PROPHYLAXIS OF THE ACUTE ASTHMATIC ATTACK IN INFANTS AND CHILDREN BY THE USE OF SYMPTOMATIC MEDICATION

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Presented in part to the Section on Allergy at the Annual Meeting, October 3, 1955.

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It is a matter of common observation than an asthmatic attack in children will often start with what appear to be symptoms of a “cold,” i.e., coryza or upper respiratory infection. It was early noted by one of us that while, in some instances, the onset of the asthmatic attack coincided with the onset of these symptoms, there was more often a variable interval of time, occasionally as long as several days, between the first premonitory symptoms of the “cold” and the beginning of the asthmatic attack. It seemed reasonable to suppose that if the “cold” could be adequately treated at its start, the asthmatic attack, which usually followed, might be aborted or perhaps reduced in severity and duration. However, with the medications then available (principally acetylsalicylic acid, atropine, codeine, papaverine hydrochloride, vasoconstricting nose drops, ephedrine, expectorants and the sulfonamide drugs) no significant success was obtained in the majority of cases.

BACKGROUND OF STUDIES

Brewster, reporting in 1949 on the effect of antihistamines in the therapy of the common cold, indicated that if such a drug were administered within the first hour after the onset of symptoms, the manifestations were aborted in about 90% of cases. The effectiveness of this method of prophylaxis decreased as the time interval between the onset of symptoms and the start of the antihistamine therapy increased.

Nevertheless, the symptoms were aborted in about 70% of the patients who received antihistamine therapy within 12 hours after the onset of symptoms.

In a small series of control cases treated with codeine and papaverine the results were very poor; 5 satisfactory results in 57 cases (about 10%). When the colds were not aborted by the antihistamines, the duration was often shortened, the severity decreased and complications reduced. Brewster also observed that even the mild, attenuated colds following antihistamine treatment conferred the usual immunity of 3 to 7 weeks which follows the common cold. Brewster felt that this method of treatment was effective because of the antiallergic effect of the antihistamine in the allergic-immunologic processes which start at the beginning of a cold.

Of Brewster’s 572 patients, only 74 (13%) were said to have suffered from some type of allergic disorder. As about 50% of the general population suffers or will suffer, from some form of major or minor allergy, it is quite likely that Brewster’s low figure represents either the result of dealing with carefully selected individuals (naval personnel) or an incomplete history.

As may well be imagined, Brewster’s publication evoked considerable interest. The common cold, according to Brewster, is estimated to cause a loss of 100 million days of work annually with a cost to the American public of between 2 and 3 billion dollars per year. Any procedure which might be effective in reducing this, particularly a simple procedure like the use of antihistamines, would be expected to be received with enthusiasm both by the medical profession and by the public. Indeed, this was what occurred. Sales of antihistamines rose to fantastic heights. Factories provided bowls of antihistaminic drugs which employees used by guest on January 1, 2018http://pediatrics.aappublications.org/Downloaded from
when it was thought that a cold was impending. Antihistamines were also provided without charge by some department stores and other commercial establishments for their customers. However, such promiscuous use of these powerful drugs, having an extremely large variety of disagreeable "side reactions," soon caused this procedure to fall into disrepute. Various more or less controlled studies testing Brewster's procedure appeared and these were summarized by Feller and associates and by Burrage, who concluded that the evidence that antihistamines could prevent the development of the common cold was inconclusive. In neither of these two studies was there any significant evidence that allergic individuals responded to this method of treatment any more favorably than others. Fortunately, our studies with the antihistamines were started before the publication of these discouraging reports.

The work of Brewster appeared to be particularly applicable to the type of patient in whom we are much interested, i.e., the child in whom the asthmatic attack is preceded by what appears to be an upper respiratory infection or "cold," and to those instances in which there is a distinct interval between the onset of symptoms of these and the onset of the asthmatic attack. The use of other measures commonly employed by us in the treatment of upper respiratory disorders and asthma also seemed desirable. However, it appeared essential to study in greater detail the exact nature of the prodromal symptoms of the asthmatic attack.

PATIENT MATERIAL AND PROCEDURE

Three hundred eighty-nine children 10 years of age or less, who suffered from bronchial asthma, were studied. They were unselected, except in so far as their records appeared serially in our files. Of these 389 children, there were 320 (82.2%) who showed prodromal symptoms of the asthmatic attack and 69 children (17.7%) who did not. Of the 320 children who showed prodromal symptoms, these were respiratory in nature in 294 (about 92%). Table I shows the nature of the respiratory symptoms. The most common symptoms were nasal discharge, sneezing and cough, commonly occurring in that order before the onset of the asthma, although these symptoms may occur simultaneously.

There was somewhat more variety to the nonrespiratory symptoms. These are tabulated in Table II. Curiously, most of these were ocular and resulted, for the most part, from edema of the conjunctivae. These symptoms are detailed in Table III.

The most common symptoms were tearing or watering of the eyes. Also occasionally noted by the parents was a peculiar, glassy, glaring or pale appearance of the eyes. The other nonrespiratory symptoms consisted chiefly of irritability, lassitude and fever, or combinations of these but, as indicated, a variety of other prodromal symptoms appeared.

### Table I

<table>
<thead>
<tr>
<th>Principle Respiratory Prodromal Symptoms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal discharge</td>
<td>180</td>
</tr>
<tr>
<td>Cough</td>
<td>104</td>
</tr>
<tr>
<td>Sneezing</td>
<td>99</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>28</td>
</tr>
<tr>
<td>Sore throat</td>
<td>12</td>
</tr>
<tr>
<td>Voice changes</td>
<td>7</td>
</tr>
<tr>
<td>Phlegm (mucus in throat)</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table II

<table>
<thead>
<tr>
<th>Nonrespiratory Prodromal Symptoms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td>90</td>
</tr>
<tr>
<td>Irritability</td>
<td>8</td>
</tr>
<tr>
<td>Lassitude</td>
<td>8</td>
</tr>
<tr>
<td>Fever</td>
<td>5</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
</tr>
<tr>
<td>Pallor</td>
<td>2</td>
</tr>
<tr>
<td>Enuresis</td>
<td>1</td>
</tr>
<tr>
<td>Stammering</td>
<td>1</td>
</tr>
<tr>
<td>Joint and muscle pains</td>
<td>1</td>
</tr>
<tr>
<td>Herpes labialis</td>
<td>1</td>
</tr>
<tr>
<td>&quot;Stomach ache&quot;</td>
<td>1</td>
</tr>
<tr>
<td>Otitis (pain in ear)</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table III

<table>
<thead>
<tr>
<th>Nonrespiratory Prodromal Symptoms (Ocular)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Glassy, glaring, staring, pale, peculiar&quot;</td>
<td>5</td>
</tr>
<tr>
<td>Tearing (watery eyes)</td>
<td>9</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3</td>
</tr>
<tr>
<td>Dark circles under eyes</td>
<td>2</td>
</tr>
<tr>
<td>Edema of eyelids</td>
<td>1</td>
</tr>
</tbody>
</table>
The prodromal symptoms were always determined by means of a carefully taken history at the time of the first visit. If the child did have prodromal symptoms, as occurs in over 80% of cases, regardless of their nature the parents were given instructions as described in Table IV. They were asked to study these carefully, and the instructions were then gone over with them in detail. The antihistamine used was given in liquid form to those children unable to swallow tablets or capsules; the nose drops could be any of the vasoconstricting preparations of the physician's choice; and the cough medication contained ephedrine or some similar sympathomimetic preparation. Details of the medications and dosage have been described.6

In our experience, the most common error in the use of antihistamines is to give infants and children too small a dose. Most physicians are accustomed to estimate dosage according to the age or weight of the patient, or, more recently according to surface area. While these methods are adequate for determining the initial trial dosage, as far as antihistamines are concerned, successful dosage, assuming the patient does not have an idiosyncrasy or allergy to the antihistamine, depends quantitatively on the severity of the condition. Logan,8 whose procedure is generally quoted, advocated Benadryl® in a dose of 4 mg/kg/24 hr. This is usually adequate. Most physicians prescribe smaller and less effective doses. Peterson and Bishop,10 on the other hand, administered as high as 16 mg/kg as single doses to small infants suffering from serum reactions. It must be remembered that, in the cases of allergic individuals whose responses to drugs cannot be predicted, the administration of any new drug is always an experiment. One must determine by experience not only the most suitable drug but also the optimum dose for each drug in each individual case.

### RESULTS

The results of this method of treatment are presented in Table V. It was felt that adequate co-operation by the parents was obtained in 174 cases (about 54%). The chief source of failure was inability of the parents to comprehend, despite repeated explanation, that the directions had to be followed exactly as given. Often, they would not give the medications immediately at the first prodromal symptom, no matter when or where it occurred, but would delay this until certain that asthma was developing. The most common explanation for delay was that they were not sure whether or not the child was actually having the prodromal symptoms they had previously described.

<table>
<thead>
<tr>
<th>Number</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Children studied</td>
<td>320</td>
</tr>
<tr>
<td>Adequate treatment and follow-up</td>
<td>174</td>
</tr>
<tr>
<td>Results satisfactory</td>
<td>168</td>
</tr>
<tr>
<td>Results unsatisfactory</td>
<td>6</td>
</tr>
</tbody>
</table>

* Complete abortion of asthmatic attack or very significant decrease in severity and duration.

Of the six failures, one developed attacks satisfactorily controlled by injection of epinephrine and five required hormone therapy for control.

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TABLE IV

**Instructions for the Prophylaxis of Asthmatic Attacks**

- **I.** Immediately, at the very first sign of an impending "cold" or asthmatic attack, which in this case is determined, means of a carefully taken history of cases, regardless of their nature, proceed as follows in an attempt to prevent the condition from progressing and developing into asthma:
  - A. Put the child to bed in a room as free as possible from house dust, feathers, wool, animals of all kinds with fur or feathers, and free from odors, particularly fresh paint, tobacco smoke, burning leaves, cooking, etc.
  - B. The following medications are to be started simultaneously and repeated every 4 hours the first 24 hours when the child is awake and thereafter as may appear desirable:
    - (a) An antihistamine:
    - (b) Nose drops: . . . . . . . drops into each nostril.
    - (c) One teaspoon of the cough mixture No. . . . . . .
      These medications must be started as soon as possible as a delay of even an hour mitigates against the best results.
  - II. Insert an aminophylline suppository every night at bedtime and repeat every 12 hours thereafter until the danger of an asthmatic attack is passed.
  - III. If the above measures fail to prevent or minimize the "cold" or asthmatic attack, then with the next episode, along with Items (a), (b) and (c) above, an antibiotic should be given. This will be prescribed by your doctor or from this office.
However, they had been told that in case of doubt the medications should be administered as this could do no harm and there was the possibility that considerable benefit might result. The second cause of failure was the fact that all the medications were not given simultaneously because the parents, again despite repeated explanations, did not grasp the import of this. They would commonly give one medication, wait and see the result and then, if the child was not doing well, give the next medication. Sometimes, this was due to the resistance of the child at taking medication. Many parents would also select one or two of the medications, usually those found the easiest to administer or those which seemed to them most appropriate for the prodromal symptoms presented, e.g., they would not give the cough mixture if there was no cough.

The use of an antibiotic was occasionally necessary. In such instances, it was believed possible that infection alone, or infection with allergy, was responsible for triggering the asthmatic attack.

In the 174 instances in which full cooperation was obtained, the results far exceeded our greatest expectations. They were satisfactory in 168 (96.4%) of cases. This refers to the individual patient studied and not to each individual attack of asthma. A satisfactory result was a complete prevention of the attack or a highly satisfactory decrease in its severity and duration. In the six failures, it was necessary to control the attacks in one by the injection of epinephrine, the remaining five required hormone therapy.

As the parents became expert in following the routine indicated in Table IV, it occasionally became apparent, particularly as the child improved, that the use of only the antihistamine was necessary. However, as in many instances, all the medications were necessary, we preferred that the parents at first follow the instructions exactly as given. Should failure occur after the use of this regimen plus antibiotics, the addition of hormone therapy (as prednisolone, adrenocorticotropin) should be considered in a prophylactic procedure. We have not as yet held the opinion that this is necessary in our cases.

**DISCUSSION**

The mechanism which produces the symptoms of an upper respiratory infection or coryza or an allergic reaction involving the nose, and also the initial symptoms of obstruction, sneezing and nasal discharge may be thought of in these terms:

1. The noxious agent, whether it be a virus, a bacterium or an allergen, first produces local tissue injury in the membrane of the upper respiratory tract.

2. As a result of tissue injury histamine is liberated.

3. Histamine acts on the capillaries of the involved tissues to produce dilatation which in turn causes congestion followed by edema. The symptoms mentioned above, sneezing, discharge and nasal obstruction, result.

4. If the initial tissue injury is produced by a living infectious agent, it may then invade the tissues and go on to produce the other symptoms of infection; purulent discharge and the systemic evidences.

5. If the tissue injury is produced by an allergen, the pathologic process may stop at this point (as it usually does in uncomplicated allergic rhinitis, e.g., that due to pollen) or the tissue injury may pave the way for complicating infection.

6. An infection, possibly by acting as a stress, can also reduce the threshold of reaction of the nasal mucous membranes, so that allergens which cause no disagreeable reactions under ordinary circumstances may react on the mucous membranes to cause further damage. This lowering of the threshold of sensitivity may also occur when the membranes are damaged by allergy instead of infection. Probably the most common example of this is the clinical sensitivity of some patients with pollinosis to house dust only during the pollen season.
It can be seen from the above that it may be difficult at times to know what should be attributed to allergy and what to infection. Under these circumstances, the nasal smear for eosinophils, as developed by Hansel is most important in the differentiation between an allergic and an infectious coryza, or the diagnosis of a combined allergic-infectious condition. It seems to be true that bacterial infection or bacterial allergy is probably a common and important cause of asthma in children as well as in adults. Whether this is due to bacteria acting as allergens or whether to infection lowering the threshold of sensitivity of the mucous membranes to non-bacterial allergens is, in the light of our present knowledge, more a matter of opinion than fact. Probably the fundamental difficulty in experimental study of bacterial allergy in man is that we must deal with dead bacteria (vaccines) rather than live bacteria; dead bacteria must possess allergenic properties different from those of living bacteria. What has been said about bacteria is probably true of viruses although our knowledge of allergy as regards viruses is even less than our knowledge of bacterial allergy.

Success in the method of prophylaxis of the asthmatic attack which has been discussed probably depends upon the neutralization of histamine produced at the time of initial injury to the respiratory mucus membrane by the antihistamine. The accessory measures probably reinforce this to a certain degree, not by the neutralization of histamine, but by suppressing edema.

**SUMMARY**

A highly satisfactory method of aborting or reducing the incidence and severity of most asthmatic attacks in infants and children is presented.

The *modus operandi* is discussed.

**REFERENCES**

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