

SENSITIZATION OF NASAL MUCOUS MEMBRANES TO BACTERIA

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BACTERIAL infection may cause "atopic" symptoms in children. Chobot¹ and his associates found it was an important cause of asthma in 87 per cent of the children they studied. In 50 per cent it was a contributory factor along with clinical sensitizations to foods and inhalants, but in 30 per cent was the only cause they could discover. Not all atopic children have asthma with their infections.² Some have only rhinitis and others rhinitis and bronchitis without frank asthmatic attacks. The symptoms of infection have been observed in children after colds which they have had in the winter. In some cases long intervals free of symptoms have intervened between epidemic infections, but in most cases interepidemic bacterial infections have been frequent all winter long. These infections have caused symptoms in either one of two ways: in some patients the respiratory mucous membranes have apparently been sensitized to bacteria, and in others infection has merely been an irritant which has enhanced the symptoms of a latent sensitization to some of the common allergens.³

The common respiratory bacteria, *Staphylococcus aureus*, hemolytic streptococcus, pneumococcus, *Streptococcus viridans*, *Micrococcus catarrhalis*, and the influenza bacillus have been cultured from the nasopharynx of patients with colds and with asthmatic attacks. The floras of these patients have always been fluid, never static.⁴ When cultures have been made from a patient in successive attacks of asthma occurring during the winter, the gram-positive cocci have been found in increasing numbers until late spring, then less and less frequently until August. This cycle has been repeated year after year. In cultures made during successive attacks in one of these patients, the same species or strains have not always been found in the nasopharynx in different attacks. In bacterial epidemic infections of the upper respiratory tract other than infections associated with asthma or colds, about one-half of the complications have been caused by some strain which has supplanted the one causing the initial infection.⁵ Nor have the floras of these complications always been stable. The species of bacteria found in sinus infections change, sometimes just as the sinus infection has become subacute, and often even in the established chronic infections.^{6, 7} Apparently bacteria cultured from the nasopharynx or foci of infection during one allergic attack may not be recovered in similar attacks occurring later. It has been impossible to predict just what the nasopharyngeal floras in these subsequent attacks may be.

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Because the floras have been so variable in patients with atopic respiratory disease, strains of all species of bacteria, enumerated in the preceding paragraph, commonly recovered from patients during infections causing allergic attacks have been included in therapeutic preparations.⁴ At times substitutions or additions have been made from autogenous cultures. Originally vaccines were used, but a mixture of filtrates of old cultures of the several species mentioned has been employed recently since they were found therapeutically superior to vaccines in comparative studies.

Although respiratory reactions have followed inoculations with vaccines, they have occurred more frequently at some level of dosage during therapeutic injections of filtrate. Depending on the degree of tolerance inoculations have been started in the early autumn with either a 1:1,000, a 1:100, or a 1:10 dilution of the mixed culture filtrates. The doses have then been increased gradually, but as rapidly as possible without causing severe local or focal reactions, up to one milliliter of the undiluted mixture. Most children have tolerated these inoculations very well, and well-defined reactions have not occurred until mid- or late winter when the doses were large. During this season when infections have been prevalent, it has been difficult to distinguish a reaction to an inoculation from a mild infection.

Although most children have been reasonably tolerant to fairly large doses of filtrate (0.5 ml. of undiluted mixture), about one in fifteen has had mild upper respiratory reactions to smaller doses. A few have been very sensitive with a critical dosage level which has been difficult to break through. As little as 0.05 ml. of a 1:100 dilution has caused upper respiratory reactions with mild fever. Reactions in the very sensitive children have occurred early in the fall when inoculations were first begun. At this time when respiratory infections have been less frequent than in the winter months, in children with a "critical level of dosage" several reactions have occurred before this level was broken through so that the doses could be increased. In a number of patients the inoculations have been given irregularly and control material has also been injected, so no question could be entertained regarding the causal relationship of the inoculations to the reactions.

In the last few years, observations to demonstrate the sensitization of the nasal mucous membranes to filtrates were started on thirty children. Only nine of the series were completed. These nine patients were seen in the spring and, because they had no symptoms during the summer, were advised to wait until September for treatment. When they were first seen all had had rhinitis during the past winter with exacerbations of infection at two- or three-week intervals. None had apparent clinical sensitizations to the common allergens. The mucous membranes were pale, swollen and boggy, and covered with a seromucoid discharge containing eosinophils. Six had had repeated attacks of bronchitis, and in three asthmatic râles had been heard during bronchitic attacks. Three of the children had had their tonsils and adenoids removed the previous spring. Cultures were made and filtrates were prepared in September. If reactions occurred following the first two or

three inoculations, a control injection was given followed by an additional dose of filtrate. Reactions were first noticed six to eight hours after an inoculation. The nasal passages were occluded and the membranes swollen and covered with a seromucoid discharge. There might be a cough, mild angina, and occasionally headache, and slight fever. The symptoms subsided in twenty-four to forty-eight hours. The significant reactions in the children have been tabulated and are shown in Table I.

TABLE I. UPPER RESPIRATORY REACTIONS TO FILTRATES

PATIENT AGE	REACTIONS							*SUBSTITU- TIONS AND ADDITIONS TO STOCK MIXTURE OF FILTRATES
	FIRST	SECOND		THIRD		FOURTH		
	DOSE DILUTION REACTION	DAYS	DOSE DILUTION REACTION	DAYS	DOSE DILUTION REACTION	DAYS	DOSE DILUTION REACTION	
J. S. 3 yr.	0.3 ml. 1 to 100 ++	8	0.4 ml. 1 to 100 +++	9	<i>Culture†</i> <i>Medium, 0.1</i> —	5	0.5 ml. 1 to 100 ++	1,6
M. R. 4 yr.	0.7 ml. 1 to 100 +++	6	<i>Culture†</i> <i>Medium, 0.1</i> —	7	0.7 ml. 1 to 100 ++			3
G. M. 5 yr.	0.1 ml. 1 to 10 ++	9	0.5 ml. 1 to 100 +	5	<i>Tetanus†</i> <i>Toxoid, 0.1</i> —	8	0.1 ml. 1 to 10 ++	3
F. A. R. 5 yr.	0.8 ml. 1 to 100 +++	7	0.5 ml. 1 to 100 +	8	<i>Tetanus†</i> <i>Toxoid, 0.1</i> —	7	0.8 ml. 1 to 100 ++	4,6
T. A. R. 5 yr.	0.2 ml. 1 to 100 ++	7	<i>Tetanus†</i> <i>Toxoid, 0.1</i> —	8	0.3 ml. 1 to 100 ++			4,6
M. L. 6 yr.	0.3 ml. 1 to 100 +++	10	0.2 ml. 1 to 100 ++	11	0.3 ml. 1 to 100 +	5	<i>Pertussis, 0.1</i> —	
F. U. 3 yr.	0.06 ml. 1 to 10 ++	7	0.4 ml. 1 to 100 +	7	<i>Diph.†</i> <i>Toxoid, 0.1</i> —		0.1 ml. 1 to 10 +++	
J. S. 3 yr.	0.8 ml. 1 to 100 +	6	<i>Tetanus†</i> <i>Toxoid, 0.1</i> —	14	0.1 ml. 1 to 10 +	14	0.3 ml. 1 to 10 ++	6
T. L. 5 yr.	0.3 ml. 1 to 10 +++	9	0.3 ml. 1 to 10 +	6	0.3 ml. 1 to 10 ++	10	<i>Diph.†</i> <i>Toxoid, 0.2</i> —	3

*A mixture of stock filtrates from cultures of selected strains of (1) *Streptococcus hemolyticus*, (2) *Streptococcus viridans*, (3) *Staphylococcus aureus*, (4) pneumococcus II, and (5) *Neisseria catarrhalis* was used in these inoculations. Substitutions of autogenous filtrates are indicated by the number.

Hemophilus influenzae was added only if found in cultures. This addition, 6, is italicized.

†Control inoculations are also in italics.

DISCUSSION

The upper respiratory mucous membranes of these children are hyper-sensitive to bacterial products in the polyvalent filtrates. The immunologic processes, such as immunity and sensitization, are apparently similar in these membranes to those in the skin. Two of the bacteria recovered frequently in the nasopharyngeal cultures cause recurrent dermal infections with sensitization of the affected areas to the nucleoproteins and filtrates of cultures

of these bacteria.⁸ They are *Streptococcus hemolyticus* causing erysipelas and *Staphylococcus aureus* found in certain erysipeloid infections. Erysipelas, which is more common and consequently has been studied more thoroughly, recurs in about 20 per cent of patients. There may be one, two, three, or even more reinfections of the same site. Local immunity to *Streptococcus hemolyticus* is effective for about three months to the type of the strain causing the infection.⁹ In these patients if the focus still harbors these cocci, reinfections may occur when this immunity is no longer protective. Infection advances along a raised margin with an accompanying severe general reaction, but successive attacks provoke milder and milder constitutional symptoms even though the local inflammation seems just as severe.

Bacteria are numerous in sections and cultures of the skin in the first two or three infections, but subsequently the inflammatory reaction is more diffuse. Then the streptococci are sparse and seldom can be found or recovered. The affected tissues are apparently so hypersensitive, that the sparse growth of a few avirulent bacteria may cause a disproportionately severe reaction. Each attack apparently leaves the area highly sensitized, because within a few days after the inflammation has resolved local cutaneous reactions have been positive and distant inoculations with streptococcal nucleoproteins or filtrates have caused regional edema, redness, and swelling. Similar reactions have been gotten with nucleoproteins and filtrates of staphylococcus in staphylococcal erysipeloid infections. Although chronic edema has been observed following several recurrences in skin which was normal when first infected, areas which are already edematous are especially susceptible to infection. Spontaneous reinfections may occur in these edematous tissues after the focus is sterile, suggesting that bacteria may lie inactive in the tissues between attacks. In patients specifically hyposensitized with filtrates of streptococcus or staphylococcus, reinfections have first been less frequent and severe and finally have ceased. Similar inoculations with polyvalent filtrates have prevented interepidemic rhinitis and bronchitis in children.²

In patients who are not atopic, filtrates of the cultures of the bacteria included in the polyvalent mixture, as well as the bacterial nucleoproteins, cause delayed tuberculin-like reactions if injected intradermally in those who are sensitive. These reactions vary from year to year, season to season, and month to month. In the late winter and spring more species cause reactions and the reactions are more intense than in the summer and early fall. The frequency with which positive reactions are obtained and their intensity has paralleled the incidence of the different species in nasopharyngeal cultures, but in these cultures the species vary greatly, and often no one species is found in such predominance that its occurrence in a culture can be correlated with the corresponding dermal reaction. Only when a species has been predominant and has been the cause of subacute or acute symptoms can a definite correlation be established. Minimal and subclinical infections must occur during the course of a winter. The behavior of these dermal reactions—the haphazard appearance and disappearance of positive reactions to different

bacteria, the occurrence of positive tests remaining positive for only a few weeks or two or three months, the varying intensity of those lasting through a winter, and the seasonal variations of those which recur year after year—can be explained in no other way.¹⁰

An immediate wheal and flare has been observed occasionally in atopic patients with staphylococcus¹¹ tetanus, diphtheria toxins or toxoids and with tuberculin.¹² The antibody which passively transfers the immediate reaction to diphtheria toxin appears to be similar to the “passive transfer antibody” in the serum of patients with pollenosis.¹³ Although typical immediate reactions have been observed with the nucleoproteins and atoxic filtrates of the upper respiratory bacteria in atopic patients, edema at the site of a dermal injection intermediate in type between the immediate wheal and flare reaction and the delayed tuberculin-like reaction has been seen more frequently. This intermediate reaction has appeared to be a modified tuberculin reaction and has not been passively transferred with the patient's serum.¹⁰ All three reactions, the wheal, the intermediate, and the delayed, occur in atopic patients, but the last two are by far the most common.

Local hypersensitization of the mucous membranes and cutaneous sensitizations to the nucleoproteins and culture filtrates of the common respiratory bacteria seem analogous in many ways to sensitizations occurring with tubercle bacilli. Infections with tubercle bacilli, even though minimal and subclinical, cause permanent sensitizations. This sensitization is most intense at the site of the lesion, but other sites, including the skin, become sensitive to a lesser degree. The sensitization varies with the activity of the infection, and can be detected with purified proteins obtained from the bacillary bodies or with tuberculin prepared from heated old cultures or from unheated culture, filtrates. Although inoculations of living or dead bacilli or of proteins carefully extracted from the bacilli will sensitize, especially when injected with adjuvants, the tuberculins, both O.T. and N.T., are nonantigenic. However, these tuberculins cause local and focal reactions in sensitive patients and will desensitize them if given in gradually increasing doses. These tuberculins are prepared from old cultures and some are heated. It is probable that they are not antigenic because the bacterial proteins are denatured or largely disintegrated.

The proteins isolated from tubercle bacilli contain more or less nucleic acid¹⁴ and are presumably nucleoproteins or degraded and disintegrated nucleoprotein fractions. These protein fractions as well as those isolated from unheated culture filtrates if given in sufficient concentration¹⁵ are antigenic and will sensitize and give typical tuberculin cutaneous reactions.¹⁶ Presumably these reactions are similar to those produced with pneumococcus nucleoprotein,¹⁷ and with filtrates of hemolytic streptococcus¹⁸ and *Staphylococcus aureus* which will sensitize, and then if inoculations are continued cause desensitization. These reactions seem to be characteristic of the bacterial nucleoproteins or of disintegrated, degraded, or denatured protein fractions in the filtrates.

CONCLUSIONS

In previous studies of recurrent infections of the skin with *Streptococcus hemolyticus* and *Staphylococcus aureus* the infected areas have been hypersensitive to the nucleoproteins and culture filtrates of these bacteria. Evidence is offered suggesting that the nasal mucous membranes of atopic children with recurrent bacterial rhinitis are similarly sensitized to the upper respiratory bacteria.

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