Treatment of Allergic Rhinitis*

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Allergic rhinitis is characterized by repeated attacks of sneezing, itching of the nose, profuse watery secretion, and nasal obstruction. These symptoms are frequently associated with eye symptom, asthmatic attack, headache, general fatigue and so on.

On the basis of our intensive studies, we consider this disease to have the following three-step mechanism:[1-7] First, antigenic chemical substance is eluted from allergen particles deposited on the nasal mucosal surface, and reacts with the sensitized basophilic cells on the same surface, causing the release of chemical mediators of allergy. Second, the released mediators stimulate the endings of the sensory nerves close to the basement membrane of the epithelium or in the epithelium itself, thereby producing sneezing and nasal discharge by nervous reflex. Third, the mediators are absorbed in the submucosa and act directly on the blood vessels, causing swelling of the nasal mucosa (Figs. 1 and 2).

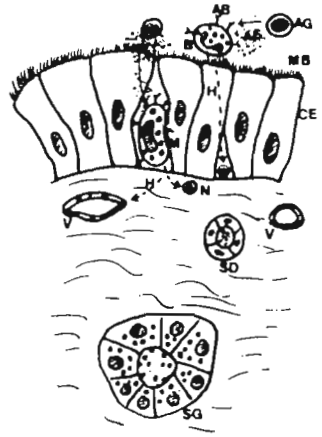
On the basis of the above concept, allergic rhinitis should be treated as reviewed in the following passages.

1. Treatments directed against contact of antigenic substance with basophilic cells on the mucosal surface

Removal of antigen from the patient's environment as well as prevention of antigen inhalation must be the most important therapy for allergic rhinitis.

Cleaning of the house and use of acaricides in cases of mite allergy, avoiding pollen floating areas in cases of pollinosis, improving the ventilation in cases of occupational allergy, elimination of pets in cases of allergy to pets and so on, are examples of remedial measures of which the importance must be emphasized. But complete avoidance of antigen is usually difficult in practice. Patients often decline to use nose masks owing to the accompanying unpleasant feeling. In spite of the difficulties all attempts should be made to minimize contact with antigen as much as possible.

Even if antigen particles are inhaled and deposited on the mucous blanket, allergic reaction does not occur without elution and diffusion of the antigenic substance from antigen particles. In order to minimize this elution and diffusion, nasal secretion must be viscid, since the antigenic substance is more easily solubilized in a watery secretion than in a viscid; the secretion becomes watery as a result of over-irritation to the secretory nerve of the nose.[8] To suppress this hypersecretion, cholinergic blockade or adrenergic stimulant is useful, and actually anti-histamine, topical cholinergic blockade, ipratropium (Hoechst, West Germany),[9] and vasoconstricting nose drops are available. According to our recent unpublished study, however, pretreatment with an α-stimulant suppressed an increase in nasal resistance only during nasal provocation with antigen, but not in nasal discharge and sneezing, while those with cholinergic blockade only an increase in nasal discharge. (Figs. 3 and 4). These results indicate that viscosity of nasal secretion may not be so important in controlling the onset of disease.



AG: Antigen particle
AS: Antigenic substance
AB: IgE antibody
B: Basophil
CE: Ciliated epithelium
MB: Mucous blanket
H: Histamine
N: Nerve ending
SG: Secretory gland
SD: Secretory duct

Fig. 1 Illustration of mechanisms in nasal manifestation of allergy, which is triggered by antigen-antibody reaction on the nasal mucosal surface. See Fig. 2 and text.

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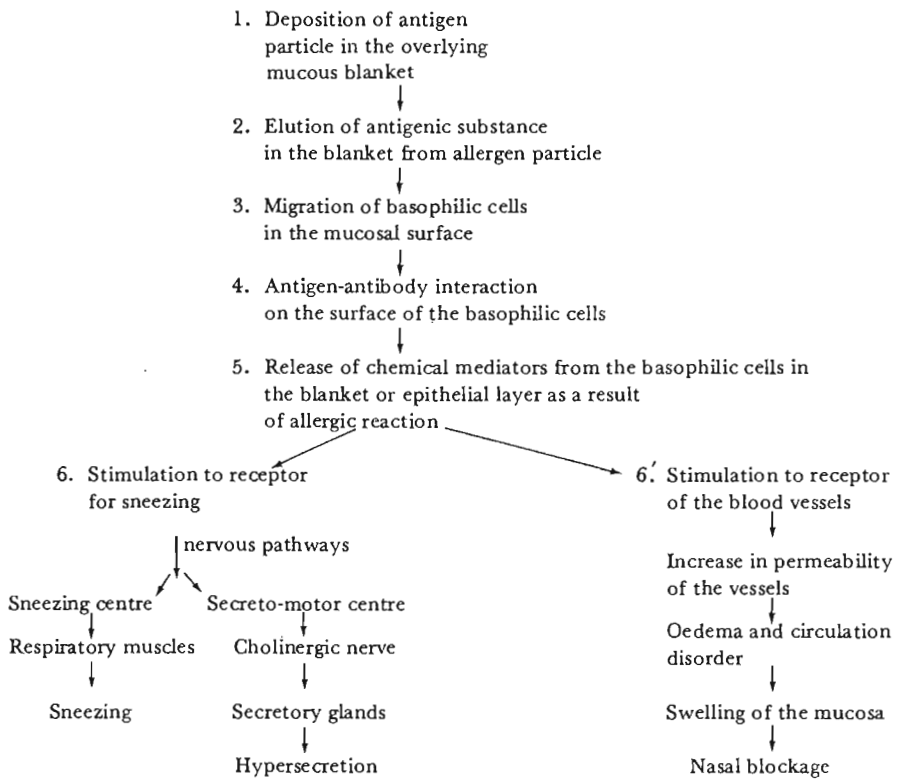


Fig. 2 Different steps of mechanisms in nasal allergy. See Fig. 1 and text.

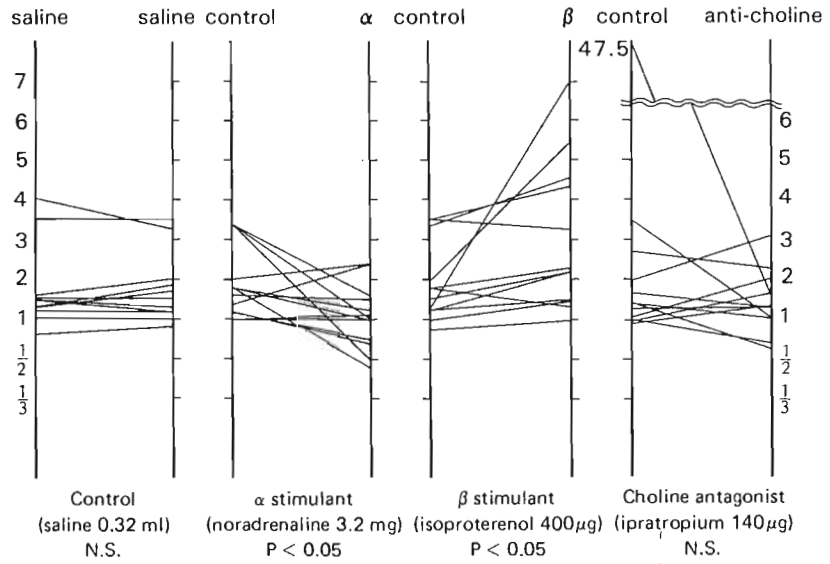


Fig. 3 Effects of α-, β-stimulants and choline antagonist on the increase in nasal airway resistance induced by nasal provocation with antigen. Fifteen minutes after spraying with saline (control), nor-adrenaline (3.2mg), isoproterenol (400 μg) or ipratropium (140 μg), the nasal mucosa was provoked with antigen. Nasal airway resistances was measured before and after provocation, and the ratios: post-/pre-provocation with saline perse and with drug were calculated. α-stimulant inhibited the increase, while β-stimulant promoted.

Even if the antigenic substance is eluted, allergic nasal reaction is not produced without an accumulation of the sensitized basophilic cells on the mucosal surface. These cells may be attracted by a specific chemotactic factor, which is reported to be C5a, a fragment of C5, or a component of lymphokine, but the details are still not well understood.[10,11] Therefore, at present we have no way to destroy or inactivate the chemotactic factor of the basophilic cells. These cells, however, are reduced in number in the mucosal surface during the long-term immunotherapy with specific antigen[3] (Fig. 5) or continuous use of topical steroid,[12] as the nasal symptom is improved (Table 1).

Even if the basophilic cells are accumulated on the mucosal surface, allergic reaction is not produced without contact of antigenic substance with the cells. It has been generally accepted that during a long-term immunotherapy, an antigen-specific IgG antibody (so-called blocking antibody) is increased in the serum and blocks the combination of IgE antibody with antigen. This blocking must occur in the nasal mucous layer rather than in the serum. Actually this blocking antibody increased in the nasal secretion and has a binding capacity for antigen when determined by the double-antibody technique.[13] The amount, however, is not sufficient to exert its blocking effect, since the nasal fluid: serum ratio was only 0.057 (Table 2). That is the reason why local immunotherapy attracts the interest of many investigators, who expect a large increase in the amount of secretory IgA, specific to antigen, in the nasal secretion, but the results of these trials are still controversial.[14]

2. Treatments directed against mediators release from the basophilic cells

Even if the basophilic cells are combined with antigenic substance, allergic tissue reaction is not produced when the release of media-

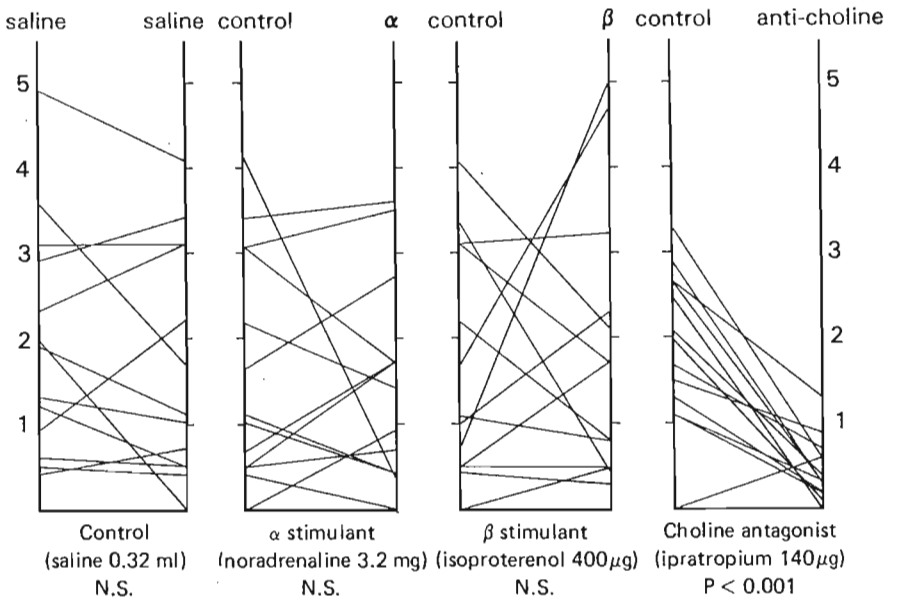


Fig. 4 Effects of α-, β-stimulants and choline-antagonist on increase in nasal secretion induced by nasal provocation with antigen. Experimental design was similar to that in Fig. 3. Instead of nasal air-way resistance nasal secretion was measured. Only choline antagonist inhibited increase in nasal secretion.

Table 1 Changes in basophilic cell counts in nasal scrapings during treatments. Beclomethasone dipropionate (4 sprays a day), disodium cromoglycate (4 capsules a day), α-chlorpheniramine maleate (2 tablets a day) or saline (4 sprays a day) were given to house-dust nasal allergy patients for 2 weeks. Basophilic cells were counted and the numbers compared before and after treatments. Only beclomethasone reduced the cell number.

	N	Increased	Unchanged	Decreased	
Bdp	28	1	9	18	**
DSCG	26	5	14	7	
H_1-blockade	25	3	12	10	
Control	26	5	14	7	

**P < 0.01 (U-test)

Table 2 Nasal fluid/serum ratio in the amounts of total immunoglobulins and specific antibody against mite. The ratio was the greatest in IgA. It was only 0.057 in IgG antibody, showing that the amount of antibody may be insufficient to block the interaction of IgE antibody with antigen.

	NF/Serum ratio		
	IgA	IgG	IgE
Specific antibody to mite	0.865	0.057	0.447
Total immunoglobulin	0.310	0.016	0.053

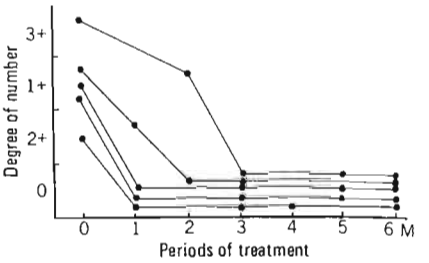


Fig. 5 Changes in the number of basophilic cells in nasal secretion during immunotherapy with house dust antigen. The number of cells decreased as the symptom improved.

tors from the basophilic cells is inhibited. The mediator release is possibly influenced by such factors as the number of IgE receptors of the basophilic cell surface, enzymic process in the cell after interaction of receptor with antigen, and production and storing of the chemical mediators in the cell. This mediator release is known to be inhibited by topical insufflation of disodium cromoglycate.[15] However, our recent studies indicate that the nasal surface basophilic cells are only slightly sensitive to this drug as the mucosal mast cells are,[16] and monoamine oxidase inhibitors, at low concentrations, have a dose-related inhibition of anti-IgE-induced histamine release from human lung fragment.[17]

Recently β-adrenergic stimulant has been shown to inhibit *in vitro* IgE dependent histamine release from the basophilic cells through augmentation of intra-cellular level of cyclic AMP (adenosine monophosphate). Further, many β-stimulating drugs such as terbutaline, fenoterol, salbutamol, isoprenaline and KWD2 have been applied to the allergic nasal mucosa without any constant result.[18] A long-term immunotherapy also induces the reduction of antigen-induced histamine released from the basophils.[19]

3. Treatment against stimulation of chemical mediators to target tissues

Even if a considerable amount of histamine is released as a result of

antigen-antibody interaction, allergic tissue response is not produced when free-type histamine is combined with protein immediately after histamine release, and before its stimulation of the nasal tissue. According to Parrot, histamine-binding capacity of the serum is reduced in atopic patients, and is normalized by injection with histamine-gammaglobulin compound, improving the clinical symptom of allergy.[20] Continuous topical use of this compound reduced nasal sensitivity to histamine and antigen, and inhibited the mediator release from the surface basophilic cells, as found in our recent preliminary study.

Even if histamine is released and stimulates the tissue, nasal response is not elicited when nasal sensitivity to histamine is suppressed. It has generally been agreed that the histamine sensitivity of the nose is increased in allergic rhinitis, and that the degree of nasal response to antigen was well correlated with the nasal histamine sensitivity.[21] Since the hypersensitivity to histamine is established by the increased sensitivity of histamine receptors for sneezing in the epithelium or close to the basement mambrane of the epithelium and of that of the blood vessels, anti-histamines, H_1-antagonist, are useful in suppressing the hypersensitivity to histamine, and are believed to act by competing with histamine in occupying the histamine receptors. This is not the case with other anti-allergic drugs such as disodium cromoglycate and beclomethasone[12] (Table 3). The inhibitory effect of H_1 antagonist, however, is insufficient to affect the increased permeability of the blood vessels, which is induced by the direct stimulation of histamine on the receptors in the blood vessels. Recently it was reported that combined use of H_1 and H_2 antagonists is effective in bringing about the inhibition.[22]

In addition, the histamine hypersensitivity is influenced by the conditions of the nervous pathways of the nose including the sensory and autonomic nervous systems.[21] Therefore, sedatives and drugs normalizing the disorder of the autonomic nervous system are used widely for the treatment of allergic rhinitis. Asthremedin, a Japanese product, is made from inflammatory tissue of rabbit skin into which cowpox virus was inoculated and is widely used in Japan as an anti-allergic drug. Intracutaneous injection of this drug also improved the nasal symptom, reducing the histamine sensitivity of the nose.[23]

Topical use of drugs for the autonomic nerve is applicable in the treatment of allergic rhinitis. Topical α_1-adrenergic stimulants such as phenylethylamine and imidazoline derivatives are effective in reducing nasal blockage through vasoconstriction, and parasympathetic blockade; ipratropium and atropine inhibit hypersecretion without any change of nasal airway resistance[9] (Fig. 2), since in the nose α_1-adrenergic fibres are predominant around the blood vessels, and cholinergic fibres are the same around the secretory glands. Effect of β-adrenergic stimulants on the nose, however, is still controversial. Psychosomatic treatment may contribute to the histamine sensitivity.

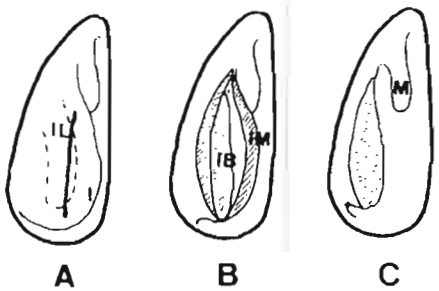
4. Surgical treatments

Surgical removal of the nasal mucous membrane or dissection of the nervous pathway is also effective in relieving the allergic nasal symptoms. Removal of the nasal mucosa, so extensive as to impair nasal function, should be avoided, even when it is effective in reducing the nasal symptoms. The present author has frequently relieved a persisting nasal blockage as well as sneezing and discharge in allergic patients by wide removal of the whole mucosa of the septal side of the inferior turbinate (Fig. 6). Approximately one month after the operation the inferior turbinate is re-epithelialized with minimum regeneration of secretory glands and vessels, resulting in a decrease in histamine sensitivity and the preservation of the normal ciliary function.[24] The dissection of the vidian

Table 3 Changes in nasal histamine sensitivity during treatment. The method of drug administration is the same as that in Table 1. Nasal histamine sensitivity was determined by the end-point test. Only α-chlorpheniramine maleate reduced the sensitivity.

	N	Increased	Unchanged	Decreased	
Bdp	26	8	12	6	
DSCG	29	6	14	9	
H_1-blockade	29	1	2	26	**
Control	29	12	11	6	**

**P < 0.01 (U-test)



A: vertical incision of the anterior portion of the inferior turbinate mucosa. B: Separation of the mucosa on the septal side from the bony structure of the inferior turbinate. C: Removal of the mucosa. I: inferior turbinate. IL: Incision line. IB: Inferior turbinate bone. IM: Inferior turbinate mucosa. M: Middle turbinate.

Fig. 6 Surgical method for wide resection of the hypertrophic inferior turbinate mucosa.

nerve supplying parasympathetic fibres to the nasal mucosa was first proposed by Golding-Wood for relieving the profuse watery secretion of vasomotor rhinitis.[25] This operation can abolish hypersecretion of the nose completely, but cannot affect sneezing and nasal blockade, if the sensory nerve in the pterygopalatine fossa is not injured. Since few allergy patients complain of hypersecretion only, and many drugs are available for reducing hypersecretion, the application of this operation for allergic rhinitis should be strictly limited. Additional reason of the strict limitation of indication is that this operation inevitably inhibits tear secretion as well as nasal secretion, with a possibility of inducing keratoconjunctivitis sicca as seen in Sjögren's syndrome.

5. Symptomatic treatment

If allergic nasal symptom occurs, symptomatic treatment should be instituted, using medicines with an immediate effect.

When used topically, α-adrenergic stimulants successfully decrease the nasal blockage, and cholinergic blockades inhibit the nasal secretion. Anti-histamines (H_1-antagonists) are also recommendable for their quick effect.

Per-oral administration of corticosteroids should be limited to patients whose symptom is resistant against other medications, and appears diffusely in the body as well as the nose. In addition, we cannot expect a quick response to steroids. Topical use of beclomethasone, flunisolide, or budisonide is preferable to systemic administration because of the minimum side-effects.

Summary

The nasal manifestation of allergy on the muscosal surface is triggered by a number of mechanisms in different steps. Therefore, the treatment should be understood on the basis of knowledge of the following steps; elution of antigenic substance from antigenic particles is inhibited by decreased hypersecretion (cholinergic blockade); interaction of antigenic substance with the surface basophilic cells is suppressed by decreased migration of these cells to the mucosal surface (topical steroid or immunotherapy) and is slightly affected by increased blocking antibody in the mucous layer (immunotherapy); mediator release from the surface basophilic cells is inhibited by a changed enzymic process or by a decrease in the production of the mediator in the cells (mast cell stabilizing agents, immunotherapy); allergic nasal tissue reaction may be suppressed slightly by quick binding of released histamine with protein (histamine-gammaglobulin compound) or is done by decreased nasal sensitivity to histamine (H_1 blockade, sedative, Asthremedine, α-stimulant, and cholinergic blockade).

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