CROUP is a syndrome in which there is inspiratory stridor, cough and hoarseness, due to varying degrees of laryngeal obstruction. A schematic representation of the pathogeneses of croup is presented in Figure 1. In an individual case, the clinical manifestations of croup may be entirely the result of spasm or edema or any combination of the two. Further, a foreign body or extrinsic mass which encroaches upon the laryngeal airway may be accompanied by varying degrees of spasm and edema. In addition to the larynx, the rhinopharynx and tracheobronchial tree may be simultaneously involved if the basic etiology is infectious.

CLASSIFICATION OF ETIOLOGY

For the purposes of this discussion, the etiology of the croup syndrome will be considered as being due to infectious, mechanical or allergic factors (Table I). Traditionally, most classifications of croup have included in addition another distinct category, i.e., "spasmodic" croup. Typically, this form of croup was described as developing suddenly at night, tending to be recurrent and usually associated with minor upper respiratory infection. This type of disease was said to be due to allergy or immaturity of the larynx and to occur in "the nervous type of child." No doubt a major portion of the laryngeal obstruction in this form of the disease is due to spasm with a lesser degree of actual subglottic edema. However, there is increasing evidence that the laryngeal spasm is apparently triggered by, and associated with, a preceding viral upper respiratory infection in a majority of cases. As an example, we have observed one child who has had three typical attacks of acute spas-
modic croup at the ages of 4, 11 and 29 months. The first attack was associated with infection with CA virus; the second, with Asian influenza; and the third, with ECHO type 13 infection. It does not seem tenable to make a sharp distinction between “infectious croup” and “spasmodic croup,” which implies that the latter is in no way related to infection.

PREDISPOSITION TO CROUP

Regardless of the direct precipitating cause of croup, there are a number of factors that are of importance in predisposing an individual child to the development of the syndrome. Even though some of these factors are poorly understood, they are worthy of consideration and are listed in Table II.

Age is an important factor. A majority of patients with croup are between the ages of 3 months and 3 years. An important exception to this is that Hemophilus influenzal and diphtheritic croup occur most commonly in children between the age of 3 and 7 years.1

The incidence of croup is higher among males than females. Even in children with postoperative or traumatic croup, the same sex incidence prevails.2 There is no obvious explanation for this.

Most cases of croup occur during the cold seasons of the year. This is in all probability a reflection of the increased incidence of respiratory infections in general during these periods.

All of the factors mentioned thus far that predispose to croup are ones which have been statistically proven by analysis of large series of cases. In addition to these, it has been postulated frequently that there are certain “endogenous factors” that predispose a given child to croup. Evidence for this includes the fact that croup tends to be recurrent in a child who has had one episode. Further, recent virologic studies reveal that all of the viruses which have been associated with croup cause other types of clinical diseases. There has been no one virus yet recovered which causes only croup. Why, then, does one 2-year-old child develop croup in association with a given viral infection while another child will have only a minor upper respiratory infection or involvement of the lower tracheobronchial tree without laryngeal involvement?

It has been postulated that an “anatomically defective larynx” or an “immaturity” of the larynx may be a factor. There is no evidence to suggest that these are important considerations. What constitutes the host factor in the pathogenesis of croup is unknown, but the concept must be accepted.

Evidence that “allergic” factors predis-
pose to development of croup is inconclusive. In one study, the family history of allergic disorders in children with croup and in a group of randomly selected children were analyzed. There was no difference. Among children with allergic diseases, there does not appear to be an increased incidence of croup.

**Clinical Observations**

Rabe made a significant contribution to the understanding of croup when he subdivided the "infectious" varieties into three types. In his detailed studies of 347 patients with "infectious croup," he was able to attribute only 14.7% to a bacterial etiology, i.e., Corynebacterium diphtheriae and Hemophilus influenza type B.

In the majority of the patients, a consistent bacterial pathogen was not cultured. The similarity of the "symptom complex, clinical course and living and morbid pathology" led him to speculate that this latter group of cases had a viral etiology. As a result of detailed clinical observations, he was able to suggest certain factors which help to differentiate croup due to Hemophilus influenza and Corynebacterium diphtheriae from that due to viral agents. In both forms of bacterial disease, the age of highest incidence was between 3 and 7 years. In diphtheritic croup, which is usually preceded by signs of an upper respiratory infection for 3 to 4 days, a membrane in the pharynx or serosanguinous nasal discharge is frequently present.

In croup due to Hemophilus influenza type B, the onset is quite rapid and follows by only a few hours the initial symptom of illness, usually a sore throat. The patients appear seriously ill out of proportion to the duration of the disease. There is marked supraglottic edema and the epiglottis is frequently fiery red in appearance and swollen. There is usually a leukocytosis with a predominance of polymorphonuclear cells.

All of the children with presumed viral infections gave a history of upper respiratory infection prior to development of croup. Although these children showed a varying degree of apprehension and restlessness, they did not show the same degree of toxemia as did children with disease due to Hemophilus influenza. The leukocyte count in patients with viral croup was usually only moderately elevated with a normal differential count. The age of highest incidence was less than 3 years.

**Recent Virologic Investigations**

With the improvement of laboratory and tissue-culture techniques in recent years further studies to elucidate the viral etiology of croup syndromes have been possible. The viruses that have been associated with croup are listed in Table III. Chanock and Beale et al. working independently reported the isolation of new viruses from the respiratory tracts of children with infections involving the larynx. It was established that these viruses, isolated separately in the United States and Canada, were antigenically similar. Chanock has designated this agent the CA (croup associated) virus and has shown it to have the characteristics of a myxovirus. The CA virus has also been recovered from sporadic cases of croup in other geographic areas including Iowa City, Boston, Washington and London. The total pathogenetic potential of this virus is as yet unknown.

During the influenza epidemic of 1918-1919, it became apparent that the same organism that caused influenza might also cause the croup syndrome. However, this was not verified until recently. During the epidemic of Asian influenza in Australia,

### Table III

**Viruses Associated with Croup**

<table>
<thead>
<tr>
<th>Viruses Demonstrated to Cause Croup</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA virus</td>
</tr>
<tr>
<td>Influenza virus</td>
</tr>
<tr>
<td>Hemadsorption virus type 2 (parainfluenza 1)</td>
</tr>
<tr>
<td>Viruses That May Cause Croup</td>
</tr>
<tr>
<td>Adenoviruses</td>
</tr>
<tr>
<td>Hemadsorption virus type 1 (parainfluenza 3)</td>
</tr>
<tr>
<td>CCA virus</td>
</tr>
<tr>
<td>U virus (ECHO 11)</td>
</tr>
<tr>
<td>? Any of recently described respiratory viruses</td>
</tr>
</tbody>
</table>
Fombesl3 observed 127 cases of croup in association with influenza infection. In recent studies by Vargosko and others11 in the Washington, D.C. area and Sabin and coworkers13 in Cincinnati, it was also shown that croup may result from infection with the Asian strain of influenza virus.

Chanock and others15, using the hemadsorption technique of Shelokov and Vogel,16 isolated two newly recognized myxoviruses. Their studies indicated that these viruses have an etiologic role in respiratory illnesses in children. More pertinent to this discussion is the fact that one of these agents, hemadsorption virus type 2 (parainfluenza type 1) was associated with 36% of the cases of croup during the study period. Hemadsorption virus type 1 (parainfluenza type 3) was recovered from a few patients with croup but the numbers were not great enough to give statistically significant results.

Various investigators have isolated different types of adenovirus from children with croup. Such data suggest that these viruses may be a cause of croup but more definitive studies in this regard are required.

The chimpanzee coryza agent17 and the "U" virus18 have been isolated from children with croup but additional data are necessary to establish an etiologic relationship.

It is to be anticipated that the importance of any one virus in the etiology of croup will vary from year to year, from geographic area to geographic area and perhaps from season to season. To pursue this further, I have obtained information from various medical centers regarding isolations of virus from patients with croup during the years 1957 to 1959. I am indebted to those investigators who supplied me with their data for this presentation. The concurrent viral infection in such patients was established by isolation of virus and/or appropriate serologic studies.

Extensive etiologic studies have been carried out in the Washington, D.C. area by Vargosko and others.11 Of 47 patients with croup, evidence of co-existing viral infection was found in 64%; 36% of the cases of croup were associated with infection by hemadsorption virus type 2, 19% with Asian influenza, and 9% with adenovirus, hemadsorption virus type 1 and CA virus.

In Cincinnati, 20 children with croup were studied virologically by Sabin et al.14 in the months of October and November, 1957. Sixteen (80%) had simultaneous viral infection; 11 of these were influenzal, 2 were hemadsorption virus type 1, 1 was hemadsorption virus type 2 and 2 had mixed influenzal and hemadsorption virus infections.

In Sweden, Philipson19 recovered adenovirus from sporadic cases of croup. Although numerous instances of hemadsorption virus infections have been observed in that country, none have been in patients with croup.

In London, likewise, Pereira12 recovered hemadsorption virus from hospitalized patients with acute respiratory disease, but none had croup. CA virus was isolated in six instances from children with croup.

Even though Sigel20 found evidence of frequent infections with hemadsorption viruses in Florida, he encountered no cases of croup.

Such information supports the earlier contention that infection with a certain virus is not sufficient in itself to produce croup. There must also be an important host factor.

In Boston, Kibnick1 reports the recovery of CA virus from four children with croup in 1957. Hemadsorption techniques were not used in testing his specimens.

In Iowa City during the past 2 years, we have isolated CA virus, influenza virus and ECHO virus type 13 from children with croup.

Because of the increasing number of viruses being isolated from specimens obtained from children, a word of caution is necessary regarding the assumption of an etiologic association between infection with such viruses and human illness. The mere isolation of a virus from an ill patient should not be interpreted as being of etiologic importance without substantiating evidence. The possibility of concurrent infection with another pathogenic agent must
be eliminated. Further, the virus should be isolated in widely separated geographic areas by different investigators from patients with similar illnesses. The same stringent criteria used to associate virus infection with other clinical syndromes should equally apply in "croup."

Undoubtedly studies in the future will yield yet other viruses that are associated with croup. If the original thesis is correct, that is, that croup may be due to many viruses, either directly or as a complication of the primary infection, then many of the presently recognized viruses may be found to cause the syndrome in future studies. In Table IV are listed some of the recently described viruses isolated from children with respiratory disease. In some instances a causal relationship with respiratory disease, and as already mentioned with croup in particular, has been established. In others, present data are not sufficient to establish such etiologic relationships. This tabulation is not intended to be all inclusive.

Virology, today, is a dynamic field. With improved laboratory techniques, gaps in our knowledge of viruses and their relationship to human disease are rapidly being lessened. Although reports of newer viruses are extensive and often confusing to those who are not actively working in the field, the information gained from these studies is being used systematically to clarify our approaches to future studies.

### Table IV
**Viruses Isolated from Patients with Respiratory Disease (Recently Described)**

<table>
<thead>
<tr>
<th>Virus Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza viruses (Asian strain)</td>
</tr>
<tr>
<td>Adenoviruses</td>
</tr>
<tr>
<td>Hemadsorption viruses</td>
</tr>
<tr>
<td>CA virus</td>
</tr>
<tr>
<td>ECHO 0 virus</td>
</tr>
<tr>
<td>JH virus</td>
</tr>
<tr>
<td>ECHO 20 (JV-1)</td>
</tr>
<tr>
<td>ECHO 10 (reoviruses)</td>
</tr>
<tr>
<td>U virus (ECHO 11)</td>
</tr>
<tr>
<td>CCA virus</td>
</tr>
<tr>
<td>HE virus</td>
</tr>
<tr>
<td>Coe virus</td>
</tr>
</tbody>
</table>

**TREATMENT**

A summary of therapy in relation to the pathogenesis of croup is presented in Figure 1. General supportive measures are important in the care of a child with croup. Since the patient is usually quite apprehensive, it is important that the child be kept as quiet as possible and that procedures be kept at a minimum. In selected instances, sedation may be quite helpful. The same caution should be exercised in administration of sedatives as is observed in any patient with respiratory difficulties.

Patients are benefited by being placed in an environment of high humidity. Although cool mist seems preferable to steam, the latter is also beneficial and is often the easier to use in the home.

If the child is quite apprehensive, it is best to give fluids intravenously at least for the first 24 hours. This obviates frequent arousal of the child, which may exaggerate symptoms.

In those instances in which spasm of the larynx predominates rather than edema, administration of syrup of ipecac may produce prompt relief of symptoms. It is assumed that ipecac has its relaxing effect upon the larynx by means of a vagal response. Ipecac is given in subemetic doses, but frequently the full therapeutic effect of the drug is not achieved without vomiting. Thus, any infant or child who receives ipecac should be closely observed in the hour following its administration to prevent aspiration of gastric contents in case emesis does occur. If symptoms subside, one can assume that the croup is largely on the basis of spasm and thus obtain valuable information without resorting to laryngoscopy. Aminophylline may also be of benefit in such patients.

As evidence has accumulated that croup is due to bacterial agents (chiefly Hemophilus influenza and Corynebacterium diphtheriae) in less than 20% of cases, it is apparent that antibiotics need only be given in selected instances. Thus, the child who rapidly develops fever and exhibits severe
toxicity out of proportion to duration of illness and is found to have a leukocytosis with increased percentage of polymorphonuclear cells should be considered to have the disease because of infection with Hemophilus influenza. Although chloramphenicol has been used most extensively in this situation, there are no controlled studies to indicate that it has any particular advantage over tetracycline. Certainly, in our experience, we have never encountered a strain of H. influenza which was resistant to tetracycline in vitro. If the disease is suspected to be due to C. diphtheriae, then penicillin or erythromycin given in conjunction with antitoxin is the treatment of choice. Other indications for the use of antibiotics occur in those patients in whom the disease is progressive and in whom secondary bacterial infection is considered to be an important factor. Administration of antibiotics to a patient with croup should never be a substitute for careful clinical observation.

The decision as to whether or not to perform a tracheotomy must always be based on the individual circumstances. If the signs and symptoms increase in spite of the aforementioned measures, then the procedure will be necessary. Extension of the inflammatory process further down into the tracheobronchial tree with increased secretions may likewise provide an indication. Careful timing of the procedure is important. Therefore, it is desirable to have an otolaryngologist see the patient as soon as possible after admission so that he may follow the progress of the disease carefully.

Lastly, I believe it is still premature to be speaking of viral vaccines for the prevention of croup. Future studies and much additional data are necessary before the importance of any one agent in the etiology of this disease can accurately be assessed.

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