SCRIPTA MEDICA (BRNO) – 74 (5): 303–344, *November 2001*

LATE TYPE OF THE NASAL ALLERGIC RESPONSE

REVIEW

PELIKAN Z.

Department of Allergology and Immunology, Institute of Medical Sciences "De Klokkenberg", 4836 AE Breda, The Netherlands

A b s t r a c t

Three types of allergy component, i.e., Type I (immediate), Type III (late) and Type IV (delayed), can be involved in allergic rhinitis. Patients with nasal allergy, when challenged with an allergen during the nasal provocation tests, may develop different types of nasal response: immediate (INR), late (LNR) or delayed (DYNR). LNR occurs in 41% of the rhinitis patients. The clinical course of LNR, as recorded by rhinomanometry, is as follows: onset within 4 to 8 h, maximum within 6 to 12 h and resolving within 24 h of the challenge with an allergen. LNR occurs either in an isolated form or in combination with INR. LNR is accompanied by severe nasal obstruction, while hypersensitivity, sneezing and itching appear to a lesser degree. LNR is regularly associated with other diagnostic parameters, such as, positive disease history (in 23%), rhinoscopic changes (in 90%, violaceous nasal musoca, in some cases also small mucosal haemorrhages), positive late skin response (in 65%, mostly induration), increased serum concentration of the total IgG (in 51%), increased blood oesinophilia (in 23%) and increased blood leukocyte counts (in 13%). LNR can also be accompanied by secondary responses of other organs (headache, palpebral oedema, conjunctivitis, otitis media, sinusitis, bronchial obstruction and general malaise symptoms). Positive LNR is accompanied by changes in the counts of various cell types in nasal secretions, such as, neutrophils (84%), eosinophils (58%), epithelial cells (73%), goblet cells (63%), basophils (8%) and lymphocytes (6%). Nasal mucosa biopsy during positive LNR reveals an oedematous epithelium with damaged integrity, sporadic breaches filled with fluid, irregular compactness of the basement membrane, an oedematous lamina propria containing eosinophil-neutrophil infiltrates, perivascular oeadema and dilatation of mucosal capillaries. LNR may also be accompanied by the appearance of total IgG in nasal secretions (46%) and an increase in concentrations of some compounds in nasal secretions (kinins, TAME-esterase, LTB_4, LTC_4, LTD_4, LTE_4, MBP, ECP, NCF, $PGF_{2\alpha}$, histamine and eosinophil-derived neurotoxin) LNR has also been recorded after food ingestion challenge. Positive LNR can significantly be prevented by topical (intranasal) application of disodium cromoglycate, glucorticosteroids or nedocromil sodium, whereas H_1- and H_2-receptor antagonists and immunotherapy have no significant effects on LNR. A possible involvement of various components on the late hypersensitivity mechanism(s) (Type III) in clinical LNR cannot be excluded.

K e y w o r d s

Late nasal allergic response, Clinical, immunological and pharmacological characteristics

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

AB, asthma bronchiale; Ab, antibody; Ag, antigen; AR, allergic rhinitis; BALT, bronchus-associated lymphatic tissue; BDA, beclomethasone dipropionate; BPT, bronchial provocation tests; BS, basophil; BUD/BSA, budesonide; Da, Dalton; DSCG, disodium cromoglycate; DYAR, delayded

asthmatic response; DYSR, delayded skin response; EALT, ear-associated lymphatic tissue; ES/EO, eosinophil; FEV1, forced expiratory volume in 1 second; FICH, food ingestion challenge; H-receptors, histamine-receptors; IAR, immediate (early) asthmatic response; IC, immune complex; i.c., intracutaneous; Ig, immunoglobulin; IH, immediate hypersensitivity; i.m., intramuscular; INR/ENR, immediate (early) nasal response; ISR, immediate (early) skin response; IT, immunotherapy; i.v., intravenous; LAR, late asthmatic response; LH, late hypersensitivity; LNR, late nasal response; LSR, late skin response; MC, mast cell; NALT, nose-associated lymphatic tissue; NAR, nasal airway resistance; NE, neutrophil; NPG, nasopharyx-nostrilpressure gradient; NPT, nasal provocation test; NR, nasal response; NS, nasal secretions; A-SH, non-specific hyper-reactivity; PRIST, paper-radio-immuno-sorbent terst; RADT, radio-allergo-sorben test, SALT, skin-associated lymphatic tissue; SBT, Salbutamol.

INTRODUCTION

The chronic, non-infectious rhinitis is characterised by nasal symptoms, such as obstruction due to mucosal swelling, hypersecretion, sneezing and itching *(1,2*). These symptoms can be caused by two different mechanisms, an allergy component and a non-specific hyper-reactivity component. They both can participate to various degrees in the nasal complaints of a particular patient *(1–4).*

The allergy component is, due to the immunological mechanism(s), initiated by an antigen-antibody (or antigen-T-cell) interaction, influencing the immuno-competent or target cell(s) (which can be changed, damaged or stimulated for selective secretion), a process which leads to the release of mediators acting either directly on various effector organs (e.g., smooth muscles, mucosal glands, goblet cells, epithelial cells, endothelial cells, capillary network, neurosynapses, receptors etc.) or indirectly through the effects on other cell types. A combined response of the effector organs results in a variety of clinical symptoms representing the particular allergic disorder *(1,2).*

The allergy mechanism may be of a seasonal or non-seasonal (perennial) character, depending on the kind of allergens involved. Of the four basic types of hypersensitivity (= allergy) reaction, as proposed by *Coombs and Gell (5),* three types can be involved in the production of symptoms in the rhinitis patient (Type I, Type III and Type IV) (2,3,6–19). These types of nasal response can be demonstrated by provocation tests with allergens (*Figs 1,2*) *(2–4,6–37).*

The non-specific hyper-reactivity component may lead to a spectrum of nasal symptoms which can partly be similar to the symptoms caused by an immunological mechanism but without any initial antigen-antibody interaction. The non-specific agents, mainly low-molecular weight chemical compounds, physical factors, such as temperature differences, vapours, smoke, perfumes, etc., or mechanical factors, such as non-organic dust, may have the following effects: i) they may influence the immuno-competent or target cell directly, causing a non-specific release of mediators, or indirectly, e.g., through the stimulation of nasal mucosal sensory nerves and/or a variety of mucosal

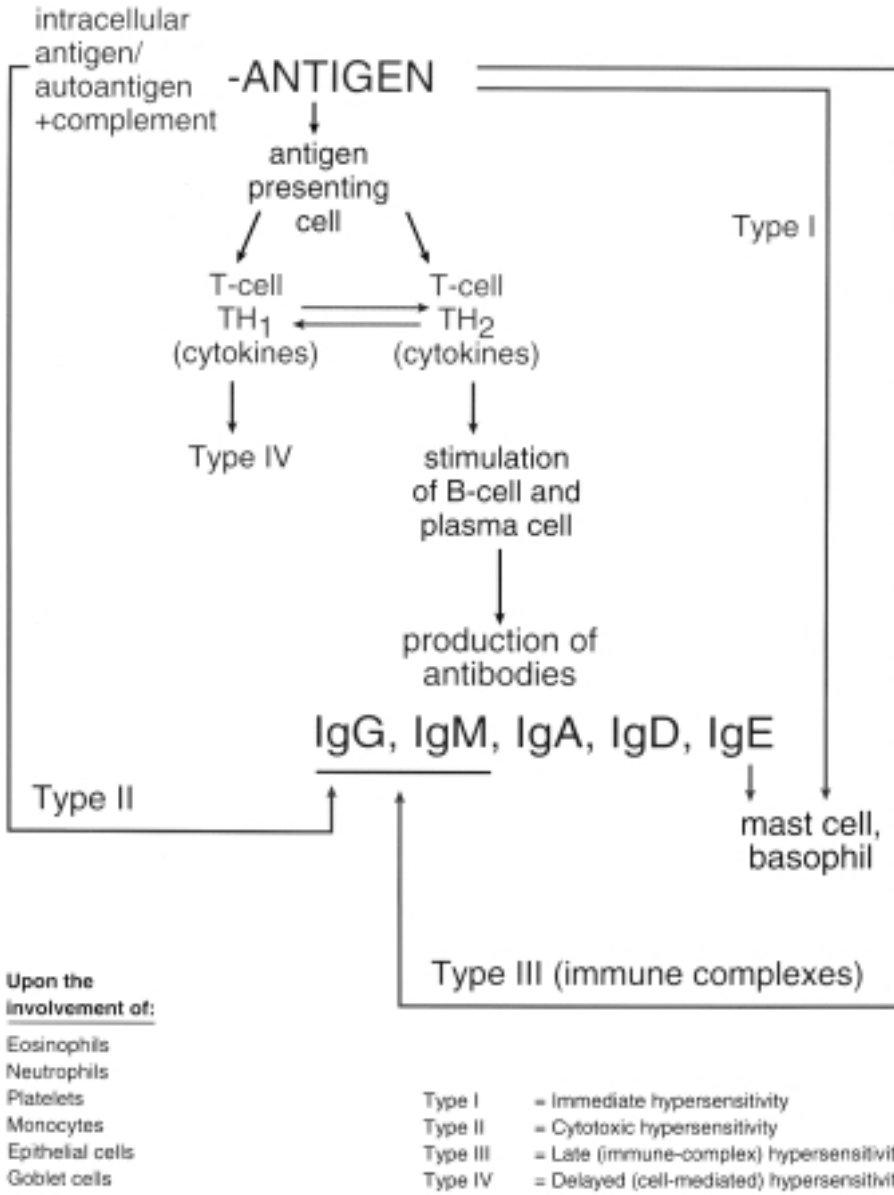


Fig. 1
Basic types of hypersensitivity (allergy) reactions

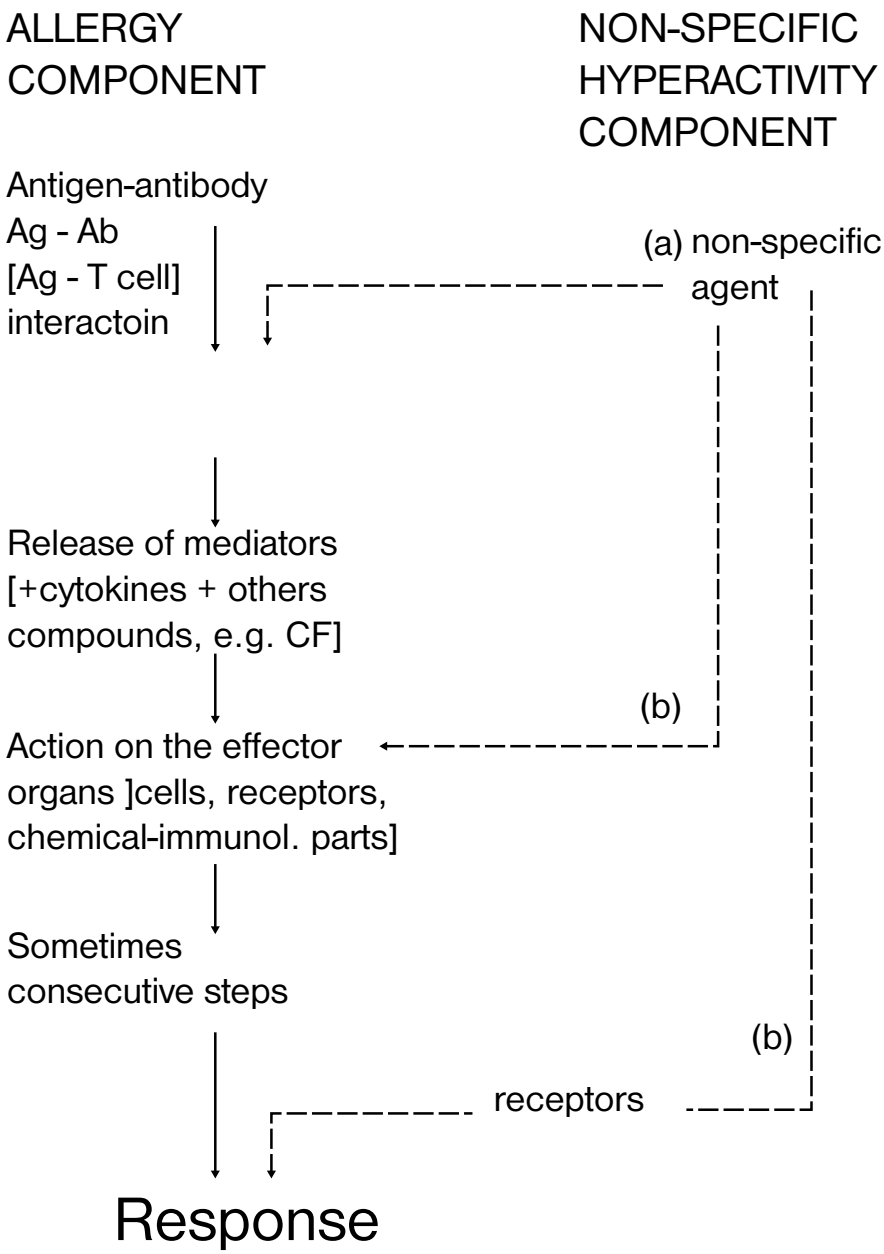


Fig. 2
Allergy and non-specific hyper-reactivity pathways

receptors, resulting in the activation and release of various neuropeptides which then affect the immuno-competent cells; ii) they may act via the stimulation of mediator precursors, firstly leading to the stimulation of mediator production, which then acts directly on the effector organs, and secondly leading to the feedback-inhibition of these mediators or immuno-competent cells; iii) they may also act on the effector organs and their receptors directly, thus causing the clinical effects (*Fig. 2*). A nasal challenge with histamine (or serotonin, acetylcholine, methacholine, cold air, etc.) may simulate and confirm the involvement of the non-specific hyper-reactivity and its degree in the nasal complaints of rhinitis patients *(3,4,25,38,39).*

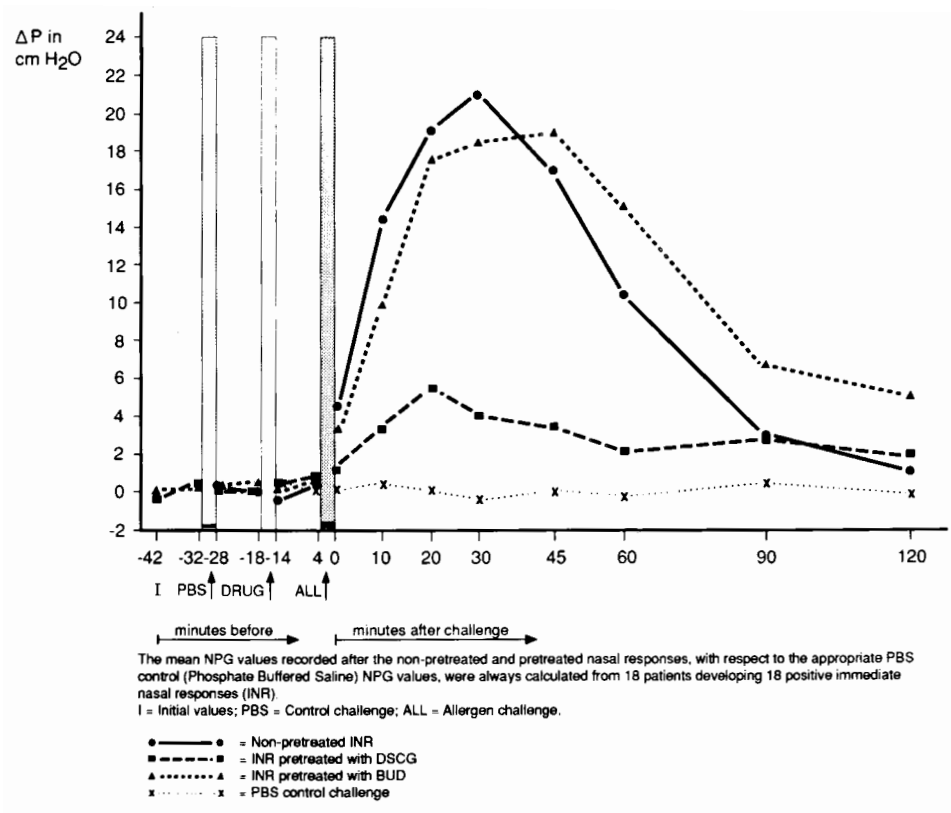


Fig. 3
Immediate nasal response to an allergen challenge and protective effects of disodium cromoglyate and budesonide

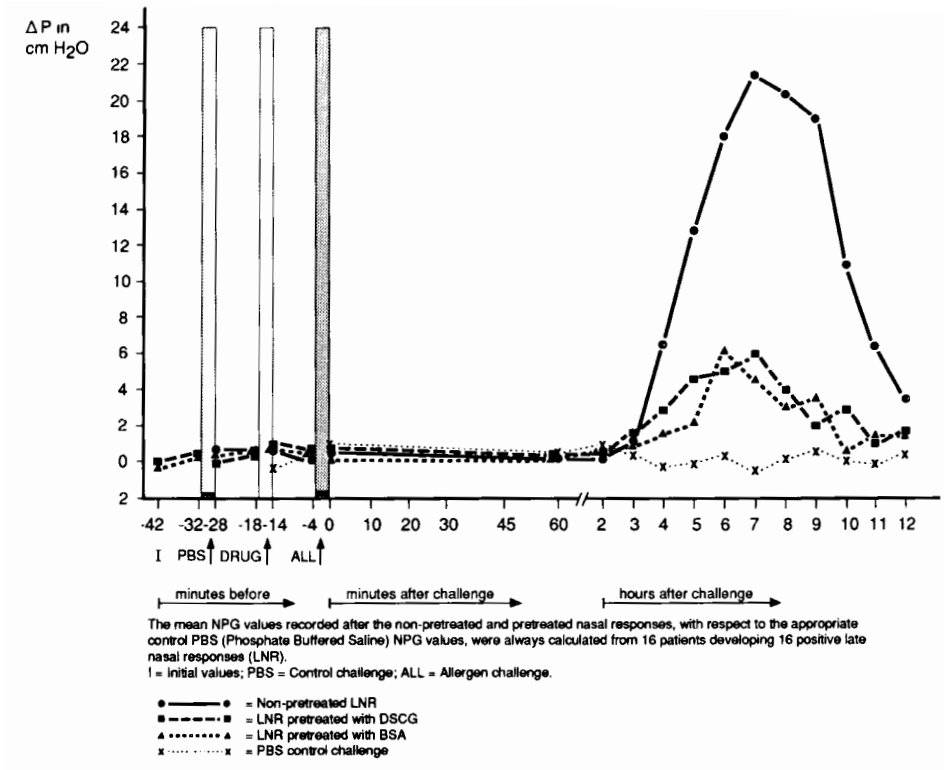


Fig. 4
Late nasal response to an allergen challenge and protective effects of disodium cromoglyate and budesonide

A positive nasal response of any of the basic types to an allergen challenge is an indicator of the involvement of an allergy component (ALL) in nasal symptoms, whereas a decreased nasal threshold of histamine (methacholine Br or Cl, cold air, etc) is an indicator of the involvement of a non-specific hyper-reactivity component (N-SH) in nasal complaints *(4,25,39).*

These two components (ALL and N-SH) may be considered to be two independent processes, each based on a principally different mechanism *(25,39).* They both can participate, to various and variable degrees, in the nasal complaints of rhinitis patients *(25,39).* They both can exist one beside the other in the same patient, but neither can be regarded as a necessary condition for the other *(25,39).* Both components have been confirmed in approximately 39% of the patients with chronic rhinitis; the allergy component alone has been found in

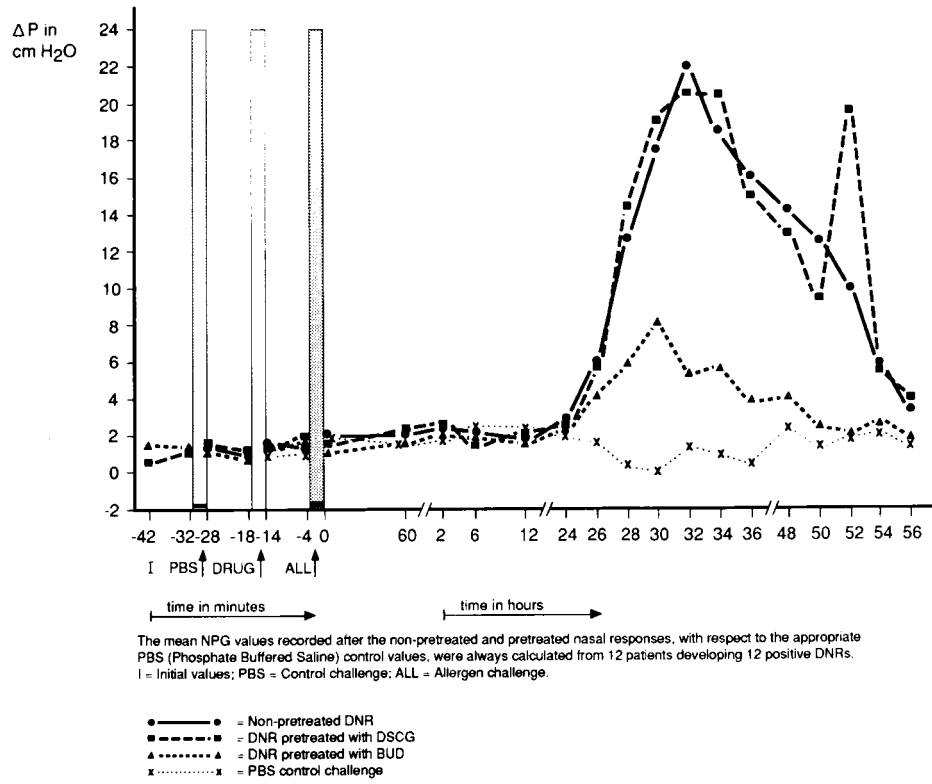


Fig. 5
Delayed nasal response to an allergen challenge and protective effects of disodium cromoglycate and budesonide

47% and the non-specific hyper-reactivity component in only 14% of the rhinitis patients *(25,39).*

Nasal provocation test

Nasal provocation tests with allergens, also called nasal challenges, are widely accepted as an important research technique and they are also considered to be ones of the most important *in vivo* diagnostic tests for the detection of the allergic component, for confirmation of the role of a particular allergen in nasal complaints of patients with rhinitis and for confirmation of the causal role of the nasal mucosa (allergy) and/or nasal response in disorders and/or responses of related organs *(2–4,6–24,26–33).*

Nasal challenges with histamine (or serotonin, methacholine, cold air etc.) may then confirm the role of non-specific hyper-reactivity in these patients *(3,4,25,38,39).*

NPT should be regarded as a model technique and as a simulated reproduction of the patient's complaints and symptoms caused by exposure to a certain allergen or non-specific agent *(3).* The nasal provocation test is the only technique that can demonstrate the particular type of nasal response caused by a certain allergen *(2–4).* Moreover, the nasal provocation test is also the only technique for confirming the participation of an allergy component and a non-specific hyper-reactivity component in a certain patient and for discriminating between these components *(2–4,9,40,41).*

Patients with nasal allergy who are challenged with an allergen during NPT, may develop different types of nasal response: immediate response (INR) or non-immediate types of response, i.e., late (LNR) and delayed response (DYNR) (*Figs 3,4,5*) (*2,6–19,22–24,26,31,40).*

The immediate hypersensitivity (Type I allergy) reaction causing the immediate nasal response (INR) has been studied most frequently and is described in the literature (*Fig. 3*) *(2,3,10,17,24,31,41).*

The existence of non-immediate nasal responses was first suggested by Taylor and colleagues *(22).* The first controlled investigation of non-immediate types of nasal response has been carried out by us (*Figs 4,5) (6).*

Since then LNR has been studied extensively by us from various points of view *(2,7–9,11–16,18,19,20,21,26–31,40),* in relation to other organs (14,15,18–21,31) and with respect to various antigens *(6,16,20);* its pharmacological modulation has also been investigated *(11,12,20,26–29,31*).

This response may play an important role in patients with chronic allergic rhinitis, but is often overlooked in practice and may be responsible for failure of the usual treatment in these subjects *(2,6,11,20,31*,*34).* LNR occurs in approximately 41% of the rhinitis patients. *(6,11*)

The clinical course of LNR, as recorded by rhinomanometry, is as follows: onset within 4 to 8 h, maximum within 6 to 12 h and resolution within 24 h after the allergen challenge (*Table 1*) *(2,6–9,11,14–16,27–31,34–37).*

LNR occurs in two sub-forms, either as an isolated late response (ILNR) or as a dual late response (DLNR) in which the immediate response appears first (within 2 h) and is followed, after a symptom-free period of 3 to 7 h, by the late response *(2,6,9,11,14,16,27–29,31,40).*

Our results suggest that the dual late nasal response, analogically to the dual late asthmatic response, may in reality be the simultaneous appearance of two independent responses (an immediate/early and a late response) due to different mechanisms, both of them caused by the same allergen *(48–55).*

LNR is usually accompanied by a variety of acute nasal complaints appearing simultaneously with the course of the clinical response. A severe nasal obstruction

Table 1

Time course of specific clinical types of nasal response to allergen challenge

Nasal response	Onset	Maximum	Resolving
Immediate (INR)	< 10	20–45	< 90–120 minutes
Late (LNR)	4–8	6–12	< 24 hours
Delayed (DYLR)	24–30	30–40	< 60 hours

Table 2

A survey of nasal complaints accompanying the nasal responses

Nasal complaints	Nasal response		
	Immediate (INR)	Late (LNR)	Delayed (DYNR)
Obstruction	++	+++	+++
Hypersecretion	+++	+	±
Sneezing	+++	+	0
Itching	+++	±	0

0, absent; ±, very slight; +, slight; ++, moderate; +++, severe

due to a distinct swelling of the nasal mucosa is the most prominent symptom, while the other nasal symptoms, such as hypersecretion, sneezing and itching, are present to a lesser degree (*Table 2*) *(6,9,11).*

A definite confirmation of the existence of the particular types of nasal response (immediate, late, delayed) due to exposure to a certain allergen, and their participation in nasal complaints of an individual patient, can only be provided by the nasal provocation test (nasal challenge) with an allergen *(2,6–14,16–19, 20–24,27–29).*

The most important aspect of the provocation test is a comparison of objective parameters and subjective complaints before and, repeatedly, after the challenge with a particular allergen (or non-specific agent) *(3).*

NPT can be supplemented with a recording of various *in vivo* as well as *in vitro* diagnostic parameters and functions, such as clinical symptoms (pulse rate, blood

pressure, body temperature), functions of other organs (tympanometry, conjunctival appearance, sinus X-ray or echography, lung functions, etc.) *(14,18,19,21,31)* or some other parameters (nasal biopsy, biochemical, cytological, and immunological investigation of nasal secretions and nasal mucosa, estimation of mediators, immunoglobulins and other compounds in nasal secretions and/or serum, physical and chemical properties of nasal secretions, such as consistency, pH, viscosity, etc.) *(6–14,16–21,23–37,42–47,56–65).*

The nasal response to allergen challenge can be recorded and assessed by various methods and techniques. There are two basic methods: *(1)* recording of subjective complaints (obstruction, hypersecretion, sneezing, itching) by means of various scores and *(2)* recording of objective parameters. The objective parameters are related to changed aerodynamics in the nose due to an increased nasal obstruction caused by swelling of the nasal mucosa and hypersecretion; these are due either to the antigen-antibody (antigen-T-cell) interaction or to the direct effects of non-specific agents *(3,6,57,65,66).*

The recording of objective parameters, mostly nasal airway resistance (NAR), by means of which the nasal mucosa response can be assessed, is preferred *(3,4,65).* NAR can be measured by means of recording air-pressure, air-flow or air-volume parameters or their derivatives, such as air-passage or conductance, which is a reciprocal value of nasal resistance *(2,3,4,41,65).*

Techniques used for NPT can be divided into 5 groups: (1) nasal peak-flow measurement, (2) plethysmography, (3) rhinomanometry (anterior, posterior, combined and/or modified techniques, performed either in an active or a passive manner), (4) acoustic rhinometry and (5) non-rhinomanometry (recording of nasal blood flow using Doppler velocimetry, the 133 Xenon washout method, or nasometry) *(6–19,22–23,41,58,65–70).*

We use a balloon method, one of the combined rhinomanometry techniques (recording of nasopharynx-nostril pressure gradients (NPG), expressed in cm of H_2O) described in detail in our previous papers *(3,4,6–19,65*), as a standard method. Passive anterior rhinomanometry is used for children, while volume-flow and volume-pressure diagrams (active posterior and active anterior rhinomanometry) are used for research purposes or as arbitrary tests.

The basic schedule of NPT used by us is as follows: (1) Baseline values are recorded at 0, 5, and 10 min. (2) Control values, after a 3-minute application of control solutions (PBS, Coca's solution or saline) are also recorded at 0, 5, and 10 min. If there are no significant changes in NPG control values, as compared with the baseline NPG values, the test may be continued. (3) Post-challenge NPG values (after an allergen challenge usually for 3 min) are recorded at 0,5,10,20,30,45,60,90 and 120 min, and then every hour up to the 11th (12th) hour and, if necessary (the response has not resolved or a delayed response is expected), every hour on the second or third day. A control challenge with the control solution

Table 3

A survey of the specific types of skin responses recorded after intracutaneous skin tests with the same allergen as that causing the corresponding type of nasal response (in %).

	Skin response			
Nasal response	Immediate (< 20 min)	Late (4–24 h)	Delayed (> 36 h)	No response
Immediate (n=246)	63	8	0	29
Late (n=225)	11	51	1	37
Delayed (n=93)	15	2	42	41
No response (n=182)	18	12	2	68

is performed in the same way on another day and NPG parameters are recorded at the time intervals used for the allergen challenge *(2-4,6–21,65).*

Association of LNR with immunological and clinical parameters

A positive history of reactivity to the allergen causing LNR has been found in 37% of the LNR cases; in 23% of them the history was indicative of the late onset of nasal complaints. During LNR, the nasal mucosa (± 90%) has been found to be violaceous and rather dry due to diminished secretions in the majority of patients. Solitary, small mucosal haemorrhages may sometimes be observed on the middle and/or inferior turbinate (*Table 4*) *(2,6,11,65,71).*

The immediate skin response (weal) to the same allergen as that causing LNR has been found in 11% of the LNR cases *(6,11,65,71).* The late skin response (induration) has been found in 51% (*Table 3*) and 65% (*Table 4*) of the LNR cases, without any significant differences in relation to the two LNR sub-forms (*Table 3,4*).

The concentration of total IgE antibodies in serum (PRIST) has been found to be significantly increased (>500 IU/ml) in only 6% of LNR cases, most of them being a part of the dual late nasal response (*Table 4*) *(6,11,65,71).*

The specific serum IgE antibodies (RAST) to the same allergen as that causing the clinical LNR have been positive (score grade 3 or 4) in 9% of the LNR cases, most of them being a part of the dual late nasal response (*Table 4*) *(6,11,65,71).*

The serum concentration of total IgG immunoglobulins has been found to be increased in 51%, the concentration of total IgM immunoglobulins in 8% and that

Table 4

The association of the particular types of nasal responses with other diagnostic parameters (in %)

	Nasal mucosa response to allergen challenge			
Response-related parameters	Immediate (n=148)	Late (n=131)	Delayed (n=63)	Negative (n=205)
Positive skin response				
Immediate	70			31
Late		65		9
Delayed			67	3
Increased total IgE in serum (PRIST)	17	6	5	9
Positive specific IgE in serum (RAST)	27	9	2	11
Increase in the serum				
Total IgG	19	51	1	3
IgG1	0	2	0	1
IgG2	0	0[a]	0	4
IgG3	2	19	0	1
IgG4	0	16	1	2
Total IgM	0	8	0	0
Total IgA	1	1	0	1
Increase in blood leucocytes	4	20	11	3
Increase in blood eosinophils	5	43	0	1
Increase in body temperature (more than 37°C = 98.6°F)	0	2	2	0
General malaise complaints	0	6	12	2
Aspects of the nasal mucosa				
Hyperaemia	34	10	0	18
Violaceous aspect	59	90	100	1
Nasal mucosa haemorrhages	0	24	43	0
Patient-related parameters				
Increased reactivity of the nasal mucosa to histamine	31	23	2	89

[a], IgG2 in serum decreased in 16% of the LNR cases.

Table 5

A survey of allergy and non-specific hyperactivity components in 166 patients with chronic rhinitis

Patients with nasal response (NR) to allergen challenge (n=166)	Non-specific hyper-reactivity in the nose, i.e., nasal responsiveness to histamine (counter-value is the nasal histamine threshold)	
	Increased	Non-increased (normal)
Positive NR (n=142)	45	97
– isolated immediate NR (n=42)	23	19
– dual late NR (n=41)	15	26
– isolated late NR (n=37)	6	31
– dual delayed NR (n=12)	1	11
– isolated delayed NR (n=10)	0	10
Negative NR (n=24)	23	1

of total IgA immunoglobulins in 1% of the LNR cases. The serum concentration of individual IgG sub-classes has been recorded during LNR as follows: elevation in IgG1, IgG3 and IgG4 was found in 2%, 19% and 16% of the LNR cases, respectively, and a decrease in IgG2 was observed in 11% of the cases (*Table 4*) *(6,11,16,65,71).*

An increase in blood eosinophil counts (more than 300 x 10^6/L) has been recorded during 23% of the positive dual late nasal responses and during 20% of the isolated late nasal responses (*Table 4) (6,11,16,65,71).*

An increase in blood leukocyte counts (more than 10 x 10^9/L) has been recorded during 13% of the isolated, and during 7% of the dual late nasal response (*Table 4*) *(6,11,16,65,71).*

An increase in body temperature (> 37 °C or 98.6 °F, measured in the armpit) has been recorded during 2% of the LNR cases (*Table 4*) *(6,11,16,65,71).*

The normal value for the nasal histamine threshold (NHT) is > 4.0 mg/ml (12 mmol/ml). Increased nasal mucosa responsiveness to histamine (PD20) or its

Table 6

A survey of nasal complaints and other organs' response accompanying the specific types of nasal response to allergen challenge (in %)

	Nasal response to allergen challenge			
	Immediate (n=148)	Late (n=131)	Delayed (n=63)	Negative (n=205)
Nasal complaints	100	100	100	0
Obstruction	69	16	9	8
Sneezing	93	18	0	10
Hypersecretion	52	3	0	0
Itching	27	46	5	1
Conjunctival injection/chemosis	12	13	3	0
Palpebral oedema				
Middle ear response (otalgia, decrease in hearing, changes in middle ear pressure)	30	23	6	7
Pressure in the sinuses (maxillary and frontal)	37	18	22	7
Acute oedema of sinus mucosa (X-ray; echography)	3	11	14	1
Cephalgia	26	47	11	2
Bronchial complaints (mostly secondary bronchoconstriction, sometimes also wheezing and/or cough)	5	4	6	2
General malaise complaints	3	1	0	0

contra-value, the so-called decreased nasal histamine threshold, has been recorded by us in only 15–20% of the patients developing LNR. The NHT mostly ranged between 2.0 and 4.0 mg/ml, i.e., 6.0 to 12.0 mmol/ml (*Table 4,5*) *(25,65,71,73,74).*

Table 7

Middle ear response to the nasal allergen challenge (NPT) in patients with secretory otitis media
A survey of otological complaints during nasal responses

Patients N=38	n	Changes in MEP			Otalgia only
		accompanied by			
		Otalgia	Decrease in hearing	Secretions	
76 positive NRs	61	56	35	13	4
21 isolated immediate	19	18	6	4	2
24 isolated late	17	17	13	5	1
15 dual late	17	10	9	1	0
11 isolated delayed	9	9	4	2	0
5 dual delayed	4	2	3	1	1
33 negative NRs	13	6	2	1	1

NR, nasal response; MEP, middle ear pressure recorded by tympanometry; secretions, rapid increase in the middle ear effusions through the mono– or bilateral ventilation tube(s)

Table 8

The specific types of nasal and paranasal sinus responses induced by the nasal challenge with an allergen and their relationship

Nasal response	Sinus response					
	Maxillary (n=135)a			Frontal (n=17)b		
N=193	ESR	LSR	DYSR	ESR	LSR	DYSR
149 positive NR						
51 immediate/early	44	3	1	3	3	0
15 immediate + late	6	4	0	1	2	0
67 late	0	61	3	0	5	0
7 immediate+delayed	1	0	4	1	0	1
9 delayed	0	0	8	0	0	1
	Maxillary (n=13)c			Frontal (n=4)d		
44 negative NR	5*	7*	1*	3*	1*	0

NR, nasal response; ESR, early sinus response; LSR, late sinus response; DYSR, delayed sinus response; a, 135=121+14; b, 17=3+14; c, 13=4+6+1+2; d, 4=1+1+2; *, primary or „non-associated“ form of sinus response; the remaining responses are of the secondary or so-called „associated“ form.

Table 9

A review of asthmatic responses induced by nasal provocation tests with allergens in 27 patients suffering from bronchial asthma with a low compliance to the usual anti-asthmatic treatment

NPT (n=133)	Secondary induced asthmatic responses					
Nasal response positive (n=119)	Isolated immediate	Dual late	Isolated late	Dual delayed	Isolated delayed	Negative
Isolated immediate (n=28)	20	1	2	0	0	5
Dual late (n=19)	1	13	1	0	0	4
Isolated late (n=46)	0	0	36	0	0	10
Dual delayed (n=9)	0	0	0	7	0	2
Isolated delayed (n=17)	0	0	0	0	11	6
Negative (n=14)	2	0	0	0	0	12
Total	23	14	39	7	11	39

NPT, nasal provocation test

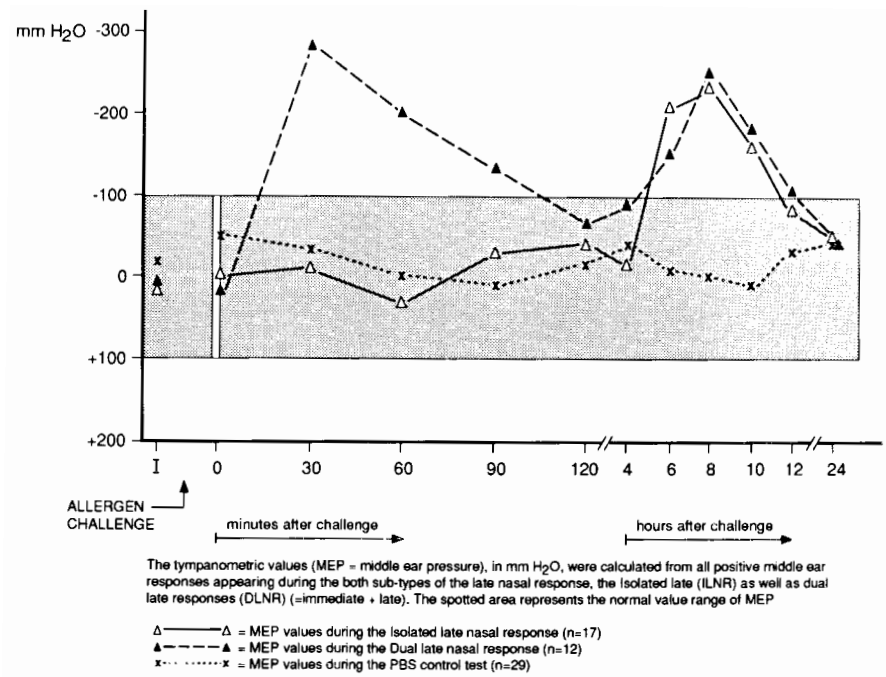


Fig. 6
Middle ear response recorded during the late nasal response to an allergen challenge

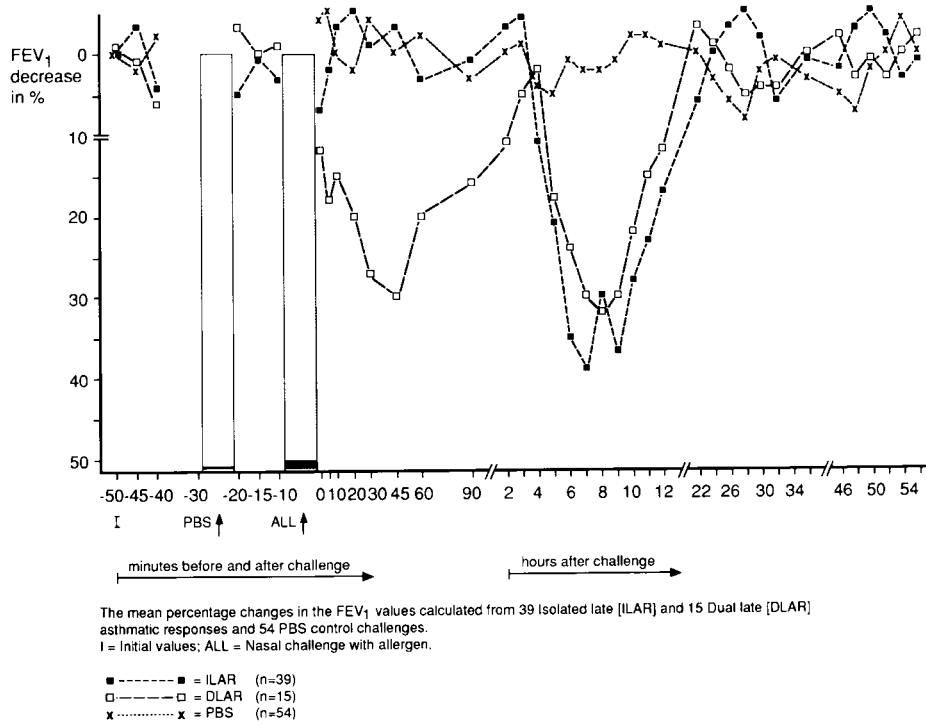


Fig. 7
Isolated late (n=39) and dual late (n=15) asthmatic responses induced by an allergic reaction originating primarily in the nasal mucosa

The normal value of nasal methacholine chloride threshold (NMCT) and that of the nasal methacholine bromide threshold (NMBT) are >8.0 mg/ml and >4.0 mg/ml, respectively. An increase in nasal mucosa responsiveness to methacholine chloride and/or bromide or its contra-value, the so-called decreased NMCT, has been recorded by us in 11% and the decreased NMBT in 9% of the patients developing LNR *(25,39,73,74).*

Histamine has been detected in the blood plasma of patients developing the positive LNR only sporadically and without any significant changes in its concentration *(74–76).* Histamine has been detected in nasal secretions during LNR only sporadically and without any significant changes in its concentration *(74,75).*

Precipitating antibodies, usually of the IgG class, can be determined by double immunodiffusion in gel (Ouchterlony & Nilsson technique) (*77*). LNR due to certain kinds of antigens, such as bird faeces and serum *(16)*, wool *(65,71)*, old paper *(71)*, cardboard *(71)*, flour *(6,11,71)* and moulds *(6,11,71)* has been found to be significantly associated with an increased concentration of the circulating precipitating antibodies of IgG and/or IgM classes in blood serum.

LNR can also induce a secondary response in related organs. A survey of the secondarily induced responses is presented in *Tables 6* to *9* and *Figs 6* and *7*. LNR can be caused by various inhalant allergens. No differences in the occurrence of LAR in relation to different allergens have been found *(65,71)*.

Nasal hypersensitive reaction

Hypersensitivity reactions in the nasal mucosa leading to the development of different types of nasal response to allergen exposure (challenge) are dynamic processes caused by specific allergens, where various types of cells, mediators, compounds and mechanisms may be involved in various steps and at various levels *(1,2,4,7–9,13,42–45,71,74*).

The hypersensitivity reactions are also exfoliative processes leading to the influx and release of various cell types as well as various factors, compounds and chemical derivates into nasal secretions *(1–3,7–10,13,17,24,27–29,32,34–37, 42–47,57,59,61–63,71,72,80,81)*.

Cellular characteristics of nasal secretions

A positive LNR in nasal secretions has been accompanied by significant changes in neutrophil counts in 84% of the cases (an increase immediately before and a decrease during the appearance of LNR, followed by an increase during the resolution of LNR), eosinophils in 58% (an increase immediately before and a decrease during the appearance of LNR), epithelial cells in 73% (an increase followed by a decrease), goblet cells in 63% of the cases (an increase followed by a decrease), basophils in 8% and lymphocytes in 6% (both cell types demonstrated a slight increase in their counts during LNR). No significant changes in the counts of other types of cells (monocytes, plasma cells, mast cells) have been recorded in nasal secretions during most of the LNR cases (*Table 10, Fig. 8*).

Cytologic changes in nasal secretions, recorded during LNR, are clearly different from those found by us during both the immediate nasal response (INR) *(2,7–10,28,42–45,80)* and the delayed nasal response (DYNR) *(13,44)*.

These results and conclusions can be supported by another aspect. The cells appearing in nasal secretions before the allergen challenge, during the PBS control and during the negative nasal response have mostly been intact, whereas those migrating and/or being released into nasal secretions during a positive LNR

Table 10

Presence of cell types in nasal secretions and changes in their counts during the late nasal response in %

LNR (n =104) NNR (n= 83) PBS (n= 187)	Presence of the cells			Changes in cell counts between the start and the end of challenge		
	LNR	NNR	PBS	LNR	NNR	PBS
Eosinophils	61	19	49	58*	5	1
Neutrophils	96	17	45	84*	3	2
Basophils	15	9	10	8*	0	0
Epithelial cells	100	23	41	73*	4	1
Goblet cells	82	13	35	63*	3	0
Lymphocytes	18	4	9	6*	0	0
Mast cells	3	2	1	0	0	0
Plasma cells	4	2	1	0	0	0
Monocytes	1	0	0	0	0	0

LNR, late nasal response; NNR, negative nasal response; PBS, phosphate buffered saline (control); *, statistically significant changes ($p<0.05$)

and shortly after its resolution, have demonstrated distinct intracellular changes, including changed cytoplasmic granules (degranulation) *(8,9,27,29,42,45).*

In most of the cells appearing in nasal secretions during the positive LNR, various cellular, intracellular and other changes, such as degranulation, disappearance of cytoplasmic granules, vacuolisation, diminished intake of stain, wrinkling of the cellular membrane and, sometimes cellular disruption, have been recorded (29,45). Neutrophils degranulated in 94% of the positive LNR cases, eosinophils in 49% and basophils in 3%, while during the negative nasal response, neutrophils degranulated in 7% of the cases, eosinophils in 7% and basophils in 0% *(29,45).*

Bascom et al. (82) and *Togias et al. (80*), using the nasal lavage technique, have observed a significant increase in the count of what they called „alcian-blue-stained positive cells", most probably basophils, but also of eosinophils and neutrophils, a slight increase in mononuclear cells and a decrease in the count of

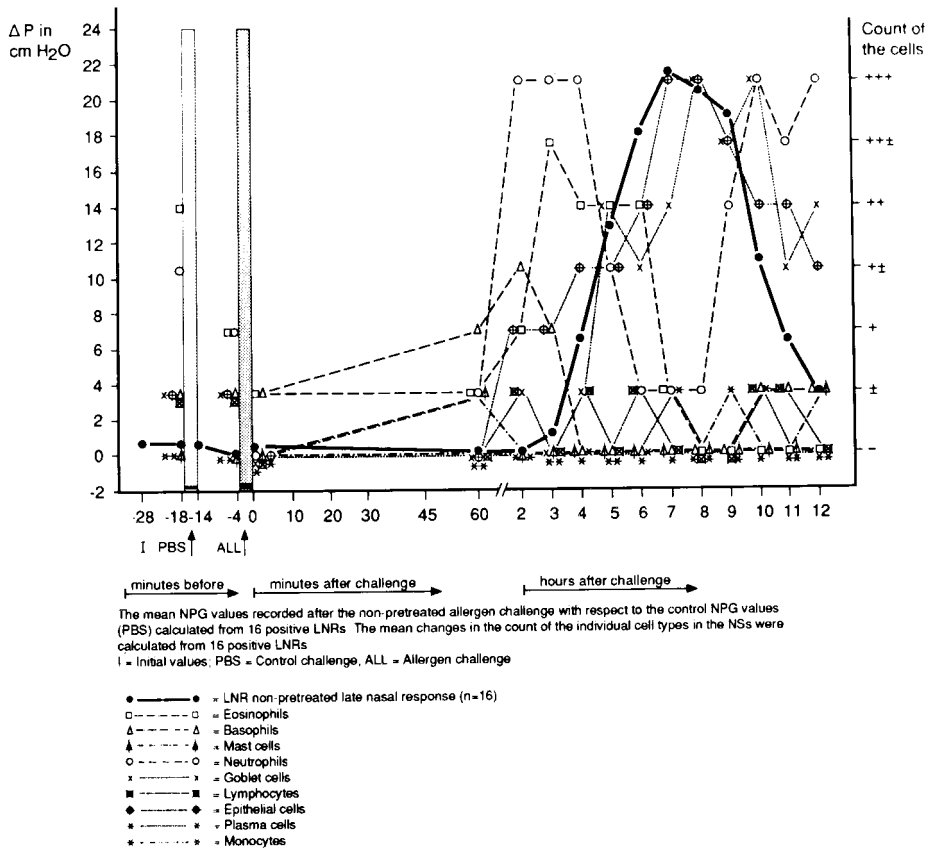


Fig. 8
Cytological changes in nasal secretions during the non-pretreated late nasal response

epithelial cells in nasal secretions during LNR to allergen challenge. *Walden and colleagues (59)* have recorded increases in total cell counts of eosinophils, neutrophils and „alcian blue cells" (probably basophils) in nasal secretions during LNR, which correlated with an increased release of some mediators (kinins, TAME-esterase activity, histamine, sulfidopeptide leukotrienes) and albumin into nasal secretions. *Iliopoulos et al (36)* have also observed an increased count of eosinophils and neutrophils in nasal secretions during LNR. However, they have found a significant increase only in the eosinophil count. The significant differences in cell influx into nasal secretions accompanying LNR and those

Table 11

Presence of immunoglobulin classes and changes in their concentrations in nasal secretions during the late nasal response, negative nasal response and PBS controls.

	Presence of immunoglobulins			Changes in immunoglobulin concentrations during the nasal response		
	LNR (n=24)	NNR (n=20)	PBS (n=24)	LNR	NNR	PBS
Total IgE	2 (8.4%)	0	1 (4.2%)	0	0	0
Antigen-specific IgE	3 (12.5%)	1 (5.0%)	1 (4.2%)	0	0	0
Total IgG	11 (45.0%)	1 (5.0%)	6 (25.0%)	8 (33.3%)	0	0
– IgG1	0	0	0	0	0	0
– IgG2	7 (29.1%)	0	2 (8.4%)	0	0	0
– IgG3	5 (20.8%)	0	1 (4.2%)	0	0	0
– IgG4	0	0	0	0	0	0
Total IgM	1 (4.2%)	0	1 (4.2%)	0	0	0
Total IgA	1 (4.2%)	1 (5.0%)	1 (4.2%)	0	0	0

LNR, late nasal response; NNR, negative nasal response; PBS, phosphate buffered saline

recorded during INR, as described by these authors *(36,59,80,82),* are generally consistent with our results *(7,42–45,65).*

Immunological characteristics of nasal secretions

A positive LNR may be accompanied by an appearance of total IgG antibodies in nasal secretions in 46% of the cases and by a decrease in IgG concentration in nasal secretions during LNR in 33% of the cases. Neither significant concentrations nor significant changes in concentrations of the immunoglobulins of other classes have been recorded in nasal secretions and blood serum during the positive LNR (*Table 11*) *(9,65,71,83).*

LNR may be accompanied by an increase in concentration of some mediators and compounds in nasal secretions, such as kinins, TAME-esterase (N-α-tosyl-L-arginine methylester), leukotrienes B4 (LTB4), C4 (LTC4), D4 (LTD4), E4 (LTE4), major basic protein (MBP), eosinophil-derived neurotoxin (EDN), bradykinin, lysylbradykinin, eosinophil cationic protein (ECP), neutrophil chemotactic factor (NCF), prostaglandin ($PGF_{2\alpha}$) and histamine. However, controversial results have been reported concerning the detectable amounts of histamine and significant changes in its concentration in nasal secretions during the positive LNR *(9,24,36,37,56,57,59,65,71,84–88).*

Finally, *Skoner et al. (88)* have measured an increased concentration of the neutrophil chemotactic factor (NCF), histamine and prostaglandin ($PGF_{2\alpha}$) metabolites in serum during LNR. In contrast to the results of other investigators *(24,36,37*), we have not detected histamine in nasal secretions during most of the LNR cases *(65,71,74,83).*

Biochemical and biophysical characteristics of nasal secretions

The biochemical and biophysical characteristics of nasal secretions during a positive LNR have not yet been studied sufficiently. There is little knowledge on this topic *(9,65,71,83).*

Biopsy findings

A positive LNR, as compared with the „pre-challenge“ baseline, may be accompanied by the following histological changes in biopsy specimens of the nasal mucosa: (1) oedematous epithelium with damaged integrity, enlarged intercellular spaces, sporadic holes filled with fluid, sporadic empty holes on the epithelial surface due to the release of some epithelial and goblet cells from the epithelial layer; (2) basement membrane with irregular structure and single breaches; (3) oedematous sub-epithelial layer of the lamina propria containing mixed eosinophil-neutrophil infiltrates and, sporadically, single mast cells, basophils, monocytes and lymphocytes; (4) perivascular oedema, dilatation of the terminal parts of capillaries and sporadic ruptures of small capillaries with erythrocyte expulsion. Histological changes recorded in the nasal mucosa during positive LNR may be qualified as slight, reversible tissue damage to the nasal mucosa with some inflammatory components (*Fig. 9*) *(35,46,47,62,64,72,83).*

LATE NASAL RESPONSE TO FOOD

The role of food allergy and of food in general, in subjects with various allergic disorders and in patients with nasal symptoms and complaints, has been repeatedly reported. Three basic types of nasal response, following a food ingestion challenge, have been recorded (*20,26,30,31,34, 65,89,90,92,93,100*):

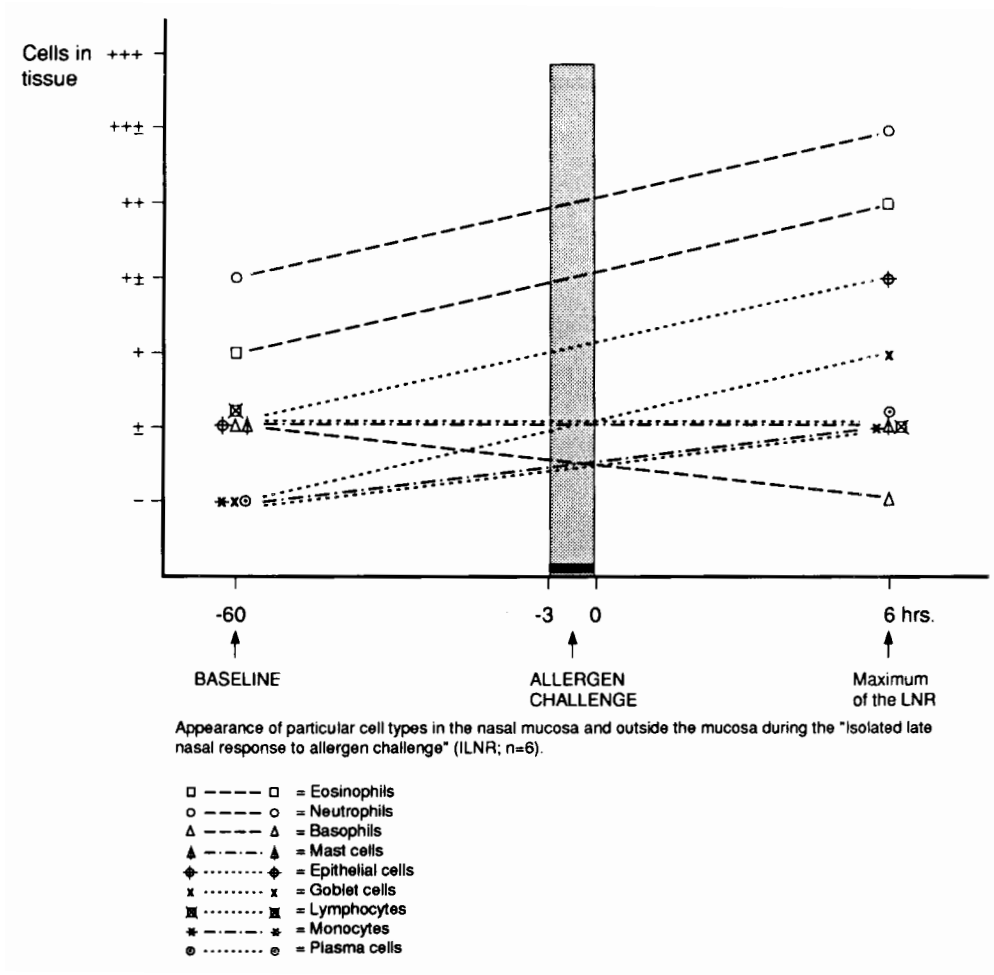


Fig. 9
Histology of the nasal mucosa during the late nasal response

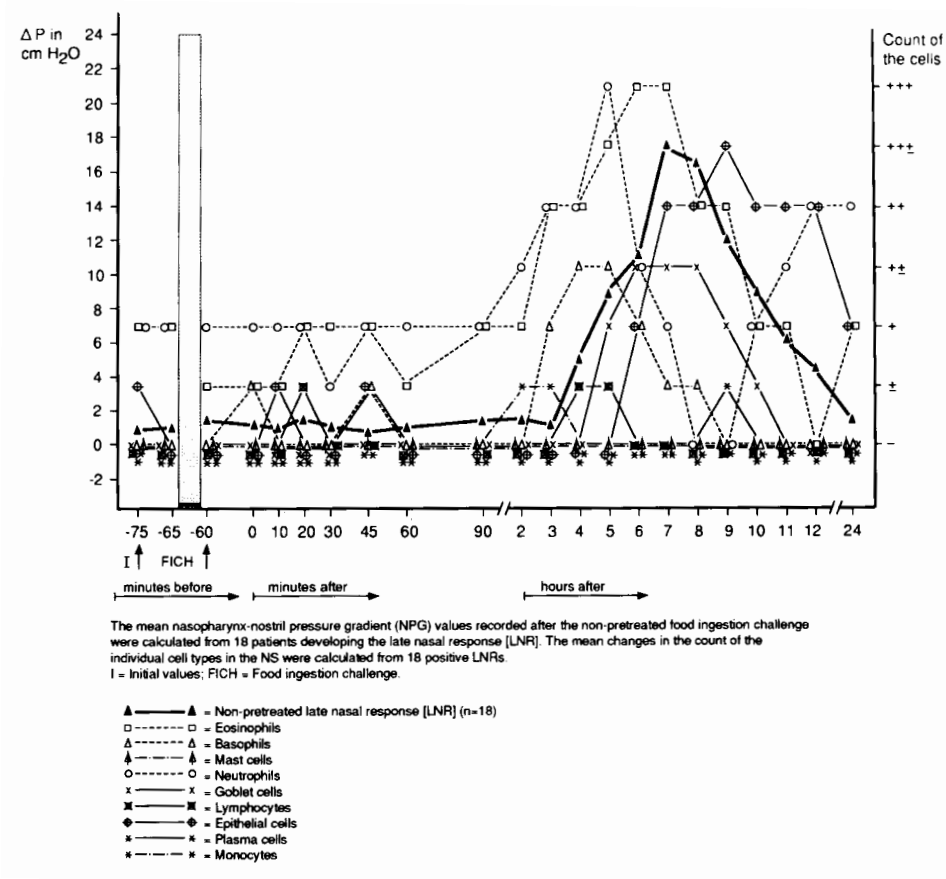


Fig. 10a
Late nasal response to the food ingestion challenge and accompanying cytological changes in nasal secretions

(1) an immediate/early response (INR/ENR), appearing within 70 min, peaking within 105 min and resolving within 180 min; (2) a late response (LNR), beginning within 6 h with a peak within 10 h and resolving within 24 h; (3) a delayed response (DYNR), starting within 24–28 h, peaking within 32–36 h and resolving within 48–52 h of food ingestion *(20,26,30,31,65,71).*

LNR caused by „adverse reactions to food" (i.e., food allergy is suspected to be one of the mechanisms involved), should be regarded as a special form of LNR (*Fig. 10a*) *(30).*

Table 12

An association of the particular types of nasal response to food ingestion challenge with other *in vivo* and *in vitro* diagnostic parameters

	Nasal mucosa response to food ingestion			
	Immediate (n=267)	Late (n=203)	Delayed (n=164)	Negative (n=309)
Positive skin response – immediate	146			48
– late		98		11
– delayed		69		3
Increase in total serum IgE (PRIST)	11	1	0	3
Increase in specific serum IgE (RAST)	38	3	1	4
Increase in blood eosinophils	14	17	2	2
Increase in blood leukocytes	10	38	11	3
Aspects of the nasal mucosa:				
hyperemia	197	48	1	5
violaceous aspect	70	155	163	0
Nasal mucosa haemorrhages	0	42	72	0
Nasal secretions				
Changes in counts of:				
eosinophils	201	128	53	21
mast cells/basophils	53	30	6	0
neutrophils	108	142	151	15
goblet cells	39	103	114	2
lymphocytes	9	5	146	0
epithelial cells	17	93	158	3

Table 13

Nasal and other complaints accompanying the particular types of nasal response to food ingestion challenge

	Nasal mucosa response to food ingested			
	Immediate (n=267)	Late (n=203)	Delayed (n=164)	Negative (n=309)
Nasal complaints				
obstruction	267	203	164	0
sneezing	19	1	0	1
hypersecretion	193	166	39	16
itching	181	75	175	13
General malaise complaints	22	54	49	1
Conjunctival irritation	35	18	6	0
Middle ear response (otalgia, decrease in hearing, changes in middle ear pressure)	31	19	13	10
Pressure in the sinuses (maxillary and frontal, acute oedema of sinus mucosa)	45	32	33	7
Cephalgia	56	91	125	42
Urticaria	4	7	8	5
Angio-neurotic oedema (labial, palpebral or elsewhere)	9	6	3	3
Increase in body temperature	4	21	1	0
Bronchial complaints	13	15	12	18
Other complaints	2	1	2	0

LNR to food occurs in approximately 47% of the patients with allergic rhinitis and is associated with a variety of other *in vivo* and *in vitro* diagnostic parameters, such as a positive disease history in 29%, a positive late skin response in 48%, an increase in total serum IgG antibodies in 24%, an increased blood eosinophil count in 8%, an increased blood leukocyte count in 9%, nasal symptoms, predominantly nasal obstruction, in 96%, which was followed by itching in 51% and hypersecretion in 14% of the patients; the nasal mucosa was hyperaemic in 23% or violaceous in 76% of the patients; changes in the count of eosinophils in nasal secretions were in 63%, neutrophils in 89%, epithelial cells in 46%, goblet cells in 51% and basophils in 15% of the patients (*Table 12*) *(9,20,30,71).*

Similarly to LNR caused by inhalant allergens, LNR due to food ingested can be accompanied by symptoms and responses in other organs, such as headache, migraine, conjunctival symptoms, middle ear response, bronchial obstruction, paranasal sinus response, gastro-intestinal symptoms, and general malaise complaints (*Table 13) (9,20,26,30,89–94).*

A positive LNR due to food ingested can be effectively prevented by oral administration of disodium cromoglycate (DSCG, Cromolyn, Nalcrom®), glucocorticosteroids (GCS) and partly prevented by intravenous administration of GCS. On the other hand, oral administration of H1- or H2-receptor antagonists and nasal topical administration of GCS have not been able to affect this form of LNR in any significant way (*Figs 10a, 10b*) *(9,20,26,65,89,92,93).*

Pharmacological modulation of LNR

A positive LNR due to inhalant allergens can significantly be prevented by topical (intranasal) disodium cromoglycate (DSCG, Cromolyn), topical glucocorticosteroids (GCS), oral corticosteroids and topical nedocromil sodium (NDS/NS), whereas most of the H1- and H2-receptor antagonists (antihistamines) have not demonstrated any significant effects on the LNR (*Fig. 4,11* and *Table 14*) *(2,9,18,19,21,27,29,31,44,65,71,83,95–100).*

DSCG, GCS and NDS have also demonstrated significant protective effects on the cell types appearing in nasal secretions during LNR by decreasing their counts (or preventing an increase in their count) and by preventing the development of various cellular and/or intracellular changes in these cell types *(7–9,11,27,29,31, 43–45,47,65,71,96–98).*

Disodium cromoglycate and glucocorticosteroids

LNR pretreated with DSCG and GCS has been accompanied by distinctly decreased counts of all cell types in nasal secretions, as compared with a non-pretreated LNR, and by non-significant changes in the counts of particular cell types, as compared before and after the allergen challenge (27,29,65). LNR pretreated with beclomethasone dipropionate (BDA) or budesonide (BSA/BUD) has also been

Table 14

Protective effects of basic drugs on the immediate, late, and delayed nasal response to a nasal challenge with inhalant allergens and protective effects on non-specific nasal hyper-reactivity represented by the nasal response to histamine challenge

	INR	LNR	DYNR	N-SH
Antihistamines				
H_1-receptor antagonists	±*	–	–	+
H_2-receptor antagonists	–	–	–	0
H_1- + H_2- receptor antagonists	–	–	–	0
Anticholinergics				
systemic (oral)[a]	–	–	–	+
topical[b]	–	–	–	+
Calcium channel blockers	0	0	0	0
Acetylsalicylic acid	0	0	0	0
cAMP modulators	0	0	0	0
Alpha2-sympathomimetics	–	–	–	±
Disodium cromoglycate	+++	++	–	±
Nedocromil sodium	+++	+++	±**	0
Corticosteroids				
systemic - oral	–	–	–	–
- injection (i.v., i.m.)	±	±	±	–
topical	–	+++	+++	+
Immunotherapy	±	–	–	–

-, no effect; ±, slight or partial effects (without significance); +, positive effects ($p<0.05$); ++, significant effects ($p<0.01$); +++, highly significant effects ($p<0.001$); 0, lack of data.
* In this category, some drugs demonstrated significant protective effects on the immediate nasal response (e.g., Cetirizine, Clemastine, Chlorphenamine, Mebhydroline and recently also Loratadine), whereas others did not (e.g., Ketotifen, Astemizole, Terfenadine and Levocabastine).
** Recent preliminary data suggest some protective effects of this drug on the delayed nasal response.
[a] Thiazinamium hydrochloride, Oxyphenonium; [b] Ipratropium bromide.

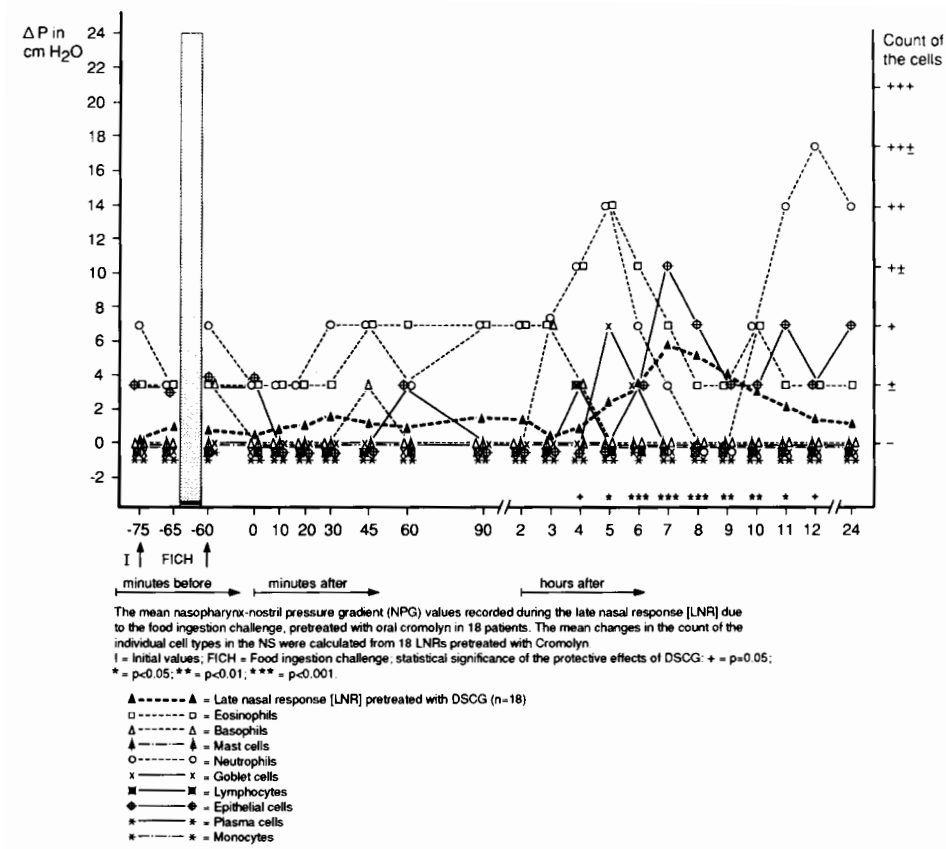


Fig. 10b
Late nasal response to the food ingestion challenge pretreated with oral disodium cromoglycate (Cromolyn), and accompanying cytological changes in nasal secretions

accompanied by the counts of all cell types in nasal secretions that were distinctly lower than those recorded during the non-pretreated LNR, and no significant changes have been found by us in the counts of the cell types studied *(27,29,65).*

DSCG treatment has significantly reduced degranulation and other intracellular changes in eosinophils, basophils and mast cells, and partly also in neutrophils. BSA treatment has effectively reduced degranulation and other intracellular changes in neutrophils, partly in eosinophils and basophils, but not in

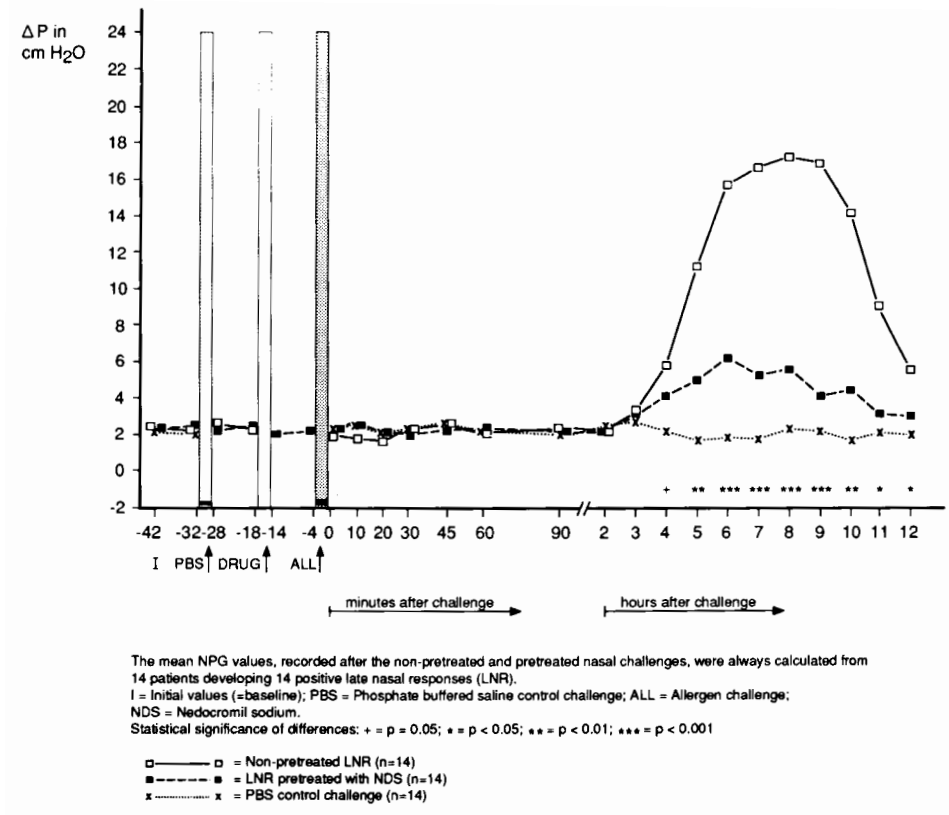


Fig. 11
Protective effects of topically administered nedocromil sodium on the late nasal response to an allergen challenge

mast cells. These results may again suggest a possible involvement of different mechanisms or, at least, different sub-mechanisms in LNR *(7–9,11,27,29,31, 43–45,47,65,71,96,97,99).*

Bisgaard et al. (86), studying timothy grass pollen-sensitive subjects who had developed a dual late nasal response to challenge with this allergen, have recorded an increase in concentration of the eosinophil cationic protein in nasal lavage fluid during LNR, but not during INR. The increase in eosinophil cationic protein has been completely inhibited by pretreatment with intranasal Budesonide, in a daily dose of 400 mg, for 2 weeks prior to the nasal allergen challenge.

Other investigators studying predominantly mediators and other factors in nasal lavage fluid have found that pretreatment with topical glucocorticosteroids (flunisolide) significantly reduced both the late nasal symptoms and the levels of histamine, TAME-esterase activity and kinins in nasal secretions, during the allergen-induced LNR *(80,101).*

Walden et al. (59) have studied subjects with pollen-related rhinitis, who developed a dual LNR to allergen challenge that consisted of an early and a late phase. The early-phase was accompanied by an increase in concentration of histamine, TAME-esterase, kinins and PGD2 in nasal secretions and by an influx of alcian blue-stained positive cells, probably basophils, into nasal lavage fluid, whereas the late phase was accompanied by an increase in histamine level, TAME-esterase, kinins, sulfidopeptide leukotrienes and albumin, but not PGD2, in nasal secretions, and by an influx of alcian blue-stained positive cells, eosinophils and neutrophils into nasal lavage fluid. A 2-day pretreatment with oral corticosteroid (prednisone) has prevented the symptoms of LNR, significantly decreased the concentration of histamine, TAME-esterase, kinins and albumin in nasal lavage fluid and significantly reduced the influx of eosinophils, but not of neutrophils or mononuclear cells. This group of investigators has reported a significant role of topical corticosteroids in reducing the symptoms as well as the levels of histamine, TAME-esterase activity and kinins during both the early and the late phase of nasal responses.

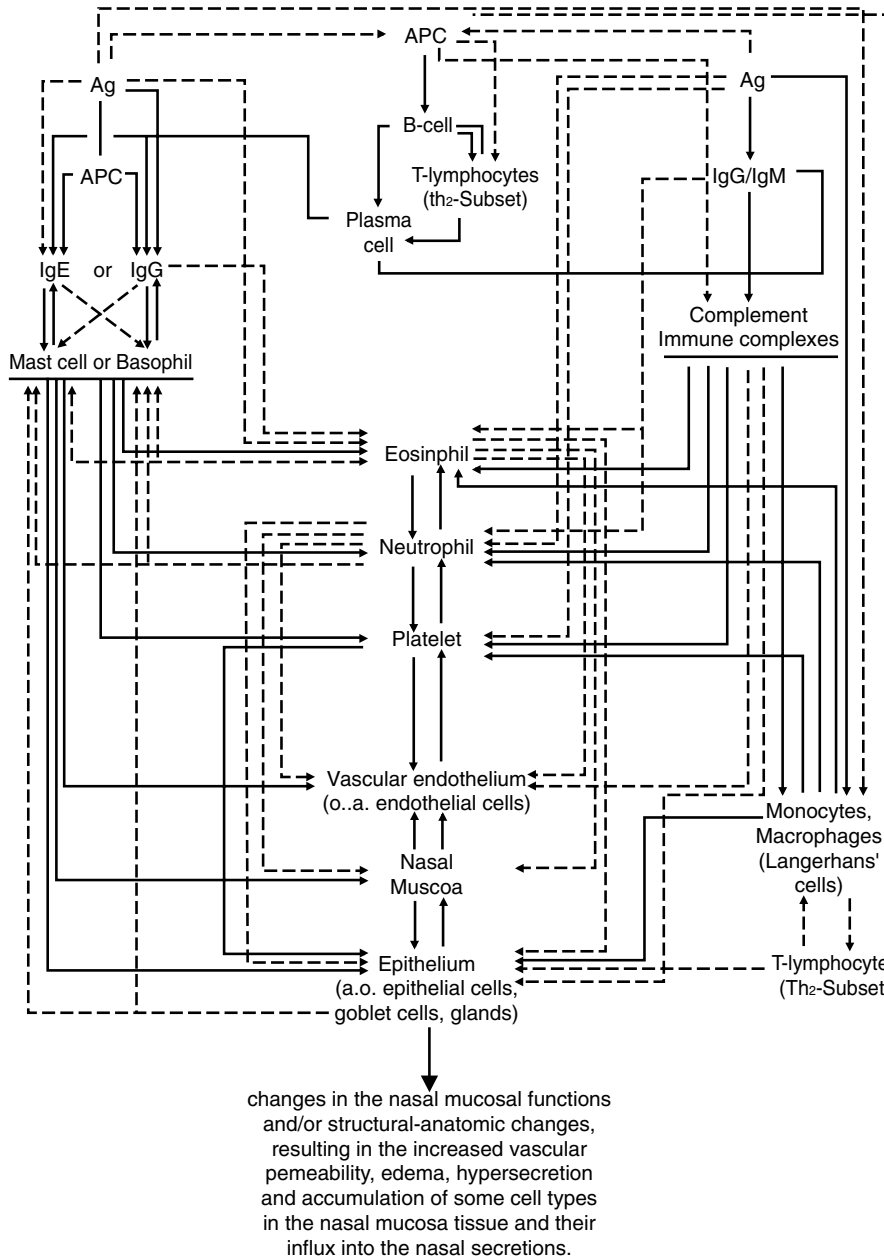
Bascom et al. (32) have reported similar suppressive effects of oral corticosteroids on the influx of eosinophils, but not of neutrophils or mononuclear cells, into nasal-lavage fluid during LNR. In another study, *Bascom et al. (102)* have recorded a significant increase in the concentration of major basic protein in nasal lavage fluid during both INR and LNR to allergen challenge, a significant increase in the concentration of eosinophil-derived neurotoxin during the late phase, and finally a significant increase in the influx of eosinophils into nasal secretions during the late phase. Treatment with oral prednisone has reduced significantly not only the eosinophil influx, but also the concentration of both major basic protein and eosinophil-derived neurotoxin in nasal lavage fluid.

H1-receptor antagonists and anticholinergic drugs

Neither antihistamines nor anticholinergics have demonstrated significant protective effects on LNR *(65,71,96–98,100).*

Nedocromil sodium

Nedocromil sodium has significantly prevented INR ($p < 0.01$) and highly significantly LNR ($p < 0.001$). Moreover, during INR, nedocromil sodium has significantly reduced the influx of eosinophils, neutrophils, mast cells and basophils into nasal secretions whereas, during LNR, it has almost completely



Ag = Antigen, APC = Anigen presenting cell; B-cells = B-lymphocytes; T-cells = T-lymphocytes

Fig. 12
Possible pathways involved in the late nasal response

prevented the influx of neutrophils, eosinophils, and basophils into nasal secretions and significantly decreased the count of epithelial and goblet cells in them (*Fig. 11*) *(103,104).*

Other drugs

Possible protective effects of other drugs, such as beta$_2$-sympathomimetics, anticholinergic drugs (ipratropium bromide), calcium channel blockers (Nifedipine, Verapamil), non-steroidal, anti-inflammatory agents (acetylsalicylic acid and its derivatives, indomethacin, flurbiprofen, ibuprofen, prostaglandin-suppressing compounds), cAMP modulators, H_2-receptor antagonists (Cimetidine, Ranitidine), eicosapentaenoic acid, antiserotonin, or new, experimentally synthesized, anti-mediator compounds (kinin-, bradykinin-, leukotriene-, PAF-, neurotoxin-, neuropeptide-antagonists, inhibitors of 5-lipoxygenase-pathway products or thromboxane-synthesis inhibitors) on LNR have not yet been sufficiently investigated *(9,44,65,83,105).*

Immunotherapy

Until now no convincing evidence has been provided for any effects of immunotherapy on the clinical LNR and/or on the mechanisms underlying this response. Immunotherapy should therefore be considered as a non-established and unproved treatment for LNR *(9,44,83,105).*

Differential diagnosis

LNR differs substantially from the immediate/early nasal response (INR/ENR) and the delayed nasal response (DYNR) in the following features: i) clinical characteristics, such as the time-course, symptomatology, appearance of the nasal mucosa, association with other *in vivo* and *in vitro* diagnostic parameters and appearance of symptoms in other organs accompanying the particular response type; ii) morphological characteristics, such as cytological changes in the nasal secretions and histological changes in nasal mucosa associated with the particular type of nasal response; iii) immunological characteristics, such as appearance of the particular classes and sub-classes of immunoglobulins in nasal secretions and blood serum and/or blood plasma and changes in their concentrations, and an appearance of particular mediators and/or other compounds and factors in nasal secretions and/or blood and changes in their concentrations during the particular types of nasal response; iv) pharmacological modulation and control of the particular types of nasal response as well as the effects of individual drugs (pharmacological agents) on the particular nasal response types *(2,7–13,20, 23,24,27,29,31,32,34,36,42–47, 49,59,61,64,65,71–75,88,99,100,103,104*).

Possible mechanism/s underlying LNR

LNR should be regarded as a clinical phenomenon, defined by the appearance of nasal symptoms and complaints, predominantly nasal obstruction, accompanied by other symptoms and changes, within 4 to 12 h of allergen exposure (antigen-antibody interaction or challenge), which can be induced by a complex mechanism *(2, 6–9, 20, 23, 31, 46, 47, 49, 61, 65, 71, 83, 88)*. Although the pathogenetic and immunological mechanisms leading to LNR can be different, the late type hypersensitivity should be regarded as one of the possible mechanisms involved in the clinical LNR, but is far from being the only one (*Fig. 12*) (*20,23,29,31,34,37,46,49,59,65,71,80,83,88,100).*

The possible role and involvement of various components of the late hypersensitivity mechanism(s), either through the complex pathways or their participation as individual and single components in the pathological mechanism leading to the development of clinical LNR, cannot be excluded. The potential components are as follows: i) immune complexes *(49,65,108,110,111);* ii) complement system and its parts, such as classical complement pathway, alternative complement pathway, membrane attack complex, receptors for complement components on the membrane of various cell types *(49,65,83,108,110–112);* iii) IgG and/or IgM antibodies *(9,20,31,34,49,65,71, 83,113*); iv) particular cell types, such as neutrophils, platelets, eosinophils, mast cells and basophils, including histamine-releasing factors, cytokines, stem cell factors, neuropeptides, prostagladins, thromboxanes, leukotrienes and various compounds activating these cell types *(9,20,31–34,37,46,49,62,65,83,114–121).*

Moreover, innervation and neurogenic control of the nasal mucosa, including neuropeptides as neurotransmitters in the human nasal mucosa, could, under certain circumstances, be involved in the development of general conditions of the nasal mucosa, thus allowing expression of some steps of the immunological pathways in the human nasal mucosa (*65,114–121).*

On the other hand, a possible role and involvement of various components of the immediate hypersensitivity mechanism(s), either through the classical pathways or as single components in the development of late-phase reactions, has already been suggested by some investigators. The potential components are as follows: i) antigen-specific IgE antibodies; *ii)* mast cells and basophils *(23,34,37, 49,59,61,64, 65, 80,87,105–107, 109*). However, our results would not support the proposed unequivocal role of either IgE antibodies, mast cells or basophils in the development of a clinical LNR *(9,31,65,71,120,121).*

NOSNÍ ALERGICKÁ REAKCE OPOŽDĚNÉHO TYPU

S o u h r n

V patogeneze alergické rhinitidy se mohou uplatňovat tři typy reakcí přecitlivělosti: časná, opožděná a pozdní. Nosní reakce opožděného typu (LNR) se vyskytuje u 41% nemocných s alergickou rhinitidou buď isolovaně nebo v kombinaci s reakcí časnou. Při rhinomanometrickém vyšetření je začátek této reakce patrný za 4–8 hodin, maximální nález bývá mezi –12 hodinou a reakce odeznívá do 24 hodin po intranasální provokaci alergenem. LNR byla pozorována i po perorálním podání potravinových alergenů. Na LNR upozorní anamnestické údaje (v 23%), rhinoskopický nález fialové nosní sliznice s nepravidelnými drobnými krevními výrony (v 90%) a opožděná kožní reakce na příslušný alergen (v 65%). U 51% pacientů je zvýšená koncentrace IgG v séru, u 13% leukocytóza a u 23% eozinofilie. Klinicky se LNR projevuje nosní obstrukcí. Hypersekrece, kýchání a svědění jsou přítomny v menší míře. LNR však bývá provázena i reakcemi v jiných orgánech – bolestmi hlavy, otoky víček, projevy na spojivkách, v středouší, v sinusech, bronchiální obstrukcí i příznaky celkovými. V biopsiích nosní sliznice se při LNR nachází porucha celistvosti epitelu s trhlinami a edémem, poškození bazální membrány, lamina propria je infiltrována neutrofilními a eosinofilními granulocyty, slizniční kapiláry jsou dilatovány a jejich okolí je prosáklé.V nosním sekretu jsou při LNR přítomny IgG i řada mediátorů, např. leukotrieny, prostaglandiny, bradykinin, produkty eosinofilních granulocytů, histamin. Vzniku a rozvoji LNR lze zabránit kromoglykany a glukokortikoidy; antihistaminika jsou neúčinná.

REFERENCES

1. *Mygind N, Weeke B.* Allergic and nonallergic rhinitis. In: Middleton E Jr, Reed CHE, Ellis EF (Eds). Allergy, Principles and Practice, (2nd Ed). St Louis Mo: The C V Mosby Co.1983;1101–1117
2. *Pelikan Z.* The role of immediate, late and delayed reactions in allergic nasal disease. In: Pepys J, Edwards AM (Eds). The Mast Cell, Its Role in Health and Disease. Proceedings of the International Symposium, Davos, Switzerland, 23–26 April. 1979, Tunbridge Wells, UK: Pitman Medical Publ. 1979;772–777
3. *Pelikan Z.* Provocation tests – a definitive confirmation of the role and involvement of a certain allergen or a non-specific hyperreactivity agent in the complaints of patients with an allergy disorder. Abstracts of the International Seminar on the Immunological System as a Target for Toxic Damage. (An International Seminar organized by the Commission of the European Communities, WHO and the United States Environmental Protection Agency), Luxemburg, November 6–9, 1984;122–126
4. *Pelikan Z.* Immediate hypersensitivity and non-specific hyperreactivity in the nose and bronchial tree – a possible double role of the mast cells and basophils, – the place and role of the chemicals. Abstracts of the International Seminar on the Immunological System as a Target for Toxic Damage. (An international seminar organized by the Commission of the European Communities, WHO and the United States Environmental Protection Agency), Luxemburg, November 6–9, 1984;127–130
5. *Coombs RRA, Gell PGH.* Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell PGH, Coombs RRA, Lachmann PJ (Eds). Clinical Aspects of Immunology, (3th Ed). Oxford: Blackwell Sci Publ. 1975;761–781
6. *Pelikan Z.* Late and delayed responses of the nasal mucosa to allergen challenge. Ann Allergy 1978; 41:37–47
7. *Pelikan Z, Pelikan-Filipek M.* Cytologic changes in the nasal secretions (NS) during the immediate (INR) and late nasal response (LNR) to allergen challenge (NPT) In: Nijkamp FP, Engels F, Hendricks PAV, Oosterhout AJM (Eds). Mediators in Airway Hyperreactivity. (Supplement No 31 to Agents and Actions). Basel, Boston, Berlin: Birkhäuser Verlag.1990;55–62
8. *Pelikan Z, Pelikan-Filipek M.* Intracellular changes of eosinophils (EO), neutrophils (NE) and basophils (BS) in nasal secretions (NS) during the early (ENR) and late (LNR) nasal response. Allergy Clin Immunol News 1994 (Suppl No 2);336 (Abstr 1205)

9. *Pelikan Z.* Late nasal response (LNR) – its characteristics, feature and possible mechanism(s). In: Dorsch W (Ed). Late phase allergic reactions. Boca Raton, Ann Arbor, Boston: CRC Press. 1990;111–155
10. *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
11. *Pelikan Z.* The effects of Disodium cromoglycate and Beclomethasone dipropionate on the late response of the nasal mucosa to allergen challenge. Ann Allergy 1982;49:200–212
12. *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
13. *Pelikan Z, Pelikan-Filipek M.* Nasal secretions (NS) cytology during the delayed nasal response to allergen challenge (DNR). Proceedings of the XIVth International Congress Allergol Clin Immunol, Oct. 13–18, 1991, Kyoto (Japan). Allergy Clinical Immunology News 1991;Suppl No 1: 334 (Abstr 930)
14. *Pelikan Z, Pelikan-Filipek M.* Role of nasal allergy in chronic maxillary sinusitis-diagnostic value of nasal challenge with allergen. J Allergy Clin Immunol 1990;86:484–491
15. *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 (Abstr 1500)
16. *Pelikan Z, Pelikan-Filipek M.* A new disease – a nasal form of pigeon breeder's disease, Allergy 1983;38:309–318
17. *Pelikan Z.* The changes in the nasal secretion eosinophils during the immediate nasal response to allergen challenge. J Allergy Clin Immunol 1983;72:657–662
18. *Pelikan M, Pelikan Z.* The role of the nasal mucosa in some cases of allergic conjunctivitis and the effects of Disodium cromoglycate (DSCG). J Allergy Clin Immunol 1985;75, (No 1, Part 2) :186, (Abstr 327)
19. *Pelikan Z, Pelikan M.* Nasal challenge with allergen in patients with secretory otitis media (SOM) and otalgia OL. Ann Allergy 1985;55 (No 2):231 (Abstr 22)
20. *Pelikan Z.* Rhinitis and secretory otitis media: a possible role of food allergy. In: Brostoff, J, Challacombe S J (Eds). Food Allergy and Intolerance, (1st Ed). London:Bailliere-Tindall, 1987;467–485
21. *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 (Abstr 535)
22. *Taylor G, Shivalkar PR.* Disodium cromoglycate: laboratory studies and clinical trial in allergic rhinitis. Clin Allergy 1971;1:189–198
23. *Dvoracek JE, Yunginger JW, Kern EB, Hyatt RE, Gleich GJ.* Induction of nasal late-phase reactions by insufflation of ragweed pollen extract. J Allergy Clin Immunol 1984;73:363–368
24. *Bascom R, Proud D, Togias AG, Peters SP, Norman PS, Kagey-Sobotka A, Lichtenstein LM, Naclerio RM.* Nasal provocation: an approach to study the mediators of allergic and nonallergic rhinitis. In: Reed Ch E (Ed). Proceedings of the XIIth International Congress Allergol Clin Immunol, Washington (DC), October 20–25, 1985. St Louis (MO): CV Mosby.1986;113–120
25. *Pelikan Z, Pelikan-Filipek M.* Non-specific hyperreactivity (N-SH) and basic types of nasal response to allergen challenge in rhinitis patients. J Allergy Clin Immunol 1992;89 (No 1, Part 2):179; (Abstr 140)
26. *Pelikan Z, Pelikan-Filipek M.* Effects of oral cromolyn on the nasal response due to foods. Arch Otolaryngol Head & Neck Surg 1989; 115:1238–1243
27. *Pelikan Z, Pelikan-Filipek M.* Cytologic changes in nasal secretions (NS) during the late nasal response (LNR) pretreated with Disodium cromoglycate (DSCG) and Beclomethasone dipropionate (BDA) or Budesonide (BSA). J Allergy Clin Immunol 1991; 87 (No 1, Part 2):281 (Abstr 566)
28. *Pelikan Z.* Effects of Cetirizine (CZ) on the immediate (INR) and the late nasal response (LNR) and on the eosinophils in the nasal secretions (NS). J Allergy Clin Immunol 1993; 91 (No 1, Part 2):193 (Abstr 210)
29. *Johansson S–Ĺ, Pelikan Z.* The effects of cromolyn (DSCG) and budesonide (BSA) on the late nasal response (LNR), changes in the cell count in the nasal secretions (NS) and their intracellular changes. J Allergy Clin Immunol 1993;91 (No 1, Part 2): 259 (Abstr 475)
30. *Pelikan Z.* Nasal response to food ingestion challenge. Arch Otolaryngol Head & Neck Surg 1988;114, 525–530
31. *Pelikan Z.* The Role of Allergies in Sinus Disease – Children & Adults. In: Gershwin E, Incaudo G (Eds). Diseases of the sinuses: A comprehensive textbook of diagnosis and treatment. Totowa (NJ, USA):The Humana Press Inc. 1996;97–165

32. *Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM*. The influx of inflammatory cells into nasal washings during the late response to antigen challenge. Effect of systemic steroid pretreatment. Am Rev Respir Dis 1988;138:406–412
33. *Freeland H. S, Pipkorn U, Naclerio RM, Adkinson NF, Lichtenstein LM, Peters SP*. The role of leukotriene B4 (LTB4) in human allergic late-phase reaction: lack of LTB4 inhibition by systemic glucocorticosteroids. J Allergy Clin Immunol 1986;77 (Suppl):244 (Abstr 493)
34. *Lemanske RF, Kaliner MA*. Late phase allergic reactions. In: Middleton E, Reed ChE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW (Eds.). Allergy, principles and practice (4th Ed). St Louis (MO, USA): Mosby-Year Book Inc.1993;320–361
35. *Varney VA, Jacobson MR, Sudderick RM, Robinson DS, Irani A-M, Schwartz LB, Mackay IS, Kay AB, Durham SR*. Immunohistology of the nasal mucosa following allergen-induced rhinitis. Am Rev Respir Dis 1992;146:170–176
36. *Iliopoulos O, Proud D, Adkinson NF, Norman PS, Kagey-Sobotka A, Lichtenstein LM, Naclerio RM*. Relationship between the early, late and rechallenge reaction to nasal challenge with antigen:Observation on the role of inflammatory mediators and cells. J Allergy Clin Immunol 1990;86:851–861
37. *Naclerio R, Togias A, Proud D, Adkinson NF, Kagey-Sobotka A, Plaut M, Norman PS, Lichtenstein LM*. Inflammatory mediators in nasal secretions during early and late reactions. J Allergy Clin Immunol 1984;73:148 (Abstr 157)
38. *Borum P.* Nasal methacholine challenge: a test for the measurement of nasal reactivity. J Allergy Clin Immunol 1979;63:253–257
39. *Pelikan Z.* Non-specific hyperreactivity of the nasal mucosa (N-SH)-comparison of histamine and methacholine challenges in rhinitis patients. Proceedings of the XIVth International Congress of Allergol and Clin Immunol, Oct. 13–18, 1991, Kyoto (Japan). Allergy Clinical Immunology News 1991;Suppl No 1:335 (Abstr 934)
40. *Pelikan Z, Pelikan-Filipek M, Stigt van B, Johansson S-A, Knottnerus I.* The asthmatic response [AR] induced by the allergic reaction originating primarily in the nasal mucosa. Proceedings of the XVIth European Congress of Allergology and Clinical Immunology (Madrid, Spain, June 25–30, 1995). Allergy 1995;50 (Supplement to No 26): 24 (Abstr 0C-052)
41. *Solomon WR, Mclean JA*. Nasal provocative testing. In: Spector SL (Ed). Provocative challenge procedures. Mount Kisco, NY (USA): Futura Publ Comp.1989;569–625
42. *Pelikan Z, Pelikan-Filipek M*. Cytological changes in the nasal secretions during the immediate nasal response (INR). J Allergy Clin Immunol 1988;82:1103–1113
43. *Pelikan Z, Pelikan-Filipek M*. Cytological changes in the nasal secretions during the late nasal response (LNR). J Allergy Clin Immunol 1989;83:1068–1079
44. *Pelikan Z, Pelikan-Filipek M*. Cytologic changes in the nasal secretions (NS) during the immediate (INR), late (LNR) and delayed nasal response (DYNR) to allergen challenge and their pharmacologic modulation by various drugs. In press
45. *Pelikan Z, Pelikan-Filipek M*. Intracellular changes in some cell types in nasal secretions (NS) during the immediate (INR) and late (LNR) nasal response to allergen challenge. Proceedings of the XIV International Congress of Allergol Clin Immunol, Oct. 13–18, 1991, Kyoto (Japan). Allergy Clinical Immunology News 1991;(Suppl No 1):273 (Abstr 689)
46. *Pelikan Z.* Histologic changes in the nasal mucosa during the immediate (INR), late (LAR) and delayed (DNR) nasal response to allergen challenge. Proceedings of the XIVth International Congress of Allergol Clin Immunol, Oct. 13–18, 1991, Kyoto (Japan). Allergy Clinical Immunology News 1991;Suppl 1:132 (Abstr 158)
47. *Pelikan Z, Pelikan-Filipek M.* Late nasal response to allergen challenge (LNR) - Cytologic changes in the nasal secretions (NS) and histologic changes in the nasal mucosa. In:Mestecky J, McGhee J, Tlaskalova H, Sterzl J (Eds). Recent advances in mucosal immunology. New York, USA: Plenum Publishing Co.1995;855–860
48. *Johansson SA, Pelikan Z.* The effects of Budesonide (BSA) and Beclomethasone dipropionate (BDA) on the late asthmatic response (LAR). J Allergy Clin Immunol 1990;85 (No 1, Part 2):145 (Abstr 5)
49. *Pelikan Z.* Concept of pathogenesis and possible mechanism(s) underlying the late phase reactions, focused on the late asthmatic response (LAR). In: Dorsch W (Ed). Late Phase Allergic Reactions. Boca Raton, Ann Arbor, Boston (USA): CRC Press. 1990;499–518
50. *Pelikan Z, Johansson S-L.* The effects of budesonide (BSA) on the late asthmatic response (LAR), administered before and at various points in time after allergen challenge. Proceedings of the XIVth International Congress of Allergol Clin Immunol, Oct. 13–18, 1991, Kyoto (Japan). Allergy Clinical Immunology News 1991; (Suppl No 1):180 (Abstr 338)
51. *Pelikan Z, Knottnerus I, Johansson S-L.* Effects of Cromolyn (DSCG), Nedocromil (NDS) and Budesonide (BSA) on the dual late asthmatic response (DLAR), administered before and after allergen challenge. Allergy 1992;47 (No 12, Supplement):129

52. *Johannson S–Ĺ, Knottnerus I, Pelikan Z.* The effect of a single dose of cromolyn [DSCG], beclomethasone dipropionate [BDA], budesonide [BUD], nedocromil sodium [NDS] and salbutamol [SBT] on the late asthmatic response [LAR] administered before and after allergen challenge. J Allergy Clin Immunol 1995;95 (No 1, Part 2):310 (Abstr 678)
53. *Pelikan Z, Knottnerus I.* Inhibition of the late asthmatic response by nedocromil sodium administered more than two hours after allergen challenge. J Allergy Clin Immunol 1993;92:19–28
54. *Knottnerus I, Pelikan Z.* The effects of cromolyn (DSCG), Nedocromil (NS) and Budesonide (BUD) on the early (EAR) and the late (LAR) asthmatic response, inhaled before and after allergen challenge. J Allergy Clin Immunol 1994;93 (No1, Part 2):198 (Abstr 211)
55. *Johansson SA, Pelikan Z.* The protective effects of cromolyn (DSCG) and budesonide (BUD) on the early (EAR) and the late (LAR) asthmatic response after a short- and long-term pretreatment. J Allergy Clin Immunol 1994;93 (No1, Part 2):166 (Abstr 22)
56. *Higgins, KG, Brostoff J.* Local production of specific IgE antibodies in allergic rhinitis patients with negative skin tests. Lancet 1975; ii:148–150
57. *Bascom R, Pipkorn U, Gleich G, Lichtenstein LM, Naclerio RM.* Effect of systemic steroids on eosinophils (EOS) and major basic protein (MBP) during nasal antigen challenge. J Allergy Clin Immunol 1986;77 (Suppl):246 (Abstr 501)
58. *Miadonna A, Tadeschi A, Leggieri E, Pastorello E, Quilizza R, Fabbri C, Froldi M, Zanussi C.* Mediators release in nasal secretions after grass pollen challenge. J Allergy Clin Immunol 1986;77 (Suppl):177 (Abstr 228)
59. *Walden SM, Proud D, Bascom R, Lichtenstein LM, Kagey-Sobotka A, Adkinson NF, Naclerio RM.* Experimentally induced nasal allergic responses. J Allergy Clin Immunol 1988;81:940–949
60. *Miadonna A, Tedeschi A, Leggieri E, Lorini M, Folco G, Sala A, Qualizza R, Froldi M, Zanussi C.* Behavior and clinical relevance of histamine and leukotrienes C4 and B4 in grasspollen-induced rhinitis. Am Rev Respir Dis 1987;136:357–362
61. *Freeland HS, Pipkorn U, Schleimer RP, Bascom R, Lichtenstein LM, Naclerio RM, Peters SP.* Leukotriene B4 as a mediator of early and late reactions to antigen in humans: The effect of systemic glucocorticoid treatment in vivo. J Allergy Clin Immunol 1989; 83:634–642
62. *Bentley AM, Jacobson MR, Cumberworth V, Barkans JR, Moqbel R, Schwartz LB, Irani A-M, Kay AB, Durham SR.* Immunohistology of the nasal mucosa in seasonal allergic rhinitis: Increases in activated eosinophils and epithelial mast cells. J Allergy Clin Immunol 1992;89:877–883
63. *Raphael GD, Igarashi Y, White MV, Kaliner MA.* The pathophysiology of rhinitis. V. Sources of protein in allergen-induced nasal secretions. J Allergy Clin Immunol 1991;88:33–42
64. *Lozewicz S, Gomez E, Chalstry S, Gatland D, Harmanyeri Y, Jordan S, D'Ardenne J, Davies RJ.* Allergen induced cellular infiltration and late reactions in the upper respatory tract. Clin Exp Allergy 1989;19:106 (Abstr S 5/7)
65. *Pelikan Z.* The late nasal response, its clinical and immunologic features, possible mechanisms and pharmacologic modulation. Thesis,1996,Free University Amsterdam, The Netherlands
66. *Pelikan Z, Feenstra L, Barre GOF.* Response of the nasal mucosa to allergen challenge measured by two different methods of rhinomanometry. Ann Allergy 1977;38,263–267
67. *Lenders H, Pirsig W.* Diagnostic value of acoustic rhinometry: Patients with allergic and vasomotor rhinitis compared with normal controls. Rhinology 1990;28:5–16
68. *Cole P, Havas T.* Nasal resistance to respiratory airflow: a plethysmographic alternative to the face mask. Rhinology 1987;25:156–166
69. *Shelton DM, Pertuze J, Gleeson MJ.* Comparison of oscillation with three other methods for measuring nasal airways resistance. Respir Med 1990;84:101–106
70. *Druce HM, Bonner UF, Patow C, Choo P, Summers RJ, Kaliner MA.* Response of nasal blood flow to neurohormones as measured by laser-Doppler velocimetry. J Appl Physiol Respir Environm Exercise Physiol 1984;57:1276–1283
71. *Pelikan Z.* Late nasal response to allergen challenge (LNR) - Clinical features and pharmacologic modulation. Proceedings of the 13th Congress of European Rhinologic Society, including the IXth ISIAN & combined with BSACI & EAFS, London, June 24–29, 1990 (The Royal Lancaster Hotel, UK), 1990;226
72. *Pelikan Z, Pelikan-Filipek M.* Immediate nasal response to allergen challenge (INR) – Cytologic changes in the nasal secretions (NS) and histologic changes in the nasal mucosa. In:Mestecky J, McGhee J, Tlaskalova H, Sterzl J (Eds). Recent advances in mucosal immunology. New York, USA:Plenum Publishing Co.1995;847–853
73. *Pelikan Z.* Allergic and non-specific hyperreactivity (N-SH) component in patients with chronic rhinitis. Proceedings of the XIVth International Congress of Allergol Clin Immunol, Oct. 13–18, 1991, Kyoto (Japan). Allergy Clinical Immunology News 1991;Suppl No 1:335 (Abstr 935)

74. *Pelikan Z.* Participation of allergy [ALL] and non-specific hyperreactivity [N-SH] components in rhinitis. Allergy Clin Immunol News 1994;Suppl No 2:415 (Abstr 1499)
75. *Pelikan Z.* Histamine (HS) in nasal secretions (NS) and its changes during the basic types of nasal response (NR) to allergen challenge. Allergy 1992;47 (No 12,suppl,):304
76. *Pelikan Z.* The concentrations of histamine in the blood plasma and their changes during the basic types of the nasal response to allergen challenge. In preparation for publication.
77. Hudson L, Hay FC. Practical immunology (2nd Ed). Oxford, London, Edinburgh, Melbourne:Blackwell Sci Publ.1980;117
78. *Pelikan Z.* Allergic conjunctivitis relationship to allergic rhinitis and the effects of Disodium cromoglycate (DSCG). Proceedings of the Xith International Congress Allergol Clin Immunol, London, October 17–22, 1982. London and Basingstoke: Macmillan Press. 1982;(Abstr 392P)
79. *Pelikan Z, Pelikan-Filipek M.* Middle ear response to the nasal allergen challenge in patients with secretory otitis media (SOM). Proceedings of the XIVth International Congress of Allergol Clin Immunol, Oct. 13–18, 1991, Kyoto (Japan). Allergy Clinical Immunology News 1991;Suppl No 1:336 (Abstr 936)
80. *Togias A, Naclerio RM, Proud D, Pipkorn U, Bascom R, Iliopoulos O, Kagey-Sobotka A, Norman PS, Lichtenstein LM.* Studies on the allergic and non-allergic nasal inflammation. J Allergy Clin Immunol 1988;81:782–790
81. *Brofeldt S, Mygind N.* Viscosity and spinability of nasal secretions induced by different provocation tests. Am Rev Respir Dis 1987; 136:353–356
82. *Bascom R, Wachs M, Naclerio RM, Pipkorn U, Galli SJ, Lichtenstein LM*. Basophil influx occurs after nasal antigen challenge, Effects of topical corticosteroid pretreatment. J Allergy Clin Immunol 1988;81:580–589
83. *Pelikan Z.* The immediate/early, late and delayed nasal response to allergen challenge, their occurrence and association with various „in vivo“ and „in vitro“ diagnostic parameters, other organsÔ responses, non-specific hyperreactivity and their pharmacologic control. In preparation as a monograph
84. *Pipkorn U, Proud D, Lichtenstein LM, Schleimer RP, Peters SP, Adkinson NF, Kagey-Sobotka A, Norman PS, Naclerio NM*. Effect of short-term systemic glucocorticosteroid treatment of human nasal mediator release after antigen challenge. J Clin Invest.1987;80:957–961
85. *Togias A, Naclerio RM, Proud D, Baumgarten C, Peters S, Creticos PS, Warner J, Kagey-Sobotka A, Adkinson NF, Norman PS*. Mediator release during nasal provocation. Am J Med 1985;79 (Suppl 6A):26–33
86. *Bisgaard H, Gronberg H, Mygind N, Dahl R, Lindqvist N, Venge P*. Allergen-induced increase of eosinophil cationic protein in nasal lavage fluid: effect of the glucocorticosteroid budesonide. J Allergy Clin Immunol 1990;85:891–895
87. *Davies RJ, Lozewicz S, Manolitsas N, Calderon M, Devalia JL.* Inflammatory cell recruitment following allergen exposure. In: Godard Ph, Bousquet J, Michel FB (Eds).Advances in Allergology and Clinical Immunology. Casterton Hall, Carnforth (Lancs), UK:The Parthenon Publishing Group.1992;233–243
88. *Skoner DP, Doyle WJ, Boehm S, Fireman P*. Late-phase Eustachian tube (ET) and nasal allergic responses associated with inflammatory mediator (IM) elaboration. J Allergy Clin Immunol 1988;81:283 (Abstr 462)
89. *Pelikan Z, Pelikan-Filipek M, Venmans, BJW.* Nasal response due to the food ingestion challenge and protective effects of oral Disodium cromoglycate (DSCG). Ann Allergy 1988;60 (No 2):149, (Abstr 25)
90. *Pelikan-Filipek M, Pelikan Z.* A comparision of double-blind and open techniques of food ingestion challenge upon recording of objective and subjective parameters. J Allergy Clin Immunol 1994;93 (No 1, Part 2):303 (Abstr 844)
91. *Pelikan Z, Knottnerus I.* Protective effects of oral Cromolyn (DSCG) on migraine due to the adverse reactions to foods. J Allergy Clin Immunol 1993;91 (No 1, Part 2):150 (Abstr 38)
92. *Pelikan-Filipek M, Pelikan Z, Van Stigt B, Miesen WMAJ*. The protective effects of oral cromolyn (DSCG) on the response the paranasal sinuses (PSR) to the food ingestion challenge (FICH). Allergy 1995;50 (Suppl to No 26):128 (Abstr)
93. *Knottnerus I, Pelikan DMV, Pelikan Z.* The effects of oral disodium cromoglycate [DSCG] on the basic types of nasal response (NR) to food ingestion challenge (FICH) and accompanying cellular changes in nasal secretions (NS). J Allergy Clin Immunol 1996; 97 (No 1, Part 3):337 (Abstr 618)
94. *Pelikan Z, Knottnerus I.* Protective effects of oral cromolyn (DSCG) on the arthritis (ART) complaints due to the adverse reactions to foods. Allergy Clin Immunol News 1994;Suppl No 2: 509 (Abstr 1867)
95. *Pelikan Z, Boorsma M.* Effects of intranasal budesonide (BUD) on the early (ENR) and late nasal response (LNR) to nasal challenge (NPT) with bird faeces extrects. J Allergy Clin Immunol 1994;93 (No 1,Part 2):165 (Abstr 14)

96. *Pelikan Z, Oers v JAH, Pelikan HMP.* Pharmacologic modulation of the cytologic changes in the nasal secretions (NS) accompanying the late nasal response [LNR]. I. Topically administered drugs. Allergy & Clin Immunol Intern 1997; Suppl No 4:260 (Abstract No 995)
97. *Pelikan Z, Oosten v MCM, Pelikan HMP.* Pharmacologic modulation of the cytologic changes in the nasal secretions (NS) accompanying the late nasal response to allergen challenge [LNR]. II. Orally administered drugs. Allergy & Clin Immunol Intern 1997; Suppl No 4:261 (Abstract No 956)
98. *Pelikan Z.* Effects of oral H1-receptor antagonists on the late nasal response [LNR] to allergen challenge. Allergy 1996;51 (Suppl to No 31):158 (Abstract P530)
99. *Pelikan Z.* Nasal cytology.In:Bascomba A, Sastre J (Eds).Syllabus of the postgraduate courses and practical workshops,(The XVIth Europ Congress of Allergol & Clin Immol, Madrid,Spain,June 25–30,1995),1995;103–123
100. *Pelikan Z.* Anti-allergic drugs and immunotherapy. In: Nijkamp FP,Parnham MJ (Eds.). Principles of immunopharmacology. Basel,Boston,Berlin:BirkhŠuser Verlag.1999;243–268
101. *Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM.* Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. N Engl J Med 1987;316:1506–1510
102. *Bascom R, Pipkorn U, Proud D, Dunnette S, Gleich GJ, Lichtenstein LM, Naclerio RM.* Major basic protein and eosinophil-derived neurotoxin concentrations in nasal-lavage fluid after antigen challenge: Effect of systemic corticosteroids and relationship to eosinophil influx. J Allergy Clin Immunol 1989;84:338–346
103. *Pelikan-Filipek M, Oostenbrink JH, Pelikan Z.* The protective effects of intranasal Nedocromil sodium on the immediate [INR] and the late nasal response [LNR] to allergen challenge. J Allergy Clin Immunol 1996; 97 (No 1, Part 3):197 (Abstr 57)
104. *Pelikan Z, Pelikan-Filipek M, Stigt v B.* Effects of Nedocromil Sodium (NDS) on the late nasal response to allergen challenge [LNR] and the accompanying cellular changes in the nasal secretions (NS). J Allergy Clin Immunol 1996;97 (No 1, Part 3):196 (Abstr 56)
105. *Meltzer LO, Schatz M.* Pharmacotherapy of rhinitis. In: Slavin RG (Ed). Immunology and Allergy Clinics of North America, „Upper Respiratory Disorders", Vol. 7, No 1. Philadelphia: WB Saunders.1987:57–91
106. *Kaliner MA.* Hypothesis on the contribution of late-phase allergic responses to the understanding and treatment of allergic diseases. J Allergy Clin Immunol 1984;73:311–315
107. *Durham SR, Caroll M, Lee TH, Cromwell O, Graneek B, Newman XX, Taylor AJ, Kay AB.* Mechanisms of early and late asthmatic reactions. In: Reed CHE (Ed).Proceedings of the XIIth International Congress Allergol Clin Immunol (Washington DC, Oct, 20–25, 1985). , St. Louis:The CV Mosby.1986;229–235
108. *Lawley TJ, Frank MM.* Immune complexes and allergic disease. In: Middleton E, Reed ChE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW (Eds). Allergy, Principles and Practice (4th Ed). St Louis (MO): Mosby-Year Book Inc.1993;990–1006
109. *O'Byrne PM, Dolovich J, Hargreave FE.* Late asthmatic responses. Am Rev Respir Dis 1987;136:740–751
110. *Henson PM.* Antibody and immune-complex-mediated allergic and inflammatory reactions. In: Lachmann PL, Peters D K.(Eds). Clinical Aspects of Immunology (4th Ed).Oxford: Blackwell Scientific Publ.1982;687–709
111. *Fearon DT.* Complement as a mediator of inflammation. In: . Fauci AS (Ed).Immune complexes in clinical medicine. Clinics in Immunology and Allergy, Vol 1, No 2WB. London, Philadelphia, Toronto: Saunders Comp Ltd.1981;225–242
112. *Goldstein IM.* Complement-biologically active products. In: Gallin JI, Goldstein IM, Snyderman R (Eds). Inflammation:basic principles and clinical correlates (2nd Ed). New York:Raven Press Ltd.1992;63–80
113. *Jefferis R, Pound JD.* Immunoglobulins. In: Gallin JI, Goldstein IM, Snyderman R (Eds). Inflammation – principles and clinical correlates (2nd Ed). New York:Raven Press Ltd. 1992;11–31
114. *Payan DG.* The role of neuropeptides in inflammation. In: Gallin JI, Goldstein IM, Snyderman R (Eds). Inflammation:basic principles and clinical correlates (2nd Ed). New York: Raven Press, Ltd. 1992;177–192
115. *Barnes PJ, Baraniuk JN, Belvisi MG.* Neuropeptides in the respiratory tract. Part I. Am Rev Respir Dis 1991; 144:1187–1198
116. *Barnes PJ, Baraniuk JN, Belvisi MG.* Neuropeptides in the respiratory tract. Part II. Am Rev Respir Dis 1991;144:1391–1399
117. *Lemanske RF Jr, Kaliner MA.* Late-phase IgE-mediated reactions. J Clin Immunol 1988;8:1–13
118. *Van Megen YJB.* Neuroreceptors in nasal allergy. Thesis, 1989. The Catholic University Nijmegen, The Netherlands.

119. *Pelikan Z.* Effects of oral H1-receptor antagonists on the late nasal response (LNR) to allergen challenge. In preparation for publication.
120. *Pelikan Z, Pelikan-Filipek M.* The late asthmatic response to allergen challenge-Part I.Ann Allergy 1986;56 (No5):421–420
121. *Pelikan Z, Pelikan-Filipek M.* The late asthmatic response to allergen challenge-Part II.Ann Allergy 1986;56 (No 5):421–435