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CHRONIC OTITIS MEDIA (SECRETORY) AND NASAL ALLERGY

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A b s t r a c t

The possible causal role of the nasal mucosa and nasal allergy in chronic otitis media with or without effusion was studied in 38 young adults by means of nasal provocation tests (NPT) with various inhalant allergens, performed by rhinomanometry and combined with tympanometry. The parameters were recorded before and up to 56 hrs after the allergen challenge. Of the 38 patients in whom 109 NPTs were performed, 31 patients developed 76 positive nasal responses (NR): 21 isolated immediate NR (IINR), 24 isolated late NR (ILNR), 15 dual late NR (DLNR = immediate + late NR), 11 isolated delayed NR (IDYNR), 5 dual delayed NR (DDYNR = immediate + delayed NR) and 21 negative responses (NNR). Seven patients did not develop any nasal response during 12 NPTs. The 61 positive NRs (80 %) and 5 negative NRs were accompanied by significant changes in the middle ear pressure (MEP), which means that the slightly negative MEP increased in negativity, by otalgia, middle ear tension, and decrease in hearing. In 6 patients the middle ear secretions increased through the monolateral ventilation tubes, during 13 positive NRs. These results suggest the possible causal role of the nasal mucosa and nasal allergy in some patients with chronic otitis media. The hypersensitivity reactions in the nasal mucosa may cause either a primary NR of various types, inducing then secondarily the middle ear response, or this reaction can lead primarily to the middle ear response without appearance of a clinical NR. Both mechanisms may have therapeutic consequences for chronic otitis media. These results stress the importance of nasal challenges with allergens, combined with tympanometry, for the diagnostic and therapeutic approach to this disorder.

K e y w o r d s

Chronic secretory otitis media, Nasal allergy, Nasal provocation tests with allergen, Rhinomanometry, Tympanometry

A b b r e v i a t i o n s u s e d

ALL, allergen; Ab, Antibody; DLNR, dual late nasal response (immediate + late); DDYNR, dual delayed nasal response (immediate + delayed); ET, Eustachian tube; I, initial value; IINR, isolated immediate nasal response; ILNR, isolated late nasal response; IDYNR, isolated delayed nasal response; ME, middle ear; MEP,middle ear pressure; MER, middle ear response; NNR, negative nasal response; NPG, nasopharynx-nostril pressure gradient; NPT, nasal provocation test; NR, nasal response; OM, otitis media; Δ P, pressure gradient expressed in cm H_2O; PBS, phosphate-buffered saline; SOM, secretory otitis media

INTRODUCTION

Otitis media (OM), especially its form associated with the presence of fluid in the middle ear cavity, so-called secretory otitis media (SOM) or otitis media with effusion (OME), in its acute as well as chronic form, is a very common disorder inchildren (*1-9*), but it can also regularly occur in adults (*10-16*). The structure and function of the middle ear and Eustachian tube have been exhaustively described (*1-8*). The pathogenesis of the inflammatory disorders of ME and ET has also been investigated from various points of view (*1-4, 6-8, 11, 14-20*). The association of OM with the dysfunction of ET and the disorders of the nose has repeatedly been confirmed (*1-4, 7, 8, 11, 14, 15, 17-30*). The diagnostic procedures and the therapeutical management of the particular forms of the inflammatory disorders of ME, however, vary (*1-62*). A number of these studies concern the role of bacterial and/or viral infections in otitis media (*1-4, 11, 16, 27, 50, 59-60*).The aetiological role of nasal allergy and its particular forms in the dysfunction of ET and in various clinical forms of OM has regularly been discussed in the literature (*1-31, 40-49, 51-57*). A number of studies deals with various immunological aspects and factors in patients suffering from the particular forms of OM, especially of SOM (*1-16, 20, 23, 27-29, 43-44, 62-81*). Moreover, some investigators have performed nasal challenges with allergens (*2, 4, 7, 18, 19- 23, 29*), or with some mediators (*32, 84-87*) in SOM patients. Their results, however, vary, because of the choice of the method of NPT and/or diagnostic parameters recorded. Nevertheless, few data are available to demonstrate a direct causal involvement of hypersensitivity mechanisms appearing primarily in the nasal mucosa and by this way leading to the dysfunction of ET and to the secondary response of ME.

The purpose of this study, being a continuation of our previous work (*88-111*) was to investigate: (1) the possible causal role of nasal allergy in chronic OM (SOM); (2) the possible mechanism(s),clinical features and types of the middle ear response in relationship to the nasal response to allergen challenge and its particular types; (3) the diagnostic value of the nasal allergen challenge, combined with tympanometry, for the assessment and therapeutical measures in patients with chronic OM and SOM.

MATERIALS AND METHODS

PATIENTS

Thirty-eight young adult patients, 17 to 26 years of age, with histories of chronic or recurrent otitis media with (SOM), with or without effusion since childhood, suffering from decreased hearing (slight to moderate degree), in whom an allergy component had been suspected, were studied.

All patients were repeatedly treated with decongestants, H_1-receptor antagonists, various antibiotics, glucocorticosteroids, inflation of ET and middle ear, in the past. In all these patients adenoidectomy, tonsillectomy, and repeated myringotomy were performed and some of them (n=7) were also fitted out with ventilation tubes. In some of them also other surgical interventions in the nose and ME, such as nasal septoplasty, conchotomy, and repeated puncture of maxillary sinuses were

carried out. None of the patients received immunotherapy, oral corticosteroids, disodium cromoglycate, long-acting H_1-receptor antagonists, H_2-receptor antagonists, antileukotrienes, immunoglobulins, or immunosuppressive drugs in the past.

All patients underwent routine diagnostic procedures consisting of complete disease history, physical examination, X-ray of the chest and paranasal sinuses, bacteriological examination of nasal secretions and sputum, basic laboratory examination, skin tests, blood eosinophil and leukocyte counts, nasal secretion cytogram, PRIST and RAST determination in the serum, screening tympanometry, and audiometry. Additionally, the nasal histamine thresholds were determined and, finally, the 109 nasal provocation tests with various inhalant allergens were performed by means of rhinomanometry, in combination with tympanometry. The patients were investigated during a period without manifest ear and nasal complaints and without symptoms of acute infection. No antiallergic treatment was given them during a 5-day period, or any short-acting H_1-receptor antagonists or nasal decongestants during the 48-hour period, prior to this study.

Allergens

Dialysed and lyophilized allergen extracts (ALK-Diephuis Laboratory, Groningen, The Netherlands) were diluted in PBS (dry weight of allergen in milligrams per 1 ml of PBS) and used for skin tests in the following concentrations: house dust mites (*Dermatophagoides pteronyssinus*) 5 NU/ml; particular animal danders and feathers 0.125 mg/ml; moulds 0.2 mg/ml, pollen kinds 100 NU/ml. The concentration of the allergen extracts used for the nasal challenges was tenfold higher. If indiated, higher dilutions of the allergen extracts were used for the nasal challenges.

Skin tests

Scratch tests (s.t.) were carried out and if they were negative, then intracutaneous tests (i.c.) were performed and evaluated 20 minutes, 6, 12, 24, 48, 72 and 96 hours after the injection. A skin wheal reaction (>7.5 mm in diameter) appearing within 20 minutes after the intradermal injection was considered a positive immediate skin response, that occurring 6–12 hours later to be a positive late skin response, and a prominent skin induration appearing later than 24 hours, usually between 36 and 72 hours, was considered to be a positive delayed skin response.

Nasal provocation tests (NPT)

NPTs with allergens were performed by means of the rhinomanometry technique (so-called "balloon method"), described in detail in our previous papers (*88-92, 94, 96-98, 100-104, 106-111*). The NPG values (Δ P, expressed in cm H_2O),recorded by this method were considered to be the basic parameters of the nasal mucosa response (nasal obstruction). The schedule of the NPT was as follows: (1) initial (baseline) values were recorded at 0, 5, and 10 minutes; (2) PBS control values were recorded at 0, 5, 10 minutes after a 3-minute application of PBS to the nasal mucosa of the non-intubated nasal cavity by means of a saturated wad of cotton wool on a nasal probe inserted under the concha media; and (3) test values were recorded similarly after a 3-minute nasal challenge with allergen at 0, 5, 10, 20, 30, 45, 60, 90, and 120 minutes, then every hour up to the 12th hour, and every second hour between the 24th and the 38th hour and between the 48th and the 56th hour.

The nasal response was considered to be positive when the mean NPG values after the allergen challenge increased by at least 2.0 cm H2O (1.2 ± 0.3, mean ± SE) with respect to the mean baseline NPG values, recorded during at least three consecutive time intervals. The NPG changes within 60 minutes after the allergen challenge were considered to be a positive immediate nasal response (INR), those appearing within 4 to 12 hours were considered to be a positive late nasal response (LNR), and those occurring later than 24 hours were considered to be a positive delayed nasal response (DYNR). Allergens for the NPTs were chosen with respect to the patient's history, skin tests, and/or RAST.

Control nasal tests with PBS

These tests were performed in each of the patients studied, in connection with every NPT with allergen, in the same way and according to the same schedule as that used during the allergen challenge. A 2-day time-interval was always inserted between the end of the previous and the beginning of the following test.

Tympanometry

The tympanometry was performed by means of "AEC American" (American Electromedics Corp., USA) and by a MicroTymp® 2 Portable Tympanometric Instrument (Welch Allyn, USA). The parameters recorded by these instruments were: (1) middle ear pressure (MEP), expressed in mm H_2O (or in daPa units; 1 daPa = 1.02 mm H_2O); and (2) compliance (so-called static admittance), expressed in cm^3. The tympanometric parameters (MEP values) were recorded at the same time-intervals as the rhinomanometric NPG values. The normal MEP values for adults vary within -100 (-150) to +100 mm H_2O (daPa). The normal compliance peak should appear within a range of 0.2 to 1.4 cm^3 at a pressure value of 0 mm H_20 (*34, 41, 42, 45, 48-57*).

Study design

The NPTs with allergen and those with PBS were performed according to the double-blind, cross-over schedule.

Statistical analysis

The nasal as well as the middle ear responses to allergen challenge were statistically evaluated by the Wilcoxon matched pair, signed-rank test, comparing the NPG or MEP values recorded after the allergen challenge with the mean NPG or MEP baseline values. A p value <0.05 was considered to be statistically significant. The nasal as well as the middle ear responses of the same type were compared and statistically evaluated by means of the Mann-Whitney U test. A p value <0.05 was considered to be statistically significant. The correlation between the nasal responses (NPG value changes) and the middle ear responses (MEP value changes) was evaluated by means of the Fisher exact test, which is a specialised chi-square test. A p value <0.05 was considered to be statistically significant.

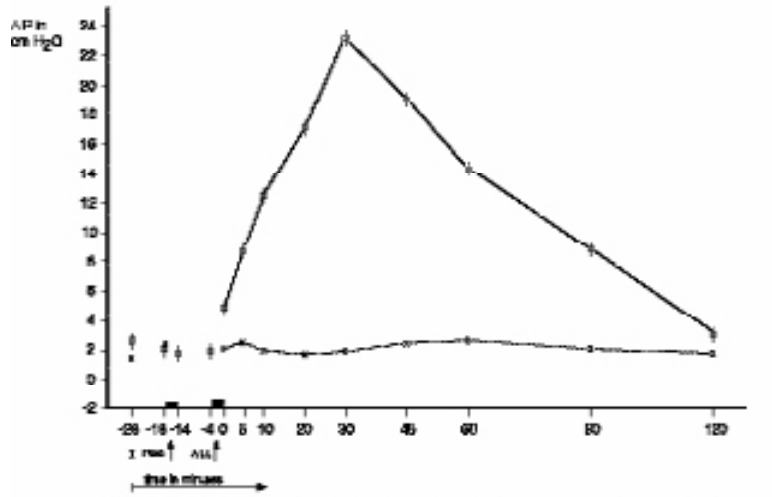
RESULTS

Nasal responses

Of the 38 patients in whom 109 NPTs were performed, 31 patients developed 76 positive NRs; 21 isolated immediate (IINR), 24 isolated late (ILNR), 15 dual late (DLNR = immediate + late), 11 isolated delayed (IDYNR), 5 dual delayed (DDYNR = immediate + delayed), and 21 negative (NNR) nasal responses. (*Figs. 1a, 2a, 3a*; *Tables 1-4*). The remaining 7 patients demonstrated 12 negative NRs. The clinical course of particular types of NR is summarised in *Table 1*. The other diagnostic parameters are presented in *Tables 2* and *4*.

The differences between positive and negative NRs were statistically highly significant ($p < 0.001$) at all time intervals. The 109 control challenges with PBS did not demonstrate any significant changes in the NPG values with respect to the NPG baseline values ($p > 0.2$).

The particular types of the NR demonstrated a highly significant positivity with respect to the appropriate PBS control responses. The significance of the particular

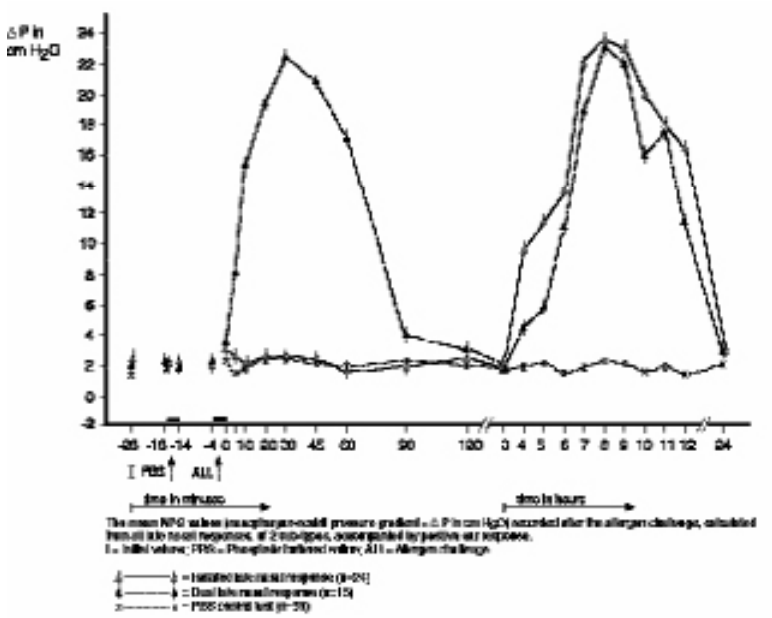


The mean NPS values (nasopharyngo-nostril pressure gradient = ΔP in cm H_2O) recorded after the allergen challenge, calculated from all isolated immediate nasal responses accompanied by positive ear responses.
I = Initial values; PBS = Phosphate buffered saline; ALL= Allergen challenge.

= isolated immediate nasal response (n=21)
= PBS control test (n=27)

Fig. 1a

Isolated immediate nasal response (IINR) to allergen challenge

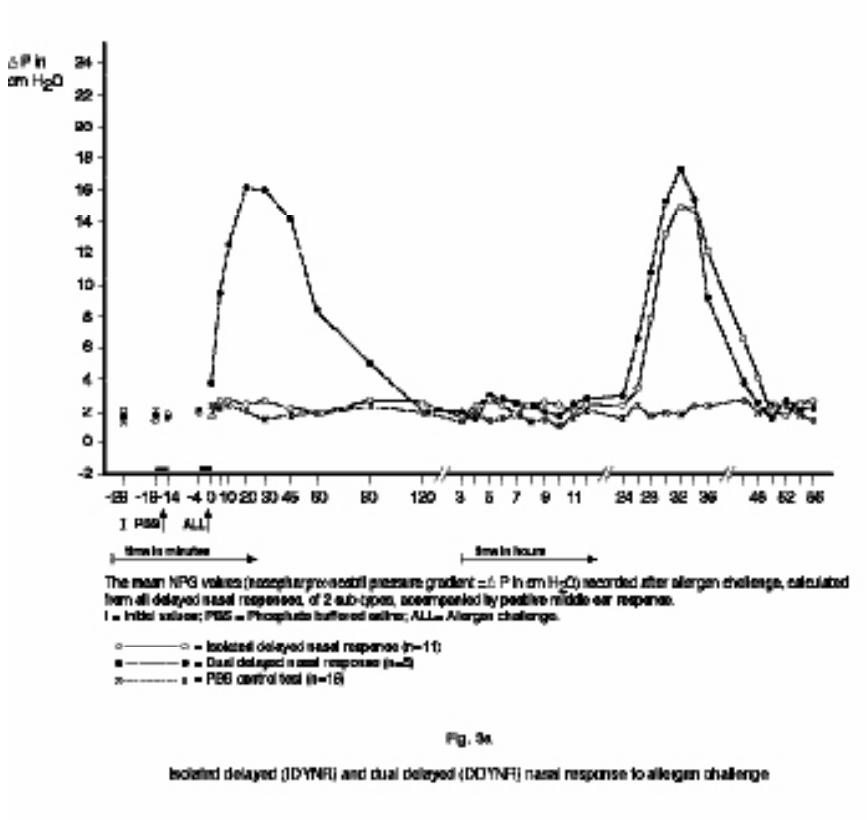


The mean NPG values (nasopharyngo-nostril pressure gradient = ΔP in cm H_2O) recorded after the allergen challenge, calculated from all late nasal responses, of 2 subtypes, accompanied by positive ear responses.
I = Initial values; PBS = Phosphate buffered saline; ALL = Allergen challenge.

= Isolated late nasal response (n=24)
= Dual late nasal response (n=15)
= PBS control test (n=39)

Fig. 2a

Isolated late (ILNR) and dual late (DLNR) nasal responses to allergen challenge



The mean NPG values (nasopharyngeal pressure gradient = Δ P in cm H_2O) recorded after allergen challenge, calculated from all delayed nasal responses, of 2 sub-types, accompanied by positive middle ear response.
I = Initial values; PBS = Phosphate buffered saline; ALL = Allergen challenge.

○———○ = Isolated delayed nasal response (n=11)
●———● = Dual delayed nasal response (n=5)
×------× = PBS control test (n=16)

Fig. 3a

Isolated delayed (IDYNR) and dual delayed (DDYNR) nasal response to allergen challenge

Table 1

Time course of the particular types of nasal and middle ear responses to allergen challenge

Response	Onset	Maximum	Resolving
Immediate (NR, MER)	0–10	20–45	90–120 minutes
Late (NR, MER)	4–8	6–12	< 24 hours
Delayed (NR, MER)	24–30	30–40	< 60 hours

Table 2
Survey of diagnostic parameters related to the response and allergen

History	unknown	probable	positive
Nasal response positive / negative n = 76 / n = 33	17 / 20	31 / 9	28 / 4
Middle ear response positive / negative n = 74 / n = 35	57 / 29	9 / 5	8 / 1
Positive response nasal = 76 / ME = 74	negative	doubtful	positive
Intracutaneous tests	28 / 34	23 / 24	25 / 16
RAST in serum	60 / 63	11 / 8	5 / 3
	not increased	slightly increased	increased
Nasal secretions eosinophilia	7 / 8	21 / 16	38 / 40

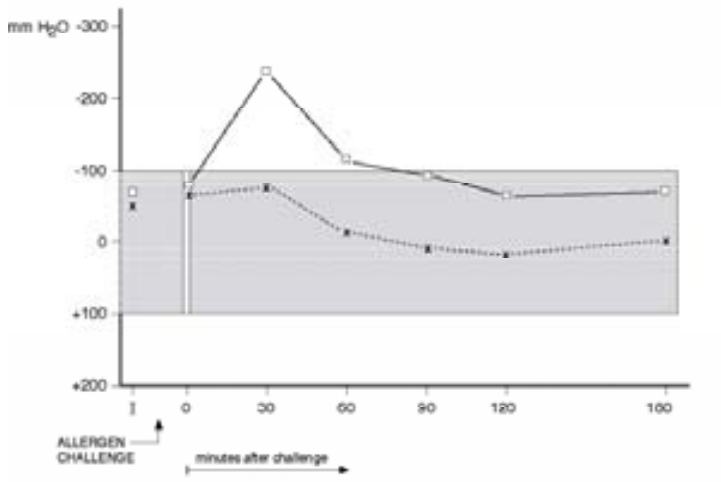
NR types was as follows: IINR ($p < 0.001$), ILNR ($p < 0.001$), DLNR ($p < 0.001$ for INR and $p < 0.001$ for LNR), IDYNR ($p < 0.01$), DDYNR ($p < 0.01$ for INR, and $p < 0.05$ for DYNR).

The 21 negative NR recorded in 31 patients and the 12 negative responses recorded in 7 patients did not demonstrate any significant changes in the NPG values as compared with the appropriate PBS control responses ($p > 0.2$ respectively $p > 0.1$).

Middle ear responses

The 61 of the 76 positive NRs (19 IINR, 17 ILNR, 12 DLNR, 9 IDYNR, 4 DDYNR) and 5 of the 21 negative NRs, recorded in 31 patients, were accompanied by significant changes in the MEP values (the slightly negative MEP increased significantly in negativity) ($p < 0.01$) (*Figs. 1b, 2b, 3b*, *Table 3*), appearance of otalgia, increase in the middle ear tension, and decrease in hearing (*Table 4*).

The significance of the changes in the MEP values recorded during the particular types of MER, with respect to the MEP values measured during the PBS control tests, was as follows: 19 isolated immediate MER ($p < 0.05$); 17 isolated late MER ($p < 0.001$); 12 dual late MER ($p < 0.05$ for immediate MER and $p < 0.01$ for late MER); 9 isolated delayed MER ($p < 0.01$); 4 dual delayed MER ($p < 0.01$ for immediate MER and $p < 0.05$ for delayed MER); 5 MER recorded during the negative NRs: 2 isolated immediate MER ($p < 0.05$) and 3 isolated late MER ($p < 0.05$). The 31 remaining MERs recorded during 15 positive NRs and 16 negative NRs were all significantly negative ($p > 0.1$).

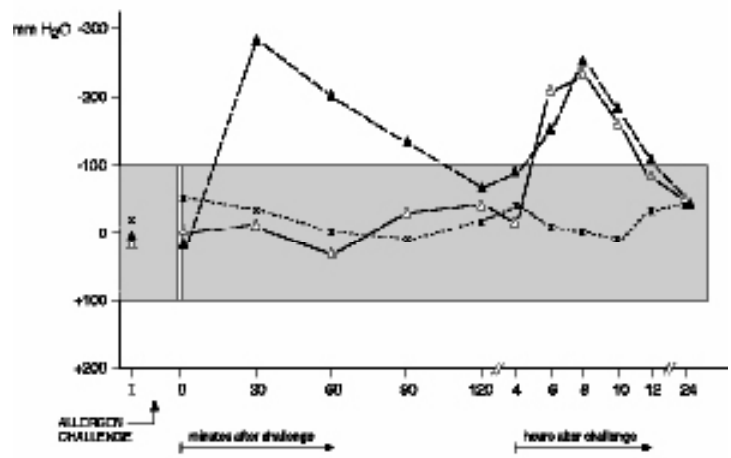


The tympanometric values (MEP = middle ear pressure), in mm H$_2$O, were calculated from all positive middle ear responses appearing during the positive isolated immediate nasal responses (IINR). The spotted area represents the normal value range of MEP.

□ ——— □ = MEP values during the isolated immediate nasal response (n=19)
x ····· x = MEP values during the PBS control test (n=19)

Fig. 1b

Isolated immediate response of middle ear (MER) to allergen challenge



The tympanometric values (MEP = middle ear pressure), in mm H$_2$O, were calculated from all positive middle ear responses appearing during the both subtypes of the late nasal response, the isolated late (ILNR) as well as dual late responses (DLNR) (=immediate + late). The spotted area represents the normal value range of MEP.

△ ——— △ = MEP values during the isolated late nasal response (n=17)
▲ - - - - ▲ = MEP values during the dual late nasal response (n=12)
x ——— x = MEP values during the PBS control test (n=19)

Fig. 2b

Isolated late and dual late response of middle ear (MER) to allergen challenge

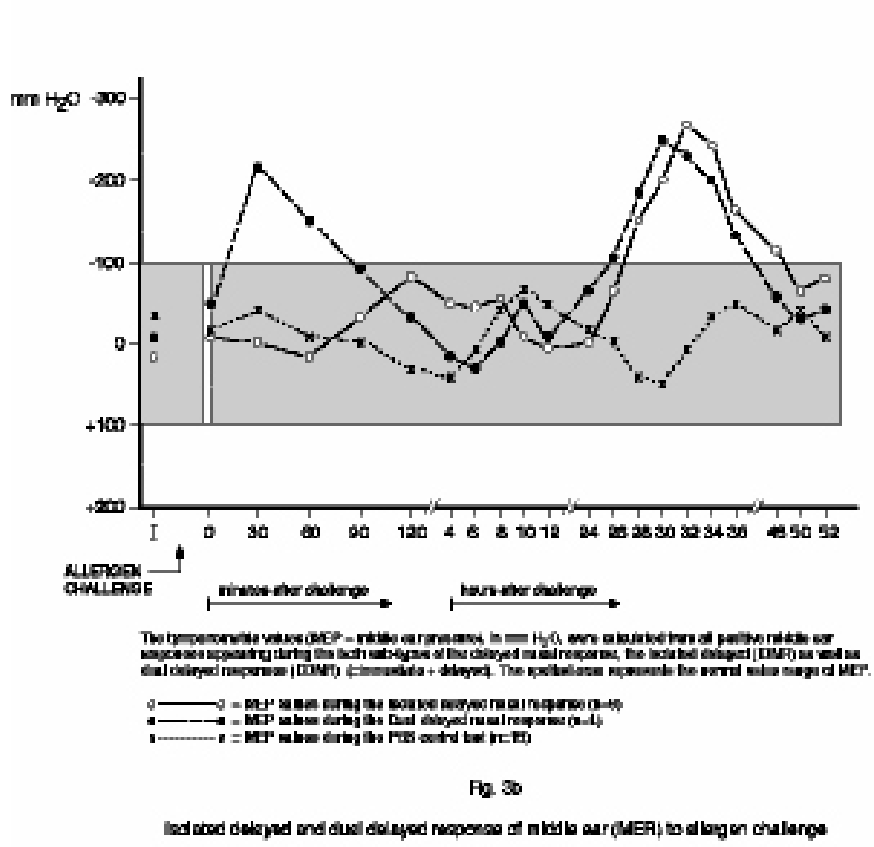


Fig. 3b

Isolated delayed and dual delayed response of middle ear (MER) to allergen challenge

Table 3

Survey of nasal and middle ear responses after nasal challenge with allergen

	Positive NR		Negative NR	
Patients	Ear response		Ear response	
n = 38	+	-	+	-
31 patients with				
76 positive NR	61	15		
21 negative NR			5	16
7 patients with				
12 negative NR	0	0	8	4
109 PBS control challenges	0	0	0	109

Table 4
Survey of the particular types of nasal and middle ear responses

	changes in MEP*				otalgia only
		accompanied by			
	n	otalgia	decrease in hearing	secretions **	
76 positive NRs	61	26	47	13	4
21 isolated immediate	19	8	16	4	1
24 isolated late	17	9	15	5	2
15 dual late	12	5	10	1	0
11 isolated delayed	9	3	5	2	0
5 dual delayed	4	1	1	1	1
33 negative NRs	13	5	9	1	1

* MEP= increase in the negativity of the slightly negative middle ear pressure
**secretions = increase in the middle ear effusion through the monolateral (or bilateral) ventilation tube(s)

In 5 of the 7 remaining patients developing 12 negative NRs only, 8 negative NRs were accompanied by significant changes of the MEP values; 3 isolated immediate MERs ($p < 0.05$) and 5 isolated late MERs ($p < 0.01$) were recorded.

No significant changes in the MEP values were recorded during the 109 control PBS tests ($p > 0.1$). The tympanometric compliance at the baseline, i.e. before the allergen challenge, was low in all patients studied (between 0.2 and 0.5 cm^3). During 58 of the 74 positive MERs and during 11 of the 35 negative MERs, a decrease in the compliance values was recorded, however, to a slight and non-significant degree ($p > 0.05$), whereas during 12 cases of the positive MER the compliance values displayed a slight and non-significant increase ($p > 0.05$), which did not exceed 1.5 cm^3. No changes in the compliance values were recorded during the other tests or the PBS control tests.

In 6 of the 7 patients with ventilation tubes (6 monolateral and 1 bilateral), a rapid increase in the middle ear secretions through the ventilation tubes was recorded during 13 positive MERs, 5 of them being associated with a positive immediate NR, 7 of them with a positive late NR, and 1 with a positive delayed NR.

The MERs were associated with subjective complaints and other diagnostic parameters to different degrees as summarised in *Tables 2* and *4*.

DISCUSSION

Otitis media is an inflammatory state of the middle ear, which may regularly be associated with middle ear effusion (secretions). The effusion can be of various aetiology, origin, and composition, such as serous, mucoid or purulent (so-called "glue ear") (*1-4, 6, 10-13, 16, 20, 24, 27-29, 46, 58-62, 112-119*). OM can be classified according to various criteria (*1-4, 6, 10-16, 24-28, 45-52, 58, 62, 112, 114-119*). With respect to the appearance and its duration, we distinguish acute, sub-acute, chronic form and recurrent form; with respect to the production of secretions we distinguish OM with or without effusion; with respect to the features of effusion we have serous, mucoid or purulent form; with respect to the aetiology involved, consequences and complications, degree and kind of the tympanic membrane damage, changes in the hearing quality, and others. The purulent form of OM, both acute and chronic sub-form, is generally caused either by bacterial agents or by upper respiratory viral infections (URI)(*1*, *3, 4, 10, 13, 16, 20, 27, 28, 58-62, 112, 114-119*). In approximately 25–31 % of the OM cases no bacteria can be identified in the middle ear effusion (*1, 4, 6, 58-62, 114, 116*).The above-mentioned classification of OM is derived from the history, symptomatology, and clinical examination. However, such classification and diagnosis of OM without the diagnostic tympanocentesis remains of a presumptive character (*1-4, 6, 25-28, 116*).

The most common cause of acute SOM is presumed to be bacterial infection, whereas hypersensitivity mechanisms are presumed to be the most frequent cause of chronic SOM (*1-4, 6-13, 15-18, 24, 26-28, 30, 37-40, 44, 46-48, 51, 57, 61, 62, 114-119*). The acute forms of OM are associated with middle-ear effusion (*1-7, 10-13, 16, 27, 37, 46, 47, 50, 56, 61, 62, 112, 114-116, 118, 119*). Generally, it is presumed that most of the chronic OM cases are also accompanied by the presence of middle ear effusion, even when this may be relatively asymptomatic in a number of cases (*1, 3, 4, 13-16, 26, 27, 28, 41, 46, 47, 50, 52-54, 115, 116*). Nevertheless, in a certain number of patients with chronic OM, especially in adolescents and adults, no evidence of middle-ear effusion may be found (1, 3, 4, 13–16, *26, 28, 34, 47-50, 116*).

The estimates in the literature report the incidence of SOM in children from 15 % to 64 % (*1-8, 10, 11, 27, 28, 45, 51, 52, 56, 61, 62, 112-116, 119*). Epidemiological data concerning SOM in adults are difficult to find (*10-15, 61, 116*).

The aetiology of OM, especially of SOM, has been shown to be of a multifactorial character. The bacterial and viral infections, immunological disorders, allergy conditions, especially those of the nasal mucosa, and dysfunctions of the Eustachian tube, belong to the most important factors involved in the pathogenesis of this disorder. The aetiological factors and their role in SOM are exhaustingly discussed in a number of excellent reviews (*1-8, 10, 11, 13-16, 24, 27, 44, 53, 58-62, 116, 118, 119*).

The pathogenesis of SOM is clearly related to the abnormal function (dysfunction) of the Eustachian tube (*1-17, 21, 23,26, 27, 29-57, 81-94, 97, 115*). The ET possessing and executing manifold functions facilitates the communication of the

middle ear cavity with the nasopharynx, nasal cavity, nasal mucosa, and indirectly also with the paranasal sinuses. By this way the ET plays a pivotal role in the disorders of the middle ear (*1-8, 10-17, 22-24, 26-42, 48-57, 61, 81-94, 96, 97, 115*). The ET executes three basic functions with respect to the middle ear: (1), protection of the middle ear from the nasopharyngeal sound pressure and secretions; (2), drainage of secretions from the middle ear into the nasopharynx; (3), ventilation of the middle ear cavity to equilibrate air pressure in the middle ear with the atmospheric pressure, to replenish oxygen that has been absorbed, and to let escape gases produced in the middle ear cavity (*1-4, 6, 7, 15, 17, 24, 26, 33, 36, 38, 40, 53, 57, 81-83, 86-94, 96, 97, 115, 116*). Under physiological circumstances the Eustachian tube is intermittently closed and open.

Active opening of ET is accomplished by contraction of the tensor veli palatini muscle during swallowing, yawning, crying or sneezing. By this mechanism the slightly negative pressure in the middle ear cavity, from 0 to -100 (-150) mm H_2O or daPa, is stabilized (*1-4, 6, 7, 17, 23, 26, 33, 41-46, 48-57, 87, 115*). On the contrary, cough, forced expiration, especially during the closed mouth, nose blowing, closed nose swallowing, diving or ascent in an airplane, may increase extremely the positive pressure in the nasopharynx, leading normally to the closing of ET and, by this way, to protection of the middle ear (*1-4, 6, 7, 17, 23, 26, 33, 41-46, 48-57*).

The major types of abnormal (disturbed) function of the Eustachian tube that may cause SOM are its obstruction, abnormal patency, and the non-optimally functioning ciliated epithelium lining the ET. The obstruction of ET can be caused either by extrinsic factors, such as adenoid hypertrophy or oedema of the mucosal membrane in the posterior nasopharynx due to infection or allergy, producing then secondarily peritubal obstruction of the nasopharyngeal orifice of ET, or by intrinsic factors, such as infection or allergy. The obstruction of ET can also be divided into two forms, a mechanical and a functional one. The mechanical form of ET obstruction is usually caused by the already mentioned extrinsic and intrinsic factors. The functional form of ET obstruction can usually be caused by increased tubal compliance due to the abnormally active opening mechanism or by nasal obstruction (so-called Toynbee phenomenon). In this form, an allergy may usually be involved. The functional obstruction may result in a persistent high negative middle ear pressure, which can be associated with a collapse or retraction of the tympanic membrane, so-called eardrum atelectasis. It is suspected that in cases in which inadequate ventilation of the ET occurs, the tube remains persistently collapsed. Such a situation results in progressively negative pressure in the middle ear associated with subsequent aspiration of nasopharyngeal secretions into the ME and development of acute otitis media with effusion. Alternatively, if an effective ventilation does not occur, because of persistent ET obstruction,an increased production of the secretions by the ME epithelium and accumulation of the sterile effusion in the ME cavity can result as a consequence of increased absorption of oxygen by the ME epithelium (local hypoxia and/or hypercapnia). All these factors, leading to

disturbance of the physiological functions of the Eustachian tube, cause its dysfunction, which then may result in a pathological state, such as otitis media. The pathophysiology, functional dysfunctions of ET, and the pathogenesis of SOM are described in detail in a number of excellent papers of Bluestone, Fireman, Skoner, Bernstein and their colleagues (*1-4, 6-8, 13, 17, 18, 24, 115, 116*).

The aetiological role of allergy in the pathogenesis of chronic SOM has already been discussed in the literature, however, from different points of view and generating different conclusions and suggestions (*1-8, 10-16, 18, 19, 20-24, 29-31, 33-39, 44, 56, 57, 62, 63, 65-94, 96, 97, 111-119*).

The involvement of allergy in chronic SOM can be realised through different mechanisms and by different pathways:(1), the allergic reaction (the antigen-antibody interaction with subsequent steps, such as release of mediators and their effects on the particular cells, receptors and structures) takes place primarily in the mucosal membrane of the ET and/or middle ear cavity; the middle ear mucosa being in this case the primary target organ; (2), the allergic reaction occurs in the mucosal membrane of the nasopharynx and/or its related structures, such as lymphatic or adenoid tissue and the released mediators affect secondarily through the nasopharyngeal secretions the peritubal and tubal mucosa of ET and then that of the middle ear cavity; (3), the allergic reaction appears in other, to the nasopharynx and ET non-related, tissues and the mediators, cytokines, various factors and the immunocompetent cells and/or immunostimulated cells reach the mucosal membrane of ET and/or middle ear cavity through the haematogenic way, and the possibly involved neuropeptides through the neurogenic ways; (4), the allergic reaction occurs primarily in the nasal mucosa and the subsequently released mediators migrating into nasal secretions are transported to the nasopharynx and then to the nasopharyngeal orifice of the Eustachian tube; this mechanism can have 2 forms, with or without accompanying nasal mucosa response; (5), allergic reaction occurring primarily in the nasal mucosa leads to the primary nasal mucosa response. The nasal mucosa response is characterised by a variety of symptoms, the oedema of the nasal mucosa causing subsequently nasal obstruction being the most prominent of them. The nasal mucosal oedema can affect the ET by two manners, either it extends directly to the nasopharyngeal mucosa and by this way it reaches the ET orifice, or it may affect the ET through the nasal obstruction. Nasal obstruction can lead either to an oedematous obstruction of the ET or to an increase in the negative pressure in the nasopharynx resulting in an obstruction of the Eustachian tube and an increase in the negative pressure in the middle ear. However, the nasal obstruction can also lead to an increase in the positive nasopharyngeal pressure, causing then aspiration of nasopharyngeal secretions into the ET and the middle ear cavity (*1-4, 7, 8, 13, 15-19, 21-24, 26, 30, 31, 33, 36-40, 46, 50, 52, 54, 57, 83, 88-97, 115, 116*).

One of the special mechanisms, which may also be considered to be involved in the development of chronic OM due to allergy, is the so-called “trapping mechanism”. The allergenic particles, passing the nasal barrier and escaping the filtering

functions of the nasal mucosa, reach the ET nasopharyngeal orifice, are trapped into the ET and cause there the antigen-antibody interaction with subsequent steps (*1, 6*). Such a mechanism has already been suggested for an alternative involvement of allergy in chronic maxillary sinusitis (*95–99, 120*).

The nasal mucosal oedema and nasal obstruction lead to an oedematous obstruction of the nasopharyngeal orifice of the ET, decreased patency of ET, and disturbance of the ciliary epithelium. This process may result in an accumulation of the secretions (effusion) and the gases in the middle ear cavity with the subsequent increase in the middle ear pressure, thickening of the ME mucosal membrane (oedema and/or infiltration) and changes in the function as well as in typical changes of the tympanic membrane. The otoscopic findings may then include an abnormal position of the tympanic membrane, such as full to bulging position, limited mobility, decreased translucency, opaque aspect, changed colour from slight bluish-red to red-yellow, disappearance of the light reflex, and increase in the eardrum vascularisation (*1–6, 10, 11, 13, 15, 20, 25–28, 40, 46, 47, 50, 51, 56, 116, 119*). This process can also lead to an increase in the middle ear pressure negativity with subsequent retraction or atelectasis of the tympanic membrane associated with its thickening, limited mobility and decrease or disappearance of the light reflex (*1–4, 11, 13, 25, 28, 40, 46, 50, 116, 119*). Chronic OM may be accompanied by a variety of other symptoms such as tinnitus, sometimes also otalgia and rarely vertigo. The most serious consequence of chronic OM, especially of that due to allergy, may be decrease in the elasticity of the tympanic membrane, appearance of fibrotic changes (otosclerosis), and decrease in hearing to various degrees (*1–16, 115, 116*).

The diagnostic confirmation of the involvement of allergy component in the dysfunction of ET and pathogenesis of chronic OM and SOM is not an easy issue. The skin tests and the determination of the total and specific IgE antibody in the serum (PRIST, RAST) have some advantages as well as disadvantages (*94–98, 101–111*). These tests are easy to perform and the results are quickly available. On the other side, these tests provide evidence for an existence of allergy component elsewhere in the body and not specifically in a particular organ or tissue. The results of these tests, being carried out on one organ, cannot be applied on the other organ without limitations. Moreover, the serum PRIST and RAST concern the IgE antibody only (type I allergy reaction), and do not provide any evidence for the involvement of antibodies of other classes or T lymphocytes. Finally, these tests are performed as a single measurement demonstrating the single data at a certain period of time, and they do not reveal any information on the dynamic aspect of the hypersensitivity process (*94–97*).

A similar problem concerns the various immunological tests estimating the appearance and/or changes in the concentrations of various mediators and factors, such as cytokines and chemotactic factors, immunocompetent cells, subtypes of leukocytes and their derivatives, in ME secretions (effusion), mucosal membrane

of ME and ET, nasal mucosa and other tissues, as a single measurement, failing the dynamic aspects of the involvement of these factors in the pathological process (*8, 14, 15, 18, 19, 63–80, 88–97, 101–103, 106, 107, 111,116–118*). The appearance and/or changes in the concentrations of these factors are indicative of their involvement and of the activation of the immunological system or its parts, as a defence mechanism. However, these data cannot discriminate the participation of different aetiological factors, from each other, such as bacterial and/or viral agents from allergens or the mode of their involvement in the particular disorder, such as chronic OM (SOM).

From this point of view, the provocation tests, e.g. NPT, combined with recording of parameters indicative of ME and ET functions and their changes (e.g. tympanometry), are the only method being able to approach this problem. The NPTs combined with tympanometry are able to demonstrate and confirm the causal role of a certain allergen in a certain organ, in this case in nasal mucosa and/or ET and ME, resulting in the appearance of a certain type of organ response, which can be quantitatively recorded in its time (dynamic) course. By this way, the causal relationship between a certain type of the hypersensitivity mechanism (allergic reaction) related to a certain allergen on one side and the disorder of an organ, in this case the ME and ET, represented by certain symptoms, on the other side, can be confirmed unequivocally (*22–24, 29–31, 34–36, 81–83, 88–97*).

Although the (nasal) provocation tests are laborious, time-consuming, to a certain degree expensive, require special equipment and facilities and specially trained personnel, they are able to generate extremely important data which cannot be gathered by other methods. They demonstrate directly the causal involvement of a certain allergen through a certain type of allergic reaction in a certain organ, which may display a certain type of response. By combination of the parameters recorded, they are also able to confirm the role of an organ in the response of another organ, as can be seen in the above-mentioned case of the nasal mucosa and ET and ME. The NPTs can also discriminate the participation of the allergy component from the non-specific hyperreactivity component in the patient's complaints. Another very important advantage of the NPT is the fact that they are record the relative values of the parameters, comparing data before with those after the allergen (or representant of non-specific hypersensitivity, such as histamine). By this way these tests are not dependent on the absolute values of the parameters, which cannot always be determined with respect to their high variations and wide range (*94–111*).

Our results, showing 3 types of nasal as well as middle ear response, are partly in agreement with the findings of other investigators using the nasal challenge model with allergen in patients (*22, 23, 29, 30, 34–36, 82– 84*) or in experimental animals (*80, 81, 83*). This agreement concerns especially the pivotal role of nasal allergy in the dysfunction of ET with subsequent development of SOM, the existence of non-immediate types of nasal and ME responses, and the very important position

of NPTs in the diagnostic procedure of allergic rhinitis as well as SOM. The nasal challenges with histamine or other chemical compounds, carried out and reported by other investigators (*32, 85–87*), concern the role and participation of the non-specific hyperreactivity component in the development of nasal complaints and subsequently the response of the ET and middle ear *(94–97*).

Our results emphasise some important aspects for the clinical practice. The dysfunction of ET and SOM can occur in adults more frequently than usually expected, because it is associated with less prominent symptoms than those usually found in children. The involvement of various hypersensitivity mechanisms may lead to the appearance of 3 basic types of the middle ear response, analogically to the 3 basic types of nasal response. The NPT with allergen, combined with tympanometry, should be considered as a very important diagnostic means in the recognition of the involvement of the allergy component and nasal allergy in the ET dysfunction and SOM, especially in its dynamic aspect. The improved diagnostic procedure permits then a better indicated therapeutical approach to this disorder.

Pelikan Z.

CHRONICKÁ OTITIS MEDIA SE SEKRECÍ A NOSNÍ ALERGIE

S o u h r n

Možná kauzální role nosní alergie v chronické sekreční otitis media (SOM) byla studována u 38 mladých dospělých pacientů (17–26 roků), kteří měli potíže od dětství a byli léčeni různými způsoby, jak medikamentózně tak i operativně.Mimo rutinní alergologickou diagnostiku bylo u těchto pacientů provedeno 109 nosních provokačních testů s různými inhalačními alergeny. Nosní reakce jakož i reakce středního ucha (oboustranně) byly monitorovány rhinomanometrií kombinovanou s tympanometrií. Dané parametry byly kvantitativně registrovány před a opakovaně do 56 hodin po nosní provokaci. U 31 pacientů bylo zaznamenáno 76 pozitivních nosních reakcí (NR): 21 izolovaných časných (IINR), 24 izolovaných opožděných (ILNR), 15 kombinovaných opožděných (DLNR = časná + opožděná), 11 izolovaných pozdních (IDYNR), 5 kombinovaných pozdních (DDYNR = časná + pozdní) a 21 negativních reakcí (NNR).U zbývajících 7 pacientů bylo zaznamenáno 12 negativních NR; 61 pozitivních NR a 5 negativních NR bylo provázeno signifikantními změnami středoušního tlaku (MEP), což znamená, že lehká negativita MEP před provokací se zřetelně prohloubila po provokaci. Změny středoušního tlaku byly provázeny subjektivními potížemi, jako otalgií, pocitem středoušního tlaku a snížením sluchu (jak objemu tak i ostrosti). U 6 ze 7 pacientů, kteří měli ventilační trubičky (5 monolaterálně a 1 bilaterálně) se objevila akutní sekrece během 13 nosních provokací. Tyto výsledky potvrzují možnou kauzální roli nosní alergie a nosní sliznice v dysfunkci Eustachovy trubice (ET) a SOM, vyskytující se také u dospělých pacientů. Alergické reakce různého typu probíhající v nosní sliznici mohou vést buď k primární nosní odpovědi (edém nosní sliznice), která pak sekundárně indukuje odpověď ET a středního ucha, nebo vyvolají primární odpověď ET a středního ucha přímo, bez předcházející nosní odpovědi. Oba tyto mechanizmy jsou důležité pro posouzení SOM z patofyziologického hlediska. Výše uvedené výsledky zdůrazňují význam nosních provokací s alergenem v kombinaci s tympanometrií pro diagnostické posouzení a terapeutický přístup k tomuto onemocnění.

REFERENCES

1. *Bluestone ChD, Klein JO.* Otitis media in infants and children. 2nd ed. Philadelphia: W.B.Saunders Comp.1995; 1–201.
2. *Fireman P.* Otitis media and nasal disease: A role for allergy. J Allergy Clin Immunol 1988; 82 (Suppl): 917–924.
3. *Fireman P.* Otitis media. In: Kay AB, ed. Allergy and allergic diseases. 1st ed. Oxford: Blackwell Sci Publ. 1997; 1632–1644.
4. *Skoner DP, Casselbrant ML.* Otitis media. In: Middleton E.Jr, Reed ChE, Ellis EF, Franklin Adkinson NJr, Yunginger JW, Busse WW, eds. Allergy, principles and practice. 5th ed. St. Louis (MO, USA): Mosby-Year Book Inc. 1998; 1036–1049.
5. *Marshall SG, Bierman CW, Shapiro GG.* Otitis media with effusion in childhood. Ann Allergy 1984; 53: 370–377.
6. *Bluestone ChD, Klein JO.* Otitis media, atelectasis and eustachian tube dysfunction. In:Bluestone ChD, Stool SE, eds. Pediatric otolaryngology, Vol.1. Philadelphia: W.B. Saunders Comp 1983; 356–412. (2nd ed). Philadelphia: W.B. Saunders Comp 1990; 320–486.
7. *Fireman P.* Otitis media and eustachian tube dysfunction: Connection to allergic rhinitis. J Allergy Clin Immunol 1997; 99: S787–797.
8. *Bernstein JM.* Recent advances in immunologic reactivity in otitis media with effusion. J Allergy Clin Immunol 1988; 81: 1004–1009.
9. *Gates GA, Wachtendorf C, Hearne E, Holt G.* Treatment of chronic otitis media with effusion: results of tympanostomy tubes. Am J Otolaryngol 1985; 6: 249–253.
10. *Bierman CW, Pierson WE.* Diseases of the ear. J Allergy Clin Immunol 1988; 81: 1009–1014.
11. *Williamson I.* Otitis media with effusion. Clin Evid 2000; 7: 469–476.
12. *Yung MW, Arasaratnam R.* Adult-onset otitis media with effusion: results following ventilation tube insertion. J Laryngol Otol 2001; 115: 874–878.
13. *Bernstein JM, Schatz M, Zeiger R.* Immunologic ear disease in adults. Clin Rev Allergy 1984; 2: 349–375.
14. *Kariya S, Okano M, Aoji K, et al.* Role of macrophage migration inhibitory factor in otitis media with effusion in adults. Clin Diagn Lab Immunol 2003; 10 (3): 417–422.
15. *Finkelstein Y, Ophir D, Talmi Y, Shabtai A, Strauss M, Zohar Y.* Adult-onset otitis media with effusion. Arch Otolaryngol Head Neck Surg 1994; 120: 517–527.
16. *Giebink GS.* Otitis media update: pathogenesis and treatment. Ann Otol Rhinol Laryngol 1992; 101: 21–23.
17. *Bluestone ChD, Doyle WJ.* Anatomy and physiology of eustachian tube and middle ear related to otitis media. J Allergy Clin Immunol 1988; 81 (Suppl): 997–1003.
18. *Bernstein JM.* The role of IgE-mediated hypersensitivity in the development of otitis media with effusion. Otolaryngol Clin North Am 1992 Feb; 25 (1): 197–211.
19. *Mogi G, Tomonaga K, Watanabe T, Chaen T.* The role of type I allergy in secretory otitis media and mast cells in the middle ear mucosa. Acta Otolaryngol Suppl 1992; 493: 155–163.
20. *Skoner DP.* Complications of allergic rhinitis. J Allergy Clin Immunol 2000; 105: S605–609.
21. *Gungor A, Corey JP.* Relationship between otitis media with effusion and allergy. Curr Opin Otolaryngol Head Neck Surg 1997; 46–48.
22. *Skoner DP, Doyle WJ, Boehm S, Fireman P.* Late phase eustachian tube and nasal allergic responses associated with inflammatory mediator elaboration. Am J Rhinol 1988; 2: 155–161.
23. *Friedman RA, Doyle WJ, Casselbrant MR, Bluestone CD, Fireman P.* Immunologic-mediated eustachian tube . obstruction: a double-blind crossover study. J. Allergy Clin Immunol 1983; 71: 442–447.
24. *Bernstein JM.* Role of allergy in eustachian tube blockage and otitis media with effusion: a review. Otolaryngol Head Neck Surg 1996; 114: 562–568.
25. *Pulec JL, Kinney SE.* Diseases of the tympanic membrane. In: Paparella MM,Schumrick DA, eds. Otolaryngology. Philadelphia: W.B. Saunders Comp 1973; 55–74.
26. *Pulec JL, Horwitz MJ.* Diseases of the Eustachian tube. In: Paparella MM, Schumrick DA, eds. Otolaryngology. Philadelphia: W.B. Saunders Comp 1973; 75–92.
27. *Paparella MM.* The middle ear effusion. In: Paparella MM, Schumrick DA, eds. Otolaryngology. Philadelphia: W.B. Saunders Comp 1973; 93–112.
28. *Proctor B.* Chronic otitis media and mastoiditis. In: Paparella MM, Schumrick DA, eds. Otolaryngology. Philadelphia: W.B. Saunders Comp 1973; 121–152.
29. *Ackerman MN, Friedman RA, Doyle WJ, Fireman P.* Antigen induced eustachian tube obstruction: an intranasal provocation challenge test. J Allergy Clin Immunol 1984; 73: 604–609.
30. *Doyle WJ, Takahara T, Fireman P.* Role of allergy in pathogenesis of otitis media with effusion. Arch Otolaryngol 1985; 111: 502–506.

31. *Yamashita T, Okazaki N, Kumazawa R.* Relation between nasal and middle ear allergy: experimental study. Ann Otol Rhinol Laryngol 1980; 89: 147–152.
32. *Doyle WJ, Ingraham AS, Fireman P.* The effects of histamine challenge on eustachian tube function. J Allergy Clin Immunol 1985; 76: 551–556.
33. *Osur SL, Bernstein JM, Enck C.* Eustachian tube obstruction in children with allergic rhinitis. J Allergy Clin Immunol 1987; 79: 259–262.
34. *O'Connor RD, Ort H, Leong AB, Cook DA, Street D, Hamburger RN.* Tympanometric changes following nasal antigen challenge in children with allergic rhinitis. Ann Allergy 1984; 53: 468–471.
35. *Cook DA, Ort H, Jalowayski A, Hamburger RN.* Otologic response to intranasal antigen challenge. J Allergy Clin Immunol 1980; 65: 215. 36. *Stuar M.* Late phase allergy and eustachian tube dysfunction. Otolaryngol Head Neck Surg 2001;125(4):339–345.
37. *Doner F, Yariktas M, Demirci M.* The role of allergy in recurrent otitis media with effusion. J Investig Allergol Clin Immunol 2004; 14(2): 154–158.
38. *Osur SL, Volovitz B, Dickson S, Enck DC, Bernstein JM.* Eustachian tube dysfunction in children with ragweed hayfever during natural pollen exposure. Allergy Proc 1989; 10(2): 133–139.
39. *Becker S, Koch T, Philipp A.* Allergic origin of recurrent middle ear effusion and adenoids in young children. HNO 1991; 39(5): 182–184.
40. *Ryding M, White P, Kalm O.* Eustachian tube function and tympanic membrane findings after chronic secretory otitis media. Int J.Pediatr Otorhinolaryngol 2004; 68(2): 197–204.
41. *Watters GW, Jones JE, Freeland AP* The predictive value of tympanometry in the diagnosis of middle ear effusion. Clin Otolaryngol Allied Sci 1997; 22(4): 343–345.
42. *Aranzon A, Ross AT, Kazahaya K, Ishii M.* Diagnosis of middle ear disease using tympanograms and digital imaging. Otolaryngol Head Neck Surg 2004; 131: 917–920.
43. *Skoner DP, Stillwagon PK, Casselbrant ML, Tanner ER, Doyle WJ, Fireman P.* Inflammatory mediators in chronic otitis media with effusion, Arch Otolaryngol Head Neck Surg 1988; 114: 1131–1133.
44. *Tomonaga K, Kurono Y, Mogi G.* The role of nasal allergy in otitis media with effusion, a clinical study. Acta Otolaryngol, Suppl. (Stockh.) 1988; 458: 41–71.
45. *Paradise JL, Smith CG, Bluestone ChD.* Tympanometric detection of middle ear effusion in infants and young children. Pediatrics 1976; 58: 198–210.
46. *Klaudt MR, Steinbach WJ, Sectish TC.* Clinical considerations in the diagnosis of otitis media. Current Allergy and Asthma Reports 2003; 3: 313–320.
47. *Karma PH.* Otoscopic diagnosis of middle ear effusion in acute and non-acute otitis media. I. The value of different otoscopic findings. Int J Pediatr Otorhinolaryngol 1989; 17: 37–49.
48. *Brookhouser PE.* Use of tympanometry in office practice for diagnosis of otitis media. Pediatr Infect Dis J 1998; 17:544–551.
49. *Onusko E.* Tympanometry. Am Fam Physician 2004; 70: 1713–1720.
50. *Kaleida PH, Fireman P.* Diagnostic assessment of otitis media. Clin Allergy Immunol 2000; 15: 247–262.
51. *Takata GS, Chan LS, Morphew T, Mangione-Smith R, Morton SC, Shekelle P.* Evidence assessment of the accuracy of methods of diagnosing middle ear effusion in children with otitis media with effusion. Pediatrics 2003; 112: 1379–1387.
52. *Margolis RH, Hunter LL, Giebink GS.* Tympanometric evaluation of middle ear function in children with otitis media. Ann Otol Rhinol Laryngol, Suppl. 1994; 163: 34–38.
53. *Shanks J, Shelton C.* Basic principles and clinical application of tympanometry. Otolaryngol Clinics North Amer 1991; 24(2): 299–328.
54. *Gates GA, Avery C, Cooper JC, Hearne EM, Holt GR..* Predictive value of tympanometry in middle ear effusion. Ann Otol Rhinol Laryngol 1986; 95: 46–50.
55. *Harford ER, Bess FH, Bluestone CD, Klein JO.* Impedance screening for middle ear disease in children. New York: Grune & Stratton 1978.
56. *Randolph CC, Frazer B.* Incidence and progress of middle ear effusion in allergy practice as detected by acoustic otoscope reflectometry. Allergy Proc 1994; 15: 157–162.
57. *Lazo-Saenz JG, Galvan-Aguilera AA, Martinez-Ordaz VA, Velasco-Rodriguez VM, Nieves-Renteria A, Rincon-Castaneda C.* Eustachian tube dysfunction in allergic rhinitis. Otolaryngol Head Neck Surg 2005; 132: 626–629.
58. *Bluestone ChD, Stephenson JS, Martin LM.* Ten-year review of otitis media pathogens. Pediatr Infect Dis J 1992; 11: S7–11.
59. *Giebink GS.* The microbiology of otitis media. Pediatr Infect Dis J 1989; 8: 218–220.
60. *Riding KH, Bluestone CD, Michaels RH, Cantekin EI, Doyle WJ, Poziviak C.* Microbiology of recurrent and chronic otitis media with effusion. J Pediatr 1978; 93: 739–743.

61. *Kraemer MJ, Marshall SG, Richardson MA.* Etiologic factors in the development of chronic middle ear effusion. Clin Rev Allergy 1984; 2: 319–328.
62. *Kubba H.* The etiology of otitis media with effusion: a review. Clin Otolaryngol All 2000; 25: 181–194.
63. *Smirnova MG, Birchall JP, Pearson JP.* The immunoregulatory and allergy-associated cytokines in the aetiology of the otitis media with effusion. Mediators Inflamm 2004; 13: 75–88.
64. *Yellon RF, Leonard G, Marucha PT, Craven R, Carpenter RJ, Lehmann WB, Burleson JA, Kreutzer DL.* Characterization of cytokines present in middle ear effusion. Laryngoscope 1991; 101: 165–169.
65. *Nguyen LH, Manoukian JJ, Sobol SE, Tewfik TL, Mazer BD, Schloss MD, Taha R, Hamid QA.* Similar allergic inflammation in the middle ear and the upper airway: evidence linking otitis media with effusion to the united airways concept. J Allergy Clin Immunol 2004; 114: 1110–1115.
66. *Himi T, Suzuki T, Kodama H, Takezawa H, Kataura A.* Immunologic characteristics of cytokines in otitis media with effusion. Ann Otol Rhinol Laryngol Suppl 1992; 157: 21–25.
67. *Sobol SE, Taha R, Schloss MD, Mazer BD, Manoukian JJ, Tewfik TL, Hamid QA.*. T(H)2 cytokine expression in atopic children with otitis media with effusion. J Allergy Clin Immunol 2002; 110: 125–130.
68. *Jang CH, Kim YH.* Characterization of cytokines present in pediatric otitis media with effusion: comparison of allergy positive and negative. Int J Pediatr Otorhinolaryngol 2002; 66: 37–40.
69. *Wright ED Hurst D, Miotto D, Giguere C, Hamid QA.* Increased expression of major basic protein (MBP) and interleukin-5 (IL-5) in middle ear biopsy specimens from atopic patients with persistent otitis media with effusion. Otolaryngol Head Neck Surg 2000; 123: 533–538.
70. *Russo E, Smith CW, Friedman EM, Smith EO, Kaplan SL.* Cell adhesion molecules and cytokines in middle ear effusion in children with or without recent acute otitis media. Otolaryngol Head Neck Surg 2004; 130:242–248.
71. *Hurst DS, Venge P.* The impact of atopy on neutrophil activity in middle ear effusion from children and adults with chronic otitis media. Arch Otolaryngol Head Neck Surg 2002; 128: 561–566.
72. *Skotnicka B, Hassmann E.* Cytokines in children with otitis media with effusion. Eur Arch Otorhinolaryngol 2000; 257: 323–326.
73. *Jung TT.* Prostaglandins, leukotrienes and other arachidonic acid metabolites in the pathogenesis of otitis media. Laryngoscope 1988; 98: 980–993.
74. *Furukawa M, Kubo N, Yamashita T.* Biochemical evidence of platelet-activating factor (PAF) in human middle ear effusion. Laryngoscope 1995; 105: 188–191.
75. *Ohashi Y, Nakai Y, Tanaka A, Kakinoki Y, Washio Y.* Soluble adhesion molecules in middle ear effusion from patients with chronic otitis media with effusion. Clin Otolaryngol 1998; 23: 231–234.
76. *Bernstein JM, Ballow M, Xiang S,O'Neil K.* Th 1/ Th 2 cytokine profiles in the nasopharyngeal lymphoid tissue of children with recurrent otitis media. Ann Otol Rhinol Laryngol 1998; 107: 22–27.
77. *Bikhazi P, Ryan AF.* Expression of immunoregulatory cytokines during acute and chronic middle ear immune response. Laryngoscope 1995; 105: 629–634.
78. *Jones EA Jr., Thomas LR, Davis NC.* The significance of secretory IgA in middle ear fluid. Ann Allergy 1979; 42; 236–240.
79. *Hurst DS, Venge P.* Evidence of eosinophil, neutrophil, and mast-cell mediators in the effusion of OME patientswith and without atopy. Allergy 2000; 55: 435–441.
80. *Pollock HW, Ebert CS, Dubin MG, White DR, Prazma J, Pillsbury HC.* The role of soluble interleukin-4 receptor and interleukin-5 antibody in preventing late-phase allergy-induced eustachian tube dysfunction. Otolaryngol Head Neck Surg 2002; 127: 169–176.
81. *Hardy SM, Heavner SB, White DR, McQueen CT, Prazma J, Pillsbury HC.* Late-phase allergy and eustachian tube dysfunction.. Otolaryngol Head Neck Surg 2001; 125: 339–345.
82. *Skoner DP, Doyle WJ, Chamovitz AH, Fireman P.* Eustachian tube obstruction after intranasal challenge with house dust mite. Arch Otolaryngol 1986; 112: 840–842.
83. *Doyle WJ, Bluestone ChD, Friedman R,* Eustachian tube obstruction following provocative nasal antigen challenge. Arch Otolaryngol 1984; 110: 508–511.
84. *Stillwagon PK, Doyle WJ, Fireman P.* Effects of an antihistamine/decongestant on nasal an eustachian tube function following intranasal pollen challenge. Ann Allergy 1987; 58: 422–426.
85. *Skoner DO, Doyle WJ, Fireman P.* Eustachian tube obstruction (ETO) after histamine nasal provocation: a double blind dose response study. J Allergy Clin Immunol 1987; 79: 27–31.
86. *Ebert Ch.* Effect of intranasal histamine challenge on eustachian tube function. Int J Pediatr Otorhinolaryngol 2002; 63: 189–198.
87. *Walker SB, Shapiro GG, Bierman CW, Morgan MS, Marshall SG, Furukawa CT, Pierson WE.* Induction of eustachian tube dysfunction with histamine nasal provocation. J Allergy Clin Immunol 1985; 76: 158–162.

88. *Pelikan Z, Pelikan M.* Nasal challenge in patients with secretory otitis media (SOM) and otalgia (OL). Ann Allergy 1985; 55: 231.
89. *Pelikan Z.* Changes in middle ear pressure (MEP) due to the nasal allergen challenge in patients with secretory otitis media (SOM) and otalgia (OL). J Allergy Clin Immunol 1987; 79: 258.
90. *Pelikan Z,Pelikan-Filipek M.* Middle ear response to the nasal allergen challenge in patients with secretory otitis media (SOM). Allergy & Clin Immunol News 1991; Suppl 1: 336.
91. *Pelikan-Filipek M, Pelikan Z, Oers v JAH, Fouchier SM.* The role of nasal mucosa and nasal allergy in the secretory otitis media (SOM). J Allergy Clin Immunol 1998; 101: 185.
92. *Pelikan Z, Pelikan-Filipek M, Miessen WMA.* The possible role of the nasal allergy in some patients with chronic secretory otitis media (SOM) and the protective effects of intranasal cromolyn (DSCG). Allergy 2002 ;57 (Suppl 73): 247.
93. *Pelikan Z, Pelikan-Filipek M.* Middle ear response due to the food ingestion challenge. J Allergy Clin Immunol 1989; 83: 239.
94. *Pelikan Z.* Late nasal response- its clinical characteristics, features and possible mechanism. In: Dorsch W (Ed). Late Phase Allergic Reactions. Boca Raton, Ann Arbor, Boston: CRC Press 1990: 111–155.
95. *Pelikan Z.* The role of allergy in sinus disease. In: Gershwin ME, Incaudo GA (Eds.). Diseases of the sinuses. Totowa (USA): Humana Press 1996: 97–165.
96. *Pelikan Z.* The late nasal response, its clinical and immunological features, possible mechanisms and pharmacological modulation. Thesis. Amsterdam: Free University Amsterdam 1996.
97. *Pelikan Z.* Rhinitis, secretory otitis media and sinus disease caused by food allergy. In: Brostoff J, Challacombe SJ (Eds.). Food Allergy and Intolerance (2nd Ed). London, Edinburgh, New York, Philadelphia, St. Louis, Sydney, Toronto: W.B. Saunders 2002: 497–528.
98. *Pelikan Z, Pelikan-Filipek M.* Role of nasal allergy in chronic maxillary sinusitis – diagnostic value of nasal challenges with allergen. J Allergy Clin Immunol 1990; 86: 484–491.
99. *Pelikan Z, Pelikan-Filipek M, Ossekoppele R.* Chronic sinusitis maxillaris (CSM) – the role of nasal allergy and the diagnostic value of echography and radiographs. Allergy Clin Immunol News 1994; Suppl 2: 415.
100. *Pelikan Z, Feenstra L, Barree GOF.* Response of the nasal mucosa to allergen challenge measured by two different methods of rhinomanometry. Ann Allergy 1977; 38: 263–267.
101. *Pelikan Z.* Late and delayed response of the nasal mucosa to allergen challenge. Ann Allergy 1978; 41: 37–47.
102. *Pelikan Z, Pelikan-Filipek M.* The effects of Disodium cromoglycate and Beclomethasone dipropionate on the immediate response of the nasal mucosa to allergen challenge. Ann Allergy 1982; 49: 283–292.
103. *Pelikan Z.* The effects of Disodium cromoglycate and Beclomethasone dipropionate on the late nasal mucosa response to allergen challenge. Ann Allergy 1982; 49: 200–212.
104. *Pelikan Z, Pelikan-Filipek M.* A new disease-a nasal form of pigeon breeder's disease. Allergy 1983; 38:309–318.
105. *Pelikan Z.* The changes in the nasal secretions of eosinophils during the immediate nasal response to allergen challenge. J Allergy Clin Immunol 1983; 72: 657–662.
106. *Pelikan Z.* The effects of Disodium cromoglycate and Beclomethasone dipropionate on the delayed nasal mucosa response to allergen challenge. Ann Allergy 1984; 52: 111–124.
107. *Pelikan Z, Pelikan-Filipek M.* Cytologic changes in the nasal secretions during the immediate nasal response. J Allergy Clin Immunol 1988; 82: 1103–1112.
108. *Pelikan Z.* Nasal response to food ingestion challenge. Arch Otolaryngol Head Neck Surg 1988; 114: 525–530.
109. *Pelikan Z, Pelikan-Filipek M.* Cytologic changes in the nasal secretions during the late nasal response. J Allergy Clin Immunol 1989; 83: 1068–1079.
110. *Melillo G, Bonini S, Cocco G, Davies RJ, Monchy de JGR, Frølund L, Pelikan Z.* Provocation tests with allergens. Allergy 1997; 52 (Suppl 35): 5–36.
111. *Pelikan Z.* Late type of the nasal allergic response- Review. Scripta medica 2001; 74: 303–344.
112. *Draper WL.* Secretory otitis media in children: a study of 540 children. Laryngoscope 1967; 77: 636–656.
113. *Phillips MJ, Knight NJ, Manning H, Abbott AL, Tripp WG.* IgE and secretory otitis media. Lancet 1974; ii: 1176–1178.
114. *Ingvarsson L, Lundgren K, Olofsson B, Wall S.* Epidemiology of acute otitis media in children. Acta Oto-Laryngol (Stockh) 1982; Suppl 388: 1–52.
115. *Bluestone ChD.* Eustachian tube function and allergy in otitis media. Pediatrics 1978; 61: 753–760.
116. *Bluestone ChD.* Recent advances in the pathogenesis, diagnosis and management of otitis media. Pediatr Clin North Am 1981; 28: 727–755.

117. *Lim DJ, Liu YS, Scram J, Birck HG.* Immunoglobulin E in chronic middle ear effusions. Ann Otol Rhinol Laryngol 1976; 85 (Suppl 25): 117–123.
118. *Ruokonen J, Holopainen E, Palva T, Backman A,* Secretory otitis media and allergy. Allergy 1981; 36: 59–68.
119. *Dockhorn RJ.* Otolaryngologic allergy in children. Otolaryngol Clin North Am 1977; 10: 103–112.
120. *Slavin RG.* Sinusitis in adults. J Allergy Clin Immunol 1988; 81: 1028–1032.