett *et al.*, 1974: Kapikian *et al.*, 1974. Recently, however, infantile gastroenteritis has been associated with fastidious adenoviruses that could be detected by EM, but failed to grow in conventional cell-culture lines (Flewett *et al.*, 1975; G. B. B. White and Stancliffe, 1975; Madeley *et al.*, 1977; Richmond *et al.*, 1979; Brandt *et al.*, 1980). These agents, termed *enteric adenoviruses*, have become a subject of several recent attempts to determine their significance and relationship to cultivatable adenoviruses (Gary *et al.*, 1979; Retter *et al.*, 1979). Waddell *et al.* (1980, personal communication) showed that enteric adenoviruses represent unique serogroups (F and G) of the human adenoviruses that have structural and some anti-

genic features in common with the other adenoviruses. Takiff and coworkers (Takiff *et al.*, 1981; Takiff and Straus, 1982) reported that in many primary or continuous cell lines, these viruses are blocked at an early stage in their replicative cycle, but that they can grow efficiently in 293 cells, a human embryonic kidney cell line transformed by Ad5. Using an enzyme immunoassay to detect viral antigen, and by cultivation in 293 cells, Yolken *et al.* (1982) showed that enteric adenoviruses are significantly associated with outbreaks of diarrheal illness in infants. In this study, most of the infected infants also demonstrated significant respiratory symptoms including frank pneumonia. The relationship of these unique adenoviruses to other infectious syndromes in normal or immunedeficient patients has yet to be assessed.

2. Other Gastrointestinal Disorders

Adenoviruses are reported to be associated with three gastrointestinal syndromes other than gastroenteritis: mesenteric adenitis, appendicitis, and intussusception. Mesenteric adenitis refers to a well-recognized pediatric condition in which inflamed mesenteric lymph nodes provoke abdominal pain that may be sufficiently severe to mimic that of acute appendicitis. Adenoviruses have been isolated from mesenteric nodes in up to 28% of cases of severe mesenteric adenitis (Kjellén *et al.*, 1957; P. M. Bell and Steyn, 1962). In a study of children with concomitant appendicitis, pharyngitis, and mesenteric adenitis, adenoviruses were cultured from 6 of 20 appendices (Kulcsar *et al.*, 1970). In addition, adenoviruslike particles have been observed in electron micrographs of inflamed appendices (Yunis and Hashida, 1973).

Much effort has been expended in studies of the relationship between adenoviruses and intussusception. Intussusception refers to a fixed telescoping of one bowel segment into that of an adjacent segment. As the segments become increasingly inflamed, the vascular supply of the segments is compromised, resulting in infarction of the bowel. The condition most commonly involves the distal ileum of children under age 2. In three studies, adenoviruses were isolated from 26–68% of stools, throat swabs, or inflamed mesenteric nodes of children with intussusception, but from only 3–8% of specimens from control patients (P. M. Bell and Steyn, 1962; Potter, 1964; Clarke *et al.*, 1969). D. O. White and Solomon (1966) observed a seasonal distribution of intussusception and postulated an association with adenovirus infection. Adenoviruses may contribute to the pathogenesis of intussusception by stimulating intestinal motility or by provoking mesenteric adenitis or in both ways. Enhanced motility may increase the possibility that bowel segments will telescope during active peristalsis, while the adenitis may prevent spontaneous release of the telescoped segments.

Mesenteric adenitis, appendicitis, and intussusception have multiple etiologies, of which adenovirus infection may be but one. Because of the

high incidence of prolonged shedding of virus following ubiquitous adenovirus infections of childhood (Fox *et al.*, 1969), the actual significance of recovering virus from patients with these disorders remains uncertain.

H. Hemorrhagic Cystitis

Numazaki *et al.* (1968) reported that acute hemorrhagic cystitis in children is significantly associated with Ad11. Since that report, they and other workers have confirmed and extended this observation (Numazaki *et al.*, 1973; Mufson and Belshe, 1976). The syndrome occurs more frequently in male than in female children, is associated with several days of urinary frequency, bladder pain, gross or microscopic hematuria, minimal pyuria, and viruria. Replication of the virus appears to be in the bladder itself, because exfoliated bladder cells have been shown by immunofluorescence microscopy to contain adenovirus antigens (Belshe and Mufson, 1974). Moreover, cytoscopy demonstrates small hemorrhagic foci in the bladder mucosa. In general, there are no concomitant respiratory symptoms to suggest involvement of other organs. This syndrome is unusual among adenovirus infections in being almost totally limited to a single serotype. Only a few cases have been associated with Ad21 (Mufson and Belshe, 1976).

I. Cancer

Since adenoviruses produce latent infection in man and are known to transform cells both *in vitro* and *in vivo*, they have been considered as a possible cause of human cancers (Pereira *et al.*, 1965). When the oncogenic potential of Ad7 was first recognized, development of a live vaccine containing this virus was halted (see Section X.C). A special collaborative effort was mounted under the auspices of the National Center Institute to assess the role of adenoviruses in human tumors. The investigators ultimately concluded that development of the Ad7 vaccine could safely be resumed because they found no antibody directed against tumor (T) antigens in sera of cancer patients (Gilden *et al.*, 1970) and no RNA homologous to Ad7 DNA in a large number of human neoplasms (McAllister *et al.*, 1972). Recent studies employing even more sensitive hybridization techniques capable of detecting latent adenovirus DNA sequences in human tonsils have failed to detect similar sequences in human tumors (Mackey *et al.*, 1976, 1979; Green *et al.*, 1979b; Wold *et al.*, 1979). The issue is not completely closed, however, because not all human cancers have been scrutinized and not all adenovirus serogroups have been used as probes.

J. Congenital Anomalies

While some viruses, such as cytomegalovirus and rubella virus, have been clearly associated with congenital anomalies, the association has been less compelling for most other viruses. In one large study, Evans and Brown (1963) could find no significant association between maternal adenovirus infection and the ultimate appearance of congenital anomalies in the offspring.

K. Other Syndromes

Adenoviruses have been suggested as etiological agents in numerous other clinical syndromes on one or more occasions. Hatch and Siem (1966) suggested that adenoviruses may have been responsible for an outbreak of infectious hepatitis. Rodriguez-Torres *et al.* (1969) studied two patients with isolated myocarditis and adenovirus infection. In a seroepidemiological study, Stechenberg *et al.* (1975) suggested that recent adenovirus infection may be a factor in the etiopathogenesis of Reye's syndrome. As a whole, these isolated reports are not compelling; they suggest future areas of investigation, but add little to the current understanding of adenovirus disease.

VIII. DIAGNOSIS

Other than epidemic keratoconjunctivitis (EKC) and possibly acute respiratory disease (ARD) of recruits or pharyngoconjunctival fever (PCF), no adenovirus-associated syndromes display clinical features sufficiently distinctive to immediately suggest their etiology. Therefore, more specific diagnostic methods are required (Taylor, 1977; Kasel, 1979). Traditionally, adenoviruses have been detected by growth in cell-culture systems, especially from specimens taken during the acute phase of illness. For viral isolation, throat, anal, or conjunctival swabs, nasal washes, conjunctival scrapings, or urine, spinal fluid, or pathological specimens should be inoculated promptly into susceptible cell lines. Primary or continuous epithelial lines such as human embryonic kidney, HeLa, KB, or Hep-2 are appropriate. Characteristic cytopathic alterations develop a few days to weeks later, depending on the viral type and multiplicity, and consist of rounding, ballooning, increasing refractility, and aggregation of cells in grapelike clusters. Newly developed antigen-detection systems, including enzyme immunoassays, are far faster, simpler, and less expensive and may eliminate the necessity for viral cultures in many cases (Yolken *et al.*, 1982). A means of establishing a diagnosis rapidly will certainly be useful when effective antiviral treatments become available.

Light microscopy of hematoxylin- and eosin-stained tissues can help determine whether adenoviruses are implicated in patients with diffuse pneumonitides or unexplained multisystem infections. Adenoviruses induce the appearance of basophilic or amphophilic intranuclear inclusions (Becroft, 1971). Indirect fluorescence microscopy of urine sediments, conjunctival scrapings, or tissue sections demonstrates both nuclear and cytoplasmic staining of viral antigens and serves, where available, as a rapid diagnostic method (Knight *et al.*, 1975).

A number of successful EM techniques have been applied to the diagnosis of adenovirus infections. One method involves examination of fixed and sectioned tissues for intranuclear paracrystalline arrays of viral capsids (Myerowitz *et al.*, 1975). Another procedure entails examination of particles concentrated by precipitation with specific antisera (Edwards *et al.*, 1975). Recently, Boerner *et al.* (1981) have reported rapid identification of adenoviruses by EM of tear samples from patients with suspected viral conjunctivitis. Enteric adenoviruses can also be detected rapidly by direct EM (Brandt *et al.*, 1981).

It is rarely necessary to type adenoviruses except for epidemiological investigations or research purposes. The schemata for grouping, subgrouping, and typing adenoviruses are relatively cumbersome and, in general, are not well suited to processing large numbers of specimens at one time. Confirmation of a cultured isolate as an adenovirus is performed by fluorescence microscopy or complement fixation (Dowdle *et al.*, 1971). Hemagglutination reactions using panels of erythrocytes from different species provide subgrouping data (Hierholzer, 1973). Assignment of specific types is performed by either hemagglutination-inhibition or neutralization methods (Rosen, 1970; Hierholzer *et al.*, 1975b). Some adenoviruses cross-react at low to modest titer with more than one typing serum (Wigand *et al.*, 1965; Stevens *et al.*, 1967; Hierholzer *et al.*, 1975). Adenoviruses that show an unusually high serological cross-reactivity have been described, but have not proved to be a serious practical problem (Wigand *et al.*, 1965; Parks *et al.*, 1967; Crandell *et al.*, 1968; Hierholzer and Pumsrola, 1976; Hierholzer and Rodriguez, 1981). The marker of cross-reactivity has even proved to be a useful epidemiological tool for investigating the long-term shedding of adenovirus of a single serotype (Brandt *et al.*, 1966).

Because adenoviruses can usually be shed in an intermittent pattern from months to years after an initial illness, recovery of virus from respiratory secretions or stool does not imply their association with a given intercurrent illness. Therefore, serological methods are often used to confirm the diagnosis of adenovirus infections. A 4-fold or greater rise in titers of complement fixing, hemagglutination-inhibiting, or neutralizing antibodies provides presumptive evidence of recent adenovirus infection (Hierholzer *et al.*, 1969; Dowdle *et al.*, 1971; Kasel, 1979). A firm diagnosis is ideally based on the combination of compatible clinical, virological, and serological findings.

IX. TREATMENT

A. General

Unfortunately, the treatment of adenovirus infections is at present limited to symptomatic and supportive care. Furthermore, physicians caring for patients with common respiratory infections generally cannot discriminate adenoviral from other infectious etiologies on clinical grounds, and rapid diagnostic techniques are not widely available. The therapeutic armamentarium consists of one or more of the following: antipyretics, antihistamines, decongestants, antitussives, hydration, and rest. Pharyngitis often warrants culturing for β-hemolytic streptococci so that antibiotics can be prescribed appropriately. Serious and life-threatening adenovirus infections may require hospitalization for laboratory diagnosis, closer observation, intravenous hydration, pulmonary toilet, assisted ventilation, or other modalities as the case demands.

B. Antiviral Therapy

Specific effective antiviral therapy is now available for herpes and influenza virus infections, but not for adenovirus infections. Drugs such as phosphonoacetic acid (Overby *et al.*, 1977), 5-iodo-2′-deoxyuridine (IUdR) (Dudgeon *et al.*, 1969), arabinofuranosyl adenine (ARA-A) (Sidwell *et al.*, 1973), acyclovir (Collins and Bauer, 1979), trifluorothymidine (Lennette and Eiferman, 1978), ribavirin (Sidwell, 1980), and amantidine (Neumayer *et al.*, 1965) exhibit little or no *in vitro* activity as inhibitors of adenovirus replication. When used in desperate clinical situations, the clinical responses to these agents have been equivocal at best. Interferons, with their broader antiviral spectrum, may hold more promise, but have not been available for administration in suitable amounts until recently.

Serious efforts to exploit the known biochemical machinery of adenovirus replication for therapeutic purposes have not been made. Inhibitors of adenovirus DNA-binding proteins or polymerase, for example, should be sought. The clinical activities of future candidate antiviral compounds that exhibit *in vitro* activity against adenoviruses are going to be difficult to assess because serious and life-threatening infections are uncommon and sporadic. EKC, ARD of recruits, and gastroenteritis would seem to be appropriate areas for controlled investigations. To date, only the treatment of adenovirus keratoconjuctivitis has been approached in an organized and deliberate fashion.

C. Keratoconjunctivitis

Ocular viral infections have been the subject of numerous therapeutic trials. The relative ease of diagnosis and sequential assessment by

noninvasive examination has facilitated these studies. Definitive evidence for the efficacy of antiviral compounds in treatment of herpes simplex keratoconjunctivitis led naturally to similar investigations with adenovirus-induced keratoconjunctivitis. Unfortunately, but not surprisingly, each agent in turn showed little if any positive impact on the courses of these infections. IUdR and ARA-A have little or no activity in inhibiting the replication of adenoviruses *in vitro* and in carefully controlled trials have not shown an alteration in the course of adenovirus-induced keratoconjunctivitis (Dudgeon *et al.*, 1969; Pavan-Langston and Dohlman, 1972; Waring *et al.*, 1976). On the basis of the results of rather preliminary uncontrolled studies, Maichuk (1980) suggests that human leukocyte interferon or interferon inducers are beneficial.

Topical corticosteroids are commonly employed in inflammatory eye disease, but are best avoided in ocular infections except when immunopathological processes are most important. For example, subepithelial corneal infiltrates are common sequelae of EKC. These are postulated to represent leukocytic infiltrates that evolve in response to viral antigens. At the time of their appearance, virus generally can no longer be recovered from the eye. In a carefully controlled study, Laibson *et al.* (1970) showed that topical corticosteroids halt the progression and speed the resolution of these infiltrates (Laibson *et al.*, 1970).

X. PREVENTION

A. General

Preventing exposure to adenoviruses can be reasonably accomplished in only a few settings. Proper sterilization of ophthalmological instruments and solutions and good hand-washing will help eliminate spread of keratoconjunctivitis. Establishing either respiratory-secretion or stool precautions or both for hospitalized patients with suspected respiratory or enteric infections may prevent nosocomial transmission of adenoviruses. In some other settings, active prophylactic measures in the form of vaccines have been required and found beneficial. The first study to demonstrate transfer of active immunity to adenoviruses was performed under the auspices of the Commission on Acute Respiratory Diseases of the United States Army during World War II, at a time when the etiology of ARD was not yet defined (Commission on Acute Respiratory Diseases, 1947a,b). Volunteers who were given filtrates of respiratory secretions developed typical symptoms of ARD, but were protected on rechallenge. Obviously, this filtrate contained unattenuated live material and could not be construed as a vaccine candidate.

B. Killed Vaccines

Shortly after the discovery of adenoviruses, Huebner *et al.* (1955) and Hilleman *et al.* (1955) reported successful preparation of formalin- or heat-

killed vaccines from monkey cell cultures infected with Ad3, 4, or 7. Parenteral injection of these reagents stimulated the appearance of type-specific neutralizing antibody and conferred immunity to later homotypic challenge. In one trial, 624 new military recruits were followed through basic training (Hilleman, 1957). Of these recruits, 311 were vaccinated with a killed Ad4 preparation. From the 2nd through the 8th week of training, 23.8% of controls and 4.8% of vaccinees required hospitalization for ARD, suggesting an 80% reduction of significant illness due to vaccination.

These early successes stimulated much wider field testing of killed vaccine, initially with bivalent vaccine (Ad4 and 7) and, after 1962, with trivalent vaccine (Ad3, 4, and 7). Several problems emerged, however (Buescher, 1967). First, the need to develop multivalent vaccines resulted from unpredictable shifts in the virus types causing epidemics among recruits. Recruits who were protected against Ad4 were still susceptible to Ad7. Thus, the incidence of ARD did not diminish sufficiently. Second, there were enormous variations in antigenic potency among vaccine lots. In all, the vaccine appeared to be only 40–70% effective. Third, the adenovirus seed stocks prepared in monkey cells were found to be contaminated with simian virus 40 (SV40). Following removal of SV40 contamination, the viral pools were found to be contaminated with adenovirus–SV40 hybrid that could not be removed (O'Conor *et al.*, 1963; Rowe and Baum, 1964; Lewis *et al.*, 1966). Thus, in 1963, the killed vaccines were withdrawn from study and licensure.

C. Live Vaccines

At about the same time, Couch and Chanock at the National Institutes of Health had begun to test live adenovirus vaccines prepared in primary human cell cultures. Volunteer trials showed that ingestion of enteric-coated capsules containing Ad4 and 7 caused inapparent enteric infection that did not spread to or cause symptoms in the respiratory tract, rarely spread to susceptible contacts, and elicited serum but not nasal secretory neutralizing antibodies (Couch *et al.*, 1963; Chanock *et al.*, 1966; Top *et al.*, 1971a–c). Over the next several years, field trials of monovalent (Ad4) and later bivalent (Ad4 and 7) live enteric vaccines demonstrated their safety and efficacy (Edmondson *et al.*, 1966; Smith *et al.*, 1970; Top *et al.*, 1971a–c). On an average, the bivalent vaccines have reduced adenovirus infection in recruits by over 80% and ARD by over 50%. Since the early 1970s, bivalent vaccine has been regularly used by the U.S. Army as well as other military groups around the world for basic combat training posts during the cooler months in which adenovirus disease is anticipated.

Three problems have beset the live adenovirus vaccine program: First, as in the killed vaccine trials, other viral types have emerged. Out-

breaks of Ad21 have occurred in American, Dutch, Russian, and Indian trainees (Zhdanov and Dreizin, 1961; Kurian *et al.*, 1966; Van der Veen *et al.*, 1969; Rose *et al.*, 1970). Initial studies of an Ad21 live enteric vaccine were successful, suggesting that the enteric immunization approach will prove effective against this agent as well (Takafuji *et al.*, 1979). Ad14 has also been detected, but its impact remains undefined. Second, the vaccines used by the military may not have practical utility for the general populace. It is conceivable that vaccines for the lower-numbered adenovirus types that commonly infect children can also be protective, but the diseases associated with most such infections may be too mild to warrant such effort. Third is the problem of the potential oncogenicity of the vaccine strains. To address this question, extensive efforts were made prior to the initiation of the live adenovirus vaccine trials to ensure that these viruses were not associated with human cancer (see Section VII.I) (Gilden *et al.*, 1970; McAllister *et al.*, 1972).

XI. ADENOVIRUS–SIMIAN VIRUS 40 HYBRIDS

Human adenoviruses do not propagate well in most simian cell lines. It is now recognized that the ability of adenoviruses to grow in monkey cells during preparation of an activated vaccine in the late 1950s resulted from helper activity provided by contaminating SV40 (O'Conor *et al.*, 1963). Suppression of the replication of SV40 by repeated passage in the presence of antibody to SV40 was accompanied by the emergence of adenovirus–SV40 hybrids (see Chapter 10). These viruses contain SV40 sequences that are inserted into the adenovirus genome (Rowe and Baum, 1964). Hybrids between SV40 and Ad1–7 and 12 have been prepared (Lewis *et al.*, 1966). Most hybrids lack or interrupt critical adenovirus sequences, so they can replicate only in the presence of coinfecting nonhybrid adenoviruses. These unusual genetic chimeras have posed difficult and as yet unresolved clinical problems. For example, does the introduction of highly oncogenic SV40 sequences into human cells in a vehicle that permits their replication in human cells predispose to human malignancy? The answer is not known, nor is there any current evidence for disease resulting from early trials with these vaccines. Nonetheless, the problem will remain more than an academic one as long as the recipients of SV40-contaminated vaccines live, because SV40-like viruses are associated with progressive multifocal leukoencephalopathy (JC virus) and other problems in the immune-compromised host (BK virus) (Gardner *et al.*, 1971; Padgett *et al.*, 1971; Weiner *et al.*, 1972).

XII. ADENO-ASSOCIATED VIRUSES

Adeno-associated viruses (AAVs) are defective parvoviruses that replicate efficiently in the presence of helper adenoviruses (Ward and Tat-

tersall, 1978). As the name implies, AAV strains were first found as contaminants in adenovirus-infected cell cultures (Atchison *et al.*, 1965). There are four AAV serotypes. AAV 2 and 3 have been recovered from anal and throat swab specimens in close association with adenoviruses (Blacklow *et al.*, 1968a). Serological responses to AAV 1, 2, and 3 commonly develop during early childhood (Blacklow *et al.*, 1968b; Boucher *et al.*, 1970). AAV type 4 appears to be a simian virus (Boucher *et al.*, 1970). In an 8-year survey of 551 hospitalized children, Blacklow *et al.* (1971) reported that about 30% of uninfected or adenovirus-infected well or ill children possess antibodies to AAV 2 or 3 or both. All but 1 of 32 children who seroconverted to AAV 2 or 3 or both showed evidence of a recent adenovirus infection.

Although AAV inhibits adenovirus growth in cell culture and adenovirus oncogenicity in hamsters (Kastow *et al.*, 1967; Parks *et al.*, 1968), it is not known whether AAV has any impact on adenovirus-induced human diseases. In the study of Blacklow (1971), children coinfected with AAV and adenoviruses were not more likely to have experienced a severe respiratory illness. Finally, even though related parvoviruses produce disease in a variety of animal species, it is now known whether AAV is associated with any human disease. Studies suggesting such associations have been unconvincing (Kasczak *et al.*, 1977).

XIII. LATENCY

The ability to establish and sustain a latent infection is a well-recognized property of adenoviruses. Adenoviruses were initially discovered because of the spontaneous expression of latent virus in human tonsillar tissues (Rowe *et al.*, 1953). Although the observation of adenovirus latency was made about 30 years ago, we know less about the process than we do about herpesvirus latency, which was proved about a dozen years ago (Bastian *et al.*, 1972). In part, the failure is due to a lack of established animal models of adenovirus infection. As discussed in Sections IV and VII.A, it is known that an individual can shed virus intermittently for months or even years after an initial adenovirus infection (Fox *et al.*, 1969). We do not know whether the intermittency of shedding results from repeated virus reactivations or from transient reductions in virus production to undetectable levels. Moreover, there are no data to determine whether reactivation can induce disease. These questions are difficult but not impossible to tackle in the absence of animal models. Restriction endonuclease analysis provides the definitive tool to distinguish reactivation from reinfection. The implications of adenovirus latency, the factors that regulate and sustain the latent state, and the extent of expression of the latent sequences are largely unexplored, but are worthy of investigation.

XIV. FURTHER RESEARCH

Three aspects of adenovirus infection are in greatest need of further research efforts. First, better animal models need to be developed so that the pathophysiology, biology, and immunology of acute and latent adenovirus infections can be examined. Second, an effort must be made to identify agents that interfere with adenovirus-specific synthetic function. Suitable animal models can then serve as the initial subject for exploring the *in vivo* activity and tolerance of such agents. Third, the fastidious enteric adenoviruses need to be further defined, in terms of their unique biology and their epidemiology, pathophysiology, and the range of illness that they provoke. The first three decades of research have obviously not closed the book on adenovirus infections of man.

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