

## One-year Aetiological Study of Nondiphtheritic Croup

By

V. MAJOR

László Central Hospital for Infectious Diseases, Budapest

(Received April 17, 1966)

Recent investigations have shown that *Myxovirus parainfluenzae* types 1—3 and the RS virus are the commonest causative agents of acute respiratory illness in infancy and early childhood. The aetiological role of these viruses in the croup syndrome has been proved [1—19].

In a previous report [17] virological and serological investigations concerning 416 infants and young children suffering from nondiphtheritic croup (pseudo-croup) were published. The cases were admitted to the Oto-rhino-laryngological Department of this Hospital in the one-year period beginning in November, 1963. In the present report the corresponding clinical experience is detailed.

### VIROLOGICAL FINDINGS IN DIFFERENT CLINICAL GROUPS

Virus isolation was attempted from 423 specimens including 416 pharyngeal and 7 tracheal swabs obtained from a total of 416 cases. We succeeded in isolating virus from 261 specimens (61.7 per cent) (Fig. 1). The iso-

lation rate was over 60 per cent for children from 6 months to 6 years of age; it was the highest from 1 to 3 years of age, whereas substantially lower both under 6 months (50 per cent) and over 7 years (40 per cent).

Based on the severity of the clinical course the children were divided into four groups. Group I (48 cases) was characterized by a sudden attack, occasionally recurrent attacks, of dyspnoea, occurring in most cases at night. The attack subsided as suddenly as it had begun. Catarrhal symptoms and fever were absent, voice of speaking and weeping was clear. Thus, the syndrome said to be characteristic of pseudocroup was observed. Virus was isolated from 27 children of this group (56.2 per cent).

The cases included in group II (285 cases) showed catarrhal symptoms characteristic of rhinitis, pharyngitis and/or bronchitis, often hoarseness and hyperthermia in addition to the symptoms shown by group I. The stenotic symptoms were transient. Virus was isolated from 172 cases (60.3 per cent).

The children with protracted dyspnoea, which occasionally lasted for several days, were classified into group III (74 cases). In this group inspiratory retractions, cyanosis and circulatory disturbances were common. As a result of energetic conservative treatment the symptoms gradually subsided. Tracheotomy proved to be unnecessary. Virus was isolated from 53 cases (72.8 per cent).

The most severe 9 cases were classified into group IV. In these cases stridor, dyspnoea and cyanosis became more pronounced in spite of the usual treatment. Because of respiratory and circulatory failure tracheotomy had to be performed. All these cases yielded virus.

It should be noted that the isolation rate for groups I—IV was directly related to the severity of illness.

Of the 416 cases 282 were primary attacks, whereas 103 children had had croup attacks earlier. In 66 cases these had occurred before the present study was begun, whereas 31 children were repeatedly admitted during the period under study, 68 times altogether. The isolation rate was 64.1 per cent for the primary cases, 59.7 per cent for the recurrent cases.

The aetiology was established both by isolating the agent and demonstrating antibody response in 128 cases, solely by virus isolation in 133 cases. In 58 cases yielding no virus, antibody response to one or another virus was demonstrated. In spite of this, these cases cannot be accepted to have been caused by the corresponding virus because, owing to the hospitali-

zation, the children might have been infected by viruses unrelated to their actual illness.

#### CLINICAL OBSERVATIONS

*Age and sex.* Distribution of the cases by age and sex is presented in Fig. 2. In accordance with literary data the pseudocroup syndrome was most frequent among children from 6 months to 3 years of age. One-year-old children were most affected. More boys than girls were affected (67 and 33 per cent, respectively). The majority of the cases occurred during the cold season.

*History.* Anamnestic data are presented in Table I. It is seen that attacks of pseudocroup had often been preceded by catarrhal symptoms. Cough, hoarseness and coryza had been observed in 85, 42 and 13 per cent, respectively. Forty-three per cent of the children had had fever.

In pseudocroup of infectious origin respiratory stenosis is due to inflammatory oedema of the subglottic area and/or infection-induced laryngeal spasm. The severity of the clinical manifestations depends on the relative partaking of these two factors, the severity of the infection and the immunological status of the patient. In mild cases the spasm, in severe cases the oedema, accounts for the laryngeal stenosis.

The length of the period from the first catarrhal symptoms to the appearance of stenotic symptoms was in close correlation with the further

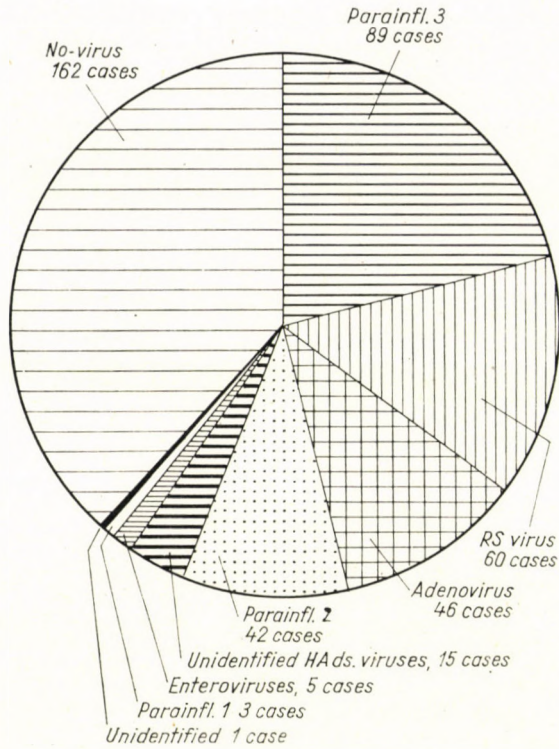


FIG. 1

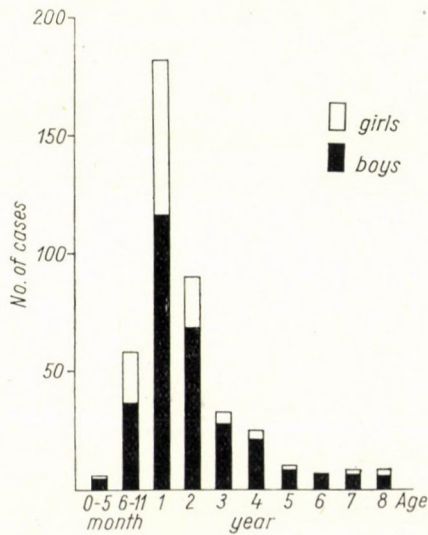


FIG. 2

TABLE I  
Symptoms introducing the croup syndrome

Clinical category	No. of cases	Cough	Hoarseness	Coryza	Fever
I	48	77*	25	10	—
II	285	86	46	16	50
III	74	93	45	7	46
IV	11	73	36	9	64
Total	418	86	43	13	44

\* per cent

TABLE II  
Fever related to croup syndrome

Clinical category	No. of cases	Fever			No fever
		<37.5°	37.5—38.5°	>38.5°	
I	48	—	—	—	100
II	285	28*	52	9	11
III	74	18	62	13	7
IV	11	—	45	55	—
Total	418	22	48	10	20
		80			

\* per cent of cases

TABLE III  
Leucocyte count in cases with croup syndrome

Clinical category	No. of cases	Leucocyte count			
		4000—8000	8000—10,000	10,000—15,000	> 15,000
I	48	50*	27	19	4
II	285	49	23	20	8
III	74	47	20	23	10
IV	9	11	33	33	22
Total	416	48	23	21	8

\* per cent of cases

clinical course. If the stenotic symptoms appear simultaneously with the catarrhal ones or even precede the latter, the child will be admitted to hospital early, often in the first hours of illness. In most of these cases dyspnoea soon subsides and the clinical course is mild. Slowly developing stenotic symptoms, on the other hand, are usually followed by a more protracted and more severe course. In group I 77 per cent of the cases were hospitalized on the first day of illness, whereas 66 per cent of the children included in group II, III and IV were admitted more than one day after onset. Indeed, stenotic symptoms in group I were mainly spastic in character, whereas in the other groups oedema played a more substantial role.

Forty-three per cent of the patients had had fever before admission. In the hospital fever was registered in 80.2 per cent. The degree and duration of fever was in general directly related to the severity of the clinical course (Table II). In group I fever was absent, whereas all children in group IV had fever; in 5 of the 9 cases fever exceeded 38.6°C.

*Haematological findings.* Leukocyte count (Table III) was elevated in 52 per cent; it exceeded 10,000 per cu. mm and 15,000 per cu. mm in 30 and 8.1 per cent respectively. However, the leukocytosis showed no correlation with the clinical course. It exceeded 15,000 per cu. mm in a few very mild, afebrile cases as well.

*Bacteriological tests.* From 59 throat secretions (14.1 per cent) pathogenic

bacteria were isolated: 24 *Staphylococcus aureus haemolyticus* (coagulase-positive), 23 *Streptococcus haemolyticus*, 2 *Diplococcus pneumoniae* and 10 strains belonging in the *Enterobacteriaceae* family (*E. coli*, *Ps. pyocyanea*, *Proteus* and *Klebsiella*). The actual role of these bacteria is questionable, considering that, 52 out of the 59 cases recovered without aimed antibiotic therapy and virus was isolated from these cases at the same rate as from bacteriologically negative cases.

The low incidence of positive bacteriological findings excluded primary bacterial aetiology in a great majority of the pseudocroup cases under study. Nevertheless, bacteria might have played a role in the complications.

*Complications.* The complications observed in the present study have been summarized in Table IV. It should be emphasized that most of these were only regarded as complications from the point of view of the laryngologist. It is well-known that the viruses isolated in the course of this study are capable of causing upper and lower respiratory disease without any concomitant infection. Adenoviruses may even cause lymphadenitis. The commonest "complications" observed into four groups, such as (i) upper respiratory catarrh; (ii) bronchitis (catarrhal or spastic); (iii) "bronchopneumonia" (true bronchopneumonia, peribronchitis and empyema); (iv) otitis media and (v) lymphadenitis. The frequencies of these complications are presented in Table IV.

TABLE IV  
Complications associated with the croup syndrome

Throat secretion		No. of cases	Complication					No complication
Virus	Pathogenic bacterium		Upper respiratory catarrh	Bronchitis	Broncho-pneumonia	Otitis media	Lymphadenitis	
Positive	Positive	29	76*	62	17	10	7	17
	Negative	225	81	56	5	6	4	17
Negative	Positive	30	80	30	10	3	10	13
	Negative	132	86	41	2	1	11	7
Total		416	82	50	5	5	7	14
					86			

\* per cent of cases

TABLE V  
Complications associated with infections due to the most frequently isolated viruses

Virus	No. of cases	Upper respiratory catarrh	Bronchitis	Broncho-pneumonia	Otitis media	Lymphadenitis
Parainfluenza 3	89	75*	55	3	6	3
RS	60	90	66	8	7	2
Adenovirus	46	100	39	9	7	9
Parainfluenza 2	42	100	36	5	7	—
Haemadsorbing viruses	15	100	47	—	7	—
Total	252	86	49	5	7	3

\* per cent of cases

In one case maxillary sinusitis, in two cases enteritis was observed. Occasionally, stomatitis was present. Only 13.7 per cent of the cases were free of complication.

For further analysis of the complications the cases were divided into two main groups, a virologically positive and a virologically negative group. Both of these groups were

subdivided according to the result of bacteriological cultivation.

There was no significant difference among the groups in the frequency of the above listed complications. Nevertheless, bronchitis, bronchopneumonia and otitis media occurred in the group of children yielding both virus and pathogenic bacterium. In the double-negative group there was no

significant difference in this respect between the children giving positive antibody response to one or another of the viruses under study on the one hand and the children either seronegative or not tested for antibody response on the other.

In Table V the virologically positive cases are subdivided according to the isolated virus. Upper respiratory catarrh was frequent, irrespec-

tive of the virus (except for parainfluenza type 3 infections which were less frequently associated with upper respiratory catarrh). The lower respiratory tract was affected in about half of the cases; in accordance with literary data, bronchitis occurred most frequently (66 per cent) in the group yielding RS virus. Bronchopneumonia was somewhat more frequent in the RS and adenovirus groups than

TABLE VI  
Recurrent attacks in three children

Case No.	Initials	Attack	Age, month	Clinical category	Virus isolated	Antibody response*	Complication
1	N. Zs.	1st	10	II	No	Parainfl. 2 0/32	Pharyngitis, bronchitis, otitis media
		2nd	11	II	Adenovirus	N. t.**	Bronchitis, otitis media Bronchopneumonia, Empyema
2	D. G.	1st	9	I	No	Parainfl. 3 0/64	Pharyngitis, bronchitis
		2nd	12	II	Parainfl. 3	N. t.	Pharyngitis, bronchitis lymphadenitis
		3rd	16	III	RS	N. t.	Rhinitis, pharyngitis, bronchitis
3	B. A.	1st	49	III	No	N. t.	Pharyngitis, lymphadenitis
		2nd	50	II	Parainfl. 3	N. t.	Spastic bronchitis
		3rd	51	II	No	N. t.	Spastic bronchitis
		4th	52	II	Parainfl. 3	N. t.	Spastic bronchitis Empyema sinus maxillaris

\* Numerator: reciprocal of the acute-phase titre, denominator: reciprocal of the convalescent-phase titre

\*\* Not tested

elsewhere. The incidence of otitis media showed no relationship to the shedded virus (extreme values, 5.6 and 7.1 per cent), whereas most of the lymphadenitic complications occurred in association with adenovirus infections.

*Recurrent attacks of pseudocroup.* The numerical data of recurrent attacks have been presented in the introduction. In Table VI virological and clinical characterization of three recurrent cases is presented. These were twice, three times and four times, respectively, admitted with a diagnosis of pseudocroup during the one-year period of this study.

*Case No. 1.* Two attacks occurred at an interval of one month. During the first attack parainfluenza type 2 infection was evidenced serologically, during the second attack adenovirus was isolated.

*Case No. 2.* Three attacks occurred at three-month and four-month intervals. During the first attack the infant gave a significant antibody response to parainfluenza virus type 3. During the second attack the patient harboured parainfluenza type 3 virus despite the still persisting homotypic antibodies. At the third admission RS virus was isolated.

*Case No. 3.* Four attacks of stenosis mainly spastic in character occurred within four months. The attacks subsided soon. At the second and fourth admissions parainfluenza type 3 virus was isolated. On the other two occasions we failed to isolate virus. Unfortunately, convalescent-phase serum samples were not tested in this case.

Cases No 1 and No 3 confirm the literary data, suggesting that the circulating antibody does not exclude homotypic reinfection.

It should be noted that case No 3 showed spastic bronchitis at each of the second, third and fourth admissions. On the last occasion X-ray examination showed empyema in the maxillary sinus. Since this had been cured by appropriate therapy, no further attacks of pseudocroup have occurred.

*Possible role of constitutional factors.* Pseudocroup often develops without hyperthermia and catarrhal symptoms. Occasionally neither virus nor pathogenic bacterium can be isolated. For this reason we have concentrated upon the constitutional factors: exudative diathesis (pasty constitution) and eosinophilia, both being considered to be allergic phenomena. Pasty constitution was found in 10.5 per cent and in this respect there was no difference between primary and recurrent cases. Eosinophilia ( $\geq 3$  per cent eosinophils) was found in 16 per cent.

*Differential diagnosis.* From the differential-diagnostic point of view diphtheritic croup raised no problem, for we had observed no such case during the preceding 10 years. In a single case differentiation from foreign body aspiration presented a problem.

*Therapy.* In general, complete rest is of great importance. Interventions, except the most important ones, should be omitted. (We endoscoped only in doubtful cases, when a correct diagnosis could not be established otherwise.)

In the mildest cases, including all the 48 cases of group I, 28 per cent of group II and 4 per cent of group



III, only sedatives, expectorants and humidifying of the air were applied. The cases with more pronounced inflammatory symptoms were given antibiotics, first of all penicillin or penicillin combined with streptomycin. In more severe cases wide spectrum antibiotics were administered.

The use of cortisone in 44 per cent of the children of group III and in 77 per cent of those of group IV rendered tracheotomy unnecessary in the most severe cases except nine (group IV). Cardiac drugs were administered to 8 cases of group III and 7 cases of group IV.

#### DISCUSSION

The present studies contributed further data to the viral aetiology of the pseudocroup syndrome. The clinical picture connected with this syndrome may be considered homogeneous albeit the aetiology is as variable as that of aseptic meningitis.

In accordance with literary data, in different seasons of the one-year period under study different viruses were predominant in the pseudocroup cases [17]. From the severity of illness no conclusion could be drawn concerning the causative virus. Nevertheless, involvement of the lower respiratory tract was more frequent in infections with RS virus than with other viruses or in cases yielding no virus.

Exudative or allergic diathesis appeared to be of minor importance in pseudocroup. Nevertheless, the con-

siderable frequency of recurrent cases support the view that there are some predisposing factors leading to the pseudocroup syndrome in the course of infections due to any of the incriminated viruses.

According to our experience there exists a positive correlation between the time elapsing between the first catarrhal symptoms and the appearance of stenotic symptoms, on the one hand, and the severity of the clinical course, on the other.

The presence of pathogenic bacteria in a considerable proportion of the cases calls for antibiotic therapy, particularly in febrile pseudocroup attacks affecting infants and young children.

\*

*Acknowledgements.* The author is indebted to Dr. Margaret Tóth for rendering the virological results available, to Drs. E. Farkas and I. Dömök (National Institute of Public Health, Budapest) for advices and criticism, to Dr. Sz. Bognár for bacteriological examinations, to Miss E. Nyitrai for assistance in taking samples and to Miss E. Schlitter and Miss E. Budai for excellent technical assistance in the virological work.

#### SUMMARY

In the one-year period beginning in November, 1963, 416 infants and young children showing the pseudocroup syndrome were admitted. Virus isolation was attempted from each of the cases, taking throat swabs at the time of admission. Two hundred and sixty-one virus strains were iso-

lated. There was no significant relationship between the isolated virus and the clinical manifestations, except that the lower respiratory tract was involved in a higher percentage in the cases yielding RS virus. Positive correlation was found between the length of the interval between

the onset of catarrhal symptoms and the appearance of stenotic manifestations, on the one hand, and the severity of the clinical course, on the other. The role of predisposing factors and associated bacterial infections and their antibiotic treatment are discussed.

## REFERENCES

- BRUČKOVÁ, M., SYRÚČEK, L., SOBE-SLAVSKY, O., SAMÁNKOVÁ, L.: Príspevek k ekológii respiračného sycyciálného vírusu v Československu. *Čs. Epidemiol.* **14**, 136—142 (1965)
- BUKRINSKAYA, A. G., BLUMENTAL, K. V.: Role of parainfluenza HA 2 virus in the etiology of pseudocroup in Moscow. Abstracts of papers presented at the Congress on Respiratory Tract Diseases of Virus and Rickettsial Origin. Prague 1961 p. 45.
- CHANOCK, R. M., PARROTT, R. H., JOHNSON, K. M., KAPIKIAN, A. Z., BELL, J. A.: Myxoviruses: Parainfluenza. *Amer. Rev. resp. Dis.* **88**, 152 (1963)
- CHANOCK, R. M., PARROTT, R. H.: Acute respiratory disease in infancy and childhood: present understanding and prospects for prevention. *Pediatrics* **36**, 21—39 (1965)
- CLARKE, S. K. R., CORNER, B. D., CAMBIER, D. M., MACRAE, J., PEACOCK, D. B.: Viruses associated with acute respiratory infections. *Brit. med. J.* **1**, 1536 (1964)
- FERRIS, A. A.: The croup viruses: bacteriological aspects. *Med. J. Aust.* **2**, 768 (1960)
- FORBES, J. A.: Croup viruses: clinical aspects. *Med. J. Aust.* **2**, 769 (1960)
- HENRY, G., CRAMBLETT, M. D.: Croup — Present Day Concept. *Pediatrics* **25**, 1071—1076 (1960)
- HILLEMAN, M. R., HAMPARIAN, V. V., KETLER, A., REILLY, C. M., MCCLELLAND, L., CORNFELD, D., STOKES, J. JR.: Acute respiratory illnesses among children and adults. *J. Amer. med. Ass.* **180**, 445 (1962)
- LANG, W. R., HOWDEN, C. W., COSTELLO, J. M.: Respiratory disease associated with parainfluenza and RS virus. *N. Z. med. J.* **63**, 508—510 (1964)
- LEWIS, F. A., LEHMAN, N. I., FERRIS, A. A.: The hemadsorption viruses in laryngotracheobronchitis. *Med. I. Ant.* **2**, 929 (1961)
- MCLEAN, D. M., ROY, T. E., O'BRIEN, M. J., WYLIE, J. C., MCQUEEN, E. J.: Parainfluenza viruses in association with acute laryngotracheobronchitis, Toronto 1960—1961. *Canad. med. Ass. J.* **85**, 290 (1961)
- MCLEAN, D. M., BACH, R. D., LARKE, R. P. B., MCNAUGHTON, G. A.: Myxoviruses associated with acute laryngotracheobronchitis in Toronto 1962—1963. *Canad. med. Ass. J.* **89**, 1257—1259 (1963)
- PARROTT *et al.*: Serious respiratory tract illness as result of Asian influenza and influenza B infections in children. *J. Pediat.* **61**, 205 (1962)
- PARROTT, R. H., VARGOSKO, A. J., KIM, H. V., CHANOCK, R. M.: Clinical syndromes among children. *Amer. Rev. resp. Dis.* **88**, 152 (1963)
- PHILIPSON, L.: Aetiology of nondiphtheritic croup. *Virologic investigation. Acta paediat. (Stockh)* **47**:4, (1958)
- TÓTH, M., MAJOR, V.: Virological investigation of hospitalized cases of pseudocroup and acute laryngotracheobronchitis. *Acta microbiol. Acad. Sci. Hung.* **12**, 189 (1965)
- TYRRELL, D. A. J.: Discovering and defining the etiology of acute respiratory viral disease. *Amer. Rev. resp. Dis.* **88**, 77 (1963)
- VAN DER VEEN, J., SMEUR, F. A. A. M.: Infections with parainfluenza viruses in children with respiratory illnesses in Holland. *Amer. J. Hyg.* **74**, 326 (1961)

Dr. V. MAJOR  
Gyáli út 5,  
Budapest IX., Hungary