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VIRAL RESPIRATORY TRACT ILLNESSES IN CHILDREN

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ANTIBIOTICS have come and antibiotics have gone but infants and children continue to have an average of six respiratory tract infections a year. This confirms the clinical impressions and epidemiologic studies which have indicated that a majority of such illnesses represent infection by agents other than bacteria. Further confirmation comes from the rapidly accumulating data on new or newly uncovered viruses and related agents in relation to respiratory tract illness. In fact, as such information accumulates it appears that *many different agents* may affect a child in a *common way*. Further, a *single* agent may result in *clinical syndromes* of varying severity or extent.

The fact that there is overlapping in the relationship of viral agents to the various clinical syndromes is not surprising since there are far more agents than there are parts of the respiratory tract, or ways in which that tract could respond to invading organisms. Further, many of the agents are capable of *reinfecting* an individual and it is reasonable to expect that first infection might bring about a more obvious clinical response whereas later infections, limited perhaps by tissue or serum antibody, would result in less severe illness.

This leads to the suggestion that we describe respiratory tract illness first on the basis of the location of the major observable pathology. Thus, we would speak of rhinitis, pharyngitis, tracheitis, bronchitis,

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TABLE I.—RESPIRATORY TRACT AGENTS

Myxovirus —	Influenza
	Parainfluenza 1, 2, 3, and 4
? Myxovirus —	Respiratory
	Syncytial
Adenovirus 1, 2, 3, 4, 5 and 7	
Picornavirus —	Coxsackie A and Coxsackie B
	ECHO
	Unclassified (H E)
	Unclassified "Rhinoviruses"
Reovirus —	1, 2 and 3
Bedsonia —	Ornithosis (psittacosis)
Mycoplasma —	Pneumoniae (Eaton agent)

laryngitis, pneumonitis or some combination of these in describing respiratory tract illness. We might then discard the terms "common cold", "ARD", or "URI" which imply specific etiology. Next, we would be concerned in respiratory tract illness so classified with the contribution of different viral and other agents to such illness as determined in large-scale studies. Then, if the various studies have paid sufficient attention to clinical detail, we can add certain clinical features to the description. For example, we might find that certain viral agents have a predilection for symptoms in one location or another, such as those affecting the laryngeal area prominently and resulting in the syndrome known as croup. We might also note systemic features that group with certain combinations of virus and clinical symptoms. Also helpful in determining which viral agent may be affecting an individual at a particular moment, or whether a particular agent would be effective and practical in a vaccine, would be certain information about the natural history of the virus, such as its occurrence in time, by season, or by age. If the clinician and epidemiologist adopt such an approach, it is hoped that clinical virological diagnosis can be more specific, and thus, there can be greater specificity in the use, or lack of use, of antibiotics in the treatment of respiratory tract illness. This approach will also offer a solid basis for defining an immune prophylactic program against infections of the respiratory tract.

The viral and related agents and mycoplasma which have been shown with varying orders of confidence to cause respiratory tract illness in

TABLE II.—THE KEY QUESTIONS

Does virus cause illness?
Which clinical syndromes?
Any distinctive clinical features?
Any effective therapy?
Natural history of virus?
Prevalence, occurrence, reinfection or immunity related to vaccine virus as vaccine antigen?

infants and children are included in Table I. Among the most important of these agents are the myxoviruses, influenza and para-influenza, the possible myxovirus respiratory syncytial, six or seven of the adenoviruses, certain picorna viruses whose classification and nomenclature is unsettled but which seem to cause respiratory tract illness, and the *Mycoplasma pneumoniae*, pleuropneumonia-like organism also called the Eaton agent. Reoviruses and the psittacosis agent do at times cause respiratory tract illness but seem not to be so prevalent as the above-mentioned agents.

Most of what I have to say further is based on studies carried out at Children's Hospital of the District of Columbia. We have attempted to define respiratory tract illnesses in a manner somewhat as described. Trying to answer the questions in Table II, we have been able to gather information on the contribution of many of the common new viral agents to different types of respiratory tract illness. Thus, we can offer some basis for an immune prophylactic program. The number of clinical or clinical laboratory features that would enable more specific clinical virological diagnosis, however, are quite limited.

METHODS

In these studies, patients with rhinitis, pharyngitis, tracheitis and/or bronchitis were grouped together but were separated according to severity of systemic response and local response, into a group of children with mild illness seen in the Out-Patient Department and another group with more severe illness who required hospitalization (Table III). Children with relatively severe *laryngitis* which, of course, is usually accompanied by inflammation in the proximal parts of the respiratory tract, were considered as having the croup syndrome. This

TABLE III.

	Hospitalized	*Ambulatory*
Study Groups	Bronchitis-Pharyngitis	Rhinitis
	"Croup"	Pharyngitis
	Bronchopneumonia	Bronchitis
	Bronchiolitis	
	No Illness	No Illness
Study Methods	Virus Isolation and CF Antibody (Good Estimate)	Virus Isolation alone (Minimal estimate)

was determined primarily by the presence of hoarseness of voice and cough accompanied by inspiratory stridor. Children with pneumonitis requiring hospitalization were subdivided further into a group with bronchopneumonia and a group with bronchiolitis. The characteristics for entry into the bronchopneumonia group included dyspnea, fine rales on auscultation and/or a patchy pneumonic infiltration on x-ray examination. Children qualified as having the bronchiolitic type of pneumonia if they had marked dyspnea, with or without fine rales, and if, on percussion of the chest and/or x-ray examination, there was evidence of emphysema in the distal lung fields. Patchy infiltration in the lung fields on x-ray was not a requisite for this diagnosis, although it was present either at the outset or later during the illness in many of the children.

Oropharyngeal specimens from all subjects and anal swab specimens from most subjects were studied by virus isolation techniques sufficient to detect adenoviruses, influenza virus, para-influenza viruses and respiratory syncytial virus, all of which could also be identified specifically by type. Enteroviruses, and some of the other entero-like viruses, were isolated but have not yet been sufficiently categorized for presentation. In addition, paired serums from a majority of hospitalized subjects were studied for evidence of a rise in complement-fixing antibody against a number of viral antigens including adenovirus group antigen, influenza A, B and C, para-influenza 1, 2 and 3, and respiratory syncytial virus antigens. A limited number were studied by indirect fluorescent antibody methods for evidence of infection with the Eaton agent.

TABLE IV.—ADENOVIRUS

Types:	1-28 (1, 2, 3, 4, 5, 7)
Size:	80-120
Nucleic Acid:	DNA
Diagnosis:	HeLa, HEp-2, (Rounding) Differential hemagglutination
Serology:	CF (group), Neut.

TABLE V.—MYXOVIRUS INFLUENZA

Types:	A B C
Size:	80-120
Nucleic Acid:	? RNA
Diagnosis:	Monkey kidney, hemadsorption Egg
Serology:	CF, hemagglutination inhibition

More specifically, and as a reminder of some of the information which Dr. Kilbourne gave you last week, the adenoviruses include 28 serotypes of intermediate size with a DNA base (Table IV). They are best recovered by inoculation into continuous cell-line tissue cultures such as the HeLa or HEp-2 cell. They can be separated into several different groups by use of a differential hemagglutination reaction and then identified by hemagglutination inhibition. The serum of a patient who is infected can be tested for antibody which will be group reactive in a complement-fixation test or type specific in a neutralization test. The cytopathic effect in tissue culture includes rounding and clumping of the cells.

Influenza viruses include three types: A, B and C (Table V). Particularly in type A there is considerable antigenic variation so that there are a number of strains within the type. An influenza agent can be recovered either in embryonated egg with the production of a hemagglutination reaction or in monkey kidney with the production of hemadsorption. Complement fixation or hemagglutination inhibition tests are useful in detecting serologic evidence of influenza infection.

There are at least four distinct serotypes of para-influenza virus

TABLE VI.—MYXOVIRUS PARA-INFLUENZA

Types: 1 (HA-2), 2 (CA), 3 (HA-1), 4 (M-25)
Size: 90-135 (200-250)
Nucleic Acid: ? RNA
Diagnosis: Monkey kidney, hemadsorption
Serology: CF, hemagglutination or hemadsorption inhibition

TABLE VII.—RESPIRATORY SYNCYTIAL

Strains: CCA, Long
Size: 90-120
Diagnosis: HEp-2, Syncytia
Serology: CF, Neut.

type 1, originally designated HA-2, type 2, which has also been called the CA virus, type 3, originally designated HA-1, and type 4 which has been called M-25 (Table VI). Some of these viruses were first recovered—and a large part of the new information on these viruses has been obtained—by virtue of the fact that red cells adsorb to the surface of monkey kidney tissue culture cells infected with these agents. This phenomenon is called hemadsorption. These are intermediate size viruses probably with an RNA core. Serological diagnosis of para-influenza infection may be made by use of complement fixation, hemadsorption inhibition or neutralization tests or by hemagglutination inhibition. In the complement fixation tests with human serums, heterotypic antibody rises are often noted, particularly with the para-influenza 3 antibody during convalescence from para-influenza 1 or 2 infection. This is probably due to the fact that these viruses share antigens and that para-influenza 3 infection is extremely prevalent and usually occurs earlier in life than the other two.

The respiratory syncytial virus (originally called chimpanzee coryza agent, and one human strain of which has been designated Long), is considered by many to be a myxovirus even though it does not fulfill such criteria as growth in eggs or hemagglutination (Table VII). To recover respiratory syncytial virus from human respiratory secretions requires that the specimens be tested immediately without

TABLE VIII.—MYCOPLASMA PNEUMONIAE (EATON)

Types: 4 (1 in resp. illness)
Size: 180-250
Diagnosis: PPLO agar, yeast extract and horse serum
Serology: ? CF, Indirect Fluor. antibody

prior freezing since the agent is extremely labile. Continuous human cell lines such as the HEp-2 are the most sensitive. When the virus is present, a syncytium occurs and eosinophilic cytoplasmic inclusions can be detected. Complement fixation or neutralization procedures may be used for study of paired human serums.

Mycoplasma organisms are not strictly viruses but include a large number of agents of at least four human types, one of which, mycoplasma pneumoniae, is also called the Eaton agent (Table VIII). This is a somewhat large agent which, unlike strict viruses, has been shown to grow in artificial PPLO media supplemented with yeast extract and horse serum. Infection with the agent is indicated either by recovery of an organism on PPLO medium or by means of fluorescent antibody techniques utilizing paired serums from infected patients in reaction against the organism growing in the bronchial epithelium of embryonated eggs. It now appears that a complement-fixation test will be feasible.

RESULTS

Agents in Various Syndromes

In these cross-sectional studies from October 1957 to May or June 1961, oropharyngeal specimens from almost 8,000 children and infants were studied, and evidence was obtained to support the etiological relationship to respiratory tract illness of influenza, para-influenza, respiratory syncytial, some of the adenoviruses and the Eaton PPLO agent.

These studies have also enabled an assessment of the contribution of these several agents to the various clinical syndromes studied. It should be remembered that the hospitalized patients were studied by serological methods as well as virus isolation, whereas those ambulatory patients with rhinitis, pharyngitis and bronchitis were studied only by virus isolation methods. Nonetheless, some virus was recovered from 22 per cent even of these latter patients. (Figure 1) Some adenovirus

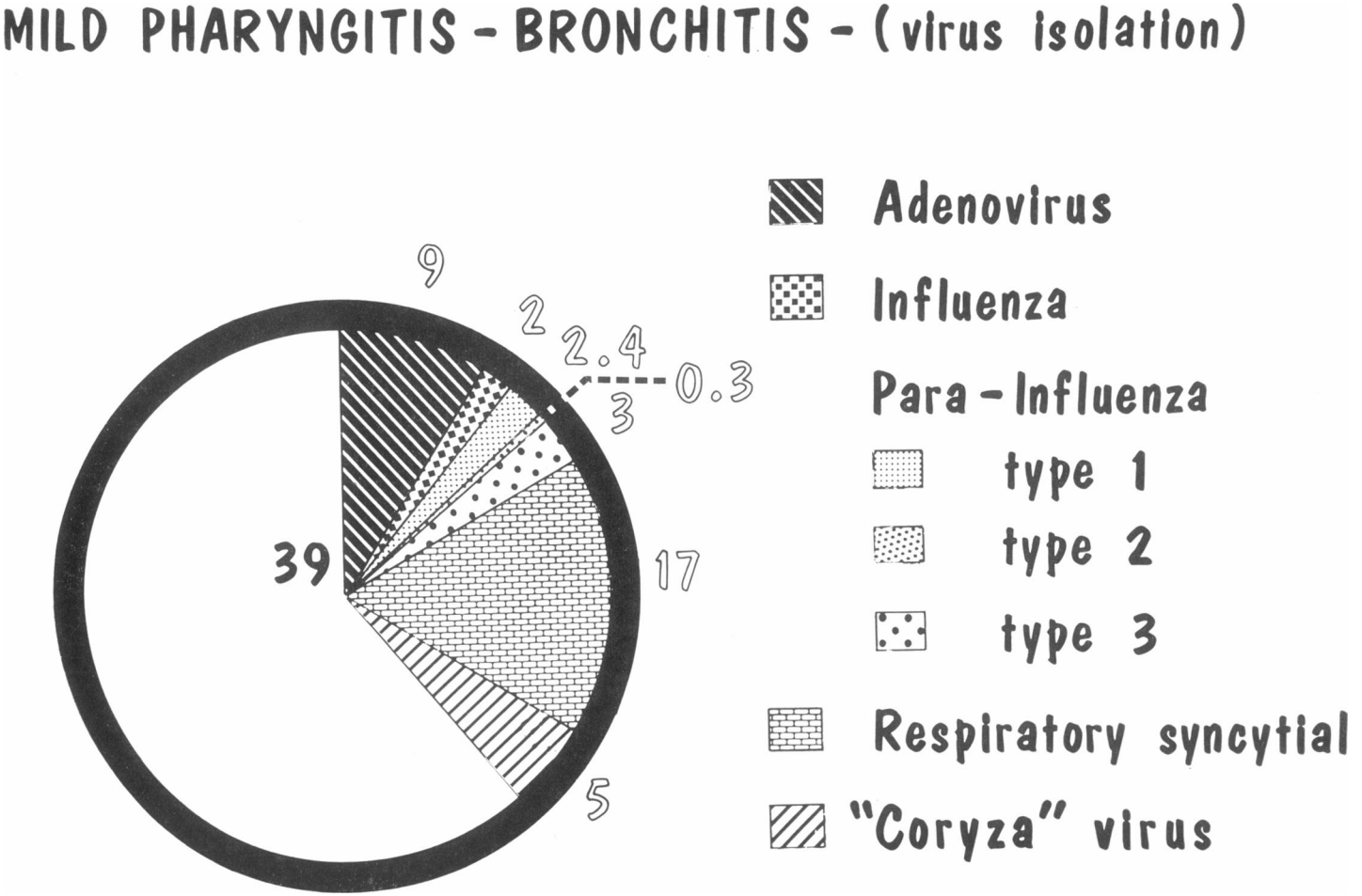
MILD PHARYNGITIS - BRONCHITIS - (virus isolation)
9
2
2.4
0.3
3
39
17
5
Adenovirus
Influenza
Para - Influenza
type 1
type 2
type 3
Respiratory syncytial
"Coryza" virus

Fig. 1

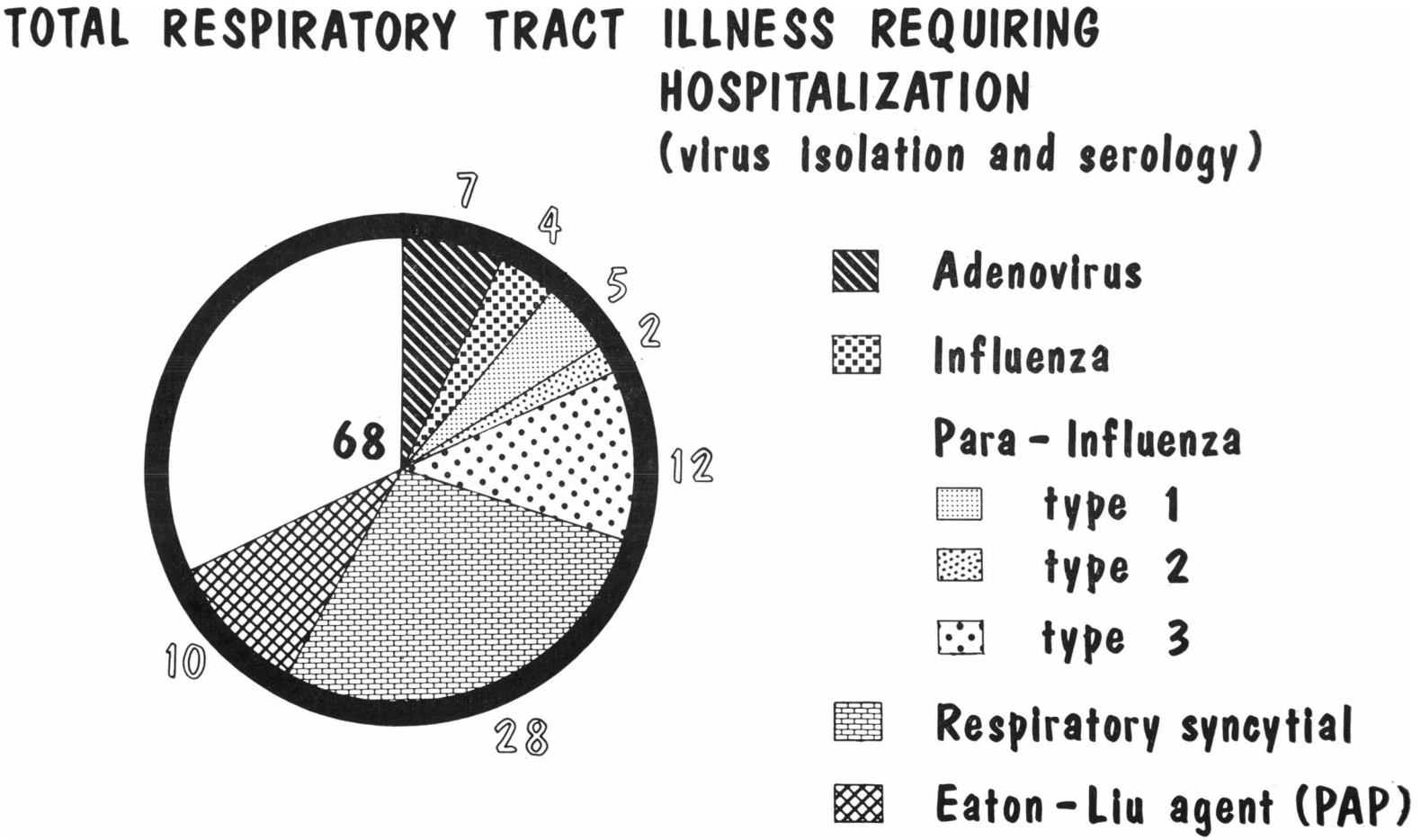
TOTAL RESPIRATORY TRACT ILLNESS REQUIRING HOSPITALIZATION
(virus isolation and serology)
7
4
5
2
68
12
10
28
Adenovirus
Influenza
Para - Influenza
type 1
type 2
type 3
Respiratory syncytial
Eaton - Liu agent (PAP)

Fig. 2

was recovered from the throat or anal swab of 9 per cent of these children seen as ambulatory patients. Adenoviruses 1, 2 and 3 and 5 were the ones most frequently found, although there were patients with types 6, 7, 9, 10, 12, 16 and 18 as well as several higher or untyped varieties. Influenza viruses were found in 2 per cent. Para-influenza viruses were found in 6 per cent with a majority of these being para-influenza 1 or 3. The respiratory syncytial agent was recovered from the throat of 5 per cent, although in Hilleman's studies of children with mild respiratory tract illness, 17 per cent were found to have respiratory syncytial infection. None of these patients was studied for Eaton agent. We feel that the estimates for association of these minor illnesses with virus infection in most instances are minimal estimates.

Our data do not yet include estimates for the contribution of the enteroviruses or the entero-like viruses, but Hilleman estimates that what he has called the "coryza" virus may be responsible for 5 per cent of respiratory tract illness in children.

In fact, it is likely that the percentage contribution of the various agents to the less severe illness would be closer to the figures derived by serologic studies in addition to virus isolation studies for somewhat more severe instances of pharyngitis and bronchitis necessitating hospitalization. (Figure 2) Here adenovirus infections were related to approximately 7 per cent, influenza to 4 per cent, the para-influenza viruses approximately to 19 per cent, with a much higher percentage relatively of para-influenza 3 infection than in the ambulatory patients, respiratory syncytial approximately to 28 per cent, and the Eaton agent to 10 per cent. In this graph, as in those immediately following, the percentage of respiratory syncytial infection is an estimate adjusted for known insensitivity of complement fixation methods in infants. The Eaton agent percentage is based on only 100 patients from different periods of study and no adjustment has been made for the fact that about 6 per cent of patients had antibody rises for two or more groups of agents.

One of the more striking associations of viruses with a clinical syndrome occurred among infants and children with severe laryngitis or infectious croup. (Figure 3) Adenovirus infections were present in 9 per cent of these patients, and influenza in 8 per cent, but the para-influenza viruses, particularly type 1, were the major contributors to infectious croup through all periods of the study. Para-influenza 1 in-

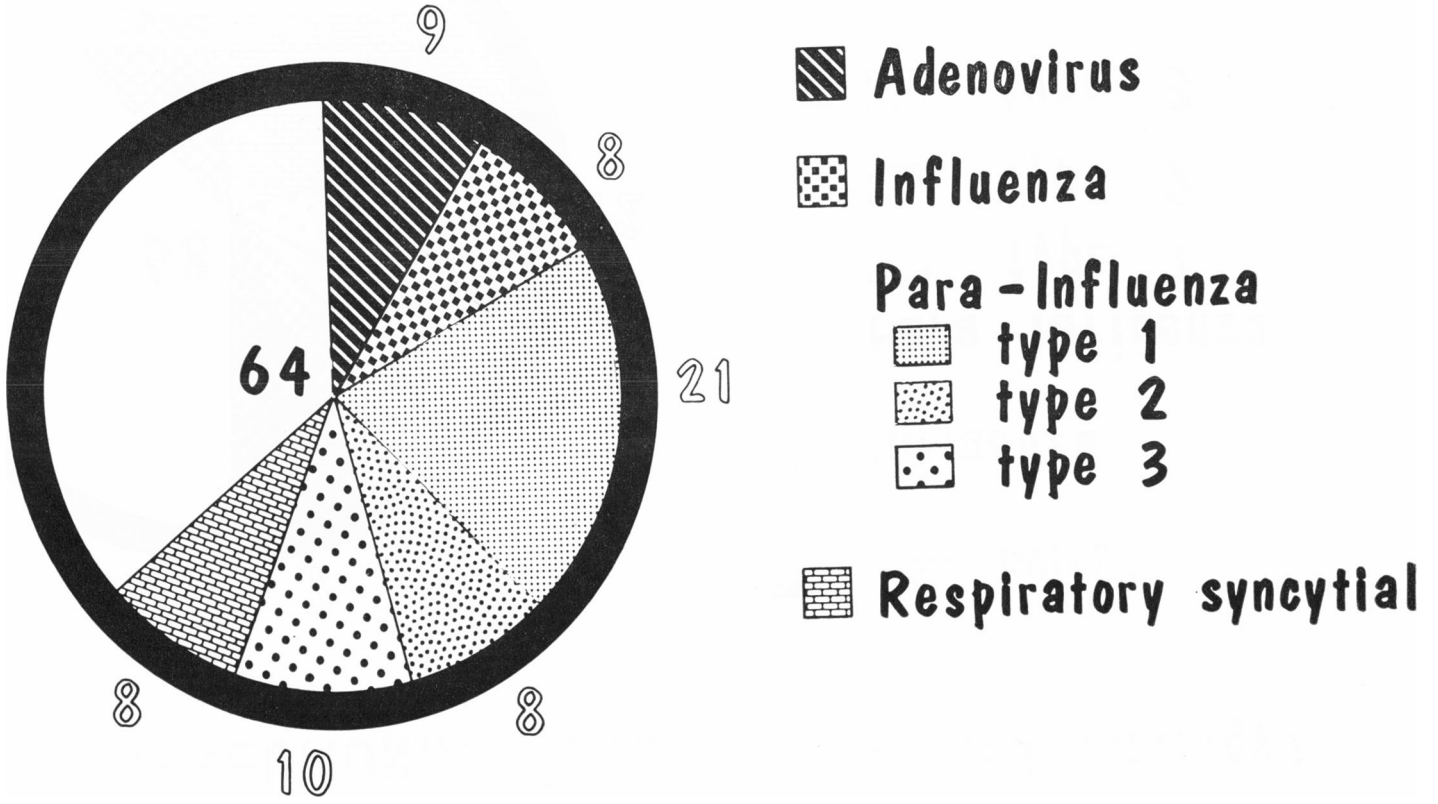
INFECTIOUS 'CROUP' (virus isolation + serology)
9
8
21
64
8
8
10
Adenovirus
Influenza
Para-Influenza
type 1
type 2
type 3
Respiratory syncytial

Fig. 3

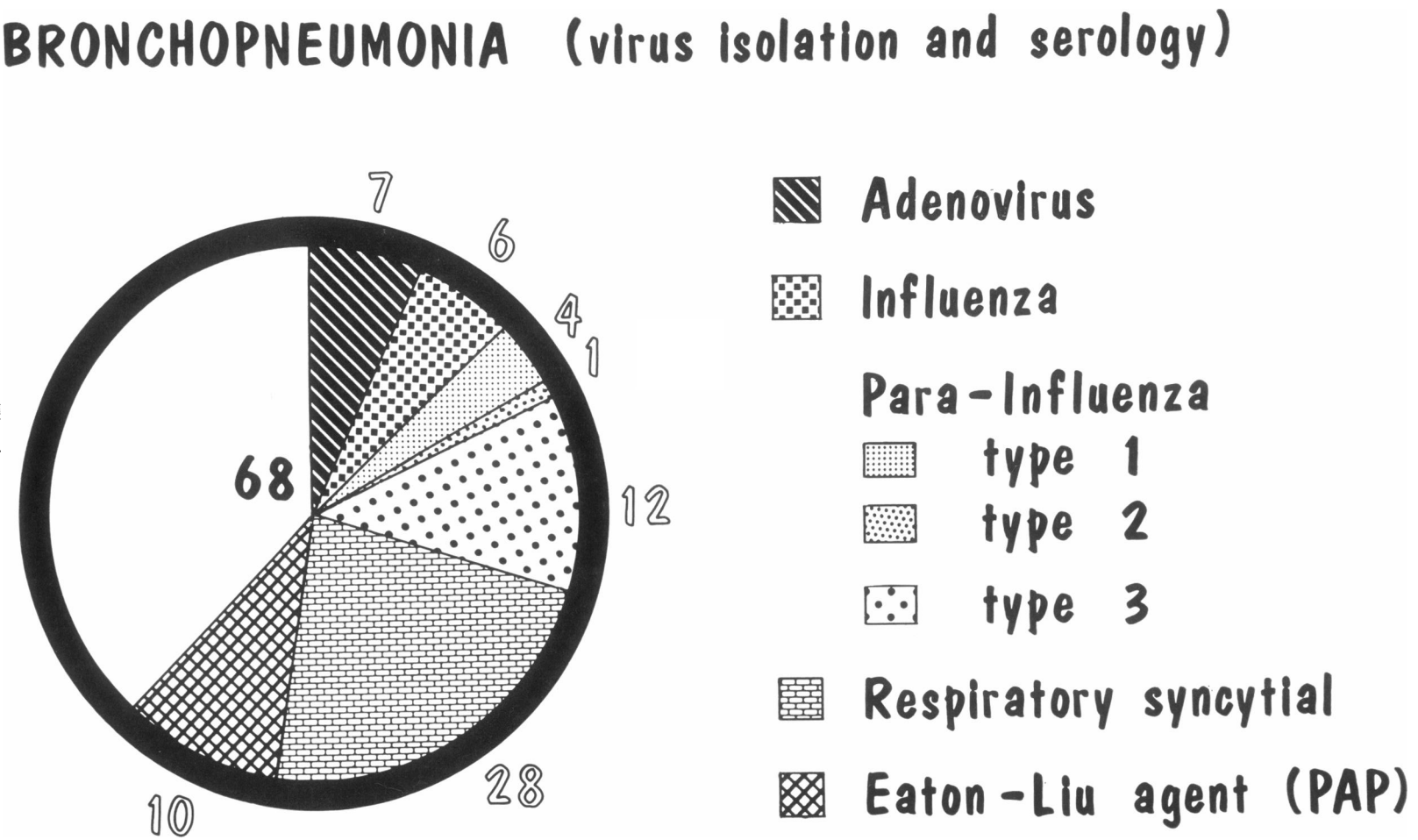
BRONCHOPNEUMONIA (virus isolation and serology)
7
6
4
1
68
12
28
10
Adenovirus
Influenza
Para-Influenza
type 1
type 2
type 3
Respiratory syncytial
Eaton-Liu agent (PAP)

Fig. 4

fection was found in 21 per cent, para-influenza 2 in 8 per cent and para-influenza 3 in 10 per cent of these patients. Respiratory syncytial infection was found in 8 per cent of croup patients, but Eaton agent rises were not found in any of the limited number of croup patients studied for this infection. The virus-associated croup cases were not particularly distinctive clinically. During the period of the study there were practically no instances of epiglottitis available for attempts at demonstrating virus infection.

Some virus or mycoplasma infection was detected in 68 per cent of the children who were admitted to the hospital with bronchopneumonia (Figure 4). Para-influenza 3 (12 per cent) and respiratory syncytial virus (28 per cent) were among the more important agents throughout all periods of the study. Ten per cent of the comparatively small segment of the total of pneumonia cases was associated with the Eaton agent.

In bronchiolitis, a majority of cases were related to respiratory syncytial virus infection (Figure 5). The estimate of 58 per cent is based on serologic evidence for infection adjusted for the insensitivity of the test in infants. Actually, respiratory syncytial virus was recovered from the oropharynx of 39 per cent of infants under seven months of age with bronchiolitis, suggesting that the estimate is reasonable.

Thus, of all children requiring hospitalization for respiratory tract illness, 8 per cent were found to be undergoing adenovirus infection, 6 per cent influenza, 4 per cent para-influenza 1, 2 per cent para-influenza 2, 13 per cent para-influenza 3, approximately 24 per cent respiratory syncytial virus and 12 per cent Eaton agent (Figure 6). This makes a total of 69 per cent of the serious respiratory tract illnesses of children which could be linked to at least one of the designated agents. Para-influenza type 3 and respiratory syncytial virus were the agents most commonly associated with illness.

Clinical Differentiation

In spite of the frequency and importance of the acute infections there have been few clinical features noted in our study—or available from others—that might enable the clinician predictably to estimate which agent is responsible. Some of the features from this or other reports follow: 1) In general, rhinorrhea and cough occur with viral infection in contrast to the typical streptococcal infection. 2) Para-in-

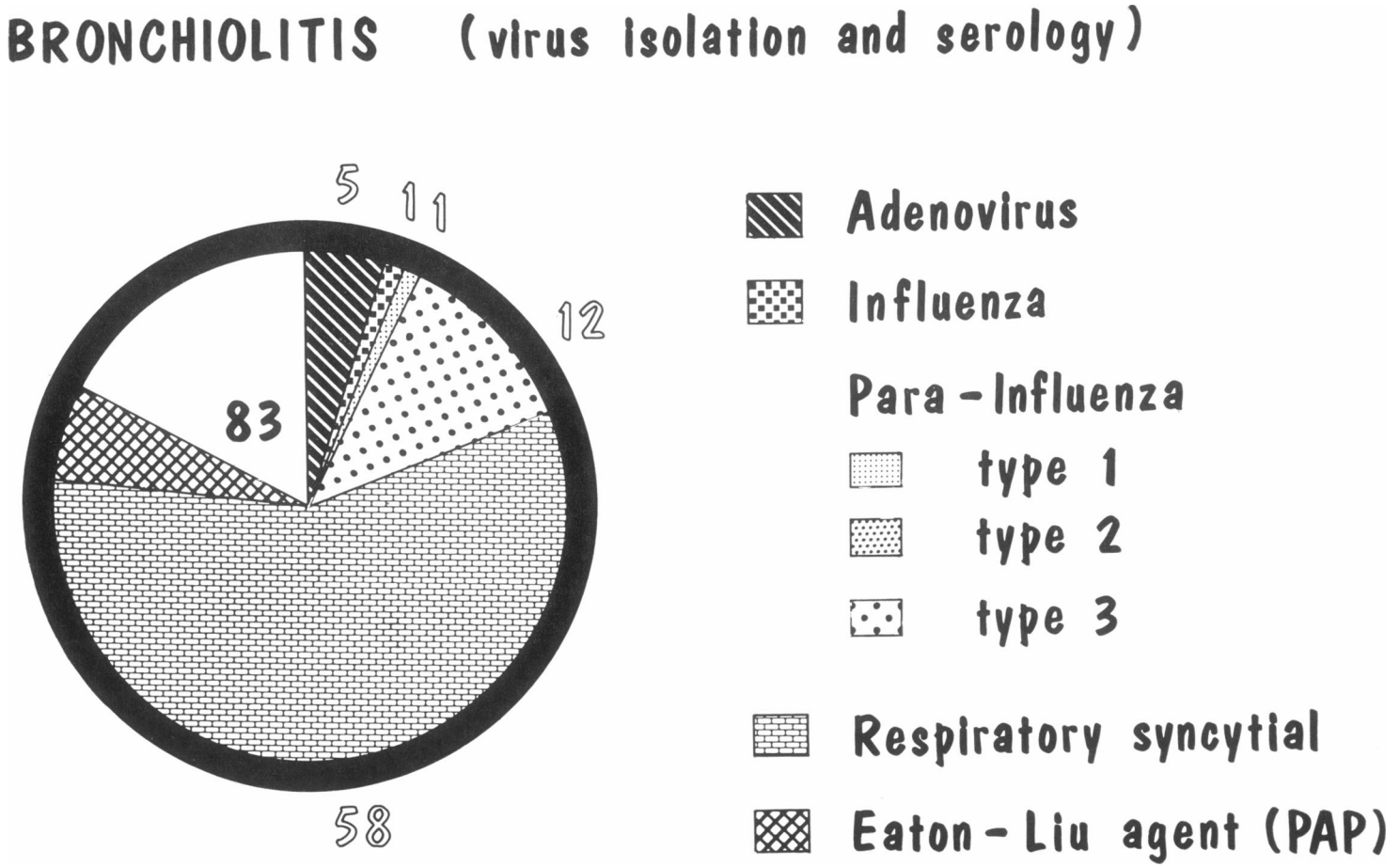
BRONCHIOLITIS (virus isolation and serology)
5
11
12
83
58
Adenovirus
Influenza
Para-Influenza
type 1
type 2
type 3
Respiratory syncytial
Eaton-Liu agent (PAP)

Fig. 5

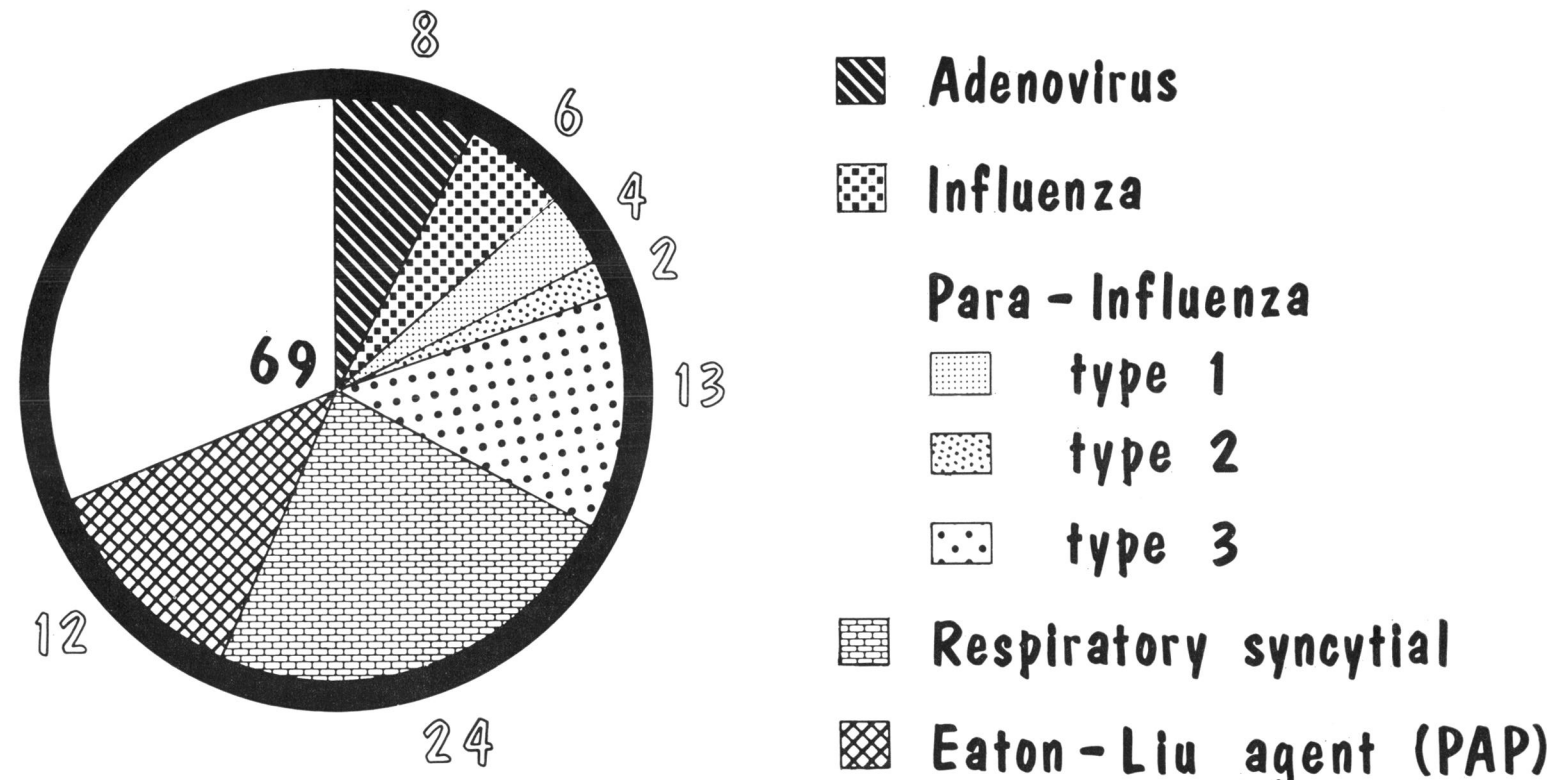
SEVERE BRONCHITIS - PHARYNGITIS (virus isolation and serology)
8
6
4
2
13
24
12
69
Adenovirus
Influenza
Para - Influenza
type 1
type 2
type 3
Respiratory syncytial
Eaton - Liu agent (PAP)

Fig. 6

fluenza and respiratory syncytial infections typically include rhinitis, pharyngitis and some bronchitis; adenoviral infection might be considered more apt to include conjunctivitis and posterior cervical lymphadenopathy, or exudative pharyngitis. 3) Hoarseness of voice suggests para-influenza 1 or 2 infections. 4) Children with influenza infection have a more sudden onset of fever and are more "toxic" at the outset than children with para-influenza and respiratory syncytial infection, although children with respiratory syncytial infection seem more often to have fever than the total of children with rhinitis, pharyngitis and bronchitis. 5) Among the more severely ill children those with the croup syndrome are likely to have infection with para-influenza 1 or 2 virus; those with the bronchiolitis syndrome are likely to have infection with the respiratory syncytial virus. However, those with bronchopneumonia of less distinct type might be infected with any of the viruses. Clinical laboratory studies and x-rays are of no real value in differentiating among these infections.

The only group of agents under discussion for which there is specific therapy is the Eaton mycoplasma group. Recent evidence in a controlled study confirms the previous clinical evidence that tetracycline variants are effective in the treatment of Eaton agent-induced, cold-agglutinin-positive, primary atypical pneumonia infections.

Thus, the major value of information obtained in these studies would be in determining which agent should be included in an immune prophylactic program; the natural history of different viruses concerned can be helpful in this determination as well as in potentially helping at an individual period in time to know which agent is likely to be affecting an individual patient.

That the agents under discussion do infect significant numbers of children is confirmed further by a study of the incidence of antibody to these agents in the serums of preschool children (Table IX). Most children have had antigenic experience with particularly the para-influenza and respiratory syncytial viruses by the age of 4 or 5. The incidence of antibody to adenovirus is somewhat more variable, and antibody to Eaton agent is not so prevalent at this age, an indication that perhaps this organism spreads more slowly through the population. In our studies over almost five years, para-influenza 1 and 3 viruses have been recovered in each year, every season and virtually every month. Para-influenza 2 infections have been encountered more sporadically.

TABLE IX.

Agent	*Occurs*	*Incubation Period*	*% Antibody Age 5*	*Reinfection*
Flu	Spor	2-3	Var	+
Para-flu				
1	Con	5-6	42	+
2	Spor	?	33	?
3	Con	2-3	81	+
4	Spor	?	?	?
R-S	Var/yr	4-9	80	+
Adeno				
1	Con	↑	35	—
2	Con	↑	60	—
3	Con	5-7	15	—
4	Var	↓	10	—
5	Con	↓	20	—
Cox A	Sum/Var	1-3	Var	—
B	Sum/EP	1-3	Var	—
ECHO	Var	1-3	Var	? +
28	Con		6	? +
Rhino	?	1-3	?	? +
Eaton	Var/yr	?	15	+

Con = Constant
Spor = Sporadic
Var = Variable
yr = yearly
EP = Epidemic
Sum = Summer

The almost continuous presence of types 1 and 3 para-influenza contrasted with the sporadic occurrence of influenza. Respiratory syncytial infection occurred during each of the five years reported in the study, although the months during which it was detected varied from year to year. For example, respiratory syncytial infection was present in the first several months of 1958 as well as toward the end of that year and early 1959. It was also present early in 1960 and during the following winter. At this time, in the Washington, D. C. area there is an upswing in respiratory syncytial infection. The peak periods of bronchiolitis prevalence were closely correlated with the peak prevalence of respiratory syncytial infection during each of the years. From studies in a closed nursery group, it has been determined that para-influenza and respiratory syncytial virus infections spread readily through a closed population of children. In several outbreaks lower respiratory tract ill-

ness was present in 33 per cent of children with no pre-existing antibody but in very few children who had any detectable neutralizing antibody when they were infected with para-influenza 3 virus. In an outbreak of respiratory syncytial infection a total of 40 per cent of nursery inhabitants had fever and pneumonia. The epidemic spread of influenza in a susceptible population is, of course, well known. Evidence is accumulating that it is possible to be reinfected with the para-influenza and respiratory syncytial viruses. However, first infection is frequently accompanied by severe febrile illness, reinfection by subclinical or less severe illness. Adult volunteers, almost all of whom had antibody to these agents, have been described as having rather typical colds after challenge with this virus. Thus, optimistically one might guess that immunization with these viruses early in infancy might prevent a major proportion of serious respiratory tract illness in children by allowing their first exposure to these agents to be in the form of a vaccine rather than natural infection with the agent.

The adenoviruses 1, 2, 3, 5 and 7 have been found during all five years of our study at a fairly constant level, although types 4 and 7 were somewhat more variable. From antibody prevalence as well as from the virus isolation studies it would appear that types 1 and 2 are the most prevalent of these agents. Adenovirus type 3 has been reported in rather explosive outbreaks of pharyngoconjunctival fever, and adenoviruses 4 and 7 spread rapidly in a military recruit population. Little is known of the rapidity of spread of adenoviruses 1, 2 and 5. Infection with adenoviruses confers rather permanent type-specific immunity.

If a majority of respiratory tract illnesses are due to virus infection, and if antibiotics and chemotherapeutic agents are not effective in therapy, it is reasonable to approach the serious problem which these agents present through an immune prophylactic program. However, despite the fact that the agents for known and suspected virus respiratory tract illness are being isolated and categorized and their importance defined, many factors must be considered.

Multivalent inactivated vaccine is available for influenza. The relative infrequency of infection with influenza in contrast to the total and the high frequency of toxic reactions to the vaccine has limited the practicality of routine influenza immunization for infants and children. In fact, routine use in normal children is not recommended by the American Academy of Pediatrics. An effective inactivated adenovirus

vaccine against types 3, 4 and 7 has been prepared and marketed but it is types 1, 2 and 5 that most often affect children and these types have not yet been prepared as potent vaccine antigens. Further, even the previously available and effective adenovirus vaccines for types 3, 4 and 7 have been contaminated with Simian viruses and must be "cleaned up" before new lots can be licensed. Experimental monkey kidney and/or egg-grown para-influenza and monkey kidney-grown respiratory syncytial vaccines are under study. The major problem faced here is to attain sufficient antigenicity of virus grown in an acceptable tissue culture system. The new viruses which have been called rhinoviruses or coryza viruses, probably to be included in the Picorna group, apparently comprise so many types that the first challenge must be to define and segregate the viruses antigenically and to assess their relative importance in order to decide on which agents to include in a potential vaccine. Thus, at the moment, there is no effective vaccine against the most important of these agents.

In summary, I would suggest that we all take a new look at our clinical classifications for respiratory tract illness in children, and perhaps in adults as well. We should start by locating the primary site of inflammation and then, with the help of major virologic studies, add any specific clinical or laboratory features which might be helpful in defining specific syndromes. Epidemiologic information, and information about the natural history of the infecting agents, can also be helpful. In our cross-sectional studies, para-influenza and respiratory syncytial viruses were among the most important of the viral agents affecting children with respiratory tract illness. Adenovirus, influenza virus and Eaton PPLO agent infections also played a significant part. All of these agents were found in children with nasopharyngitis and bronchitis; para-influenza 1 and 2 viruses were most important in the laryngitis syndrome; para-influenza 3, respiratory syncytial and Eaton agent in bronchopneumonia and respiratory syncytial in bronchiolitic bronchopneumonia. These findings are being borne out by studies from all parts of the world, as recently summarized by Hilleman. Thus, approaches to the vaccine prevention of at least the serious respiratory tract illnesses in children must include attention to all of these agents but, at the present time, no effective vaccines are available for the agents which seem to be most important.

(Collateral Reading List on page 648)

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