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II. ADENOVIRUSES

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ADENOVIRUSES were first recognized in 1953,[1] and during the past eight years 28 serotypes[2] have been found in man. Still other types have been found in animals but there is no good evidence that the types found in animals induce human infection. On the other hand there is good evidence that many adenovirus types are directly transmissible from man to man, and the incubation periods for the few types known to cause disease range from three to eight days. Types 1, 2, 3, and 5 may remain in tonsils and adenoids for long periods as latent agents. They have been isolated from 50 per cent to 90 per cent of such tissues surgically removed from children. There are no antibiotic or chemotherapeutic agents known to influence the course of adenovirus infection or disease but prophylactic vaccines have been shown to be effective for homologous types.[3,4]

In the laboratory adenoviruses are fairly stable and grow readily in HeLa cells. The earlier types were commonly isolated from conjunctival, nasopharyngeal and anal specimens, but the more recently found types have been isolated chiefly from anal specimens. Serologically the adenoviruses share common complement-fixing antigens, but specific types are differentiated by hemagglutination-inhibition or neutralizing antibody tests. Laboratory evidence indicates that some types have world-wide distribution.

To be more specific, adenovirus Types 3, 4, 7, 14, and 21 cause respiratory illnesses in military recruits. In the United States Types 4 and 7 cause some 60 per cent of the acute respiratory illnesses

which require hospitalization of military recruits.[5] The infection causes an acute grippe-like disease which usually lasts from four to seven days and is generally characterized by fever, headache, malaise, and anorexia. Physical findings may be meager but often include lymphoid hyperplasia on the posterior pharyngeal wall and occasionally pulmonary involvement. Epidemics are common at recruit training centers and seriously interfere with costly training programs. It is strange that Types 4 and 7 cause so much disease in military recruits and, although substantial numbers of adult civilians have serologic evidence of past infection with Types 4 and 7, these types are rarely isolated from civilians with respiratory illness in the United States.

Adenovirus Type 3 commonly causes pharyngoconjunctival fever, which is an acute respiratory disease predominantly of children.[6] The clinical manifestations, fever, pharyngitis, and so forth, are quite similar to those described for Types 4 and 7, but differ chiefly in that a conjunctivitis is commonly present. It is a follicular, nonpurulent unilateral or bilateral conjunctivitis which involves the bulbar and palpebral conjunctiva, and may persist from a few days to two or more weeks. It seldom affects the cornea and produces no residual effects. In outbreaks which frequently occur in summer camps associated with swimming, the conjunctivitis is a striking feature of the disease. Perhaps eye irritation from swimming increases the severity of conjunctivitis. In such outbreaks, three-fourths of camp children may become ill within a few weeks time. During other seasons the conjunctival component of the disease is generally mild and of short duration, and the disease may not be clinically differentiable from other common acute febrile illnesses. On the other hand, Type 3 causes many sporadic cases of acute follicular conjunctivitis with little or no respiratory manifestations. Many of the common, nonpurulent, acute conjunctivitides seen by ophthalmologists are caused by adenoviruses, notably Type 3, but occasionally other types.

Adenovirus Type 8 is apparently the chief cause of epidemic keratoconjunctivitis but other types are occasionally involved.[7] Like adenovirus Type 3, Type 8 induces a unilateral or bilateral conjunctivitis, but unlike Type 3, Type 8 involves the cornea, causing opacities. The corneal infiltrates do not usually ulcerate, but in some cases they result in a residual impairment of vision. The disease occurs sporadically and in outbreaks, and is often associated with trauma to the cornea, such as from ultraviolet light, ophthalmologic tonometers, and the like.

As previously reported,[8] when nursery children of the Junior Village welfare institution were routinely cultured every week (Wednesday) for adenoviruses, they had an unusually high illness attack rate at the time of infection with adenovirus Types 1, 3, and 5. Table 1 shows the Junior Village data from which it was concluded that a temporal association existed between the occurrence of illness and infection with adenovirus Types 1, 3, and 5, but not with Type 2. These data were based upon the illness experience at the time a specific virus was first isolated from a routine specimen, and did not take account of homologous infections that may have occurred before admission to Junior Village or of observed repeated episodes of shedding the same type virus by the same child after intervals of one or more months of no shedding. It was not uncommon for a child to have a second and occasionally a third such episode of infection, particularly with adenovirus Types 1, 2, and 5.

Recently a substantial number of the blood serums collected at time of admission to Junior Village were tested for adenovirus neutralizing antibodies. Epi-

Table 1—Relationship Between Occurrence of Acute Febrile Illness and Adenovirus Infection

Adenovirus Type	No. of Illnesses/No. of Child-weeks*					
	Illnesses in Children During Week When Adenovirus Was First Isolated from Their Routine Specimens		Illnesses in Same Children During Two Prior and Two Subsequent Weeks		Illnesses in Other Children During Same Weeks That New Infections Were Occurring	
1	28/66	42%	33/243	14%	549/2448	22%
2	13/56	23%	36/204	18%	419/2008	21%
3	68/128	53%	113/457	25%	606/2798	22%
5	22/57	38%	49/211	23%	416/1822	23%

* Child-weeks expressed in whole numbers, but fractions used in computations.

sodes of infection occurring after admission were detected by routine weekly cultures. It thus became possible to classify children by prior homologous experience and to compare acute febrile illness attack rates during weeks of onset of infection with rates for the same children during the two prior and two subsequent weeks, according to such classification. Figure 1 shows this comparison for infection episodes with adenovirus Types 1, 2, 3, and 5. Illness rates were based on the population of nonill children at risk of a new illness. Week of a new infection was the first week of an infection episode in which an isolation was made in a routine weekly specimen. It may be seen that children who had no prior homologous experience had strikingly high illness rates during weeks of infection with adenovirus Types 1, 3, and 5 (each significant) but not with Type 2. Children who had had prior infection experience had slightly higher illness attack rates during week of infection with adenovirus Types 1 and 5 (neither significant) and no increase in illness attack rates during week of infection with Types 2 and 3. Thus analyses taking account of prior homologous experience support previous evidence that Types 1, 3, and 5 induced definite illness, and that Type 2 did not induce illness detectable by the study methods used. It appears that when a child first experiences an infection with adenovirus Types 1, 3, and 5 he is very likely to become ill; however, upon reinfection (or latent shedding?) he is much less likely to have illness.

Many of the 28 known adenovirus types have been isolated from ill persons, and good epidemiologic evidence has been obtained to indicate that Types 1, 3, 4, 5, 7, and 8 are causing illness. Aside from these, and perhaps Types 2, 14, and 21, little is known about the epidemiology of the other types. In civilians of North America and Europe, adenovirus Types 1, 2, 3, and 5 have been frequently isolated from children and seldom isolated from adults. Figure 2 shows the percentage of children who, by neutralizing antibody test, were found to have been infected with Types 1, 2, 3, and 5 while living in the general population of more congested residential areas in Washington, D. C. It should be noted that by the tender age of 2½ years, 30 per cent had been infected with Types 3 and 5, and from 50 per cent to 75 per cent had been infected with Types 1 and 2. Obviously, young preschool children bear the brunt of infection with these highly prevalent types.

Inactivated vaccines containing ade-

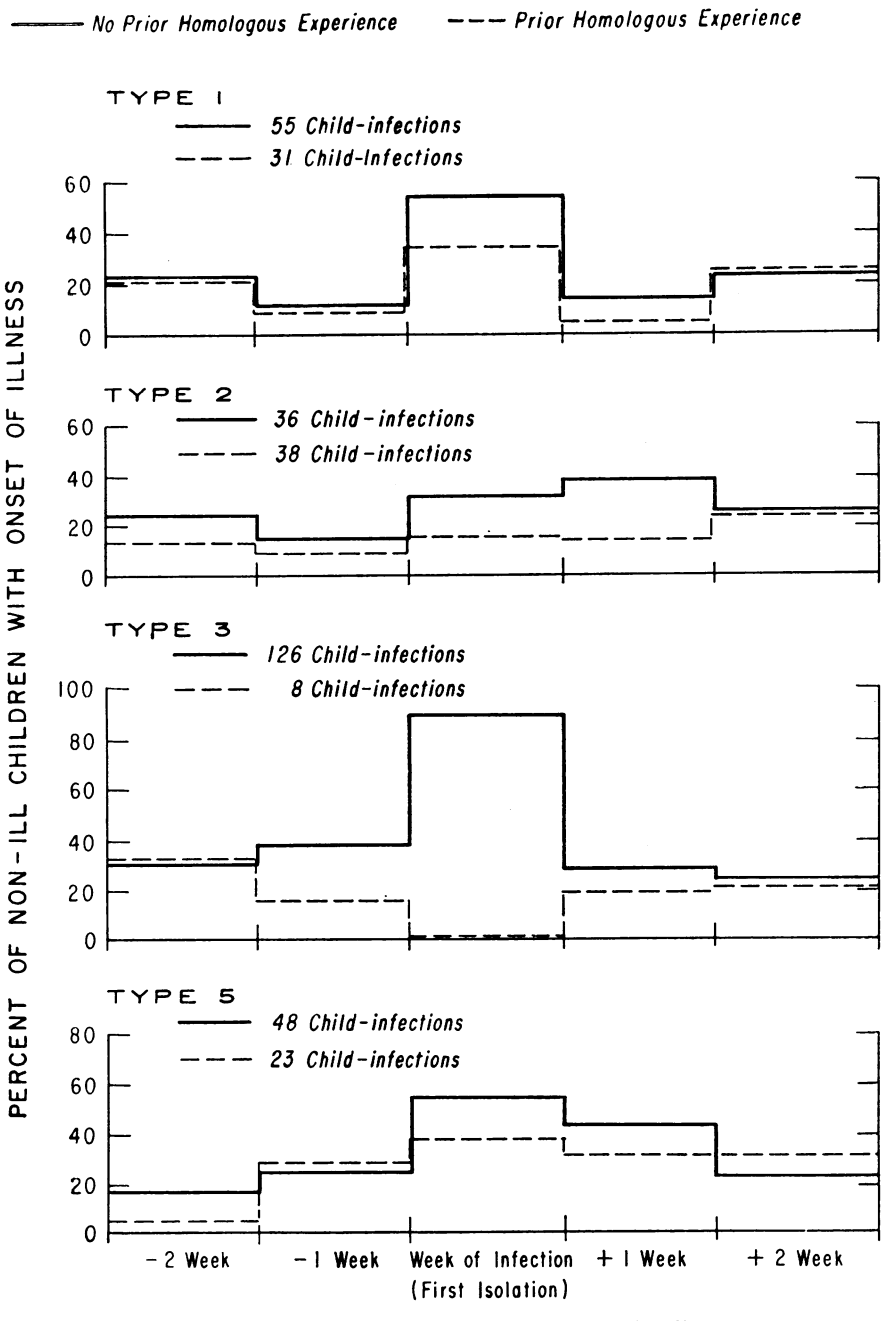

Figure 1—Relationship Between Occurrence of Acute Febrile Illness and Adenovirus Infection According to Prior Homologous Experience

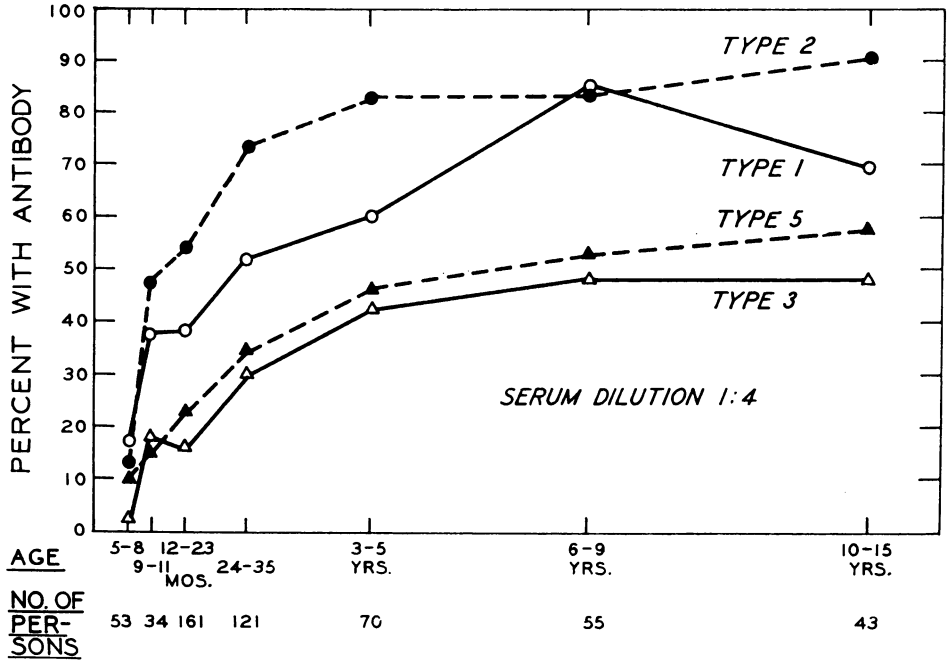

Figure 2—Serum Neutralizing Antibodies to Adenovirus Types 1, 2, 3, and 5, in 537 Infants and Children, 1955-1958

novirus Types 3, 4, and 7 have been shown to protect military recruits from illness caused by these types. It is surmised that similar vaccines, containing Types 1, 3, and 5, can protect children from illness caused by these types, but multiple doses and more potent products may be necessary for children. General population studies have shown that adenovirus Types 1, 3, and 5 were seldom isolated from febrile illnesses in adult civilians but they were isolated from 5 or more per cent of the many febrile illnesses in preschool children. Although this represents a large number of illnesses, the percentage is so small that the beneficial effect of an effective vaccine would hardly be detectable in mass clinical studies. It is believed that general widespread public health use of such vaccines must await (1) the development of a multipolyvalent product incorporating adenoviruses with other common agents known to be pathogenic for children, e.g., influenza, parainfluenza, respiratory syncytial, and certain enteroviruses; and (2) must await epidemiologic studies demonstrating that benefits of such a vaccine far outweigh any hazard, inconvenience, or expense of its widespread use. Whether such a vaccine should be an attenuated live, or an inactivated product or both is unknown. However, it seems clear that for practical general public health use, any parenterally administered vaccine must have many highly purified and potent antigens incorporated in a single product. Basic research has already progressed far enough to permit development of a multipolyvalent product which would hold promise of preventing perhaps one-third of the more severe acute febrile respiratory illnesses of

children. Although the cost of development would be high, at present this is the most promising approach toward control of the acute respiratory diseases.

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III. MYXOVIRUSES: PARAINFLUENZA

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PARAINFLUENZA viruses, of which there are four types, are members of the myxovirus group, and they are immunologically distinct from influenza and other myxoviruses.[1,2,3,4,4a] Most of the information on these agents, including the original uncovering of Types 3 and 4, has become available because certain erythrocytes adsorb to the surface of monkey kidney tissue culture cells infected with these viruses.[5] This phenomenon is called hemadsorption. Recovery of parainfluenza viruses was facilitated by the hemadsorption technic since many naturally occurring strains failed to produce a cytopathic effect during initial tissue culture passage. In fact cytopathic effects with Types 1 and 4 viruses are minimal even with well adapted strains.[1,3] After isolation, parainfluenza viruses were identified by the use of type-specific rabbit antiserums in a hemadsorption inhibition test.[1] In our studies a modified Bengtson method complement-fixation test[6] was used for serological diagnosis and a fourfold rise in antibody was considered evidence for infection.

Sensitivity of Serological Methods

The complement-fixation test was quite sensitive in detecting evidence of infection but, particularly with human