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ALLERGIC RHINITIS AND ITS IMPACT ON ASTHMA

ARIA WORKSHOP REPORT

In collaboration with the World Health Organization

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AMERICAN ACADEMY OF ALLERGY
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Recommendations

1- **Allergic rhinitis is a major chronic respiratory disease due to its:**
   - prevalence,
   - impact on quality of life,
   - impact on work/school performance and productivity,
   - economic burden,
   - links with asthma.

2- **In addition, allergic rhinitis is associated with sinusitis and other co-morbidities such as conjunctivitis.**

3- **Allergic rhinitis should be considered as a risk factor for asthma along with other known risk factors.**

4- **A new subdivision of allergic rhinitis has been proposed:**
   - intermittent
   - persistent

5- **The severity of allergic rhinitis has been classified as "mild' and "moderate/severe" depending on the severity of symptoms and quality of life outcomes.**

6- **Depending on the subdivision and severity of allergic rhinitis, a stepwise therapeutic approach has been proposed.**

7- **The treatment of allergic rhinitis combines:**
   - allergen avoidance (when possible),
   - pharmacotherapy,
   - immunotherapy.

8- **The environmental and social factors should be optimised to allow the patient to lead a normal life.**

9- **Patients with persistent allergic rhinitis should be evaluated for asthma by history, chest examination and, if possible and when necessary, the assessment of airflow obstruction before and after bronchodilator.**

10- **Patients with asthma should be appropriately evaluated (history and physical examination) for rhinitis.**

11- **A combined strategy should ideally be used to treat the upper and lower airway diseases in terms of efficacy and safety.**

Introduction

Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose. Symptoms of rhinitis include rhinorrhea, nasal obstruction, nasal itching and sneezing which are reversible spontaneously or under treatment. It is subdivided into "intermittent" or "persistent" disease (Table 1). The severity of allergic rhinitis can be classified as "mild" or "moderate-severe."

TABLE 1: Classification of allergic rhinitis

1- "Intermittent" means that the symptoms are present:
  • Less than 4 days a week,
  • Or for less than 4 weeks.
2- "Persistent" means that the symptoms are present:
  • More than 4 days a week,
  • And for more than 4 weeks.
3- "Mild" means that none of the following items are present:
  • Sleep disturbance,
  • Impairment of daily activities, leisure and/or sport,
  • Impairment of school or work,
  • Troublesome symptoms.
4- "Moderate-severe" means that one or more of the following items are present:
  • Sleep disturbance,
  • Impairment of daily activities, leisure and/or sport,
  • Impairment of school or work,
  • Troublesome symptoms.

Previously, allergic rhinitis was subdivided, based on the time of exposure, into seasonal, perennial and occupational diseases (1-3). Perennial allergic rhinitis is most frequently caused by indoor allergens such as dust mites, moulds, insects (cockroaches) and animal danders. Seasonal allergic rhinitis is related to a wide variety of outdoor allergens such as pollens or moulds.

However, this is not entirely satisfactory as:
• There are some places where pollens and moulds are perennial allergens (e.g. grass pollen allergy in Southern California and Florida (4) or *Parietaria* pollen allergy in the Mediterranean area (5)).
• Symptoms of perennial allergy may not always be present all year round.
• The majority of patients are sensitised to many different allergens and therefore present symptoms throughout the year (6). In many patients, perennial symptoms are often present and patients present seasonal exacerbations when exposed to pollens or moulds.
• Many patients allergic to pollen are also allergic to moulds and it is difficult to define the pollen season (7).
• Due to the priming effect on the nasal mucosa induced by low levels of pollen allergens (8) and minimal persistent inflammation of the nose in patients with symptom free rhinitis (9), symptoms do not necessarily occur strictly in conjunction with the allergen season.

Thus, a major change in the subdivision of allergic rhinitis has been proposed in this document with the terms "intermittent" and "persistent". However, in the present document, the terms "seasonal" and "perennial" are still retained to enable the interpretation of published studies.

Allergic rhinitis is characterised by nasal obstruction, rhinorrhea, sneezing, itching of the nose and/or post-nasal drainage. It is often associated with ocular symptoms. Several other conditions can cause similar symptoms: infections, hormonal imbalance, physical agents, anatomical anomalies and the use of some drugs. Therefore, a detailed and correct aetiological diagnosis forms the basis for selecting optimal treatment.

Allergic rhinitis represents a global health problem. It is an extremely common disease worldwide affecting 10 to 25 % of the population (1, 10-12). However, this figure probably underestimates the prevalence of the disease, as many patients do not recognise rhinitis as a disease and therefore do not consult a physician (10). An increasing prevalence of allergic rhinitis over the last decades has been recognised (13, 14). Allergic rhinitis has been identified as one of the top ten reasons for visits to primary care clinics (15). Although allergic rhinitis is not usually a severe disease, it significantly alters the social life of patients (16, 17) and affects school learning performance (18, 19) as well as work productivity (20). Moreover, the costs incurred by rhinitis are substantial (21).

Other conditions associated with allergic rhinitis are asthma, sinusitis, otitis media, nasal polyposis, lower respiratory tract infection and dental occlusion. The cost of treating these conditions should be considered when evaluating the socio-economic impact of allergic rhinitis (22).

Asthma and rhinitis are common co-morbidities suggesting the concept of "one airway, one disease" (23). Rhinitis and asthma are linked by epidemiological, pathological and physiologic characteristics and by a common therapeutic approach (24-27). Although not universally accepted (28), the term "allergic rhinobronchitis" has been proposed to link the association between allergic asthma and rhinitis (29). Non-allergic asthma and rhinitis are also associated (30) but the mechanisms underlying the two diseases are not fully understood except, possibly, for aspirin-induced asthma (31). Moreover, costs for asthma are significantly increased in patients with allergic rhinitis (32). Patients with persistent allergic rhinitis should therefore be evaluated for asthma, and patients with asthma should be evaluated for rhinitis. A strategy combining the treatment of both upper and lower airway disease in terms of efficacy and safety appears to be optimal.

Clinical guidelines are systematically developed statements designed to help practitioners and patients make decisions about appropriate and effective health care (33). Guidelines have existed in various countries for decades and hundreds of them have been published for

many diseases (34) including asthma (35, 36) and allergic rhinitis (1-3, 37-40). There is considerable interest in guidelines as a tool for implementing health care based on proof of effectiveness. Guidelines should be informative, simple, easy to use and in a form that can be widely disseminated within the medical community in order to improve patient care. Unfortunately, many guidelines are not tested and may be difficult to use by non-specialists. Evidence-based medicine is an important method of preparing guidelines (41). Moreover, the implementation of guidelines is equally important.

New knowledge on the pathophysiological mechanisms underlying allergic inflammation of the airways has resulted in better therapeutic strategies. New routes of administration, dosages and schedules have been studied and validated. In addition, asthma co-morbidity should be well understood in order to achieve optimal treatment for patients.

The present document is intended to be a state-of-the-art for the specialist as well as for the general practitioner:
- to update their knowledge of allergic rhinitis,
- to highlight the impact of allergic rhinitis on asthma,
- to provide an evidence-based documented revision on the diagnosis methods,
- to provide an evidence-based revision on the treatments available,
- to propose a stepwise approach to the management of the disease.

The ARIA Paper is not intended to be a standard of care document for individual countries. It is provided as a basis for physicians and organisations involved in the treatment of allergic rhinitis and asthma in various countries to develop relevant local standard of care documents for their patients.

1- Classification

Rhinitis (rhinosinusitis) is classified as follows (Table 2). The differential diagnosis of rhinitis is presented in Table 3.

1-1- INFECTIOUS RHINITIS

Acute viral rhinosinusitis is one of the most common health complaints, affecting millions of people annually (42). It has been estimated that 0.5-2% of viral upper respiratory tract infections progress to an acute bacterial infection. Chronic rhinosinusitis affects 5-15% of the urban population (43) and thus exceeds the prevalence of many other chronic conditions (44). Four principal clinical types are recognised:
- acute,
- recurrent acute,
- chronic,
- acute exacerbations of chronic disease.

Attempts have been made to define these in terms of pathophysiology, microbiology, radiographic imaging, severity and duration of symptoms (45-47). This latter criterion has proved to be the most widely utilised, although, in the case of acute infectious rhinosinusitis, the accepted duration of symptoms may range from one day to less than twelve weeks (48-50).

In acute infectious rhinitis Rhinovirus, Influenza and Para-influenza, viruses are the most frequent initiators, whilst *Streptococcus pneumoniae* (20-35%) and *Haemophilus influenza* (6-26%) remain the most common bacteria (51). However, other agents including *Moraxella catarrhalis, Staphlycoccus aureus* and anaerobic bacteria are also found.

The same bacteria are regarded as significant in chronic infectious rhinosinusitis where they are found in high titres from sinus aspirates. They may also cause acute exacerbations of the chronic disease. In conditions such as cystic fibrosis, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are regarded as important pathogens. In addition, many other bacteria may be encountered whose role is as yet undetermined (52). Fungi such as *Aspergillus* or the Dermataceous fungi, *Alternaria, Bipolaris* or *Curvularia*, appear to be assuming greater importance (53-57). Other organisms such as *Mycobacterium tuberculosis, Klebsiella rhinoscleromatis, Mycobacterium leprae and Treponema pallidum* can also occur and both protozoan infection (leishmaniasis) and parasitic infection have been described.

Ciliary abnormalities, both congenital and acquired, immunodeficiency and direct trauma may all predispose individuals to the development of both acute and chronic infection (58-60).

1-2- ALLERGIC RHINITIS

Allergic rhinitis is subdivided into "intermittent", "persistent", "mild" and "moderate-severe" (Table 1).

TABLE 2: Classification of rhinitis
- Infectious
    Viral
    Bacterial
    Other infectious agents
- Allergic
    Intermittent
    Persistent
- Occupational (allergic and non-allergic)
    Intermittent
    Persistent
- Drug-induced
    Aspirin
    Other medications
- Hormonal
- Other causes
    NARES
    Irritants
    Food
    Emotional
    Atrophic
    Gastroesophageal reflux
- Idiopathic

TABLE 3: Differential diagnosis of rhinitis
- Polyps
- Mechanical Factors
    Deviated septum
    Adenoidal hypertrophy
    Foreign bodies
    Choanal atresia
- Tumours
    Benign
    Malignant
- Granulomas
    Wegener's Granulomatosis
    Sarcoid
    Infectious
    Malignant - midline destructive granuloma
- Ciliary defects
- Cerebrospinal Rhinorrhea

1-3- OCCUPATIONAL RHINITIS

Occupational rhinitis arises in response to an airborne agent present in the workplace and may be due to an allergic reaction or non-allergic hyperresponsiveness. Many occupational agents are irritant. Causes of occupational rhinitis include laboratory animals (rats, mice, guinea pigs, etc.), grains (bakers and agricultural workers), wood dust, particularly hard woods (mahogany, Western Red Cedar, etc.), latex and chemicals such as acid anhydrides, platinum salts, glues and solvents (61).

1-4- DRUG-INDUCED RHINITIS

A range of medications is known to cause nasal symptoms. These include:
- aspirin and other non-steroidal anti-inflammatory agents (NSAID). Aspirin intolerance is characterised by nasal secretion, eosinophilia, frequent occurrence of polyps, sinusitis, non-allergic asthma and usually by a good response to glucocorticosteroids (see chapter 3-3-2),
- reserpine (62),
- guanethidine (63),
- phentolomine,
- methyldopa,
- angiotensin converting enzyme (ACE) inhibitors (64),
- α-adrenoceptor antagonists,
- intra-ocular ophthalmic preparations such as ß-blockers (65),
- chlorpromazine,
- oral contraceptives.

The term rhinitis medicamentosa (66, 67) applies to the rebound nasal obstruction which develops in patients who use intranasal vasoconstrictors chronically. Rhinitis medicamentosa can be a contributing factor to non-allergic non-infectious rhinitis, which may be the reason the patient uses the vasoconstrictor.

Cocaine sniffing is often associated with frequent sniffing, rhinorrhea, diminished olfaction and septal perforation (68, 69).

1-5- HORMONAL RHINITIS

Changes in the nose are known to occur during the menstrual cycle (70), puberty, pregnancy (71, 72) and in specific endocrine disorders such as hypothyroidism (73) and acromegaly. Hormonal imbalance may also be responsible for the atrophic nasal change in post-menopausal women.

Persistent hormonal rhinitis or rhino-sinusitis may develop in the last trimester of pregnancy in otherwise healthy women. Its severity parallels the blood oestrogen level. Symptoms disappear at delivery.

In women with perennial rhinitis, symptoms may improve or deteriorate during pregnancy (74).

1-6- OTHER CAUSES

1-6-1- Nasal symptoms related to physical and chemical factors

Physical and chemical factors can induce nasal symptoms which may mimic rhinitis in subjects with sensitive mucous membranes, and even in normal subjects if the concentration of chemical triggers is high enough (75, 76). Skier's nose (cold, dry air) (77) and gustatory rhinitis (hot spicy food) (78) have been described as distinct entities. However, the distinction between a normal physiological response and a disease is not clear; all rhinitis patients may exhibit an exaggerated response to unspecific physical or chemical stimuli. Little information is available on the acute or chronic effects of air pollutants on the nasal mucosa (see chapter 3-2) (79).

1-6-2- Food-induced rhinitis

Food allergy is a very rare cause of isolated rhinitis (80). However, nasal symptoms are common among the many symptoms of food-induced anaphylaxis (80).

On the other hand, foods and alcoholic beverages in particular may induce symptoms by unknown non-allergic mechanisms.

Some spicy food such as red pepper can induce rhinorrhea, probably because it contains capsaicin. This is able to stimulate sensory nerve fibres inducing them to release tachykinins and other neuropeptides (81).

Dyes and preservatives as occupational allergens can induce rhinitis (82), but in food they appear to play a role in very few cases (80).

1-6-3- Eosinophilic rhinitis

Persistent non-allergic rhinitis with eosinophilia is a heterogeneous syndrome consisting of at least two subgroups: NARES and aspirin intolerance.

Non-allergic rhinitis with eosinophilia syndrome (NARES) was defined in the early 1980s (83, 84). Although it probably does not represent a disease entity on its own, it may be regarded as a subgroup of idiopathic rhinitis. It can be characterised by the presence of nasal eosinophilia and perennial symptoms of sneezing, itching, rhinorrhea, nasal obstruction and occasionally a loss of sense of smell in the absence of demonstrable allergy. It occurs in children and adults. Asthma is uncommon but approximately 50% of patients have non-specific bronchial hyperreactivity (85). NARES seems to evolve in three stages (86):
- migration of eosinophils from vessels to secretions,
- retention of eosinophils in the mucosa which might be linked to activation of unknown origin,
- nasal polyposis.

It has been suggested that some NARES represent an early stage of aspirin-sensitivity (87).

NARES is not responsive to DSCG (88) but responds usually although not always to intranasal glucocorticosteroids (89).

1-6-4- Emotions

Stress and sexual arousal are known to have an effect on the nose probably due to autonomic stimulation.

1-6-5- Atrophic rhinitis

Primary atrophic rhinitis is characterised by progressive atrophy of the nasal mucosa and underlying bone (90), rendering the nasal cavity widely patent but full of copious foul-smelling crusts. It has been attributed to infection with *Klebsiella ozaenae* (91) though its role as a primary pathogen is not fully documented. The condition produces nasal obstruction, hyposmia and a constant bad smell (ozaenae). It must be distinguished from secondary

atrophic rhinitis associated with chronic granulomatosis conditions, excessive nasal surgery, radiation and trauma.

1-6-6- Gastroesophageal reflux

Gastroesophageal reflux can be associated with rhinitis, especially in children (92, 93).

1-7- Unknown aetiology (idiopathic rhinitis)

Otherwise sometimes termed "vasomotor rhinitis", these patients (usually females aged between 40-60 years) manifest an upper respiratory hyperresponsiveness to non-specific environmental triggers such as changes in temperature and humidity, exposure to tobacco smoke and strong odours.

2- Epidemiology and genetics

2-1- EPIDEMIOLOGY OF ALLERGIC RHINITIS

Despite the recognition that allergic rhinitis is a global health problem and is increasing in prevalence (94-98), there are insufficient epidemiological data with regards to its distribution, aetiological risk factors and natural history. However, new national or multinational studies are rapidly improving our knowledge in the prevalence of rhinitis and its possible risk factors. These include:
- the second National Health and Nutrition Examination Survey (NHANES II) (99, 100),
- the European Community Respiratory Health Survey (ECRHS) (101),
- the International Study on Asthma and Allergy Asthma in Childhood (ISAAC) (12),
- the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) (11),
- the Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen (SCARPOL) (102) .

2-1-1- Epidemiological definitions

Before defining rhinitis for epidemiology, several terms need to be determined (36).

2-1-1-1- General definitions
- Prevalence is the percentage of the population with a disease or an abnormality. Cumulative prevalence is the total number of individuals who have had the disease at any time. Point prevalence is the number of individuals with the disease at any given time.
- Incidence is the number of individuals who develop an abnormality within a given time (usually a year).
- Morbidity is the degree to which quality of life is impaired.
- Atopy: The epidemiological definition of atopy is not based on the definition of atopy found in the glossary. The epidemiological definition of atopy is based on skin prick test positivity to allergens or allergen-specific serum IgE. Therefore, depending on the definition of skin prick test criterion used, there have been considerable differences in estimations of prevalence and incidence of atopy in populations.

2-1-1-2- Definition of rhinitis
The clinical definition of rhinitis is difficult to use in epidemiological settings of large populations where it is not possible either to visit every person or to obtain laboratory evidence of the immune response.

Initial epidemiological studies have assessed allergic rhinitis on the basis of simple "working definitions". Various standardised questionnaires have been used to this effect (103, 104).
- The first questionnaires aiming at assessing seasonal allergic rhinitis dealt with "nasal catarrh" (British

Medical Research Council, 1960) (105) and "runny nose during spring" (British Medical Research Council, 1962) (106).
- Successively, questions introducing the diagnostic term of "seasonal allergic rhinitis" were used: "Have you ever had seasonal allergic rhinitis?" or "Has a doctor said that you suffer from seasonal allergic rhinitis?"
- In the ECRHS full-length questionnaire, the question asked on rhinitis was: "Do you have any nasal allergies including "seasonal allergic rhinitis"?" (107). In order to identify the responsible allergen, the ECRHS study has included potential symptom triggers.
- A score considering most features (clinical symptoms, season of the year, triggers, parental history, individual medical history, perceived allergy) of allergic rhinitis has recently been proposed (108). Taking the doctor's diagnosis (based on questionnaires, examinations and skin tests to common aeroallergens) as a gold standard, such scores had good positive and negative predictive values (84% and 74% respectively) for identifying patients suffering from allergic rhinitis. Perennial rhinitis has been defined as having frequent non-seasonal nasal or ocular symptoms ("rhinoconjunctivitis").
- In a study, the length of the disease was also taken into consideration in order to differentiate perennial rhinitis from "the common cold" (a viral upper respiratory infection) (109).

Objective tests for the diagnosis of IgE-mediated allergy (skin prick test, serum specific IgE) can also be used (110-112). The diagnostic efficiency of IgE, skin prick tests and Phadiatop® was estimated in 8,329 randomised adults from the SAPALDIA. For the diagnosis of allergic rhinitis, the skin prick test had the best positive predictive value (48.7%) compared to Phadiatop® (43.5%) or total serum IgE (31.6%) (113). Future working definitions are intended to encompass clinical symptoms, immune response tests, nasal function and, eventually, specific nasal challenge (114).

2-1-2- Prevalence

2-1-2-1- Monocentric studies
Estimates of the prevalence and incidence of allergic rhinitis have varied with the populations studied, definitions of the conditions and methods of assessment ("working definitions").
- Most data concern seasonal allergic rhinitis, but not exclusively (6, 99, 100, 109).
- The prevalence of seasonal allergic rhinitis ranges from 1 to 40% (Table 4).
- The prevalence of perennial rhinitis varies from 1 to 18% (Table 4).
- In a survey, skin prick testing with 8 non-standardised

TABLE 4: Prevalence of rhinitis by questionnaire or examination

Study		Year	Number of subjects	Study	Age group	Country	Seasonal	Perennial	Nasal symptoms
Varjonen	(116)	1992	1712	Quest	15-16	Finland	14%		
Harf	(117)	1992	629	Quest	Adult	France	5.9%		
Vervloet	(111)	1991	2067	Exam	20-60	France	18.5%		
Pariente	(109)	1997	35615	Quest	>18	France		4.1%	
Dold	(118)	1992	3984	Quest	9-11	Germany	9.5%		
Weiland	(119)	1994	2050	Quest	13-16	Germany	22.7%		
Droste	(112)	1996	2167	Quest	20-70	Holland	6.6%	12.7%	29.5%
Astarita	(120)	1998	915	Quest	9-15	Italy	13.1%		
Matricardi	(121)	1997	1649	Quest	Men	Italy	13.3%		
Ogino	(122)	1990	471	Exam	18-22	Japan	32.7%		
Okano	(123)	1999	431	Quest	school				22.5
Okuma	(124)	1994	1013	Quest	6-15	Japan	12.9%		
Min	(125)	1997	9069	Exam	All	Korea		1.14%	
Bakke	(126)	1990	4492	Quest	15-70	Norway	10%		
Dotterud	(127)	1994	551	Quest	7-12	Norway	20.6%		
Breborowicz	(128)	1995			6-15	Poland	16.7%		
Ng	(129)	1994	2868	Quest	20-74	Singapore	4.5%		10.8%
Goh	(130)	1996	6238	Quest	6-7	Singapore			13.4%
Azpiri	(131)	1999	2216	Quest	10-40	Spain (Basque)	10.6%		
Hattewig	(132)	1990	1654	Exam	7	Sweden		8%	
Aberg	(133)	1995	2481	Quest	7	Sweden	13%		
Norrman	(134)	1994	1112	Exam	13-18	Sweden	17%		
Varonier	(135)	1984	4781	Exam	5-6	Switzerland	0.46%	0.56%	
Varonier	(135)	1984	2451	Exam	15	Switzerland	4.4%	1.0%	
Wuttrich	(11)	1995	8357	Exam	16-60	Switzerland	14.2%		
Kalyoncu	(136)	1999	738	Quest	6-13	Turkey			18.7%
Burr	(137)	1989	965	Exam	12	UK	14.9%		
Howarth	(138)	1989	1792	Quest	16-20	UK	18%		
Jones	(257)	1998	2114	Quest	>14	UK	19.8%	8.6%	
Ninan	(139)	1992	1989	Quest	8-13	UK	11.9%		
Sibbald	(6)	1991a	2969	Quest	16-65	UK	3%	13%	24%
Richards	(140)	1992	813	Quest	5-59	UK	29%		
Strachan	(141)	1995	12355	Quest	23	UK	16.5%		
Hagy	(142)	1969	1836	Exam	16-21	USA	21.1%	5.2%	
Broder	(143)	1974b	9226	Exam	4-7	USA	10.2%		
Turkeltaub	(144)	1988		Quest		USA			20.4%
Wright	(145)	1994	747	Quest	6	USA	42%		

Modified from (115)

extracts of inhalant allergens confirmed that perennial rhinitis was often associated with allergy as there was an excess of skin prick test positivity to cats or dogs among individuals suffering from perennial rhinitis (99, 100).
- Non-allergic rhinitis was reported to account for 30 to 70% of patients with chronic perennial rhinitis (146).
- In the Tucson study, it was found that 42% of children had physician diagnosed rhinitis at the age of 6 years (145).
- The prevalence of seasonal allergic rhinitis is higher in children and adolescents than in adults. Perennial rhinitis is more common in adults than in children but little reliable data exist (146).
- In many parts of the world, pollen allergy is very common, but in Eastern Asia, Latin America and tropical areas, mite allergy is more common (see chapter 3-1).
- In a study carried out in the US, the prevalence of aspirin-induced rhinitis and asthma was approximate-

ly 10% of the adult asthmatics (147). This percentage may be even higher when aspirin provocation tests are routinely carried out (148). In a recent Scandinavian population-based study, aspirin intolerance was higher in those with allergic-like rhinitis than in those without (2.6% versus 0.3%) (149). However, there may be differences between geographical areas in the world concerning aspirin intolerance. More data are needed.

2-1-2-2- ISAAC
The aetiology of asthma and allergic disease lacks understanding despite considerable research. The ISAAC was founded to maximise the value of research into asthma and allergic disease, by establishing a standardised methodology and by facilitating international collaboration. Its specific aims are (150):
- to describe the prevalence and severity of asthma, rhini-

tis and eczema in children living in different centres, and to make comparisons within and between countries,
- to obtain baseline measures for the assessment of future trends in the prevalence and severity of these diseases,
- to provide a framework for further aetiological research into genetic, lifestyle, environmental and medical care factors affecting these diseases.

The ISAAC design comprises three phases (151):
- Phase 1 uses core questionnaires designed to assess the prevalence and severity of asthma and allergic disease for two age groups. It was completed in 156 collaborating centres in 56 countries and a total of 721,601 children participated. In the 13-14 year-old age group, 155 centres from 56 countries participated, of which 99 centres completed a video questionnaire (463,801 children). For the 6-7 year age group, there were 91 collaborating centres in 38 countries (257,800 children). Rhinitis was described as "a problem with sneezing", or "a runny or blocked nose when you (your child) did not have a cold or the flu". Additional questions were asked about rhinitis associated with itchy-watery eyes, interference with activities and a history of seasonal allergic rhinitis. One of the major problems raised within this study was that only a questionnaire was applied and that responses for rhinitis may overestimate the real prevalence of the disease. In the SCARPOL (152), the validity of the ISAAC core questions on rhinitis was tested on a population of 2,954 Swiss school children by comparing them to skin prick test results. The specificity of the ISAAC questions was high, ranging from 77.5 to 97.6%, but the sensitivity was low (2.6 to 42.7%). The positive predictive value for atopy among children with symptoms was 63% for sneezing accompanied by itchy-watery eyes, 67% for symptoms occurring only during the pollen season and 70% for reported seasonal allergic rhinitis. The authors concluded that the ISAAC core questions on rhinitis are highly specific and therefore useful in screening children without atopy. In addition, they have a high positive predictive value in detecting atopy among children with symptoms. However, they are not helpful for detecting atopy in a general population of children (low sensitivity). Moreover, there was a season-of-response effect on questions concerning rhinitis symptoms suggesting a recall bias relating to recent symptoms (153).
- Phase 2 will investigate possible aetiological factors, particularly those suggested by the findings of Phase 1.
- Phase 3 will be a repetition of Phase 1 to assess trends in prevalence.

ISAAC Phase 1 has demonstrated a large variation in the prevalence of asthma and rhinitis symptoms in children throughout the world. The prevalence of rhinitis with itchy-watery eyes ("rhinoconjunctivitis") in the past year varied from 0.8% to 14.9% in the 6-7 year-old age group and from 1.4% to 39.7% in the 13-14 year-old group (12, 130, 154-174) (Figure 1). The overall correlation between the prevalence of asthma and rhinitis in

school children was significant (σ = 0.65, p<0.0001) (12, 154). In particular, it was found that countries with a very low prevalence of asthma (<5%) such as Indonesia, Albania, Romania, Georgia and Greece had low prevalences of rhinitis. On the other hand, the countries with a very high prevalence of asthma (>30%) such as Australia, New Zealand and the United Kingdom had a high prevalence of rhinitis (15-20%). Other countries with a very high prevalence of rhinitis (Nigeria (>35%), Paraguay (30-35%), Malta, Argentina, Hong Kong (25-30%), Brazil (7-25% in different centres)) had asthma prevalences ranging from 10 to 25%. It is likely that environmental factors were responsible for these major differences between countries.
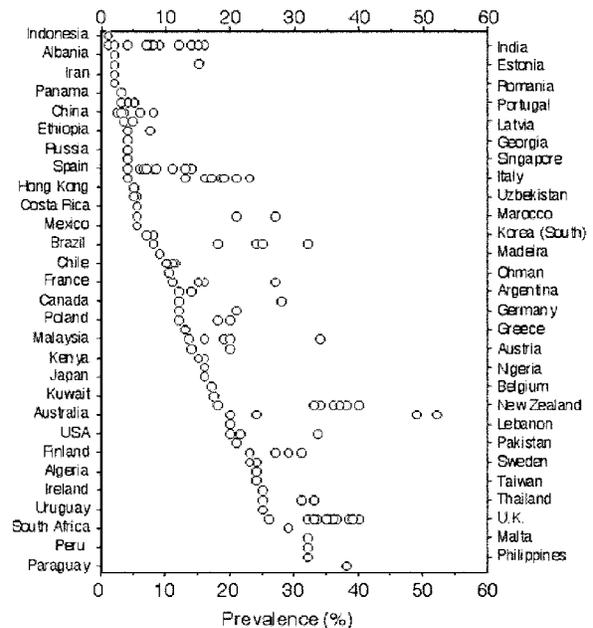
FIGURE 1: Prevalence of "hay fever" in 13-14 year-old children in ISAAC centres. Data from Strachan et al (12).

The results provide a framework for studies between populations in contrasting environments. These are likely to yield new clues about the aetiology of asthma and rhinitis.

2-1-2-3- ECRHS

No co-operative study on allergic rhinitis has been carried out among adults but the ECRHS asked for comparable representative samples on "nasal allergy" (107). The ECRHS was carried out in order to answer specific questions about the distribution of asthma and health care given for asthma in the European Community. Specifically, the survey is designed:
- to estimate variations in the prevalence of asthma, asthma-like symptoms and airway responsiveness,
- to estimate variations in exposures to known or suspected risk factors for asthma,
- to assess to what extent these variations explain the variations in the prevalence of disease,

- to estimate differences in the use of medication for asthma.

The protocol provides specific instructions on the sampling strategy adopted by the survey teams, on the use of questionnaires, the tests for allergy, lung function measurements, tests of airway responsiveness, blood and urine collection.

Results for the prevalence of "nasal allergy" were published in a few studies only (30, 101, 112, 175-177). The findings of Droste *et al.* (112) confirmed the close relationship of skin test positivity with reported symptoms of nasal allergy in a general population. Specific IgE positivity also shows a close relationship with nasal symptoms in response to allergen exposure in a general population. Skin testing and specific IgE measurement may be considered complementary to one another when diagnosing allergic rhinitis.

2-1-2-4- SAPALDIA

SAPALDIA focuses on the long-term health effects of low to moderate levels of air pollutants as typically seen in different parts of Switzerland. The aim of the SAPALDIA cross-sectional study carried out in 1991-1993 was:

- to determine the prevalence of bronchial asthma, chronic bronchitis and allergic conditions in the adult population of Switzerland,
- to identify and to determine the respective importance of potentially influencing factors (178). These could be both personal (smoking habits (179), allergy status, family history, occupation) and environmental (outdoor and indoor pollution (180), aeroallergens, climate).

SAPALDIA investigated a random population sample (18-60 year-olds) in eight Swiss areas with different environments. In total, 9,651 adults (60%) participated in the cross-sectional investigation (part 1, 1991) which consisted of the following standardised procedures: questionnaires (interviews), forced expiratory lung function tests, bronchial challenge with methacholine, atopy assessment (Phadiatop®, total serum IgE), allergy skin tests (113) and end expiratory CO-measurements. Subjects with a history of respiratory symptoms, increased bronchial reactivity, reduced lung function (FEV_1/FVC < 80% predicted) and 150 healthy persons who had never smoked were included in the subsequent diary study (part 2; n = 3281, 1992/93). Peak flow (morning and evening), symptoms, medication, personal activity and visits to the doctor were monitored. A further aim of the cross-sectional study consisted in the identification of individuals susceptible of presenting symptoms during a two year observation period and who could be included in the SAPALDIA follow-up study (181).

The prevalence of allergic rhinitis was also assessed in the SAPALDIA (11).

- On the basis of a positive Phadiatop® and/or a positive skin prick test to common aeroallergens, 32.3% of the study population were considered atopic (males 35.7%, females 28.8%; p < 0.001).

- The highest rate of positive skin prick tests was observed for grass pollen (12.7%), followed by house dust mite (8.9%), silver birch (7.9%), cat (3.8%) and dog (2.8%). Moulds and *Parietaria* elicited less than 1% of positive skin prick tests.
- The prevalence of allergic rhinitis (rhinitis symptoms associated with atopy) was 13.5% (males 14.3%, females 12.6%; p < 0.05).
- The prevalence of current seasonal allergic rhinitis varied between 9.1% (questionnaire answer and a positive skin prick test to at least one pollen), 11.2% (questionnaire answer and presence of atopy) and 14.2% (questionnaire answer only) with no significant difference whether male or female.
- In multivariate logistic regression models, the prevalence of positive Phadiatop®, positive skin tests and atopy decreased significantly with age. The odds of having a positive Phadiatop and skin test, or being atopic, were found to decrease on average by 23, 21.1 and 21% respectively, with every 10-year increase in age (182).

Smoking was found to increase total serum IgE but was associated with a lower prevalence of allergic rhinitis (182).

Air pollution had effects on the prevalence of dyspnea, on symptoms of chronic bronchitis, on FEV_1, on the incidence of respiratory symptoms and on the length of symptom free intervals, but not on the prevalence of asthma (183). Environmental tobacco smoke showed an impact on wheezing, asthma, bronchitis and chronic bronchitis (179).

2-1-2-5- SCARPOL

The impact of long-term exposure to air pollution on respiratory and allergic symptoms and illnesses was assessed in a cross-sectional study of school children (aged from 6 to 15 years, n = 4,470) living in 10 different communities in Switzerland (184). Air pollution measurements (particulate matter of less than 10 µm in diameter (PM10), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and ozone) and meteorological data were collected in each community. Reported symptom rates of chronic coughs, nocturnal dry coughs and bronchitis, adjusted for individual risk factors, were positively associated with PM10, NO_2 and SO_2.

In the SCARPOL, rhinitis was studied in a population of 2,954 school children (152). Sensitisation to any allergen was most strongly associated with reported seasonal allergic rhinitis (OR = 5.7), nose problems accompanied by itchy-watery eyes (OR = 4.4), symptoms occurring only during pollen season (March to September) (OR = 4.9) and a combination of these two latter symptoms (OR = 5.8). Finally, the under-diagnosis of allergic rhinitis was found to be common.

The prevalence of seasonal allergic rhinitis and allergic sensitisation in farmers' children and their peers living in the same rural community was then studied. Children growing up on a farm were less likely to be sensitised to common aeroallergens and to suffer from allergic diseases than children living in the same villages but in non-farming families (adjusted OR = 0.31) (102).

2-1-3- Risk factors

Allergic rhinitis is highly related to asthma and eczema. However, the geographical and temporal distributions as well as the associations of such diseases differ largely and these differences can be used to better understand the mechanisms of allergic diseases. Risk factors of rhinitis may intervene at all ages in life and epidemiology has greatly contributed in exploring them.

2-1-3-1- Genetics and familial history

A genetic component in allergic rhinitis as well as in other allergic disease has been shown (185) and the best established risk factor for allergic rhinitis is a family history of allergy, especially allergic rhinitis (186). Furthermore, seasonal allergic rhinitis increases the risk of asthma significantly on the basis of analyses of all individuals and of discordant twin pairs (187). For the past decade, various antigens of the HLA system have been identified as being responsible for seasonal allergic rhinitis (185). Some genes have also become candidates for explaining the genetic component of allergic rhinitis but problems with the definition of the studied phenotypes prevent us from generalising them (see chapter 2-2). It is clear that the recent increase in prevalence of allergic rhinitis cannot be due to a change in gene pool.

2-1-3-2- Early life risk factors

Several studies have provided evidence that sensitisation to allergens may occur in early life (188). However, early life risk factors have rarely been related to rhinitis (189). As a consequence, existing results are contradictory and need to be confirmed.

- Young maternal age, multiple gestation, prematurity, low birth weight, growth retardation and perinatal asphyxia were all significantly related to a decreased risk of allergic rhinitis among male conscripts in Sweden (190).
- Prospectively, in the Tucson Children's Respiratory Study, early introduction of solid foods, heavy maternal cigarette smoking in the first year of life (at least 20 cigarettes per day) and higher IgE were all associated with the development of rhinitis in the first years of life (145). This supports the fact that allergic rhinitis is an early manifestation of an atopic predisposition triggered by early environmental exposures.
- Maternal age during pregnancy, birth weight, gestational age and *in utero* smoking were not related to seasonal allergic rhinitis in off-springs of a British birth cohort (104).
- However, in two British birth cohorts, there were significant trends in the increase of allergic rhinitis prevalence with decreasing birth order, increasing maternal age, *in utero* smoking and increasing duration of breast feeding (191).
- The month of birth has been related to allergic rhinitis but findings could have been biased by the absence of consideration of negative studies (192-196).

2-1-3-3- Ethnic groups

Although some studies have been carried out in asthma, few studies have examined the role of ethnic origins in the development of allergic rhinitis. In England, native persons were at lower risk than those born in Asia or the West Indies (197). Similarly, Maori people suffered more from allergic rhinitis than New Zealanders from English origin (198). Little evidence as to whether this is related to genetic, environmental, socio-economic or cultural factors exists up to now (99, 199).

2-1-3-4- Sib-ship size and order and infections in the neonatal period

Several studies have found an inverse relationship between atopy, seasonal allergic rhinitis (and asthma) and sib-ship size and order (191, 200, 201). Seasonal allergic rhinitis is less frequent in large families even after taking the month of birth into account (104). The apparent protective effect of large household size and asthma and/or rhinitis could not be explained by an increase in reported early respiratory illness. The timing and mechanism of the inverse association between increasing sibling numbers and atopic disease are not yet understood (202).

A possible but unproven explanation has been demonstrated using the Th1/Th2 paradigm (203). In children of large families where infections are common, the immune system may be Th1 cell oriented to respond to the aggression of external agents such as viruses and bacteria (204, 205). With children living in small families where infections are rare, Th2 cells may develop instead of Th1 cells. As a consequence, IgE responsible for immediate sensitivity is produced. Moreover, there are probably as many pros and cons in this theory. It has been observed that various confounders intervene in the relationship between infection and allergy (206), for instance the age of entry into nursery where infections are also very common (207). Some studies have proposed that early BCG exposure was associated with a reduction of atopy (208), but other studies have found no relationship (209). The measles infection was also associated with a reduction in allergic disease in some but not all studies (210-212).

Another hypothesis has recently been proposed (213). Bacterial antigens may favour the development of Th1 cells from naive CD4-positive T-cells through a CD14-dependent pathway. The CD14 gene maps to chromosome 5q31.1, a candidate region for loci regulating total serum IgE. Genetic variants in the CD14 gene could influence Th-cell differentiation and thus total serum IgE. CD14/-159 plays a significant role in regulating serum CD14 levels and total serum IgE levels.

2-1-3-5- Allergen exposure

Allergens are known risk factors for the development and the triggering of allergic rhinitis (214). They operate early in life (188, 215). Outdoor allergens appear to constitute a greater risk for seasonal rhinitis than indoor allergens (152). In NHANES II, the prevalence of perennial rhinitis increased significantly in four years with positive skin prick tests to indoor allergens such as house dust, cats or dogs (100). Recently, new hypotheses have been raised on the effect of allergenic exposure (157, 216, 217), as early exposures to feather bedding, pillows and cats or dogs might have protective effects in some

individuals. However, although challenging, these hypotheses need to be confirmed by further studies.

2-1-3-6- Rural-urban differences and modification of life style

Different studies in North America (100), Europe (103, 218) and South Africa (219) have shown that the prevalence of atopy (defined as positive skin tests to common aeroallergens) and allergic rhinitis is higher in urban areas than in rural areas. Besides the fact that selection bias acts in selecting people who live in the countryside (11, 100, 220-222), pollution, which is higher in town than elsewhere, increases the allergenic potency of pollens (223, 224). Furthermore, it is not excluded that observed differences could be due to confounders such as socio-economic factors, variations in the diagnosis and in the management of the disease. Recently, it has been found that farmers' children have less allergic rhinitis than other children, suggesting therefore that lifestyle in the countryside could protect children from the development of allergy (102). The putative role of endotoxins has been raised but not yet confirmed (212).

Asthma and allergy in developing countries may be associated with the adoption of an urbanised "western" lifestyle (225, 226). In Africa, urbanisation leads to an increase in asthma and allergy. This was largely explained by urban-rural differences in environmental factors, including indoor animals, sharing a bedroom with a smoker, parental education, house ventilation and exposure to motor vehicles.

In 1989, in East German children, there was a reduced prevalence of atopy and seasonal allergic rhinitis compared to West German children (218, 227). Similar trends have been observed in the Baltic States and in Scandinavia (228). Although there is some controversy (229, 230), it seems that the prevalence rate of atopy and seasonal allergic rhinitis is now similar in all parts of Germany (189).

2-1-3-7- Outdoor and indoor air pollution

Environmental studies of the health effects of air pollution have contributed to the understanding of such effects.

2-1-3-7-1- Acute effects of outdoor air pollution

Acute effects on humans due to the outdoor and indoor exposure to several gases/fumes and particulate matter (PM) have been demonstrated in studies (231). However, these effects have not been clearly studied on nasal symptoms.

2-1-3-7-2- Chronic effects of outdoor air pollution

The chronic effects of atmospheric pollutants have been studied but, except for the known effects of particulate matter on lower airways, they have not been studied conclusively (232). There are ongoing studies concerning the chronic effects of certain pollutant classes such as ozone, acid rain, airborne toxics and the chemical form of particulate matter (PM) (including diesel exhaust) (233). However, there are some studies assessing the effects of outdoor air pollution on rhinitis:

- As demonstrated in Mexico City, pollution is an important cause of nasal symptoms in non-allergic subjects (79, 234, 235).
- In Turkey, high school students living in polluted areas have significantly higher prevalence rates for symptoms of allergic rhinitis (22.8%) than those living in unpolluted, residential areas (6%) (236).
- In Italy, Corbo *et al.* (237) showed that 7-11 year-old children living in a polluted area (n = 1477) had 1.7 times more ENT symptoms than those not exposed (n=749).
- In Thailand, policemen working in heavy traffic have more cough and rhinitis symptoms and lower FEV_1 and FVC than the normal Thai population (238).
- In Taiwan, nasal symptoms of children living in the petrochemical communities were more prevalent than in those living in the rural community (239).
- Outdoor pollution appears to induce symptoms in patients with allergic rhinitis (76, 119).

Diesel exhaust particles may induce a Th2-like inflammation (see chapter 3-2), but epidemiogical data on the occurrence of rhinitis and/or asthma are still lacking.

2-1-3-7-3- Chronic effects of indoor air pollution

Since most of the time spent by the Western population is indoors, the effect of indoor air pollution is of great importance (240).

- Pre-natal (145, 191) and early post-natal exposure to tobacco smoke enhances allergic sensitisation in some groups of subjects such as boys (241) or children with atopy in the first three years of life.
- In the French ISAAC study which involved approximately 15,000 children, dermatitis (242, 243) was increased in smoking households.
- A study of 9 to 11 year-old children in South Bavaria has found a reduced risk of seasonal allergic rhinitis in homes where coal and wood were used for heating. Coal and wood, which are used in lower social classes, increase the risk of respiratory infections for reasons that are uncertain (244).
- The effect of gas cooking in the epidemiology of rhinitis is still unclear (245).

2-1-3-7-4- Future studies

Key elements of further studies are:

- The assessment of total exposure to different pollutants (occurring from indoor and outdoor sources) and the interactive effects of pollutants.
- Major research areas include: (i) determination of the contribution of indoor sources and of vehicle emissions to total exposure, (ii) how to measure such exposures and (iii) how to measure human susceptibility and responses (including those at the cellular and molecular level). Cotinine levels should be measured if passive smoking is studied.
- Biomarkers of exposures (246, 247), doses and responses, including immunochemicals, biochemicals (248) and deoxyribonucleic acid (DNA) adducts (249, 250), are beginning to promote some basic knowledge of exposure-response, especially concerning mechanisms.
- These will be extremely useful additions to standard physiological, immunological and clinical instruments, and to the understanding of biological plausibility.

2-1-3-8- Active smoking

The effect of active smoking differs according to age. Cross-sectional studies showed that children or adolescents with allergic rhinitis smoke more than others (119). In another study, it was found that allergic patients are more frequently ex-smokers than others (251). Conversely, smokers suffer less seasonal allergic rhinitis than non-smokers (251). However, in the absence of longitudinal studies, it is difficult to establish whether smoking is a causative factor of allergy or not (252, 253).

Tobacco smoking may increase allergenic sensitisation to haptens in occupational settings (254, 255).

2-1-3-9- Social class and occupation

These factors may also be involved in the prevalence of rhinitis:

- In the 1958 British birth cohort, children of fathers with higher social class occupations were more likely to have seasonal allergic rhinitis (145, 256).
- Similarly, the Tucson Children's Respiratory Study indicated a higher prevalence of seasonal allergic rhinitis in children whose mothers had more than a high school education (145).
- In Nottingham, in a study of 2,114 individuals, those with perennial symptoms were no more likely to have been working in a dusty or smoky environment (257).
- In the Guinea-Bissau study, children born from more educated mothers had more allergies than those born from poorly educated ones (212).

2-1-4- Increase in prevalence of allergic rhinitis and putative factors

An increase in the prevalence of allergic rhinitis has been observed over the last 40 years (95, 133, 139, 145, 191, 199, 258) (Table 5).

These studies propose different reasons for such trends which may be related to allergen load or co-factors:

- Changes in lifestyle (265),
- Increase in exposure to allergen (266), pollution and irritants (smoke, gas…) (267),
- Modification in diet responsible for the diminution of protective nutrient intake,
- Decrease in infections (268),
- Stress.

Thus, interaction between the environment and individual susceptibility (269) might be responsible for the observed increase in prevalence. One study has specifically attempted to examine the reasons for the increase of allergic rhinitis prevalence. No factors were found apart from the increase of mould exposure. However, this study encountered a few methodological problems. The same definition of allergic rhinitis as well as objective assessments of exposure have to be taken into account in studies which attempt to explore the causes of increase in prevalence.

2-1-5- Natural history

Most longitudinal studies have explored the development of asthma in individuals suffering from allergic rhinitis. Few have reported directly on the prognosis of allergic rhinitis.

- Prognosis of allergic rhinitis depends on age and sex.
- Remission may be observed after long periods of time, especially in seasonal allergic rhinitis.
- Rhinitis symptoms tend to become milder (99, 145, 191) and simultaneously the allergic skin reactivity decreases (270).
- Some studies found an increased prevalence of allergic rhinitis in young adults (142, 271-278).
- After a ten year course of the disease, 20% of patients with non-allergic rhinitis reported spontaneous disappearance and 36% reported improvement (146).

2-1-6- Conclusion

Allergic rhinitis is a very common disease in western lifestyle countries. It tends to be more common in developed countries. Furthermore, an increase in the prevalence of allergic rhinitis is commonly observed. However, knowledge of allergic rhinitis is far from complete. More studies on the epidemiology of allergic rhinitis should be advocated as they may provide useful clues to the interpretation of the immunological abnormalities associated with allergic diseases in general.

2-2- THE GENETICS OF ALLERGIC RHINITIS

The hereditary character of allergic rhinitis and other atopic diseases was shown in the first studies of families and twins (220). Genetic studies were focalised on the genes of the immune response, whether specific to the allergen or not. The genetics of rhinitis has not been studied as much as that of asthma and atopy. One of the principal reasons for this is the difficulty of the precise and discriminating "allergic rhinitis" phenotype characterisation in a general population or in families and the fact that numerous rhinology disorders can show the same symptoms. However, atopy, which is a frequent cause of allergic rhinitis, has been the subject of many genetic studies and some of the susceptibility genes for atopy have been determined.

2-2-1- Family segregation studies

In 1916, Cooke and Vander Veer, whilst studying 504 families, concluded that the "sensitisation tendency" was transmitted by a dominant Mendelian autosomic mode (279). However, from 1950-1960, the "multifactorial theory" replaced the "monogenic theory". Another study suggested control by several genes, each one transmitted according to a recessive Mendelian autosomic mode (280). Studies using a clinical definition of allergy are not therefore concordant (this definition only detecting 30% of atopic subjects).

Whilst atopy is defined partly as the aptitude of the immune system to secrete excessive quantities of IgE in response to minimal allergenic stimulation, the results of the studies founded on the elevation of total serum IgE are not concordant. This is probably due to a non-negligible percentage of atopics who have only a low level of

TABLE 5: Changes in the prevalence of seasonal allergic rhinitis

Country	Study	Years	Age (yrs)	Prevalence (%)
Australia				
Australian bureau of statistics (1991)	(259)	1977-1990		No change
Denmark				
Linneberg *et al.* (1999)	(258)	1989	15-41	22.3%
Linneberg *et al.* (1999)	(258)	1997	15-41	31.5%
Finland				
Alanko (1970)	(260)	1970	10-19	2.7%
Rimpela *et al.* (1995)	(261)	1977-9	12-18	5%
Rimpela *et al.* (1995)	(261)	1991	12-18	14.9%
Haahtela *et al.* (1980)	(262)	1980	15-17	22%
Varjonen *et al.* (1992)	(116)	1991	15-16	14%
Sweden				
Aberg *et al.* (1989)	(195)	1971	Army recruits	4.4%
Aberg *et al.* (1995)	(133)	1979	7	5.45%
Aberg *et al.* (1989)	(195)	1981	Army recruits	8.4%
Aberg *et al.* (1995)	(133)	1991	7	8.08%
Switzerland				
Rehsteiner (1926)	(263)	1926		0.28%
Varonier (1970)	(135)	1970	15	4.4%
Varonier *et al.* (1984)	(135)	1980	15	4.4%
Wütrich *et al.* (1989)	(264)	1985	15-24	16%
Wütrich *et al.* (1995)	(11)	1991	18-60	14.2%
United Kingdom				
Butland *et al.* (1997)	(191)	1958	Cohort to 16	12%
Butland *et al.* (1997)	(191)	1970	Cohort to 16	23.3%
Ninan and Russel (1992)	(139)	1964	8-13	3.2%
Ninan and Russel (1992)	(139)	1989	8-13	11.9%
Burr *et al.* (1989)	(137)	1973	12	9%
Burr *et al.* (1989)	(137)	1988	12	15%
Richards et al. (1992)	(140)	1990	15-59	29%

Modified from (115)

total IgE. A recessive autosomal monogenic transmission has been proposed for "high IgE responders" (281). For other authors, the transmission of atopy, and more particularly low IgE response, occurs through monogenic autosomic dominant inheritance (282). In 1988, Cookson and Hopkin (283) showed that atopy was transmitted according to a dominant hereditary maternal autosomal mode. In 1995, Martinez *et al.* (284) and Meyers *et al.* (285, 286) recognised the influence of several genes, in particular one major gene which was transmitted according to a respectively co-dominant autosomal and recessive autosomal mode.

Some other familial segregation studies are currently being carried out in different countries throughout the world.

2-2-2- Twin studies

The study of twins confirmed the hereditary transmission of atopy. The concordance of allergy in monozygotic, genetically identical twins is higher than in dizygotic twins (220). The role of heredity is however small in the clinical expression of atopy and in the sensitivity to a particular allergen (here, environmental factors appear to dominate genetic factors).

2-2-3- Molecular studies

2-2-3-1- Candidate gene approach versus genome wide search

Some genetic linkages have been demonstrated using molecular markers located in and around genes whose products are involved in the pathophysiology of atopy or spread along the whole genome (287, 288).

The first approach using "candidate genes" has allowed the localisation of six chromosomal regions of susceptibility:
- 5q31.1q33.1 (containing the genes of the interleukin cluster 4 or IL4) (289, 290),
- 6p21.3 (containing the genes of the major histocompatibility complex HLA D and the TNF-α gene),
- 11q13 (containing the gene of the ß chain of the high affinity IgE receptor or FcεRIß) (291),
- 12q15-q24.1 (containing the interferon gamma gene or IFNγ) (292),
- 14q11.1 (containing the T-cell receptor gene alpha/delta or TCRα/δ) (293). Evidence for linkage between the development of asthma in childhood and the T-cell receptor ß chain gene was found in the Japanese (294). Chromosome 14q may contain a locus close to TCR

A/D at 14q11.2 linked to skin prick reactivity and a locus at 14q13- 23 linked to total serum IgE (295).

- 16p12 (which contains the IL4 receptor gene) (296).

The genome wide search approach has demonstrated an association between certain phenotypes and markers on chromosomes 4 (with bronchial hyperreactivity), 6 (with total serum IgE and eosinophilia), 7 (with total serum IgE, eosinophilia and bronchial hyperreactivity), 11 (with total serum IgE, positive allergy skin tests and asthma), 13 (with atopy) and 16 (with total serum IgE, bronchial hyperreactivity and asthma) (297). However, in another study (298), no single locus generated overwhelming evidence for linkage in terms of established criteria and guidelines for a genome-wide screening. This supports previous assertions of a heterogeneous aetiology for Der p-specific IgE responsiveness. Two novel regions, 2q21-q23 and 8p23-p21, that were identified in this study, merit additional studies.

No fine mapping or particular genetic polymorphisms has been described so far in allergic rhinitis subjects.

2-2-3-2- Candidate genes

Some of these genes are involved in the specific immune response (HLA D, TCR), others are genes of the (total) IgE response (IL-4, IL-4R, IFNγ, FcεRIß) or genes involved in the inflammatory process (TNF-α).

2-2-3-2-1- Genes associated with the HLA system

The genetic control of the specific IgE response is different to that of the total IgE response. The presentation of allergens to T lymphocytes by antigen presenting cells involves both HLA class II molecules and the T-cell receptor (TCR). These molecules are logically gene candidates. The genes susceptible to numerous illnesses have been localised in the HLA region (psoriasis, rheumatoid arthritis, diabetes). These illnesses are all characterised by an abnormal immune response. The expression of particular HLA haplotypes could also favour thymic maturation of T lymphocytes, reacting more with certain allergens.

In subjects monosensitised with a low level of total serum IgE (low responders) (282), a linkage disequilibrium has been observed between particular HLA haplotypes and the sensitisation to a purified allergen. For example, the IgE response to Amb a 5 antigen of ragweed (Ambrosia artemisiifolia) pollen is strongly associated with haplotype HLA D2/Dw2 (299), and that of rye grass (*Lolium perennae*) pollen or *Dermatophagoides pteronyssinus* is strongly associated with haplotype HLA-DR3. Allergy to rag-weed allergen was also found in DRB1*1501, 1601, 1602, 0103, 0402, 0404, 0801, or 1101 sequences (300).

In a group of patients allergic to ragweed pollen, a significant association was found between the presence of a specific haplotype and a particular clinical phenotype: the haplotype HLA-B7, SC31, DR2 was found almost exclusively in asthmatics and the haplotype HLA-B8, SC01, DR3 was more frequent in rhinitis-only sufferers (301).

2-2-3-2-2- Genes non-associated with the HLA system

A genetic association has also been found between the TCR α-chain of the lymphocytes (localised on chromosome 14) and the sensitisation to Der p 1 (major allergen of *Dermatophagoides pteronyssinus*), Amb a5 (302), Fel d 1 (major allergen of the cat) and grass pollen allergens. This was found in both English and Australian subjects (293).

The genes whose products regulate the synthesis of IgE are not linked to the HLA system. The genes of IL-4 and IL-13, localised on the 5q chromosome, are therefore, in "classical" genetics, candidate genes for atopy, as is the IL-5 gene. Marsh *et al.* (289) found an association between markers in 5q31.1 and the presence of a high level of total serum IgE. This study, confirmed in the general population (303), is undergoing thorough genetic exploration.

In 1989, in a study of 20 families, Cookson and Hopkin used a serological definition of atopy and localised a gene on the chromosome 11q12-13 (291). They then found different polymorphisms on the beta chain of the high affinity IgE receptor (FcεRI-ß-Leu181 and FcεRI-ß-E237G variants), whose gene is localised in this region (304-306). However, some discrepant results have been found (307).

A linkage and an association between atopic asthma and markers on chromosome 13 was found in the Japanese population (308).

Susceptibility loci on chromosome 12q have been described for both asthma and allergic rhinitis (309).

2-2-4- Conclusion

The present data are fragmented. They require reproduction by other teams and confirmation in the general population. One should remain cautious (most of the data are to be confirmed) and patient (we are still far from a precise physical identification of all the susceptible genes). The final stage will consist of modelling the interaction of all these genetic and non-genetic factors (notably those of the environment), which lead to the phenotype "allergic rhinitis".

3- Allergens and trigger factors

3-1- ALLERGENS

Allergens are antigens which induce and react with specific IgE antibodies. Since drugs or insect venoms, reactive haptens from occupational agents or drugs and the discovery by Charles Blackley in the 1860s that pollens can cause allergic diseases, the number of allergenic substances which have been identified has expanded enormously. Allergens originate from a wide range of animals, insects, plants and fungi or are small molecular weight chemicals. They include proteins or glycoproteins from inhalant allergens, foods, drugs or insect venoms, reactive haptens from occupational agents or drugs and, more rarely, glycans (as in the case of *Candida albicans* allergy (310)).

3-1-1- Nomenclature of allergens

The allergen nomenclature has been established by the WHO/IUIS Allergen Nomenclature Subcommittee (311). Allergens are designated according to the taxonomic name of their source as follows: the first three letters of the genus, space, the first letter of the species, space and an Arabic number. The numbers are assigned to the allergens in order of their identification and the same number is generally used to designate homologous allergens of related species. For example, Der p 1 was the first *Dermatophagoides pteronyssinus* allergen identified and Der f 1 refers to the homologous allergen of *Dermatophagoides farinae*. If necessary, an additional letter is added to the genus or species abbreviation to avoid ambiguity. For example, a distinction is made between antigen 5 of *Vespula vulgaris* and *Vespula vidua* by Ves v 5 and Ves vi 5.

In the allergen nomenclature, a definition of "major" and "minor" allergens has been proposed. When over 50% of the patients tested have the corresponding allergen-specific IgE, allergens can be considered as "major".

3-1-2- Molecular characteristics and function of allergens

The first purified allergens were obtained in the 1960s by protein chemistry (312). However, major advances have been made on allergen characterisation and sequence determination using chemical, immunochemical, biochemical and molecular biology techniques (313). Since 1988 when the first cDNA sequence of an allergen was published, tremendous progress has been made in identifying, cloning and expressing major allergens (314). The cDNAs of a large number of important allergens including mites, insects, Hymenoptera venoms, animal proteins, pollens, moulds and foods have now been isolated and sequenced (for review see 315, 316).

These new technologies make it possible to characterise the structure of allergens and thus improve the standardisation of allergen vaccines (317). Also, they are likely to improve the diagnosis and treatment of allergic patients. As an example, Bet v 1, the major allergen of birch pollen, is one of the best studied allergens and is part of of a multigene family. Several Bet v 1 isoforms and homologous proteins from closely related species (alder, hazel and hornbeam) have been isolated and their cDNAs cloned and characterised. This considerable degree of heterogeneity has been attributed to glycosylation (or other post-translational modifications), to isogenes coding for Bet v 1 isoforms and/or to allelic variants (318). It was shown that individual birch trees produce various subsets of isoallergens which display differences in reactivity both towards IgE antibodies and T-cells in humans (319). Recombinant isoforms of Cor a 1, the major allergen of hazel pollen which shares a large homology with Bet v 1, show different reactivities with allergen-specific T-lymphocyte clones (320). The dissection of IgE and T-lymphocyte reactivity of isoforms of the major birch pollen allergen Bet v 1 suggests a potential use of hypoallergenic isoforms for immunotherapy (321). X-ray crystal structures of Bet v 1, birch pollen profilin and Phl p 2 have been studied (322, 323). New forms of specific immunotherapy may be found since a detailed description of the major reactive epitopes may help to design tight-binding monovalent ligands which can prevent receptor aggregation, thereby reducing allergic response. Another promising strategy to increase the safety of specific immunotherapy is through the use of allergen derivatives, which do not cause anaphylaxis. Such hypoallergenic isoforms have been produced *in vitro* for Der p 2 and Bet v 1 by site-directed mutagenesis (324, 325).

Most allergens have associated activities with potent biological functions. The majority of allergens can be divided into several broad groups based either on their demonstrable biological activity or on their significant homology with proteins of known function (326). They include enzymes, enzyme inhibitors, proteins involved in transport and regulatory proteins. Profilin, ubiquitous low molecular weight (13,000-15,000 M(r)) actin binding protein (327), regulates the formation of F-actin structures *in vivo*. It is localised to specific cellular regions through interaction with proline-rich sequences. It was shown to be essential for cytoskeletal rearrangements such as those essential to the process of pollen tube growth (328). The major birch pollen allergen, Bet v 1, shows ribonuclease activity (329). It may include a subset of defence-related genes that are activated in the presence of microbial pathogens (330) and may be involved in anther ontogeny (331). Most mite allergens are associated with enzymatic activities. Many of these are digestive enzymes (332) whose specificities may differ depending upon the substrate on which the mites are growing, e.g. human skin scales for *Dermatophagoides* or grain and fungi for storage mites.

3-1-3- Inhalant allergens

Aeroallergens are very often involved in allergic rhinitis (333).

The increase in domestic allergens is partly responsible for the increase in the prevalence of allergic respiratory disease or in the severity of asthma (266). The allergens present in the bedroom are derived principally from mites, pet animals, insects or from plant origin (e.g. *ficus*).

3-1-3-1- Mites

3-1-3-1-1- House dust mites

Mites make up a large part of house dust allergens. Asthma and perennial allergic rhinitis therefore dominate the clinical picture. The majority of asthmatics and patients suffering from persistent allergic rhinitis are sensitised to mites.

House dust mites belong to the Pyroglyphidae family; subclass Acari, class of Arachnid, phylum of Arthropods (334, 335). The most important are:

- *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f) (336-341),
- *Euroglyphus maynei* (Eur m) (342-344),
- *Lepidoglyphus destructor* (Lep d) (345),
- *Blomia tropicalis* (Blo t) (343, 346-348) and *Blomia kulagini* (349), particularly, but not only, in tropical and sub-tropical regions (350-352). These mites can induce both asthma and rhinitis (353).
- Other house dust mite species present in tropical environments (354).

Mites of the species of *Dermatophagoides* and *Euroglyphus* feed on human skin danders which are particularly abundant in mattresses, bed bases, pillows, carpets, upholstered furniture and fluffy toys (355-360).

Their growth is maximal under hot (above 20°C) and humid conditions (80% relative humidity). When humidity is lower than 50%, the mites dry out and die (361). This is the reason why they are practically non-existent above 1,800 metres in European mountains as the air is too dry.

In fact, even though mites are present in the home all year round, there are usually two peak seasons (September/October and April/May) in many but not in all European countries (362, 363). Patients allergic to mites therefore have symptoms all year round but with a recrudescence during these peak periods (364). Moreover, the symptoms of patients allergic to mites are aggravated when it is humid.

House dust mite allergen is contained in faecal pellets (10-20 μm). Airborne exposure occurs with the active disturbance of contaminated fabrics and settles rapidly after disturbance.

It has been shown that 100 mites per gram of house dust (or 2 μg of allergens per gram of dust) are sufficient to sensitise an infant. With approximately 500 mites per gram of house dust (or 10 μg of allergens Der p1 (major allergen of *Dermatophagoides pteronyssinus*)), the sensitised patient shows a relative risk of around 5 of developing asthma at a later date (365-367). The higher the number of mites, the earlier the first episode of wheezing (366). The prevalence of sensitisation to mites in the general population is higher in humid regions (20-35%) than in dry ones (15%).

3-1-3-1-2- Other dust mites

Certain types of so-called storage mites (*Glycyphagus domesticus* and *destructor, Tyrophagus putrecentiae* and *Acarus siro*) are present in stocked grains and flour (368). These species are not found in bedding but have a definite allergic importance in the house dust of very damp houses, in tropical environments where the growth of moulds increases their development, and in rural habitats. These mites are particularly important in agricultural allergies (369-371) and can induce persistent rhinitis (372, 373).

Other species of mites intervene in other selected environments such as spider mites (*Panonychus ulmi)* in apple growers, *Panonychus citri* in citrus growers and *Tetranychus urticae* (374-377) and *Ornithonyssus sylviarum* in poultry breeders (378).

3-1-3-2- Pollens

Pollens were among the first allergens identified. The pollen grain is the male gametophyte of the vegetable kingdom.

According to their mode of transport, one can distinguish anemophilous and entomophilous pollens.

- The anemophilous pollens are very aerodynamic and are carried by the wind. They represent a major problem for sensitised patients as they are emitted in large quantities, can travel long distances (such as 200 km) and consequently can affect individuals who are far from the pollen source. It is, however, those who are nearest the emission of the pollen who generally show the most severe symptoms.
- The entomophilous pollens are those carried by insects. Attracted by colourful and perfumed flowers they carry the pollens from the male flower to the female portion of the flower. The pollens are sticky and adhere to the antennae or other parts of the insects. Little pollen is liberated into the atmosphere and sensitisation thus requires direct contact between the subject and the pollen source. This is the case, for example, with agriculturists (379) or florists (380) who are in contact with weeds or trees. However, atopic patients may occasionally develop sensitisation to these entomophilous pollens (381, 382).
- Certain pollens such as dandelion are both entomophilous and anemophilous.

The capacity of pollens to sensitise is theoretically universal, but the nature and number of pollens varies with geography, temperature and climate (383-385). The pollen concentration in the atmosphere depends on the vegetation and climate of a given geographic zone. There are important regional differences. The pollens causing most allergies are found among:

- grasses,
- certain weeds such as the Compositeae family (mugwort and ragweed (*Ambrosia*) (386)) and the Urticaeae family (*Parietaria* (5, 387-391)),
- trees such as the birch, other Betulaceae (392-397), Oleaceae (the ash and olive tree (398-400)), the oak

(Fagaceae family), the plane tree (401), Cupressaceae (the cypress tree (402-405)), junipers (406), thuyas (407), the Japanese cedar (408) and the mountain cedar (409, 410) .

Trees generally pollinate at the end of winter and at the beginning of spring. However, the length, duration and intensity of the pollinating period often vary from one year to the next, sometimes making the diagnosis difficult. Moreover, those patients allergic to tree pollen are often sensitised to other pollens, but the first pollen season "induces" inflammation of the nasal mucous membrane ascribed to the priming effect (8) (see chapter 4-5-2). Grasses pollinate at the end of spring and beginning of summer, whilst weeds such as *Ambrosia* flower at the end of summer and beginning of autumn. *Parietaria* often pollinates over a long period of time (March-November) and is considered a perennial pollen.

The size of the pollen varies from 10 to 100 μm on average. This explains pollen deposition in the nostrils and more particularly in the eyes and also why most patients allergic to pollen have rhinitis and conjunctivitis. However, pollen allergens can be borne on micronic and sub-micronic particles (411, 412) and can induce and/or contribute to the persistence of rhinitis and asthma. This is particularly the case in asthma attacks that occur during thunderstorms (413-417).

Cross-reactivities between pollens are now better understood as they have been extensively studied and using molecular biology techniques (418-420). However, it is not clear as to whether all *in vitro* cross-reactivities observed between pollens are clinically relevant (421). Major cross-reactivities include pollens of the Gramineae family, Oleacea family (398, 422, 423), Betuleacea family (424) and Cupressaceae family (425) but not those of the Urticaceae family (426, 427). Moreover, there is clinically little cross-reactivity between *Ambrosia* and other members of the Compositae family (428-430). For the grass pollen family, cross-reactivity is often extensive (431-433) except for *Cynodon dactylon* (434, 435) and Bahia grass (436).

3-1-3-3- Animal danders

3-1-3-3-1- Cat and dog allergens

The modification of relationships between man and animals, and in particular the increase in the number and variety of domestic animals, means that exposure and therefore sensitisation to animal allergens have considerably increased in the last 20 years, especially in urban environments within industrial countries. It is estimated that in many European countries, cats are present in 1 in 4 residences.

The dander and secretions of many animals carry or contain powerful allergens capable of causing severe hypersensitivity reactions (437). Cats and dogs are the main culprits, especially since they are often in the bedroom. The major cat allergen (Fel d 1) is a glycoprotein which is transported in the air by particles smaller than 2.5 μm (438). These particles can remain airborne for prolonged periods. They are also adherent and can thus contaminate an entire environment for weeks or months

after the animal is removed (439). Additionally, they adhere to clothing and are carried to areas in which the pet has no access such as schools and public buildings.

The principal allergen sources are the sebaceous glands, saliva and the peri-anal glands. The principal allergen reservoir is cat fur. Fel d 1 is also present in high amounts in domestic dust, in upholstered furnishings and, to a lesser degree, in mattresses. However, cat and dog allergens can be found in various environments where animals do not live such as schools (440-442) and hospitals (360, 443). The low level cat exposure that occurs in many homes without cats is capable of inducing symptoms in some patients who are very sensitive to cats (444). Sensitisation to cats ranges from 2 to 30% of the general population and 15 to 50% of children with rhinitis or asthma are sensitised.

The major dog allergen (Can f 1) is principally found in the dog's fur and can also be found in the saliva (445), skin and urine (446). This allergen can be transported in airborne particles.

Patients allergic to cats and dogs frequently display IgE reactivity against allergens from different animals (447, 448). Serum albumins have been recognised as relevant cross-reactive allergens (449). Moreover, there are common, as well as species-restricted, IgE epitopes of the major cat and dog allergens which can be demonstrated by IgE inhibition studies (450).

3-1-3-3-2- Horse (Equus caballus, Equ c)

After a decrease in the last 20 years, allergy to horses is becoming more frequent. Most patients allergic to horses initially develop nasal and ocular symptoms but life-threatening asthma exacerbations are not uncommon.

The allergens being very volatile, sensitisation is made by direct or indirect contact (451). The allergens are found in the mane, sweat and urine. The major allergen of horse dander, Equ c1, has been identified (452, 453).

Cross-sensitisation can sometimes be found with other equidae (pony, mule, donkey, zebra) and with cat, dog and guinea pig albumin.

3-1-3-3-3- Cattle (Bos domesticus, Bos d)

Cow's dander allergy still remains present in rural environments within cattle breeding areas (454-456). The allergens are found primarily in the danders and fur, but also in urine, saliva, tears and the meat. Cross-reactions with mutton, goat and even deer allergens have been described (457).

3-1-3-3-4- Rabbit (Oryctolagus cuniculus, Ory c)

5 to 7% of patients sensitised to animals are allergic to rabbits (breeding rabbits in rural environments, domestic animals in urban environments, laboratory animals). The allergens are found in the fur and saliva (but are not present in the urine or serum). Cross-reactions with other rodents have been described.

3-1-3-3-5- Other rodents: guinea pigs, hamsters, rats (Rattus norvegicus, Rat n), mice (Mus musculus, Mus m), gerbils

These animals can induce occupational sensitisation in laboratory personnel (10-40% of the exposed subjects) (458). Allergy to laboratory animals was also found to

occur in children whose parents were occupationally exposed to mice, rats and hamsters (459). Two distinguishable syndromes were identified (460). The first is characterised by rhinitis with negative skin prick tests. The second consists of rhinitis leading progressively to asthma with positive skin prick tests. Atopy (461, 462) and active smoking (463) represent a risk for the development of laboratory animal allergy. Prick tests are diagnostically useful only in the latter. Allergens are contained in the fur, urine (464), serum (465) and saliva. Cleaning the cages of these mammals mobilises large quantities of allergens.

It has been shown that children can be sensitised to rodents in less than one year when directly exposed to them.

Cross-reactive allergens between different rodents and rabbits have been demonstrated.

3-1-3-4- Fungal allergens

Superior fungi, moulds and yeast, are plants which do not possess chlorophyll but which liberate large quantities of allergenic spores into the atmosphere. Widespread in the air and resulting from putrefying organic matter, fungi and moulds are present everywhere except in areas of low temperatures or snow, which hinders their growth. Their development is increased particularly in hot and humid conditions, which explains their seasonal peaks and abundance in certain hot and humid areas.

The mould spores are small in size (3-10 μm) and penetrate deeply into the respiratory tract. They can provoke rhinitis as well as asthma. For unknown reasons, children are more often sensitised to mould than adults (466).

Three important types of mould and yeast can be distinguished according to their origin (467).

- The principal atmospheric moulds are represented by *Cladosporium* (468)*, Alternaria* (469-471) and *Stemphylium.* They peak during the summer whereas *Aspergillus* and *Penicillium* do not have a defined season. Large regional differences are found (472-478).
- Domestic moulds are also very important allergens (475, 477, 479, 480). Microscopic fungi present inside houses are capable of producing spores all year round and are responsible for persistent symptoms, especially in hot and humid interiors. Indoor moulds have been associated with dampness (481-484). These moulds can also grow in aeration and climatisation ducts (central heating and air conditioning) and around water pipes. They are particularly abundant in bathrooms and kitchens. The moulds also grow on plants which are watered frequently or on animal or vegetable waste, furnishings, wallpaper, mattress dust and fluffy toys.
- In food, one can observe a certain number of moulds, which can be responsible not only for inhalant allergies but also food allergies. The predominant moulds are *Penicillium, Aspergillus* and *Fusarium* and, more rarely, *Mucor.*
- Moulds and yeasts are present in some foods as they are used in the fabrication of numerous foodstuffs and may be allergenic.

Candida albicans, Saccaromyces cerevisiae and *minor* (485) and *Pityrosporum* (486) are the most allergenic yeasts. IgE-mediated sensitisation to yeast has been shown, in particular in atopic dermatitis (486-489). Most yeast presents cross-reactive antigens (490). Yeast can be found in the atmosphere and *Sporobolomyces roseum* is responsible for asthma and rhinitis in Great Britain and in the Mediterranean region.

Basidiomycetes and Ascomycetes spores are found in large quantities in the atmosphere and were found to be allergenic in patients with asthma and rhinitis (491, 492) but their role as an atmospheric allergen is still difficult to define. Occupational allergy to superior fungal spores has been described (493).

3-1-3-5- Insects

Inhalation of insect waste can induce an IgE immune response and respiratory allergies. In this case, IgE is directed against the protein fragments of insects, which become airborne. However, allergen concentration must be very high to induce sensitisation. Certain allergens such as haemoglobin of Diptera have been identified (494, 495).

- Allergy to insects such as the cricket can occur from occupational exposure (496).
- In certain hot and humid regions of the United States (497, 498) or tropical areas (499-501), allergies to cockroaches are as frequent as, or even more frequent than, allergies to *Ambrosia* pollen or to house dust mites. However, cockroaches are also prevalent in many European countries (443, 502, 503). Cockroaches are particularly important in low income housing ("inner city") where they cause severe asthma (504). Cockroach allergen is found in gastrointestinal secretions as well as on the chitin shell. The allergen is distributed in large particles that do not become airborne. Cockroaches tend to cluster in hiding places and forage after dark. Seeing cockroaches during the day suggests that they are present in very large numbers. The allergen is usually distributed throughout an infested home (505).
- Chironomides are particularly important in some tropical areas like the Sudan (506, 507).

3-1-3-6- Other inhalants

Ficus benjamina, known as Java willow, Ceylon willow or Bali fig tree, is a tropical non-flowering plant used ornamentally in many homes and public places. Inhalant allergy to *Ficus* has been reported (508) and appears to be relatively common, probably because *Ficus* allergens are cross-reactive with those of latex (509). The allergens originally located in the sap of the plant are also present in dust collected from the leaf surfaces as well as in floor dust where the allergen may persist over months after removal of the plant (510).

The allergic role of bacteria is controversial.

- At the present stage of our knowledge, it can be estimated that asthma or rhinitis induced by a bacterial allergy is exceptional, even though specific IgE to bacteria have been found.
- However, the enzymes originating from bacteria used in industrial environments can cause a high prevalence of asthma or rhinitis (511, 512).

- Telluric bacteria, whose genes are used in certain transgenic plants, could also cause allergies but the demonstration is not yet conclusive (513).

3-1-4- Food allergens

Food allergy is a rare symptom in subjects with allergic rhinitis and without other symptoms. On the other hand, rhinitis is a common symptom of food allergy in patients with multiple organ involvement. Despite the wide variety of foods ingested, only relatively few cause allergic reactions. In infants of less than 6 months, the majority of allergic reactions are due to milk, egg or soya. In adults, the most common food allergens causing severe reactions are peanuts (514), tree nuts, fish, Crustacea, egg, milk, soya beans, sesame, celery and some fruits like apples and peaches (for review see 515).

Most food allergens are native proteins but the allergenic activity of some food allergens may be destroyed by heating (516) or during storage (e.g. in apples (517)). Others (e.g. casein, egg and fish) are not denatured by cooking and digestion. Neo-allergens can also be produced by heating and cooking (518).

Differences may occur in the protein profiles of food as a result of agronomic factors. For example, agronomic conditions may affect the allergenicity or the storage proteins in peanuts and soya beans (80).

Concern has been expressed about the introduction of allergenic proteins into food plants by genetic engineering. The US Food and Drug Administration has directed developers and manufacturers of new plant varieties to consider the allergenic potential of donor organisms in assessing the safety of foods derived from genetically engineered plants (519). Such a concern was justified since 2S albumin from Brazil nuts can be transferred into another food (soya beans) by genetic engineering, enabling the transgenic soya to induce positive skin tests in Brazil nut allergic patients (520). Since numerous crop plants developed by plant technology have been introduced into the marketplace, assessment of the allergenic potential of the foods derived from these crops has been a critical component of the overall food safety assessment of these products.

3-1-5- Cross-reactive allergens between food and inhalant allergens

Cross-reactive allergens between food and inhalant allergens are common.
- Patients with allergic rhinitis/conjunctivitis due to birch and, to a lesser extent, other Betulaceae (hazel, alder) pollen are frequently allergic to tree nuts, fruits and vegetables, including apples, carrots and potatoes (521). Most patients develop mild symptoms but anaphylaxis may occur from these cross-reacting foods. Some birch or hazel pollen allergens cross-react with those of apple, other fruits (522, 523) or various nuts (424). Most patients with food hypersensitivity are severely allergic to pollens (521).
- Some Compositae pollen allergens (mugwort) cross-react with foods of the Ombelliferae family (celery, in particular) (524). Although IgE antibodies to food

allergens are highly prevalent in patients allergic to Betulaceae and Compositeae pollens, only a proportion of patients present food allergy symptoms (525, 526).
- Ragweed (*Ambrosia*) (527) or grass pollen (528) sensitive individuals may present symptoms when eating banana or melon.
- On the other hand, clinically insignificant cross-reactivity exists among cereal grains and grass pollens (529).
- Cross-reactive antigens have been identified between latex and banana, chestnut or kiwi fruit (530, 531).
- Although it is common to find positive skin tests and IgE antibodies to a range of legumes in peanut allergic patients, only a small percentage of the individuals also have clinical responses to legumes other than peanut. Such reactions are often less severe than to the peanut itself (532). However, recent concern has been raised for lupine, another member of the legume family, which appears to induce systemic reactions in peanut allergic patients.

Molecular biology-based approaches have also improved knowledge about cross-reactivity among allergens. The identification of allergens in fruits and vegetables showed IgE cross-reactivities with the important birch pollen allergens, Bet v 1 (533) and Bet v 2 (birch profilin) (534-537). Many other cross-reactive antigens have also been identified and characterised. Depending on the main cross-reactive allergen, different symptoms may be observed. Bet v 1 in apples, cherries, peaches and plums primarily causes mild symptoms such as the oral allergy syndrome (538). However, Bet v 1 associated with other allergens may cause generalised symptoms. Sensitisation to Bet v 2 is more often associated with generalised symptoms, in particular urticaria and angioedema (539). Lipid-transfer proteins are relevant apple and peach allergens and, considering their ubiquitous distribution in tissues of many plant species, could be a novel pan-allergen of fruits and vegetables (540, 541).

3-1-6- Occupational allergens

Occupational rhinitis is far less well documented than occupational asthma. Symptoms of rhinoconjunctivitis are often associated with occupational asthma and in one study, it was found that 92% of the subjects with occupational asthma experienced associated rhinitis (542).

Rhinitis is less common than asthma in occupational reactions to low molecular weight agents. It more often appears before occupational asthma (542, 543).

In Finland, furriers, bakers and livestock breeders had the highest relative risk of developing occupational rhinitis (543). The prevalence of rhinitis in allergy to laboratory animals is high (chapter 3-1-3).

3-1-6-1- Latex

Latex allergy has become an increasing concern to patients and health professionals because of the overwhelming use of latex gloves (544) and its extensive use in many devices such as catheters. Health professionals should therefore become aware of this problem and develop strategies for treatment and prevention.

Latex is almost exclusively obtained from the tree *Hevea brasiliensis* (Euphorbiaceae family). The first clinical case of immediate-type allergy (urticaria and angioedema) was apparently reported in 1927 by Stern. In 1979, Nutter *et al.* reported a case of contact urticaria to latex gloves (545).

Rubber is an important industrial and consumer product encountered in many household items and medical devices. The chemical additives used in its manufacture were a well recognised cause of delayed-type hypersensitivity (allergic contact dermatitis) (546). However, during the past decade, immediate-type allergy to natural rubber latex proteins (latex allergy) has emerged as a serious health issue. Frequent, prolonged wearing of natural rubber latex gloves (547), especially amongst physicians, nurses and health professionals (548-551), and workers (552) using rubber is a major risk factor for such sensitisation. Moreover, natural rubber latex allergy is common in patients who have had multiple surgical procedures or in those with spina bifida (553).

Immediate type hypersensitivity reactions to latex are caused by an IgE-mediated allergic reaction and a Th2-type response (554). Eosinophilic inflammation (555) of the nasal mucosa has been observed.

Symptoms of latex allergy include contact dermatitis (type IV reaction), contact urticaria, rhinitis, asthma and, more occasionally, anaphylaxis (556).

Skin tests and serum specific IgE can be used for the diagnosis of latex allergy (557, 558). If needed, provocative challenge can be carried out.

3-1-6-2- Low molecular weight compounds

Many occupational agents inducing rhinitis are low molecular weight compounds such as isocyanates (559), aldehydes (560), ninhydrin (561), pharmaceutical compounds (562) and others (563). More than 250 different chemical entities have been identified. Although these can act as reactive haptens, non-immunological mechanisms are common. Some compounds like chlorine can induce irritant rhinitis in 30 to 50% of exposed workers (75, 76).

Formaldehyde is a low molecular weight volatile chemical widely used in industry and as a sterilising agent in medicine. At high concentrations, it is toxic and can induce irritant reactions, but as a reactive, hapten can become allergenic and can cause an IgE-mediated reaction or contact dermatitis. However, IgE-mediated allergic reactions appear to be related mainly to the pharmaceutical use of formaldehyde (564, 565). In homes, schools or occupational settings, formaldehyde may become an irritant (566, 567) and can cause, exceptionally, an IgE mediated reaction (568, 569).

3-1-6-3- Other occupational allergens

Bakers often present with rhinitis and asthma (570-572). Sensitisation to bakery allergens seems to be the main cause of baker's asthma and rhinitis, but not in all cases (573). Swedish bakers studied in the 1970s and 1980s had a higher (x2) risk of developing rhinitis than non-bakers (574). Nasal inflammation in bakers exposed to flour dust can be mediated by neutrophils (575).

Many other high molecular weight allergens can induce IgE-mediated rhinitis and asthma. These include coffee beans (576), proteolytic enzymes (511, 577, 578), other enzymes (579), plants and flowers (580).

Wood dust can induce rhinitis and asthma but the mechanisms for these reactions are still unclear (581-583).

3-2- POLLUTANTS

Epidemiological evidence suggests interaction between pollutants and rhinitis (see chapter 2-1-3-7). The mechanisms by which pollutants cause or exacerbate rhinitis are now better understood (584).

3-2-1- Characteristics of air pollution

3-2-1-1- Evolution of outdoor air pollution

In the 1960s and 1970s in Europe and the USA, episodes of atmospheric winter pollution were frequently responsible for acute mortality epidemics of cardiovascular and respiratory diseases. The responsibility for such effects was given to high concentrations of sulphur dioxide (SO_2) and particulate matter (PM) in the air of cities, usually due to unfavourable meteorological conditions and air stagnation. There has been a significant reduction of industrial pollution in Western countries with the use of efficient filters in factory chimneys and of combustibles such as petrol and electricity, which pollute less than coal. Such an effort is however not operative in many developing countries. Moreover, urban-type pollution is still of major concern in Western countries due to several factors:

- improvement in the quality of life in Europe and the United States implicating a larger consumption of energy *per capita*,
- substitution of petrol in place of coal,
- and above all, since the 1970s, an increase in the number of cars and, in Europe, diesel motors.

3-2-1-2- Automobile pollution

Urban-type pollution originates essentially from automobiles. The principal atmospheric pollutants emitted by automobiles can be classified as:

- oxidant pollutants which are likely to chemically evolve in the troposphere due to sunrays. These are:
  - carbon monoxide (CO), a result of incomplete coal combustion, but with no apparent involvement in rhinitis.
  - nitric oxides (NO_x) and especially NO and NO_2, a result of nitrogen oxidation in the air at high temperatures.
  - volatile organic compounds (VOC) including hydrocarbons and some oxygen composites.
- The formed secondary pollutants are mainly ozone but there are also other species of oxidants (peroxyacetyl-nitrates, aldehydes, nitric acid, oxygen peroxide…).
- sulphur pollutants such as SO_2 formed from diesel sulphur. High levels of SO_2 sign acid-particulate pollution of industrial origin in relation to the combustion of coal and fuels, rich in sulphur.

- <u>organic chemical agents</u> including polyaromatic ones such as benzo(a)pyrene, benzo(k)fluoranthene, benzo-(b)fluoranthene, benzo(g,h,i)pirylene and benzo(a)-anthracene. The heavy composites, which are quantitatively the most important, are adsorbed on the surface of the microparticles, whereas the volatile composites remain in the gaseous phase.
- <u>carbon dioxide</u> (CO_2), produced by the oxidation of the carbon of fuels.
- <u>metals</u> (notably lead), present initially in oils and fuels.
- <u>particles</u> (particulate matter, PM), produced mainly by the incomplete combustion of fuels and lubricants.

3-2-1-3- Characteristics of diesel emission

These emissions are made up of a complex mixture of relatively light gases and of particles with a carbon core on which are adsorbed organic composites of high molecular weight.

The gaseous phase of diesel exhaust contains toxic or irritant substances:

- <u>gases</u> which are typically produced during the combustion of fuels (carbon monoxide, sulphur dioxide and nitric oxides, precursors to the formation of ozone). The emissions of CO are comparable or slightly inferior to those of a petrol engine.
- <u>the low molecular weight hydrocarbons</u> and their derivatives.

The particulate phase of diesel emission is composed of aggregates of spherical micro-particles with a carbon core (approximately 0.2 μm of aerodynamic median diameter), on which are adsorbed organic composites of high molecular weight. These nano-particles represent a unique model in pulmonary toxicology, as they possess a very large specific surface, which is available for the adsorption of toxic organic composites such as polyaromatic hydrocarbons. Typically, 10-40% of the mass of diesel particles is made up of these organic chemical molecules, of which some are known carcinogens. Nevertheless, recent progress in the preparation of diesel fuels has reduced the particle content by approximately 95% compared to older diesel engines.

3-2-1-4- Indoor air pollution

Indoor air pollution is of great importance since subjects in industrialised countries spend over 80% of their time indoors. Indoor pollution includes domestic allergens and indoor gas pollutants (156, 585), among which tobacco smoke is the major source. However, other pollutants may have a role, especially when a fuel or wood-burning stove is present in the house (586, 587) with the emission of carbon oxides, nitric oxides, PM, VOC and SO_2. Gas cooking may also be involved in respiratory symptoms (245), especially in women and atopics (588). Certain furniture may also liberate compounds utilised during the manufacturing process (plywood, glue, fabric, giving off formaldehydes and isocyanates) (567). However, in these studies, nasal symptoms were not usually examined.

3-2-2- Pollutants of possible relevance in allergic rhinitis

3-2-2-1- Ozone

Ozone (O_3) is a secondary pollutant formed from NOx and VOC, through a chain of sunlight dependent chemical reactions. This transformation can take several hours or days, in such a way that ozone is only usually formed at a distance from the source of primary gases (NOx and VOC) on the outskirts of large urban centres (589). The production of ozone is maximal in steep-sided or very sunny geographical sites such as Southern California (590), Switzerland, Austria, Germany, the south of France and around large cities. The ozone peaks occur from April to September in the Northern Hemisphere. During recent years, the situation seems to have worsened because of a deterioration in the quality of the air or the climatic conditions.

Nearly 40% of the inhaled ozone is absorbed by the nasal mucosa. *In vitro*, ozone can induce inflammation (591). Ozone challenge results in nasal congestion, increased levels of histamine, neutrophils, eosinophils and mononuclear cells in nasal lavage fluid (592-595). Ozone increases the late-phase response to nasal allergen challenge (596) but has no effect on the early-phase reaction (597). In a longitudinal study (598), in order to investigate nasal inflammation after ambient ozone exposure, nasal lavage fluid was collected from 170 school children on 11 occasions between March and October. The results showed acute inflammation of the nasal mucosa after the first increase in ambient ozone levels. There was a significant dose-dependent increase in leukocyte and ECP levels, and a possible adaptation of the nasal mucosa in spite of constant high levels of ozone exposure in the children during the summer season. After one month of exposure to air pollution (Mexico City) and high levels of ozone, most subjects developed nasal symptoms with significant nasal epithelial lesions (79).

Zwick *et al.* (599) have compared one group of 218 children exposed to high levels of ozone (more than $120\mu g/m^3$ during 45% of the period with a maximum of $376\mu g/m^3$) to another group of 281 children exposed to low doses of ozone (less than 1% of the period to a concentration of more than $120\mu g/m^3$ with a maximum of $190\mu g/m^3$). The concentrations of NO_2 and SO_2 were identical in both groups. No significant difference between the two groups was found in the frequency of allergic rhinitis, total IgE levels and positive skin tests to common aeroallergens. Bronchial hyperreactivity was however higher in the group exposed to high levels of ozone. However, no correlation between the symptoms of rhinitis and high ozone peaks was observed and there was no difference between atopic and non-atopic children.

3-2-2-2- Sulphur dioxide (SO_2)

In Eastern European countries, SO_2 pollution was still common in 1989. However, in Western Europe and North America where, at the present time, most measuring networks indicate an annual average SO_2 below $30\mu g/m^3$, or

TABLE 6: List of the NSAIDs that cross-react with aspirin in respiratory reactions

Generic names	Brand names
Indomethacin	Indocid, Metindol
Piroxicam	Feldene
Ibuprofen	Motrin, Rufen, Advil
Naproxen	Naprosyn, Anaprox, Aleve
Fenoprofen	Nalfon
Ketoprofen	Orudis, Oruval
Diclofenac	Voltaren, Cataflam
Diflunisal	Dolbid
Tolmetin	Tolectin
Mefenamic acid	Ponstel, Mefacit
Flurbiprofen	Ansaid
Sulindac	Cilnoril
Ketoralac	Toradol
Etodolac	Lodine
Nabumetone	Relafen
Oxaprozin	Daypro
Metamizol	Analgin,
Noramidopyrine,	Novalgin
Aminophenazone	Isalgin
Propylphenazone	Pabialgin, Saridon
Oxyphenbutazone	Tanderil
Klofezon	Perclusone

* *Paracetamol* is well tolerated by the majority of patients, especially in doses not exceeding 1000 mg/day. *Nimesulide* and *meloxicam* in higher doses might precipitate nasal and bronchial symptoms. The tolerance of the selective inhibitors of COX-2 (*celecoxib = Celebrex* and *rofecoxib = Vioxx*) remains to be tested.

even less than $10\mu g/m^3$ (EU 24 hour limit : $250\mu g/m^3$, WHO 24 hour limit : $125\mu g/m^3$), the prevalence of seasonal allergic rhinitis and skin test reactivity to aeroallergens is more frequent (218). Thus, SO_2 does not greatly influence clinical sensitisation to aeroallergens. In contrast, high automobile pollution appears to be involved.

It has been shown that exposure to SO_2 decreases the secretion of nasal mucous and increases the resistance of the nasal airways (600, 601). Ten teenagers suffering from allergic asthma were exposed to $1400\mu g/m^3$ of SO_2 during 5 consecutive days and during physical effort. There was a significant increase in the upper airway resistance.

3-2-2-3- Nitric dioxide (NO_2)

In Europe, NOx are emitted in approximately equal quantities from energy sources and road traffic. NO_2 levels do not generally exceed the EU limit value ($200\mu g/m^3$ per hour). Moreover, for a complete evaluation of the effect of NOx on respiratory health, one must also take into account the production of these gases inside homes, in particular the domestic use of natural gas should be considered.

The effect of exposure to NO_2 was studied in 625 0-5 year-old Swiss children living in three different areas: cities (31 and $22\mu g/m^3$ of NO_2), sub-urban areas ($19.4\mu g/m^3$ of NO_2) and rural zones ($11.1\mu g/m^3$ of NO_2)

(602). Symptoms of irritation of the upper respiratory tract were higher in the zones with high concentrations of NO_2.

3-2-2-4- Particulate matter (PM)

They can be classified according to their diameter: PM 10 (less than $10\mu m$), PM 2.5 (less than $2.5\mu m$) and nanoparticles (less than $1\mu m$). The finer the particles, the deeper they penetrate into the respiratory tract. They are also capable of passing through the air-blood barrier (603).

Pope *et al.* (604) studied the relationship between upper respiratory tract symptoms and exposure to PM10 in two groups of subjects: one group consisted of 591 9-10 year-old children and the other comprised 66 asthmatics. They found a 1.5 increased risk of ENT symptoms with regard to the rise of PM10 concentrations in the group of 591 children only. In another study (605), the same authors studied 60 asthmatic children and 60 non-asthmatic children. In the group of asthmatics, the ENT symptoms increased with the concentrations of PM10, from 21 to 33%. No difference was found in the non-asthmatics.

3-2-2-5- Volatile organic compounds (VOC) and formaldehyde

Even though formaldehyde and VOC are mainly indoor pollutants, they are detectable in some cities such as Los Angeles ($6-100\mu g/m^3$), at concentrations able to induce irritating symptoms of the upper respiratory tract (606): from 0.1-20 ppm ($120\mu g$ to $20,000\mu g/m^3$) (see chapter 3-1-6).

3-2-2-6- Automobile pollution

There is growing evidence that fossil fuel combustion products act as adjuvants in the immune system and may lead to the enhancement of allergic inflammation (607, 608). Through this mechanism, particulate air pollutants may be an important contributor to the increased prevalence and morbidity of asthma and allergic rhinitis. Diesel exhaust particles were shown to skew the immune response towards IgE production (609) and induce allergic inflammation (610-612). Experimental studies in animals (613-617) and humans (618) have shown that diesel exhaust particulates enhance IgE production by a variety of mechanisms. These include effects on cytokine and chemokine production (619), as well as activation of macrophages and other mucosal cell types including epithelial cells (620-623). Diesel exhaust particulates may also act as an adjuvant of pollen allergens (624). Metabolic and cellular activation pathways were linked to chemicals such as polycyclic aromatic hydrocarbons contained in diesel exhaust particulates (625). Cross-sectional studies have demonstrated that allergic rhinitis in general and pollinosis to Japanese cedar pollen in particular (626, 627) is more prevalent in subjects living in areas of heavy automobile traffic (627). However, these epidemiological studies need confirmation.

3-2-2-7- Tobacco smoke

In smokers, eye irritation and odour perception are more common than in non-smokers (628). Moreover, there are smokers with reported sensitivity to tobacco

smoking, some of the symptoms being headaches and nose irritation (rhinorrhea, nasal congestion, postnasal drip and sneezing) (629). The more the subjects smoke, the more they report chronic rhinitis (251). Objective assessments have confirmed that smoke-sensitive patients present with rhinorrhea and/or nasal obstruction when challenged with tobacco smoke (630). Tobacco smoke does not appear to be allergenic in contradistinction to tobacco leaves in exposed workers (631, 632). Tobacco smoke can alter mucociliary clearance (633) and can cause an eosinophilic and "allergic" like inflammation in the nasal mucosa of non-atopic children (634).

3-3- DRUGS

3-3-1- Aspirin intolerance

Aspirin and other non-steroidal anti-inflammatory drugs (NSAID) commonly induce rhinitis and asthma (Table 6). In a population-based random sample, aspirin-intolerance was more frequent among subjects with allergic rhinitis than among those without (2.6% vs. 0.3%, p.<0.01) (149). In about 10% of adult patients with asth-ma, aspirin and other NSAID that inhibit cyclooxygenase (COX) enzymes (COX-1 and -2) precipitate asthmatic attacks and naso-ocular reactions (148, 635). This distinct clinical syndrome, called aspirin-induced asthma, is characterised by a typical sequence of symptoms, intense eosinophilic inflammation of nasal and bronchial tissues, combined with an overproduction of cysteinyl-leukotrienes (CysLT). After ingestion of aspirin or other NSAID, an acute asthma attack occurs within 3 hours, usually accompanied by profuse rhinorrhea, conjunctival injection, periorbital edema and sometimes a scarlet flushing of the head and neck. Aggressive nasal polyposis and asthma run a protracted course, despite the avoidance of aspirin and cross-reacting drugs. Blood eosinophil counts are raised and eosinophils are present in nasal mucosa and bronchial airways. Although at one time aspirin-induced asthma was thought not to occur in atopic patients, positive skin test responses to common aeroallergens can be present in patients with aspirin-induced asthma.

3-3-2- Other drugs

See chapter 1-4.

4- Mechanisms

Allergy is classically considered to result from an IgE-mediated allergy associated with nasal inflammation of variable intensity.

However, it is now also appreciated that allergens, on account of their enzymatic proteolytic activity, may directly activate cells (636). House dust mite allergens have been shown to activate epithelial cells *in vitro* (637). They induce cytokine and chemokine release (638) and thus have the potential to induce airway inflammation independent of IgE. Moreover, Der p1 is able to alter the epithelial tight junctions (639) thereby increasing epithelial permeability (640). The relative importance of non-IgE to IgE-mediated mechanisms is undetermined.

Pollen-induced rhinitis is the most characteristic IgE-mediated allergic disease and is triggered by the interaction of mediators released by cells which are implicated in both allergic inflammation and non-specific hyperreactivity (641). This disease can be mimicked by nasal challenge with pollen allergens (642) but such a challenge differs from the natural course of the disease in that it is a single provocation and does not reflect the multiple triggers which occur during the pollen season. In persistent allergic rhinitis, allergic triggers interact with an on-going inflammatory situation. Symptoms are caused by this complex interaction.

Histamine was discovered just after the turn of the century and rapidly became known as the mediator of allergic and anaphylactic reactions. In the late 1930s, it appeared that other chemical mediators such as the slow reacting substances of anaphylaxis (SRS-A) were involved in allergic reaction. The mechanisms of allergic reaction are now better understood and although histamine (released by mast cells and basophils) is still one of the major effectors of the allergic reaction, many other mediators produced by different cell types are involved. Thus, mediators, cytokines, chemokines, neuropeptides, adhesion molecules and cells co-operate in a complex network provoking the specific symptoms and the non-specific hyperreactivity of allergic rhinitis.

Allergic rhinitis is characterised by an inflammatory infiltrate made up of different cells. This cellular response includes:
- chemotaxis, selective recruitment and transendothelial migration of cells,
- localisation of cells within the different compartments of the nasal mucosa,
- activation and differentiation of various cell types
- as well as a prolongation of their survival,
- release of mediators by these activated cells,
- regulation of the local and systemic IgE-synthesis,
- communication with the immune system and the bone marrow.

These events take place only in subjects who have already been sensitised to allergens, e.g. allergen-specific IgE-antibodies have been formed and bound to the membrane of mast cells and other cells. They do not take place in healthy individuals, who do not show a measurable reaction of the nasal mucosa to the same allergens.

Understanding the mechanisms of disease generation provides a framework for rational therapy in this disorder, based on the complex inflammatory reaction rather than on the symptoms alone.

4-1- THE NORMAL NASAL MUCOSA

4-1-1- Anatomy and physiology of the nose

Whereas the form of the external nose is shaped by the upper and lower cartilages wrapped by skin and facial muscles in prolongation of the nasal bony pyramid, the internal nose mainly consists of a bony framework, covered with respiratory mucosa. The nasal septum divides the nasal cavity into two sides and is composed of cartilage and bone, again covered by mucosa. Only the first few millimetres are covered by skin. The continuous slow growth of the septum up to the age of 30 might explain frequently observed septal deviations in adults, leading to some degree of nasal obstruction.

From an aerodynamic point of view, the nose may be divided into:
- the vestibule, lined with stratified squamous epithelium,
- the isthmus region, accounting for approximately 50% of the total resistance to respiratory airflow,
- the nasal cavity, where the inferior, middle and superior turbinates are located, lined with pseudostratified columnar ciliated epithelium. The turbinates increase the mucosal surface of the nasal cavity to about 150 to 200 cm^2 and facilitate humidification, temperature regulation and filtration of inspired air.

Nasal air flow changes from laminar to turbulent depending on the speed of inspiration and the anatomical situation. Together with the differential pressure between the nostril and the nasopharynx, it can be measured by active rhinomanometry (643).

The olfactory mucosa is located above the middle turbinate, inferior to the cribriform plate. It contains odour-receptor cells and also receives taste signals. Severe nasal obstruction, caused by nasal deformities, congestion or nasal polyps impairs olfactory sensations. Another chemosensory structure, the vomeronasal organ, which detects chemical signals that mediate sexual and territorial behaviours, has been described in vertebrates and may also be functional in the human nose.

The lateral nasal wall receives the openings of the maxillary, anterior ethmoidal and frontal sinuses as well as drainage from the naso-lachrymal duct, whereas the sphenoid drains into the posterior wall. In the middle meatus, lateral and below the middle turbinate, the

ostiomeatal complex is located where the anterior ethmoidal cells, the maxillary sinus and the frontal sinus are drained into the nasal cavity. Any obstruction, caused by anatomical deviations or mucosal swelling and scar formation, may heavily impair the drainage and ventilation of these sinuses with a consecutive sinus disease.

The nasal mucosa consists of three layers (Figure 2):
- the ciliated epithelium,
- the basement membrane
- the *lamina propria* or submucosa.
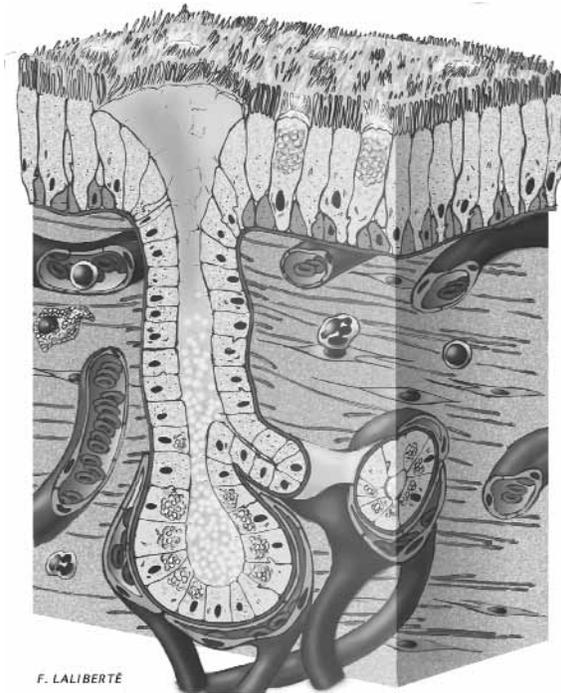
FIGURE 2: The nasal mucosa.

Three types of cells are identified within the epithelium:
- basal cells,
- goblet cells,
- ciliated or non-ciliated columnar cells, which are all attached at the basement membrane. They also adhere to neighbouring cells, forming the epithelial barrier.

The submucosa contains cellular components, serous and seromucous nasal glands, nerves and a complex vasculature.

A thin layer of mucus, consisting of a low viscosity sol phase and a viscous gel phase, covers the nasal epithelium and is constantly transported to the nasopharynx by ciliary movements. Nasal secretions have multiple sources such as the submucosal glands, goblet cells, tears and exudation from blood vessels. Secretions consist of albumin, immunoglobulins, proteolytic and bacteriolytic enzymes, mediators and cells, forming an unspecific protection against infection. Mucociliary transport is dependent on the right consistence of the mucus and on the effective movement of the cilia, which beat about 1,000 times per minute, moving the superficial gel layer and the debris

trapped therein at a speed of about 3 to 25 mm/minute. Viral or bacterial infections as well as allergic inflammation have been shown to heavily decrease or abrogate mucociliary clearance (644). When airborne allergen particles are inhaled through the nose, the majority of particles larger than 5 mm in size are deposited on the surface of the nasal mucosa and then transported from the nose to the pharynx within 15 to 30 minutes. During this process, particles do not appear to penetrate directly into the nasal mucosa due to their large size. However, water-soluble antigenic substances are eluted from the particles and may be absorbed quickly by the nasal mucosa.

4-1-2- Nasal microvasculature

The microvasculature of the nose consists of (645) (Figure 3):
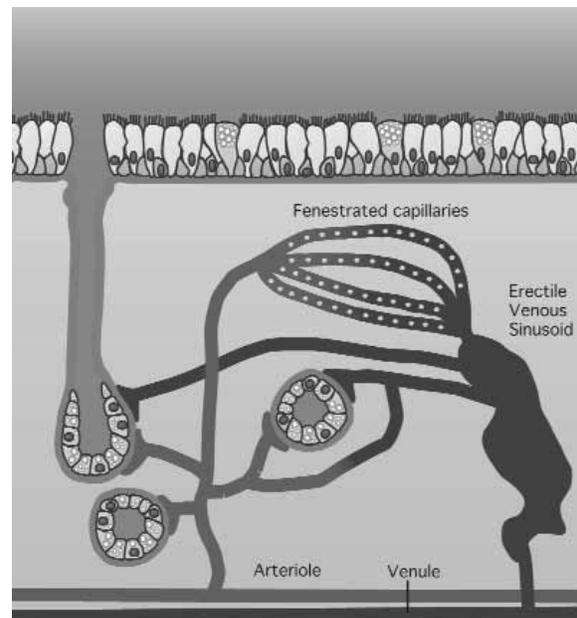
FIGURE 3: Nasal vasculature.

- a dense subepithelial network of capillaries, with fenestrations between the endothelial cells. This network provides nutrients to the epithelium and glands and allows passage of water into the lumen for evaporation and air-conditioning.
- arteriovenous anastomoses which allow rapid passage of blood through the mucosa. They are probably important in air-conditioning and in the counter current mechanisms that tend to keep the brain cool in a hot dry climate. The anatomical interrelationships between these different systems are not well understood, nor is their differential control in terms of mediator and nerve actions.
- a system of capacitance vessels or sinuses which, when they distend, block the nasal lumen, and when they empty, open the nasal passages. Changes in their volume will affect the filtering and air-conditioning functions of the nose. The arteries are surrounded by a

smooth muscle layer that controls blood supply into the venous sinusoids, also referred to as capacitance vessels. With these elements, the nasal mucosa can shrink or expand rapidly by changing the blood volume in response to neural, mechanical, thermal or chemical stimuli. The high degree of vascularisation is one of the key features of the nasal mucosa and changes in vasculature may lead to severe nasal obstruction (646). Changes in the blood content of these structures also regulate the free lumen of the two nasal cavities. In most individuals under normal conditions, this results in a rhythmic alternating congestion and decongestion of the mucosa, referred to as the nasal cycle (647, 648).

4-1-3- Mucous glands

Nasal fluid is a heterogeneous substance. Fluid accumulated in the nasal cavity can be produced by the nasal mucous membrane, derived from the eyes or from the paranasal sinuses. In normal subjects, it consists largely of a secretory product derived from the small seromucous glands (649). Secretory products from glands and goblet cells are of importance for the composition of fluid on the mucosal surface. Furthermore, water and electrolyte transport over the surface epithelium and glandular ducts are also significant.

4-1-3-1- Goblet cells and mucous glands

The density of goblet cells in the nose and in the large airways is approximately 10,000/mm^2 (650). The number of goblet cells and mucous glands does not appear to increase in chronic rhinitis (651-653).

Anterior serous glands consist of 200 purely serous glands located to the entrance of the nose, the internal ostium. Their contribution to the total amount of rhinorrhea is unknown.

Small seromucous glands are present in the submucosa of the nasal mucosa (650). After birth, the density of nasal glands decreases constantly. At birth, the number of glands in the nose reaches a maximum of 34 glands/mm^2, while there are 8.3 glands/mm^2 in the adult nose. These differences may explain why rhinorrhea is common in infants and children. There are only slight differences in gland density within different parts of the nose. The total number of glands in the nose is approximately 100,000.

Normal paranasal sinuses have very few glands (50-100 glands in each sinus), while pathologically inflamed sinus mucosa contains newly developed and pathological glands which are purely mucous (650). Therefore, sinus secretions, derived from mucous elements in glands and surface epithelium, consist of highly viscoelastic mucus. This does not contribute to watery rhinorrhea but to post-nasal drip.

4-1-3-2- Sources of nasal fluid in rhinorrhea

In rhinitis, hypersecretion from nasal glands is of paramount importance. However, an active secretory process in the nose appears to be the main cause of watery rhinorrhea (654). Moreover, there is an enhancement in mucus discharge from the inferior turbinate goblet cells

of patients with perennial allergic rhinitis, attributed to a non-hyperplastic increase of nasal goblet cell functional activity (655).

Plasma exudation is a sign of inflammation and it has been proposed that plasma exudation contributes significantly to the volume of nasal surface fluid (656).

A normal production of nasal secretions can be associated with nose blowing when the mucociliary transport system does not work at all. This is the case in primary ciliary dyskinesia (657) and when its function is reduced.

4-1-3-3- Control of the secretory process

The airway glands are controlled by the parasympathetic nervous system. Stimulation of sensory nerves, e.g. by cold air or by histamine, initiates a reflex arc, which results in the stimulation of glandular cholinoceptors. Consequently, the effect of anticholinergics can be used as a measure of the contribution of parasympathetically stimulated glandular secretion to the volume of nasal fluid.

4-1-4- Cells of the nose

The structure of the nasal mucosa of normal subjects has been widely studied. It has been found that there are many different cell types present including CD1$^+$ Langerhans-like cells, mast cells, CD4$^+$ T-cells, B-cells, macrophages and some eosinophils (658-662).

Secretory immunity is central in primary defence of the nasal mucosa. B-cells involved in this local immune system are initially stimulated in mucosa-associated lymphoid tissue, including tonsils and adenoids. They then migrate to secretory effector sites where they become immunoglobulin (Ig)-producing plasma cells (663). Locally produced secretory IgA (a dimeric immunoglobulin with an incorporated secretory component and J chain to facilitate external transport), as well as IgG and to a lesser extent pentameric IgM and IgD form the humoral defence of the nasal mucosa. Plasma cells can be seen in the nasal mucosa of patients with allergic rhinitis (664).

4-1-5- Nerves of the nose

The nerves present in nasal mucosa have been characterised and include cholinergic nerves and nerves of the non-adrenergic, non-cholinergic system (NANC). Sensory C fibres from the trigeminal ganglion contain substance P (SP), neurokinin A and K (NK) and calcitonin gene-related peptide (CGRP). These are contained within nerve endings around the sphenopalatine ganglion cells and around blood vessels as well as beneath or within the epithelium. Pre-ganglionic cholinergic fibres synapse in the sphenopalatine ganglion, and activated nicotinic receptors in post-ganglionic cholinergic neurons also contain vasoactive intestinal peptide (VIP). Some post-ganglionic sympathetic adrenergic neurons innervating arteries also contain neuropeptide Y (NPY). The neurons around sinusoid contain an adrenergic innervating peptide (NPY) (665-674).

Neuropeptides have various bioactivities:
- Neurotransmitters and neuropeptides released within the autonomic nervous system exert homeostatic control of nasal secretion.

- Parasympathetic nerve stimulation induces glandular secretion, which is blocked by atropine and causes vasodilatation. These effects are used for testing nasal reactivity with methacholine, a cholinomimetic agent.
- Sympathetic nerve stimulation causes vasoconstriction and thus decreases nasal airway resistance.

Peptides from sensory nerves, such as calcitonin gene related peptide (CGRP), substance P and neurokinin A, are suspected to play a role, both in normal subjects and allergic patients, in vasodilatation, plasma extravasation, neurogenic inflammation and in mast-cell nerve interactions (675, 676). However, the nasal reaction to neuropeptides is still controversial (677).

- Substance P and gastrin releasing peptide (CGRP) may induce glandular secretion (672, 678-682), but intranasal provocation needs high dosages of exogenous peptides to provoke positive responses.
- Intranasal Substance P did not induce hypersecretion (683) or any other symptom (684).
- Intranasal Substance P and Neurokinin A increased nasal airway resistance without a clear dose-response-relationship (685).
- Eosinophil recruitment also requires a very high dose of Substance P compared to the amount released locally (686).
- Intranasal CGRP did not induce hypersecretion (683).
- On the other hand, intranasal application of NPY evoked a dose-dependent reduction of nasal mucosal blood flow (687) and probably functions as a long-acting vasoconstrictor (688).
- Bombesin was found to stimulate human nasal mucous and serous cell secretion *in vivo* (689).
- Cholinergic effects are primarily responsible for mediating parasympathetic reflexes, but vasoactive intestinal peptide may regulate acetylcholine release, augment glandular secretory responses and have a vasodilatory effect (690).

4-2- CELLS, MEDIATORS, CYTOKINES, CHEMOKINES AND ADHESION MOLECULES OF NASAL INFLAMMATION

4-2-1- Cells

Using immunohistochemistry, it was shown in the late 1980s that not only eosinophils and metachromatic cells but also IgE-positive cells migrate into the nasal epithelium. Compared to the status outside season, they are then redistributed towards the epithelial surface due to seasonal allergen exposure. Later, it was also found that macrophages and monocyte-like cells invade the mucosa after artificial, seasonal and perennial allergen exposure The same phenomenon is observed for Langerhans cells representing strong antigen presenters to the local immune system. Furthermore, a subset of T-cells, activated T helper cells, were shown to increase in number or at least increase in activity within the mucosa under natural allergen exposure.

4-2-1-1- Mast cells

Since the discovery of the granule laden mast cell (*Mastzellen*) in 1879 by Paul Ehrlich and the description by Riley *et al.* (691) about the presence of the preformed mediators, histamine, in the mast cell, much has been learnt about its biochemical characteristics and functional properties. In 1966, Enerback first classified mast cells (in rats) based on the morphology, size and density of granules as well as on their staining properties (692). Subsequently, Irani *et al.* classified human mast cells into two phenotypically distinct subpopulations. These were based on the type of neutral proteases they express, namely MC(T) that contain only tryptase and MC(TC) that contain chymase, cathepsin G and carboxypeptidase in addition to tryptase (693).

Mast cells are derived from CD34+ hematopoietic progenitor cells (694, 695), which migrate to and mature in the peripheral tissues (696). Interactions between the tyrosine kinase receptor c-kit expressed on the surface of mast cells and their precursors and the c-kit ligand, stem cell factor (SCF), are essential for normal mast cell development and survival (697). Stem cell factor is expressed on the plasma membrane of a variety of structural cells like fibroblasts and vascular endothelial cells. The extracellular domain of SCF can be released from these cells by proteolytic cleavage (698). In fact, CD34+ c-kit-tryptase-IgE-cells (presumably progenitor cells) were detected in the surface compartment of allergic nasal mucosa (699, 700).

When activated by an IgE-dependent or independent mechanism, mast cells release:

- histamine and granule proteins such as tryptase, by degranulation,
- arachidonic acid metabolites including CysLT by activation of membrane phospholipids
- cytokines. These are present in mast cells as preformed mediators. When mast cells are activated via the high affinity IgE receptor (FcεRI), a release of several cytokines has been observed. This release is faster than that of T-cells in which cytokines are not preformed. These include Th2 cytokines such as IL-4, IL-5 and IL-13 (701-703) and pro-inflammatory cytokines such as IL-6, IL-8, IL-10 and TNF-α (704, 705). Mast cells were also shown to release cytokines and chemokines such as GM-CSF, MCP-1, IC-8 RANTES, MIP-1α and CC-chemokines. Mast cells also possess CCR-3 receptors and are responsive to MCP-3, MCP-4, RANTES and eotaxins. There is some heterogeneity in the cytokine expression between subsets of mast cells: MC(T) mast cells preferentially express IL-5, 6 and 7, whereas MC(TC) mast cells preferentially express IL-4 (706, 707). The release of Th2 cytokines by mast cells may be of great importance in the regulation of the IgE immune response. It has been shown that nasal mast cells can induce the synthesis of IgE (707) (Figure 4).

Mast cells were recently shown as being sentinels of innate immunity (708).

In the nasal mucosa of patients with allergic rhinitis, there is a significant increase in the numbers of intraepithelial MC (T) mast cells (700). Morphologically, mast
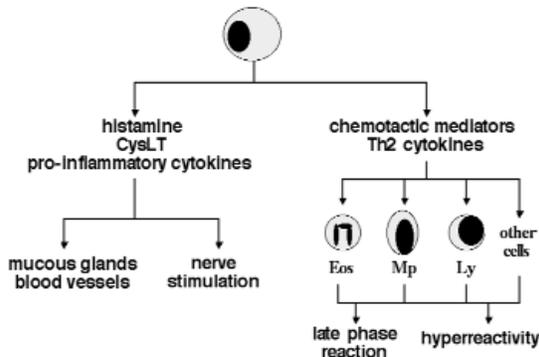
FIGURE 4: The role of mast cells in rhinitis. *EOS*, Eosinophils; *MP*, macrophages; *Ly*, lymphocytes.

cells in the nasal epithelium and superficial *lamina propria* resemble MC(T) and those in the deep *lamina propria* resemble MC(TC) (709). Several studies have shown that nasal mast cells are activated in rhinitis (641, 710). Several mast cell derived mediators like histamine (642), PGD_2 (642, 711), CysLT (712) and tryptase (713) can be detected in nasal secretions after allergen challenge and during the season in pollen-induced rhinitis. Nasal mast cells recovered from patients with allergic rhinitis can release IL-4, IL-6 and IL-13 when stimulated by mite allergen (707, 714).

Recently, it has been shown that mast cells in the allergic nasal mucosa exhibit increased expression of VLA-4 and VLA-5 (715). Mast cell extra cellular matrix interactions increase cytokine secretion from these cells (716). Such a mechanism may contribute to the enhancement of mast cell activation, especially when the levels of antigen in the microenvironment are rather low.

Thus, mast cells are not only effector cells of the immediate-phase response. They also act as immunoregulatory cells of the late-phase allergic reaction as well as of the on-going allergic inflammation via the mast cell cytokine cascade (717, 718).

4-2-1-2- Basophils

Like other granulocytes, basophils are derived from pluripotent $CD34^+$ hematopoietic progenitor cells. They ordinarily differentiate and mature in the bone marrow and then circulate in the blood (694, 719). Interleukin 3 (IL-3) appears to be an important developmental factor for basophils, although other growth factors may also influence basophil development (720). The basophil is the least common blood granulocyte in humans, with a prevalence of approximately 0.5% of total leukocytes and 0.3% of nucleated marrow cells. While human basophils appear to exhibit kinetics of production and peripheral circulation similar to those of eosinophils, the basophil, unlike the eosinophil, does not normally occur in peripheral tissues in significant numbers (717). Basophils can infiltrate sites of many immunological or inflammatory processes, often in association with eosinophils (721).

Basophils are not normally detected in the nasal mucosa or surface lining fluid. Basophilic granulocytes

have been demonstrated in the lung and sputum of allergic asthmatics, in the nasal mucosa and secretion of allergic rhinitis patients and in skin lesions of atopic dermatitis patients. The number of basophils correlates with the severity of the disease (722). Analyses of mediator profiles and cellular contents of lavages of the nose, skin and lung during allergic late-phase reactions (LPR) have demonstrated histamine, but not tryptase or PGD_2. The histamine-containing cells have been characterised as basophilic granulocytes (723). This indicates that infiltrating basophils are activated and release their inflammatory contents in the LPR.

Although the ability of basophils to produce cytokines has been less extensively studied than mast cell cytokine production, several reports have demonstrated that mature human basophils isolated from peripheral blood can release IL-4 and IL-13 in response to FcεRI-dependent activation (724, 725). This release can be enhanced in basophils exposed to IL-3 but not to certain other cytokines (726). Basophils may also participate in the Th2-type immune response. As they can be activated rapidly after allergen challenge, it has been postulated that they may have a prominent effect in the early regulation of the IgE immune response (727).

4-2-1-3- Eosinophils

Eosinophils were described by Paul Ehrlich in 1879 based on their specific staining behaviour. Over the following decades, they rapidly became associated with asthma, cutaneous and parasitic diseases as bystander cells. However, today, their pro-inflammatory functions and their important role in chronic allergic diseases are clearly recognised (728), turning them into major targets for basic and therapeutic research. They may however possess some anti-fibrosis effects (Figure 5).
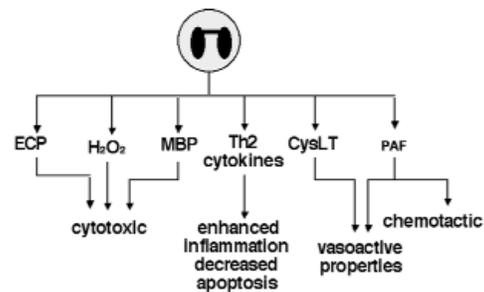
FIGURE 5: The role of eosinophils in rhinitis. *ECP*, Eosinophil cationic protein; *MBP*, major basic protein.

Eosinophils derive from the bone marrow from a progenitor cell (CD34+) that may develop into either eosinophils or basophils (729). Eosinophil progenitors can be found in the nasal mucosa in seasonal allergic rhinitis (730) and in nasal polyps (731). Eotaxin appears to be critical for the maturation and release of eosinophils from the bone marrow. In the peripheral blood, where they represent only a small fraction (about 1%) compared to tissues, eosinophils have a short half-life of about 8 to 18 hours. They migrate into tissue upon an appropriate signal by a

mechanism involving cytokines, chemokines and adhesion molecules. IL-5 (732, 733) and GM-CSF act to enhance eosinophil recruitment, terminal maturation and the expression of their adhesion molecules (734-736). Chemokines such as RANTES (737, 738) and eotaxin (739) also act on eosinophil recruitment to enhance their recruitment and possibly their activation. Within the tissue, eosinophils mature and stay alive for several days or even weeks. They are dependent on survival signals from the environment which overcome programmed cell death (apoptosis) (740, 741). The regulation of apoptosis by cytokines, surface receptors and intracellular signal pathways is now better understood, opening new perspectives for the treatment of eosino-philic diseases (742).

Mature eosinophils are easily recognisable by their bilobed nucleus and specific granules consisting of an electron dense core and an electron lucent matrix (crystalloid) containing:
- major basic protein (MBP) (743),
- eosinophil cationic protein (ECP) (744),
- eosinophil-derived neurotoxin (EDN) (745),
- eosinophil peroxidase
- ß-glucuronidase.

Furthermore, small granules contain enzymes including acid phosphatase and arylsulfatase B (746) which is able to inhibit CysLT.

In addition, eosinophils synthesise and release:
- cytokines such as IL-3, IL-5, GM-CSF (747) and pro-inflammatory cytokines,
- chemokines (RANTES, IL-8, MIP-1α) (748) and TGF-ß1 (involved in fibrosis),
- lipid mediators (CysLT (749), PGE$_1$, TXB$_2$ and PAF) (728),
- reactive oxygen intermediates,
- and different enzymes, including Charcot-Leyden crystal proteins (750) and histaminase (751).

Eosinophils express various membrane receptors for IgG, IgA and IgE (752-754), adhesion ligands (755) and soluble mediators such as cytokines and lipid mediators.

During the late-phase reaction following allergen challenge, eosinophils increase in number (756, 757) and release mediators such as ECP or MBP (723). Eosinophils also increase in the nasal epithelium and submucosa of patients with seasonal (758) or perennial allergic rhinitis (661). In house dust mite allergic patients, eosinophils and their mediators are also found in nasal secretions, even when patients are symptom-free (9, 759). Eosinophils also increase in the nasal secretions of patients with NARES (83). Intranasal glucocorticosteroids profoundly reduce nasal eosinophilic inflammation (760).

Once activated, products from eosinophils increase vascular permeability and mucus secretion. Eosinophils may also be deleterious in rhinitis by the release of highly toxic products (MBP, ECP, EDN and oxygen free radicals) which induce an alteration of the surface epithelium.

4-2-1-4- T-lymphocytes

T-lymphocytes are among the principal factors that regulate and co-ordinate immune responses in allergic diseases. Although a strict dichotomy is not as clear as in the murine system (761-764), two helper T-cell subsets have been identified in humans (203, 765):
- Th1 T-cells which mainly release IFN-γ and IL-2 and are involved in the delayed hypersensitivity immune reactions,
- Th2 T-cells, which mainly release IL-4 and IL-5 and are involved in IgE-mediated allergic inflammation (Figure 6).
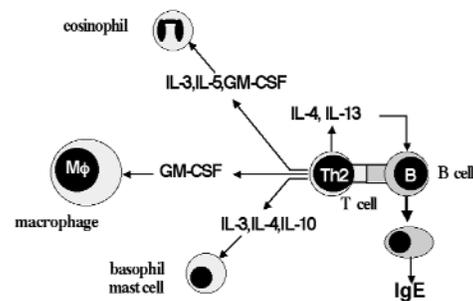
FIGURE 6: The role of Th2 lymphocytes in rhinitis.

An imbalance of Th1 and Th2 cells has been proposed in various diseases. In atopy, Th2 cells are thought to predominate regulating IgE synthesis and cell recruitment at the sites of inflammation. T-cell differentiation, activation and cytokine production is determined by several factors (766) including cytokines (767), growth factors (768), inflammatory mediators (769) and hormones (770).

There is growing evidence that Th1 and Th2 subsets can be differentially recruited into tissues to promote different types of inflammatory reaction (771). Th1 but not Th2 cells are recruited through P and E selectin into inflamed tissues, where they induce delayed-type hypersensitivity reactions. The human eotaxin-receptor CCR3, originally described on eosinophils and basophils, was also found on Th2 cells. The attraction of Th2 cells by eotaxin could represent a key mechanism in allergic reactions because it promotes the allergen-driven production of IL-4 and IL-5 necessary to activate basophils and eosinophils (772). Other chemokines are important in the recruitment of Th1 and Th2 cells (773).

Mucosal inflammation in allergic rhinitis is characterised by the tissue infiltration of T-lymphocytes (CD4^{+} T-cells and CD25^{+} (activated) T-cells) both in the submucosa and the epithelium (756, 774). There is a significant correlation between the increase in CD4^{+} T-cells during the late-phase allergic reaction following an allergen challenge and the number of infiltrating eosinophils in the mucosa (756). This is associated with an increased expression of IL-3, IL-4, IL-5, GM-CSF at mRNA levels in the nasal mucosa (757). In perennial rhinitis, there is an increase in CD4^{+} T memory cells, CD4^{+} T cells and B-cells in the nasal mucosa (774). This is associated with an increase in the number of IL-4, IL-5 and IL-13 positive cells suggesting a Th2 pattern (775-777). Moreover, there is an increase in intra-epithelial γ/δT-cells in perennial allergic patients (774, 778). γ/δT-cells are of impor-

tance as they are able to regulate allergic immune responses through their capacity to induce IgE synthesis by B-cells (779-782).

4-2-1-5- B-lymphocytes

In the bone marrow, B-cells mature in close association with stromal cells (783) which interact by direct contact or via cytokines to induce differentiation (784). Most of the progenitors, precursors and immature cells will die within the bone marrow. However, after screening for auto reactivity, some B-cells will complete their maturation and express not only IgM but also IgD (mature virgin B-cells) (785). These mature cells will then migrate to secondary lymphoid tissues (spleen, tonsils and lymph nodes) and form part of a re-circulating lymphocyte pool. There, in the T-cell zones, they are activated by T-cells after contact with antigen-presenting cells (APC). They enter the lymphoid follicle to proliferate and establish a germinal centre. Within the light zone of the germinal centre, B-cells undergo a selection process based on the affinity of the antibodies synthesised and controlled by follicular dendritic cells. These cells are capable of retaining antigen-antibody complexes for prolonged periods of time. This affinity maturation process results in isotype switching, the production of highly efficient antibody-secreting plasma cells and the development of memory B-cells.

B-cells can be found in the epithelium and the *lamina propria* of the nasal mucosa (786). In the nasal mucosa of patients with perennial allergic rhinitis, B-cells comprise about 20% of the total lymphocyte population (774). Recent studies have shown that in seasonal allergic rhinitics, B-cells can undergo class switch to IgE locally in the nasal mucosa (787). Nasal CD23^{+} B-cells decrease in allergic patients during provocation, indicating that mature virgin CD23^{+} B-cells switch into a memory B-cell phenotype with loss of CD23 expression (788).

4-2-1-6- Macrophages and dendritic cells

Allergic reactions occur in a mucosal environment that is rich in both dendritic cells and macrophages. However, there are significant differences between the lower and upper airways: alveolar macrophages form more than 90 % of the cell population in bronchial alveolar lavage (789), but airway macrophages on the nasal epithelial surface account for just 1 to 2 % of the cells (790). The number of nasal macrophages increases after non-specific stimulation of the mucosa such as lavage or brushing (790, 791). However, in seasonal and perennial allergic rhinitis, a significant increase in macrophages has also been found in the nose (790).

Langerhans cells represent an important group of dendritic cells in the nose, characterised by the expression of CD1 and Birbeck granules (792). These cells increase after allergen challenge (791) or in patients with allergic rhinitis (658, 793).

Antigen presentation is a critical first step in the T-cell activation process. In the primary immune response, dendritic cells in the respiratory tract form a tightly meshed network at the epithelial surface and are the principal antigen presenting cells (APC). In the secondary response, any cell expressing surface Major Histocompatibility Complex (MHC) class II may serve in this function.

4-2-1-6-1- Macrophages

The mononuclear phagocyte system consists of a migratory, specialised family of cells derived from haemotopoietic precursors that circulate in blood as monocytes and are widely distributed as macrophages in tissues and body fluids. Mononuclear phagocytes have always been the scavenger cells of the body (794). Although this traditional role remains critical, these cells have a much wider function in biology and pathology. By virtue of their specialised plasma membrane receptors and versatile biosynthetic and secretory responses, macrophages play a major role in inflammation (795, 796) and repair (797). Macrophages are capable of secreting growth factors and cytokines such as IL-1, TNF-α, TGF-ß, PDGF and interferons, depending on their state of maturation and elicit immune modulatory functions. It has long been known that macrophage function is controlled by activated T-cells (798). Macrophages also have a role in specific immunity by their accessory cell function. However, compared to dendritic cells, macrophages do not function efficiently as APC for T-cells (799).

4-2-1-6-2- Dendritic cells

Dendritic cells are a highly potent APC-population. They specialise in the presentation of antigen to naive T-cells and deliver antigen specific activating signals to T-memory cells (800-802). For the interaction between dendritic cells and T-cells, with the T-cell receptor recognising an antigen associated with an MHC-molecule, co-stimulatory signals such as CD28 and B7 or CD40 ligand and CD40 are necessary (801). Resting Langerhans cells are well equipped for antigen binding and processing, but require maturation in order to efficiently stimulate resting T-cells. There is recent evidence that antigen presentation by airway dendritic cells leads to the preferential development of a Th2 response, possibly by the selective production of cytokines (803).

Dendritic cells form a network of APC in the human respiratory mucosa. The density of dendritic cells is at its highest in the epithelial surface of the upper airways and decreases in the peripheral bronchi (799, 804).

The airways are continuously bombarded by pathogens, allergens and other irritants. Airway mucosal dendritic cells play an important role in the primary sensitisation or tolerance to antigens (805).

Airway dendritic cells are also essential for presenting inhaled allergen to previously primed Th2-cells (805, 806). Further studies have to clarify, however, whether the maturation of Langerhans cells takes place within the nasal mucosa or is dependent on the migration of these cells to mucosa associated lymphoid tissue. The depletion of dendritic cells in animals leads to an almost complete suppression of eosinophilic airway inflammation (807).

Glucocorticosteroids are the most effective treatment for reducing dendritic cell numbers and functions (808). Such an effect has been found in the nasal mucosa (760,

809) whereas these drugs are ineffective on the number of macrophages.

4-2-1-7- Epithelial cells

The nasal epithelium forms an interface between internal and external environments acting as the first line of defence against invading organisms or inhalant allergens. For many years, epithelial cells were considered as barriers while being involved in the secretion of mucus or removal of foreign agents by their cilia. However, recent studies have shown that epithelial cells have a much wider range of activities including the release of eicosanoids, endopeptidases, cytokines and chemokines (810-812). They are also involved in the degradation of neuropeptides and fibronectin release (812, 813). Epithelial cells in allergic individuals (asthmatics and rhinitics) are in an activated state, as shown by:

- the increased expression of adhesion molecules like ICAM-1 and VCAM-1 (814-819),
- the increased expression and production of inflammatory mediators like IL-6, IL-8, GM-CSF and TNF-α thus contributing to the enhancement of allergic inflammation (820-824).
- Furthermore, epithelial cells in atopic asthmatics and allergic rhinitics release significantly greater levels of eosinophil chemoattractants like RANTES (825) and eotaxin (826, 827), as well as growth factors (828, 829) and metalloproteases (830).
- Epithelial cells are also an important source of growth and of survival factors like SCF for mast cells (831) and GM-CSF for eosinophils.

It has also been shown that epithelial cells in allergic individuals are more sensitive to air pollutants like diesel exhaust particles. This has been attributed to the greater constitutive and pollutant induced release of pro-inflammatory cytokines (622).

Again, under normal conditions, it is difficult for allergens to penetrate the epithelial layer and come into contact with the effector cells (lymphocytes, macrophages and mast cells). However, in allergic individuals, there is an increased permeability of the epithelial layer.

It has been shown that epithelial cells from asthmatics express FcεRI and FcεRII. The activation of these receptors in asthmatic patients leads to the release of eicosanoids or pro-inflammatory mediators (832, 833). More recently, it has been shown that epithelial cells can directly interact with allergens resulting in the increased production of IL-6, IL-8, MCP-1 and GM-CSF (834). This interaction was considered to be protease dependent as well as protease independent. Moreover, epithelial cells can be activated by inflammatory mediators released from mast cell/ basophils like histamine (835-837), IL-4 (838) and IL-13, which can induce an increased production of cytokines and chemokines in epithelial cells. Mucous secretion is regulated by cytokines such as IL-4 and IL-13 (839, 840). Finally, a proportion of epithelial cells from allergic rhinitics express HLA-DR and CD86 and may also play a role in antigen presentation (824). Thus, the epithelial cell can participate in the genesis and development of allergic inflammation.

4-2-1-8- Endothelial cells

The infiltration of effector cells is crucial to the development of allergic diseases like asthma and allergic rhinitis. Structural cells like endothelial cells appear to play a dual role in the pathogenesis of bronchial asthma and allergic rhinitis (816, 841). These cells participate in the recruitment of leukocytes to the site of the allergic response by releasing neutrophil chemotactic factors and modulating leukocyte-adhesion molecules (842). An increased expression of ICAM-1 and VCAM-1 was reported on nasal endothelial cells obtained in the nasal biopsies of patients with perennial allergic rhinitis as compared to non-atopic healthy volunteers (843). Endothelial cell VCAM-1 is over-expressed during the pollen season (844). Moreover, the expression of VCAM-1 in nasal tissues was related to the number of infiltrating eosinophils (845, 846) and T-cells (844). There is also increasing evidence that cytokines like IL-1 (847), IL-4 (755, 848), IL-13 (849), TNF-α, IFN-γ and chemokines such as eotaxin (850) and RANTES play a key role in enhancing the expression of these adhesion molecules.

Cells from allergic patients increase endothelial cell activation through the release of cytokines and chemokines (851). Endothelial cells in allergic rhinitics and asthmatics are also an important source of several cytokines and chemokines like RANTES and eotaxin (852). Moreover, like epithelial cells, endothelial cells also express the H1 receptor, and stimulation with histamine induces the activation of these cells (853, 854).

4-2-1-9- Fibroblasts

Structural cells like fibroblasts play an important role in allergic inflammation through the production of an array of cytokines and chemokines such as GM-CSF (855), IL-8, RANTES (855-858) or eotaxin (859). They appear therefore to be essential for the recruitment of effector cells and for the growth and survival of mast cells and eosinophils (860, 861). Interaction with fibroblasts results in the modulation of the proteoglycan content in mast cells and in the preferential development of MCTC type mast cells. However, in rhinitis, the role of fibro-blasts is much less studied than in asthma where it seems to be a critical cell in airway inflammation (862).

4-2-2- Pro-inflammatory mediators

4-2-2-1- Histamine

Histamine, a ubiquitous cell-to-cell messenger, was identified in 1910 by Dale and Laidlaw (863) and was recognised in the 1920s as a major mediator of allergic disorders such as rhinitis, asthma, urticaria and anaphylaxis. Histamine consists of a single heterocyclic ring (imidazole) connected directly to the ethylamine group, the unsubstituted amino-terminal. The real mechanism of the action of histamine remained unknown until 1966 when the H1-histamine receptor was identified (864). Knowledge of the histaminergic system evolved with the later discovery of the H2-receptor (865), responsible for gastric acid secretion, and the H3-receptor (866), apparently represented mostly in the central nervous system of humans.

In the 1950s, Riley *et al.* described the presence of his-

tamine as a preformed mediator in the mast cell (691). Histamine is released upon activation by allergen after the IgE mediated activation of mast cells and basophils through FcεRI. However, histamine can also be released by non-specific triggers such as codeine. Histamine is quantitatively the major mediator released after immuno-logical challenge by mast cells and basophils.

Histamine can mimic many symptoms of the nasal allergic reaction (rhinorrhea, sneezing, pruritus and nasal obstruction (867-869)). However, the effects of hista-mine on nasal obstruction are not marked and require rel-atively high concentrations. The response is of short duration (870). Action on sensory nerves induces itching and sneezing (871), whereas the action of histamine on blood vessels, possibly by direct action on endothelial cells (872-874), causes vasodilatation, plasma exudation and edema formation. Histamine stimulates secretion by a direct action that increases plasma protein extravasa-tion and by an indirect reflex mechanism that stimulates glandular secretion (875-877). Histamine increases glan-dular secretion in the ipsilateral side by direct effect on mucous cells and vessels and in the ipsilateral and contra lateral sides through neural reflexes. (878).

Histamine is probably the major mediator of the early-phase reaction following an allergen nasal challenge (642) but it is also important in the late-phase response (723). Basophils and mast cells release histamine during the early-phase reaction (642) whereas basophils are considered to be the main source of histamine in the late-phase reaction (723). Increments of histamine have also been observed in seasonal and perennial allergic rhinitis in some (879) but not all studies (759, 880), possibly because of its rapid metabolism (870, 881, 882). More-over, a few molecules of a given mediator released *in situ* may cause allergic symptoms without any release in the nasal secretions (883).

Histamine also possesses pro-inflammatory and immunomodulatory properties (884, 885). It has been shown to cause a profound increase in the numbers of rolling leukocytes within minutes of exposure to allergen (886, 887). The duration of adhesion of these cells to the endothelium was increased with histamine and was medi-ated by P-selectin. Histamine also increases the TNF-α-induced expression of E-selectin, ICAM-1 and LFA-1 on vascular endothelial cells (888). Moreover, histamine can increase the production of cytokines like IL-6 and IL-8 in endothelial cells (853). In fact, H1 antihistamines can inhibit histamine-induced cytokine production or adhe-sion molecule expression in endothelial cells. Recent studies have shown that histamine induces increased ICAM-1 expression in nasal epithelial cells and this is inhibited by H1 antihistamines (817). Histamine directly upregulates ICAM-1 expression on bronchial and nasal epithelial cells and the production of key cytokines and chemokines from bronchial epithelial cells (835-837).

In conclusion, histamine plays a key role in allergic reactions of the nose, not only through its effects on sen-sory nerves, glands or vessels, but also through its pro-inflammatory effects.
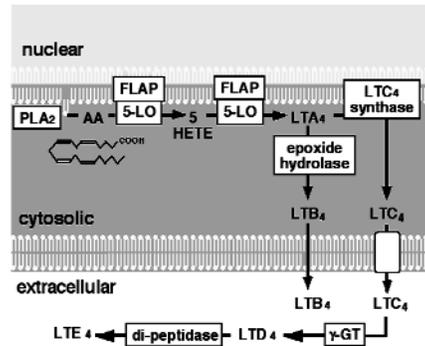
FIGURE 7: Production of leukotrienes. *PLA$_2$*, Phospholipase A2; *5-LO*, 5 lipoxygenase; *FLAP*, 5LO activating protein.
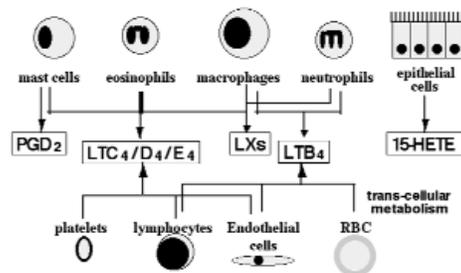
FIGURE 8: Cell origin of leukotrienes. *RBC*, Erythrocytes.

4-2-2-2- Arachidonic acid metabolites
Written in collaboration with C. Chavis

The arachidonic acid metabolic pathway leads to the formation of compounds named eicosanoids and includes prostanoids, hydroxyeicosatetraenoic acids (HETEs), leukotrienes (LTs) and lipoxins (LXs) (889). These pro-inflammatory mediators have potent effects in rhinitis (890-892).

Upon physiological stimulation, arachidonic acid is released from cell membrane phospholipids and submit-ted to oxidation (893) by:
- enzymatic lipid peroxidation which leads to eicosanoids,
- free radicals catalysed by lipid peroxidation which lead to iso-eicosanoids (894) (Figures 7 and 8).

Eicosanoids are extremely potent. They are able to cause profound physiological effects at very dilute con-centrations and act locally at the site of synthesis through receptor mediated G-protein (by paracrine (or even autocrine) effects). Two major and one minor pathways are involved in the enzymatic synthesis of eicosanoids:
- prostaglandins (PGs) and thromboxanes (TXs) occur-ring from the cyclic pathway by cyclooxygenases (COX),
- HETEs, LTs and LXs from the linear pathway by lipoxygenases (LO).
- Other epoxygenases belonging to the cytochrome P450 family. These lead to some HETEs and epoxy-eicosatetraenoic acids, the exact function of which remains to be demonstrated in airway diseases (895).

4-2-2-2-1- Cyclooxygenase pathways: Biosynthesis and biological properties of prostanoids

Prostanoids belong to the family of eicosanoids generated by the COX pathways. COXs are ubiquitous, heminic proteins of the cytochrome b family, localised in reticulum endoplasmic and nucleus membranes (896). They cyclise arachidonic acid into the hydroendoperoxide PGG_2 which is reduced into PGH_2, the common precursor of prostanoids. PGH_2 metabolism leads to PGE_2, PGD_2, PGF_2, PGI_2 and TXA_2. There are two COX isoforms (897, 898):

- the constitutive COX1 which regulates physiological activities and is inhibited by aspirin but not by dexamethasone (899),
- the inducible COX2 which is probably more related to inflammatory states (900-902). However, in the nasal mucosa of normal subjects, there exists a small COX2 expression (903). COX2 is rapidly induced by LPS, cytokines or growth factors and is inhibitable by dexamethasone (904).

Prostaglandins are divided into several groups. PGD_2 is the predominant prostanoid released following mast cell degranulation. Nasal challenge with PGD_2 induces a sustained nasal obstruction (905, 906). It appears that PGD_2 is ten times more potent than histamine (870). PGE_2 and PGI_2 induce vasodilatation and increased mucosal oedema (907). However, it has been suggested that PGE_2 may have different effects in the bronchi and in the nasal cavities. Whilst there is little doubt that PGE_2 generally acts as a vasodilator, there have been reports that this mediator has vaso-constrictor effects in the nasal mucosa and for this reason it has been tested as a nasal decongestant (908).

Prostaglandins (PGD_2, PGE_2, $PGF_{2\alpha}$ and 6-keto-$PGF_{1\alpha}$) have been measured in the nasal secretions of normal subjects and patients with seasonal allergic rhinitis (909-911). Concentrations of PGD_2 were found to increase after allergen challenge (early but not late-phase reaction) and during seasonal allergic rhinitis (912). On the other hand, no significant differences were observed in concentrations of either $PGF_{2\alpha}$ or 6-keto-$PGF_{1\alpha}$ between control and allergic subjects (911). The blockage of prostaglandin release by NSAID does not improve ocular symptoms of allergic patients, suggesting that in these patients, prostaglandins alone may not play a major role in the mediation of symptoms (913). In a nasal challenge study, Flurbiprofen was nearly as effective as chlorpheniramine in reducing the severity of induced rhinitis suggesting the role of prostaglandins (914). The combined blockage of histamine and COX products appears to improve symptom control in ragweed hay fever (915).

In aspirin-intolerant patients with rhinitis, studies of eicosanoid biosynthesis in the nose have stirred considerable interest (31). Recent data indicate that COX-2 mRNA expression is down regulated in the nasal polyps of patients with aspirin-intolerant rhinitis/asthma (916). In keeping with these findings, it has been reported that cultured epithelial cells obtained from patients with aspirin-intolerant asthma produce less PGE_2 than those cultured from rhinitis patients who tolerate aspirin (917). Whether these abnormalities are linked to distinct changes in bronchial COX function in aspirin-induced asthma (918) or to enhanced LTC_4 synthase over-expression (919, 920) deserves further investigation.

4-2-2-2-2- Lipoxygenase pathways: Biosynthesis and biological properties of leukotrienes

Leukotrienes belong to the family of eicosanoids generated by the LO pathways. Lipoxygenases are dioxygenases, which incorporate one molecule of oxygen at a certain position of unsaturated fatty acids such as arachidonic. Arachidonate 5-LO is responsible for leukotriene synthesis (921). This mechanism differs from radical lipid peroxidation in that singlet oxygen attacks both sides of the molecular plan and leads to a racemic mixture (922). Among essential polyunsaturated fatty acids (PUFA), eicosatetraenoic acid or arachidonic acid presents three activated methylene groups (on the carbons in positions 7, 10 and 13). It is thus a privileged target for LO after it is released from membrane phospholipids by phospholipase A2 (PLA2). Three mammalian lipoxygenases have been purified, cloned and expressed. They are differentiated by a number which corresponds to that of the carbon atom where oxygen attacks preferentially: 5, 12 and 15. Lipoxygenases are cytosolic, calcium-dependent and translocable to nuclear membranes after activation. Four types of AA metabolites are biosynthesised. The steps of the LO pathways are:

- Mono hydroxyeicosatetraenoic acids (HETEs): the initial oxygenation of arachidonic acid, catalysed by the action of one LO, leads to the formation of hydroperoxy-eicosatetraenoic acids (HPETEs). These highly reactive and short-lived intermediates are converted to HETEs by cellular peroxidases, such as glutathione peroxides. The three most important HETEs are 5,12 and 15-HETE generated by 5, 12 and 15-LO respectively.
- Di-hydroxyeicosatetraenoic acids (di-HETEs): two successive oxygenation steps by 2 different LO lead to the generation of di-HETEs. The most common derivatives are 5(S),15(S)-diHETE (unknown physiological role) and 14(R),15(S)-diHETE reported to show the same activity as PGE_2 on natural cell killer toxicity.
- Leukotrienes (LTs): LTB_4 and LTC_4 are generated following 2 successive steps from the same bi-functional LO (923). LTD_4 and LTE_4 are the metabolites generated by g-glutamyl transpeptidase and dipeptidase actions on LTC_4.
- Lipoxins (LXs): LXA_4 and LXB_4 are generated by the interaction of 2 different LO. At least one of these is bi-functional.

In the eicosanoid nomenclature, number 4 indicates that the eicosanoids come from AA metabolism and have kept the 4 double bonds of their precursor.

LO enzymes are involved in inflammatory process but the most important in allergic rhinitis and asthma are 5-LO and 15-LO. 5-LO has been cloned (924). In many cells, particularly macrophages, blood monocytes and granulocytes, 5-LO translocation is dependent on an 18

kDa membrane protein named "five lipoxygenase activating protein" (FLAP) (925). In activated leukocytes, 5-LO and FLAP have been localised in nuclear envelop and endoplasmic reticulum, but neither in other cell compartments nor in plasma membrane.

The LT and LX biosyntheses are described in Figure 7. Firstly, 5-LO catalyses arachidonic acid oxidation on the carbon atom in position 5 and leads to 5-HPETE. Secondly, 5-LO transforms 5-HPETE into the intermediate epoxide LTA_4. Enzymatic opening by LTA_4 hydrolase leads to LTB_4 whereas glutathione conjugation leads to LTC_4 (926). LTC_4 may be metabolised by the elimination of glutamic residue to LTD_4 and then to LTE_4 by the elimination of glycine. The LTs from the glutathione conjugation, also named sulfido-peptide or cysteinyl leukotrienes (CysLT), are the constituents of the unknown lipid material characterised in early investigations of mechanisms of asthma as "slow reacting substance of anaphylaxis" (SRS-A). They play an essential role in asthma and rhinitis. Generally, LTs are synthesised inside a determined cell type and released in the extracellular medium. However, in the peripheral circulation, LTC_4 may be synthesised by cellular cooperation between neutrophils and platelets: LTA_4 released by neutrophils from the 5-LO pathway is taken by platelets which lack 5-LO but have LTC_4 synthase enzymes.

Several physiological properties of the eicosanoids from the 5-LO pathway have been observed:

- CysLTs induce vascular permeability and oedema in the nose and bronchi and bronchial obstruction by contraction of the airway smooth muscle, vasodilatation and mucous production (927, 928).
- CysLTs are involved in eosinophil recruitment in the airways (929).
- CysLTs are probably important mediators in allergic rhinitis (930).
- LTB_4 induces the recruitment of neutrophils.
- In contrast, anti-inflammatory properties are conceded to LXA_4, and LX presence in asthma has suggested their impact in cell regulation (931).

CysLTs are released in nasal lavage fluid obtained during the early and late-phase reactions after allergen challenge (712, 932, 933) and in seasonal (934) and perennial rhinitis (759). LTB_4 was found to be released in nasal secretions after allergen challenge but little is known about this mediator in seasonal or perennial allergic rhinitis (932, 934).

4-2-2-2-3- Leukotriene receptors

The actions of LTB_4, LTC_4, LTD_4 and LTE_4 on target cells are mediated through specific receptors. The cDNA for LTB_4 receptor was cloned from a guinea-pig leucocyte cDNA library (935). Pharmacological studies have determined that cysteinyl leukotrienes activate at least two receptors, designated CysLT(1) and CysLT(2). The CysLT receptor was recently cloned (936, 937). Both zafirlukast and montelukast have affinities that are approximately two times greater than that of the natural ligand LTD_4. The CysLT(1) receptor has been found in human airways. The CysLT(2) receptor, however, has not yet been found in human airway smooth muscle.

4-2-2-2-4- Aspirin-induced asthma and rhinitis

Attacks of sneezing, rhinorrhea and nasal blockage that appear within 20-120 minutes after aspirin ingestion, and are often followed by bronchoconstriction, are related to the inhibition of COX in the airways (938). Original observations (635, 939) that drug intolerance can be predicted on the basis of its *in vitro* inhibition COX have since been consistently reaffirmed (940, 941). After aspirin desensitisation, cross-desensitisation to other NSAIDs which inhibit COX also occurs.

At the baseline, CysLT urinary excretion is augmented and aspirin administration leads to its further temporary increase. After aspirin challenge, CysLTs are released into nasal and bronchial secretions and can be collected in the urine (918). LTC_4 synthase, the terminal enzyme for CysLT production, is markedly over expressed in eosinophils and mast cells from bronchial biopsy specimens of most patients with aspirin-induced asthma (919). An allelic variant of LTC_4 synthase that enhances enzyme transcription is associated with aspirin-induced asthma (920).

Aspirin-induced asthma should be clearly differentiated from other forms of aspirin-associated reactions. Up to 10% of patients with chronic urticaria develop an obvious increase in wheals and swelling after taking aspirin or NSAID. Usually, urticaria is not associated with rhinitis and asthma. These reactions, often accompanied by nasal blockage, usually occur when urticaria is active. Although the reason for these reactions is not known, it appears that different mechanisms may be responsible in different patients. Another distinct clinical entity which needs to be differentiated from aspirin-induced asthma is allergy to pyrazolone drugs (942).

4-2-2-3- Kinins

It has been proposed that kinins are involved in the mechanism of virus induced (943) allergic and perennial rhinitis (944). The effects of kinins in the human nasal mucosa (sneezing, pain and discomfort, as well as reduced patency, protein secretion and nasal discharge) are characteristic of rhinitis due to different causes. Increased concentrations of kinins have been reported in nasal secretions after allergen challenge (945, 946). Some studies with bradykinin antagonist B2 have also been performed on patients with allergic rhinitis.

The application of tachykinins to the nasal mucosa results in:
- an increase in plasma exudation,
- nasal discharge,
- blockage in a manner independent from histamine (947, 948).

Substance P is generated *in vivo* following nasal challenge of allergic individuals with bradykinin (949).

Application of capsaicin to the nasal mucosa causes painful sneezing and nasal secretion (950-953). However, a repeated application of capsaicin to the nasal mucosa ameliorates the symptoms of perennial rhinitis (954).

Therefore, kinins are considered to play a role in rhinitis.

4-2-3- Cytokines

"Cytokine is one term for a group of protein cell regulators, variously called lymphokines, monokines, interleukins and interferons, which are produced by a wide variety of cells in the body, play an important role in many physiological responses, are involved in the pathophysiology of a range of diseases and have therapeutic potential" (955).

Most cytokines usually have a short action radius and act through an autocrine or paracrine mode of action. However, some cytokines also display a hormone type effect acting at a distant site (e.g. TNF, IL-1 and IL-6 in septic shock).

Cytokines control growth, differentiation, death and function of cells in lymphocytic, hemopoietic systems. Together with nerve cells, they provide a pertinent model for studying intercellular communications and intercellular signal networks (956).

The action or production of cytokines is mediated through a number of signal transduction pathways, which have recently been elucidated. These include (i) pathways integrating the activation of extracellular receptors and subsequent intracellular events leading to alterations of gene expression, (ii) cytoskeletal organisation, (iii) DNA synthesis and cell survival and (iv) the direct activation of intracellular transcription factors via cell permeable hormones (957, 958).

Cytokine functions are (959, 960):
- pleiotropic (a cytokine has more than one function),
- redundant (structurally dissimilar cytokines have an overlapping spectrum of actions),
- synergistic (the effect of two cytokines on a target cell is not just additive) or
- antagonistic.

Furthermore, a cytokine may start the synthesis of a cascade of other cytokines It may also induce the synthesis and release of its own antagonists and, in addition, downregulate its biological activity at the level of cytokine receptor expression. As a consequence, a very complex network of effects and relations can be observed.

For didactic reasons, cytokines are divided into pro-inflammatory and Th2-related factors in this document.

4-2-3-1- Pro-inflammatory cytokines

Pro-inflammatory cytokines such as interleukin (IL)-1, TNF (tumor necrosis factor), IL-6 and IL-18 are multifunctional unspecific enhancers of inflammation. They host defence and display multiple biological effects. Among them, they are involved in:
- endothelial cell adherence and the accumulation of inflammatory cells. Pro-inflammatory cytokines have been shown to induce the expression of E-selectin
- the activation of T- and B-lymphocytes in the enhancement of basophil histamine release,
- the induction of arachidonic acid metabolism,
- the release of antagonists to pro-inflammatory cytokines (for review, see 961).
- Recently, a new pro-inflammatory cytokine, IL-18, has

been identified. It is related to the IL-1 family in terms of structure, synthesis, receptor family and signal transduction pathways (962, 963). Similar to IL-1, IL-18 activates T- and B-cells, induces the expression of adhesion molecules and stimulates the release of pro-inflammatory cytokines and chemokines. Interestingly, IL-18 might preferably be involved in chronic inflammatory processes.

The release of pro-inflammatory cytokines into the tissue leads to regulatory processes involving the synthesis of IL-1rα and sIL-1RII, both being antagonists to IL-1, as well as the down regulation of the expression of the active IL-1 receptor on the cell membrane (964). These processes are naturally limiting the effects of IL-1 *in situ* and prevent the spreading of inflammation. Their failure may be connected to disease persistence (961).

These cytokines are involved in the early and late-phase allergic response (for review, see 965, 966). After allergen challenge of the nasal mucosa, increased concentrations of IL-1ß, TNF-α and IL-6 are measured in nasal secretions during the early-phase reaction and are further increased in the LPR (967-969). They may therefore be involved in the early initiation of the adhesion cascade by the induction of adhesion molecule expression on endothelial cells. Histamine increases the adhesion of leukocytes to the endothelium (970) and may thus potentiate the effect of cytokines (868).

Furthermore, under natural exposure conditions such as seasonal and perennial allergic rhinitis, increased concentrations of IL-1 were found in nasal secretions of allergic subjects compared to controls (971-973). Interestingly, this release persists for several weeks after the pollen season (973) suggesting that a persistent inflammatory process continues after allergen exposure, and supports the recently proposed concept of "minimal persistent inflammation" (9, 817).

In nasal secretions of normal subjects, a strong molar excess of IL-1 antagonists has been measured (973). In normal subjects, there is approximately a 3,000-fold excess of IL-1rα and a 17-fold excess of the soluble IL-1 RII over IL-1ß in nasal secretions. In serum, sIL-1RII excess is approximately 14,000-fold and IL-1rα excess about 1,500-fold higher. This points to the importance of the receptor antagonist to limit inflammation in tissue by binding to the receptor without biological activity, whereas in serum, sIL-1RII seems to be of greater importance. However, IL-1rα requires a 100-fold excess to prevent binding of IL-1ß to the receptor. As sIL-1RII binds to IL-1ß at a ratio of 1:1, this molecule may also have strong antagonistic properties *in vivo*.

During the pollen season, IL-1ß and also IL-1rα and sIL-1RII are upregulated during pollen exposure and there was a significant correlation between these factors (Bachert, unpublished data). This again indicates that pro-inflammatory effects of IL-1ß are a tightly regulated event protecting the host from harmful effects. However, the ratio of the agonist to its antagonists showed a relative deficit of the antagonistic systems under natural allergen exposure. This indicates that the balance

between agonist and antagonists may play a crucial role for the net biological effect of this cytokine. Soluble receptors with antagonistic properties (TNF-α binding proteins) also exist for TNF-α. Their upregulation has recently been demonstrated in nasal secretions during the pollen season (974).

A significant increase of IL-18 concentration in nasal secretions occurred later in the season compared to IL-1ß (Bachert, unpublished data). This suggests that IL-18 might be involved in sustaining a persistent inflammatory process. As discussed for IL-1, possible antagonists have been suggested for IL-18, but nothing is known so far about the occurrence and activity of these factors in allergic rhinitis.

Little is known about the cell source of pro-inflammatory cytokines in allergic rhinitis. It is likely that these cytokines are initially released by IgE-dependent mechanisms but that they are re-released by inflammatory cells through the cytokine cascade. TNF-α has been co-localised to mast cells in the nasal mucosa of perennial allergic rhinitis patients (705, 714). However, mast cells do not produce sufficient amounts of IL-1ß to explain the levels of this cytokine in nasal secretions. A possible source for this cytokine, however, could be the macrophage, able to release IL-1ß (975), and its naturally occurring receptor antagonist IL-1rα (976). Eosinophils can also release pro-inflammatory cytokines.

4-2-3-2- Th2-related cytokines

Other cytokines are classified as Th2-cytokines since, in initial studies, they were mainly released by Th2-type lymphocytes (203, 763, 977, 978). These include IL-3, IL-4 and IL-5. GM-CSF is released by Th1 and Th2 cells. IL-13 has an effect close to IL-4 but does not act on T-cells. On the other hand, IFN-γ and IL-12 are Th1-related cytokines. Although the dichotomy between Th1 and Th2 cells is less evident in humans (764) than in mice (761), this concept is important in the understanding of allergic diseases.

IL-4 and IL-13 are important in the regulation of IgE (chapter 4-3-1). On the other hand, IL-3, GM-CSF and IL-5 play a significant role in increasing the production of eosinophilic progenitors, in activating eosinophils and in supporting the recruitment, maturation and survival of these granulocytes. However, these cytokines have many other properties. IL-13 and IL-4 may be mucous secretagogues.

In allergic rhinitis, mRNA for Th2-type cytokines has been shown to be upregulated after allergen challenge (757). The release of IL-5 into nasal secretions could be demonstrated hours after allergen challenge (968, 979).

During the pollen season, patients allergic to pollens show an increased number of cells expressing Th2 cytokines (968, 972, 980-982). Allergen-induced synthesis of interleukin-5, but not of IgE, appears to be linked to symptomatic episodes of seasonal allergic rhinitis in sensitised individuals (983). Topical glucocorticosteroid treatment results in the inhibition of IL-5 mRNA expression and eosinophil infiltration (981, 984). In patients with perennial allergic rhinitis, there is also an increase

in some Th2 cytokines (776, 985). In contrast, there was no difference in the number of subjects expressing IFN-γ mRNA (986).

Apart from IL-4 and IL-5, the IL-4 and IL-5 receptors have been shown to be upregulated due to allergen challenge in allergic rhinitis subjects, whereas the receptor for IFN-γ was down regulated. Receptor expression correlated with eosinophil infiltration in the tissues. Pre-treatment with intranasal glucocorticosteroids before nasal allergen challenge resulted in a decreased expression of IL-4 and IL-5 receptors and an increased expression of IFN-γ receptors. Thus, cytokine receptor expression follows a similar pattern to the corresponding cytokines (987).

However, the source of Th2 cytokines within the nasal mucosa is not clear, as *in situ* hybridisation and immunohistochemistry show that they can be released by T-cells, mast cells, basophils, eosinophils and epithelial cells (707, 775, 988, 989).

IL-12 is a structurally distinct Th1-associated cytokine produced by B-cells and macrophages, which may play a suppressive role in the development of allergic sino-nasal mucosal responses (990).

4-2-3-3- Other cytokines and growth factors

Apart from pro-inflammatory and Th2-related cytokines, a variety of other cytokines and related factors may well be involved in the regulation of allergic inflammation. In culture, nasal epithelial cells produce stem cell factors (SCF), a cytokine supporting mast cell growth and differentiation. SCF was present in nasal lavage fluids in seasonal allergic rhinitis patients and correlated to the mast cell chemotactic activity, which was not suppressed by intranasal glucocorticosteroid or H1-antihistamine treatment (991). Also, in a second study, SCF production was correlated to the number of mast cells and the histamine content within allergic nasal mucosa. Therefore, SCF may be important for the attraction and activation of mast cells in allergic inflammation in the nose (831).

Recently, increased levels of NGF (nerve growth factors) have been shown in allergic subjects compared to controls. This correlates to an increased sensitivity of the sneezing reflex, increased secretion and plasma extravasation due to sensory nerve stimulation (992). NGF levels are increased in the serum of allergic patients (993). Thus, this neurotrophin may be implicated in neural hyperresponsiveness and in rhinitis.

4-2-4- Chemokines

Over the past ten years, more than 30 chemokines have been identified as attractants of different types of blood leukocytes to sites of infection and inflammation (994). They are produced locally in the tissues and act on leukocytes through selective receptors (995-997). Chemokines are now known to function also as regulatory molecules in leukocyte maturation, in traffic and homing of lymphocytes and in the development of lymphoid tissues. Not only a specific expression of adhesion molecules, but also the presence of chemokines may be responsible for preferential migration processes of sub-

sets of cells. Chemokines form several families, which can be differentiated according to their structure and to their target cells. Whereas CXC chemokines such as IL-8 act especially on neutrophils (998, 999), CC chemokines such as RANTES or eotaxin mediate eosinophilic migration (1000).

Nasal epithelial cells from atopic individuals release significantly greater amounts of RANTES and other factors than those from non-atopic individuals. In the atopic individuals, those exposed to pollen again released greater amounts than those not exposed to allergen (1001). When allergic patients are challenged with allergen, there is an increased release of RANTES (748). Challenge with RANTES induces the influx of eosinophils, basophils and lymphocytes (1002).

Eotaxin mRNA was found upregulated in nasal tissues from patients with allergic rhinitis (1003, 1004). It is mainly released by epithelial cells. Eotaxin is probably a key eosinophilic chemokine (1005). However, it also represents a major regulator of allergic reactions acting on Th2 cell chemotaxis, migration and differentiation of mast cells and on bone marrow progenitors (1006). Although eotaxin is not the only chemokine acting on eosinophil progenitors, it is central to the release of eosinophils from bone marrow to peripheral blood (1007). Glucocorticosteroids inhibit eotaxin expression in nasal tissues (1008).

IL-8 is released after allergen challenge in sensitised patients during early and late-phase reaction. This release is accompanied by an increased number of neutrophils in nasal lavages. However, the effect of neutralising IL-8 antibodies *in vitro* to the chemotactic activity of lavage fluid was only marginal, suggesting that IL-8 acts in connection with other chemotactic factors (1009). IL-8 can regularly be found in the nasal secretion of controls and is strongly upregulated during viral infections (1010), but seems to be unchanged or even decreased during the pollen season in allergic rhinitics (973, 1011).

In contrast, MCP-1, a monocyte and basophil activating factor, increases during the pollen season. MCP-1 is constantly produced by macrophages (999) and can be detected in the nasal mucosa of patients with seasonal and perennial allergic rhinitis (1011-1012). MCP-3 and MCP-4, belonging to the sub-family of CC chemokines (1013), have been shown to upregulate in biopsy specimens during allergen challenge, this response being abrogated when pre-treated with intranasal glucocorticosteroids. MCP-s induce chemotactic activity, particularly in eosinophils, T-cells and monocytes. They may be closely related to the influx of these inflammatory cells and thus contribute to the pathogenesis of allergic rhinitis (1014).

Furthermore, chemokines may elicit histamine-releasing activities, which might be of interest in the allergic late-phase reaction. The histamine releasing activity of chemokines for basophils is significantly increased by pre-incubation or co-stimulation with cytokines such as IL-3 and GM-CSF (1015, 1016). Further studies will be needed to completely understand the function of chemokines in rhinitis.

4-2-5- Adhesion molecules

4-2-5-1- Endothelial adhesion molecules

Cellular adhesion molecules (CAMs) play an essential role in tethering circulating leukocytes to the vascular endothelium at sites of inflammation. There is accumulating evidence for their involvement in the pathophysiology of airway mucosal allergic inflammation, such as that found in rhinitis (1017). The best characterised adhesion molecule families are the integrins, the immunoglobulin supergene family and the selectins (1018, 1019). Neutrophils or eosinophils have little ability to adhere to resting endothelium *in vitro*. Endothelial cells can be activated by cytokines such as IL-1, IL-4, IFN-γ, TNF-α, IL-5 and IL-13 (842, 849). Chemokines such as RANTES and eotaxin activate eosinophils (737); IL-8 activates neutrophils (738). Pro-inflammatory mediators such as PAF or histamine also activate neutrophils. Following activation, these cells adhere to eosinophils, basophils or neutrophils. E-selectin (1020), ICAM-1 and CD18 integrins participate in the adherence of these three types of blood cells. However, only eosinophils and basophils express VLA-4 and can bind to VCAM-1 which appears to be a major ligand for eosinophil adhesion to activated endothelium.

In the resting nasal mucosa, selectins are not expressed until their induction is caused by pro-inflammatory cytokines and other mediators such as histamine. Using an *ex vivo* model of the nasal mucosa, E-selectin expression is inducible as early as 1 hour after exposure to allergen in sensitised individuals. This expression is partly inhibited by TNF-binding proteins (TNF-BP) and by the IL-1 receptor antagonist (1021). Selectins are found to be preferentially expressed in the sub-epithelial vasculature and have been shown to increase in seasonal allergic rhinitis specimens compared to controls (1021). E-selectin expression and VCAM-1 expression were also enhanced 24 hours after local allergen challenge (1022). An increase in VCAM-1 expression is found on nasal endothelial cells in perennial rhinitis patients, probably due to a persistent activation of the mucosa (843). The expression of VCAM-1 on endothelial cells is likely to be related to a selective recruitment of eosinophils.

4-2-5-2- ICAM-1

Immunoglobulin supergene family members are membrane-bound protein molecules that are characterised by the presence of one or more immunoglobulin domains. They can be found on mast cells, lymphocytes, eosinophils, epithelial and endothelial cells. ICAM-1, the major rhinovirus receptor (1023), is constitutively expressed, but may also be induced 1 to 24 hours after stimulation (1024, 1025).

ICAM-1 and its counter molecule LFA-1 are increased in nasal epithelial cells of patients with seasonal (817, 1026) and perennial rhinitis (9). ICAM-1 and LFA-1 expression is increased in nasal endothelial cells in perennial rhinitis (843).

Topical glucocorticosteroids and most H1-antihistamines (835, 1027-1029) inhibit the upregulation of ICAM-1 on epithelial cells during early and late-phase reactions following allergen challenge.

4-2-5-3- Soluble adhesion molecules

Most of these adhesion molecules might also be shed from the cell surface and be present in nasal secretions and serum as markers of inflammation. Soluble ICAM-1 was found to increase in the serum of allergic rhinitis patients compared to non-atopic controls in perennial allergic rhinitis (1030). It also increased systematically and locally in patients with seasonal allergic rhinitis under natural conditions (819, 1031). Moreover, nasal ICAM-1 levels remained increased after the pollen season (819). However, the concentrations of soluble adhesion molecules such as soluble VCAM-1, E-selectin and ICAM-1 were not different in another study comparing perennial allergic rhinitis subjects to controls (1032).

4-2-6- Survival of inflammatory cells

The survival of inflammatory cells at the site of the allergic reaction depends on several factors. They may undergo cell death during the evolution of airway inflammation (1033) depending on their adhesion to extracellular matrix (1034) or other cells like epithelial cells (1035).

Programmed cell death or "apoptosis" is involved in the removal of superfluous and damaged cells in most organ systems. In contrast to necrosis, which may also be seen at inflamed sites, apoptosis represents granulocyte fate whereby a number of mechanisms would tend to limit inflammatory tissue injury and promote the resolution rather than the progression of inflammation. Preliminary characterisation of the recognition mechanism implicates the integrin αv-ß3 (vitronectin receptor) and CD36 (thrombospondin receptor). Eosinophil survival was shown to be increased in asthma due to decreased apoptosis which was further linked to GM-CSF (1036). *In vitro* eosinophils were shown to release increased amounts of various cytokines including GM-CSF (1037) and others. Supernatants from nasal epithelial cells were found to increase the survival of inflammatory cells (1038). However, direct apoptosis has never been studied in the nasal mucosa even though the survival of eosinophils in nasal polyps was shown to be associated with reduced apoptosis (740). Moreover, serum-soluble Fas levels were used as a marker to distinguish allergic and non-allergic rhinitis (1039).

The expression of adhesion molecules on epithelial cells rapidly increases after exposure to cytokines (IFN-γ or TNF-α) or to eosinophil-derived proteins (MBP and ECP) (1035). The enhanced expression of adhesion molecules on epithelial cells was found to increase the persistence of inflammatory cells *in vitro* (1035).

4-2-7- Conclusions

The inflammatory reaction in the nose results from an increased recruitment of inflammatory cells and a prolonged survival of these cells in the nasal mucosa. This is due to interactions with adhesion molecules and probably altered apoptosis (Figures 9 and 10).
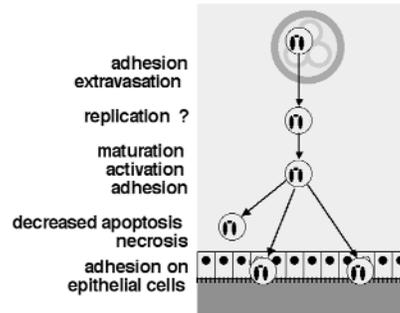
FIGURE 9: The nasal inflammatory response.
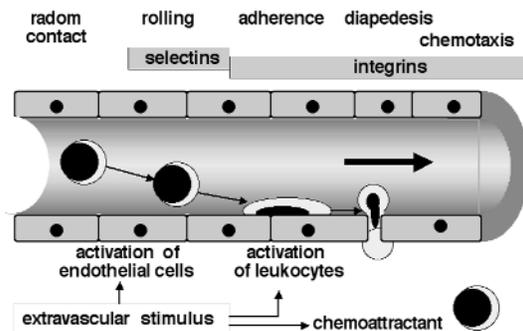
FIGURE 10: Recruitment of cells in the nasal mucosa.

4-3- NEUROTRANSMITTERS

4-3-1- Non-adrenergic, non-cholinergic system

In addition to classical neurotransmitters like acetylcholine and noradrenaline, NANC peptide neurotransmitters (neuropeptide) are identified in central and peripheral neurons and are presumed to be involved in the events related to allergic reaction (neurogenic inflammation) (676) (see chapter 4-1-5). However, the amount of these neuropeptides released in nasal fluid present in biopsies and the threshold concentrations for the positive manifestation of symptoms in nasal provocation are controversial and are still being discussed. Thus, neuropeptides may be of less importance than the classical neurotransmitters in nasal allergic reaction. Further investigations are necessary to confirm their specific involvement in the mechanisms of allergic rhinitis as has been discussed for mediators in allergic rhinitis.

4-3-2- Nitric oxide

Nitric oxide (NO) is an endogenous soluble gas acting as an intercellular transmitter, both in the central and peripheral nervous system. It is synthesised from arginine by an enzyme nitric oxide synthase (NOS) of which there are three isoforms. In addition to nerve cells, NO is also produced by epithelial cells and by the endothelium. NO plays a key role as a vasodilator, neurotransmitter and inflammatory mediator (1040-1042). A significant increase of NO in the nose is detected in patients with allergic rhinitis (1043,

1044) and sinusitis (1045). However, in other studies, nasal NO was not significantly different from controls outside the pollen season and did not increase significantly in the pollen season (1046). The production of NO is increased in patients with perennial nasal allergy (1047, 1048), but the blood flow in the nasal mucosa of patients is reduced (1049). In the same study, nitrotyrosine formation suggests that there is a process of ONOO(-)-induced damage in the mucosa of patients with perennial nasal allergy. This damage may limit the dilatation of blood vessels, despite the presence of excessive NO. Nasal nitric oxide does not appear to control basal nasal patency or acute congestion following allergen challenge in allergic rhinitis (1050). Nitric oxide may be an important mediator of the effector arm of the naso-nasal reflex that increases vascular permeability but it is not involved in the sensory nerve afferent pathway (1051). Further studies on the role of NO in allergic rhinitis are necessary for a final conclusion.

4-4- THE IgE IMMUNE RESPONSE

Allergy is generally caused by a sustained overproduction of Immunoglobulin E (IgE) in response to common environmental antigens such as pollen, foods, house dust mite, animal danders, fungal spores and insect venoms. Elevated levels of serum IgE are thus a hallmark of atopic diseases like allergic rhinitis. IgE itself constitutes a very minute fraction of the total antibody in the human serum (50-300 ng/ml of IgE versus 10 mg/ml of IgG). However, the biological activities of IgE are powerfully enhanced by the activities of specific cell surface receptors to which it binds and which may be of high or low affinity phenotype.

4-4-1- Regulation of the IgE immune response

Written in collaboration with H. Yssel (F)

One of the typical aspects of airway inflammation in allergic rhinitis is the infiltration of the nasal mucosa by T helper type 2 (Th2) cells (203, 763, 764), basophils, Langerhans cells, eosinophils and mast cells. Each of these cells contributes to the physiological changes that characterise rhinitis. It is believed that this inflammatory process is initially triggered by the presentation of allergens in the micro-environment of the nose, in the presence of an appropriate cytokine milieu. This results in the induction of IgE via the isotype switching of B-cells (Figure 11).

4-4-1-1- Antigen presenting cells

The role of antigen presenting cells in the airways appears to be of importance for the development of immune response. In particular, in animal experiments, the balance between dendritic APC and macrophages and/or the reaction of the T-cell system to the stimuli given by these cells plays an important role in the occurrence of Th1 tolerance or Th2 hypersensitivity (1052). Antigen presentation by airway Langerhans cells leads to the preferential development of a Th2 response which can be short lived (a short boost of IgE production, followed by active suppression) or persist to develop a polarised, long lived Th2 response (806). Moreover, monocyte-derived dendritic cells from allergic asthmatic patients, when compared to healthy controls, already showed phenotypic differences in the expression of HLA-DR, CD11b and the high-affinity receptor for IgE (1053).

4-4-1-2- Th2 cytokines

Differentiation of B-cells into IgE-secreting plasma cells is a complex cascade of events in which cytokines play a crucial role (for review see 1054). Cytokines do not only induce Ig synthesis, but also regulate isotype switching. Human IL-4, and more recently IL-13, have been shown to induce IgE synthesis *in vitro* in cultures of mononuclear cells derived from peripheral blood, tonsils and spleen (1055, 1056). In addition, IL-4 induces IgE synthesis in B-cells obtained from cord blood, foetal spleen and liver, whereas even foetal bone marrow-derived B-cells, characterised by the absence of surface IgM expression, can be induced to produce IgE *in vitro*. This indicates that these cells are mature in their capacity to produce IgE (1057).

Both IL-4 and IL-13 induce the transcription of germline ε mRNA in purified B-cells (1058). With appropriate co-stimulatory signals (see chapter 4-4-1-3), this results in the switching and production of IgG_4 and IgE of B, as well as pre-B cells (1059, 1060). However, IL-13 induces the synthesis of IgG_4 and IgE, independently of IL-4 (1057). Furthermore, IL-4 and IL-13 do not have synergistic effects or additional effects on IgG_4 and IgE synthesis. Although both cytokines are human B-cell growth factors of equal potency, IL-4-induced IgG_4 and IgE synthesis is about three folds higher, at saturating concentrations, compared to that induced by IL-13 (1057). Consistent with this motion, it has been found that IL-13 is most effective in inducing IgE synthesis in situations where little or no IL-4 is present (1061).

In addition to their inducting effect on IgE synthesis, IL-4 and IL-13 share many other biological functions (reviewed in 1062):
- Both cytokines promote the growth and differentiation of pre-activated B-cells,
- they induce the expression of several surface antigens on B-cells, including CD23, CD71, CD72, MHC class II and sIgM,
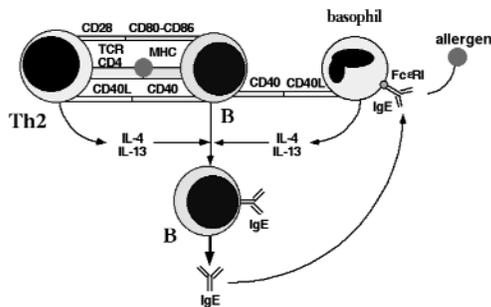
FIGURE 11: The IgE immune response. *TCR*, T-cell receptor; *MHC*, major histocompatibility complex.

- they inhibit the production of pro-inflammatory cytokines by monocytes. However, in allergic inflammation, the anti-inflammatory properties of IL-4 may be less effective (1063).

Despite these functional similarities and the utilisation of shared signal transduction components of their respective receptors, there are some major differences in the biological activities of IL-4 and IL-13, which may partly reflect their different roles in the immune response to allergens.

- Unlike IL-4, IL-13 is not preferentially produced by human Th2 cells, but is produced by both Th1 and Th2 cells (1064).
- Furthermore, IL-13 is produced earlier following the activation of T-cell clones and peripheral blood T-cells,
- its production is sustained for much longer periods as compared to that of IL-4 (1064, 1065).
- IL-13 fails to activate T-cells because of the absence of a binding component of the IL-13 receptor on T-cells (1064).
- These findings suggest that IL-13 may not only be involved in early immune responses. It may have a unique function in inducing and sustaining B-cell growth and differentiation, including the induction of IgE synthesis in the absence of T-cell expansion.
- IL-4, unlike IL-13, is not only a potent growth factor for T-cells. It is required for the differentiation of immunologically naive T-cells into IL-4- and IL-5-producing Th2 cells.
- IL-13, in contrast to IL-4, is not able to directly induce its own production. The enhancement of IL-13 production by Th2 cells is dependent on the presence of IL-4.
- IL-13, but not IL-4, is produced by immunologically naive CD45RA^{+} T-cells isolated from cord blood, as well as peripheral blood, following activation (1065). This may induce IgE synthesis in situations where no IL-4 is present, underscoring the observation that activated CD45RA^{+} T-cells efficiently modulate IgE synthesis *in vitro* (1066).

4-4-1-3- Co-stimulatory signals

IgE production by B-cells not only requires the presence of IL-4 or IL-13, but also a physical interaction between T- and B-cells, involving a number of surface and adhesion molecules. This T-B cell-mediated signal can be replaced by an antibody directed against CD40 (1060), as well as transfectants expressing CD40 ligand (CD40L) (1067). This indicates that the CD40/CD40L interaction is pivotal in the induction of B-cell switching leading to IgE synthesis. The process during which T-cells help B-cells for the production of Ig, including IgE, is thought to be the result of a reciprocal dialogue between these populations which starts if either the T-cell or the B-cell is activated (reviewed in 1068). Upon activation, T-cells transiently express CD40L and induce resting B-cells to express CD80, whereas subsequent interaction between CD80 and its ligand CD28 enhances cytokine production and CD40L expression by T-cells.

This series of mutual T- and B-cell activation, via interactions between CD28/CD80 and CD40/CD40L respectively, is thought to be short-lived, as a consequence of the transient expression of CD40L on activated T-cells. This results in the loss of signal transduction through CD40 and in the abrogation of induction of IgE synthesis.

4-4-1-4- Cells involved in Th2-cytokine synthesis

The production of IL-4 and IL-13 is not restricted to T-cells. Preformed IL-4 is expressed in human mast cells and released upon cell activation (701, 702, 988). It is found in the cytoplasm of *in-vitro* activated human peripheral blood basophils (724). After IgE-dependent activation, IL-4 and IL-13 mRNA are transcribed in basophils which produce IL-4 and IL-13 in addition to various mediators (1069-1071). Although basophil numbers are low in peripheral blood, these cells are stronger producers of IL-4 than T-cells (727). Moreover, human recombinant histamine-releasing factor directly stimulates IL-4 and IL-13 secretion from basophils of selected atopic donors in a reaction requiring the expression of a particular type of IgE, referred to as IgE[+] (1072-1074). This broadens the possible role, in chronic allergic inflammation, of this cell type. Basophil production of IL-4 and IL-13 early in the course of allergen stimulation may therefore shape subsequent T-cell responses both *in vivo* and *in vitro*. Moreover, it has been shown that freshly isolated mast cells and basophils can be induced to express CD40L and that IgE synthesis can be induced by the interaction of B-cells with mast cells in the presence of exogenous IL-4. Basophil-mediated IgE synthesis can even take place in the absence of exogenous IL-4 or IL-13 (1075). These results suggest that mast cells and basophils can induce the production of IgE, independently of T-cells. Nasal mast cells in perennial allergic rhinitics exhibit increased expression of FcεRI, CD40L, IL-4 and IL-13, and can induce IgE synthesis in B-cells (707, 714).

Conclusions

In conclusion, IgE production results from complex interactions between B-cells, T-cells, mast cells and basophils. It involves a series of surface molecules, as well as the presence of IL-4 and IL-13cytokines. In view of the location of the tissue distribution of these various types of cells, it is likely that IgE synthesis takes place not only in the germinal centres of the lymph node, but also in the nasal mucosa.

4-4-2- Local IgE immune response

Local production of specific IgE in the nasal mucosa has been proposed in the past (1076). During the pollen season, there is an increase in the level of allergen-specific serum IgE (1077). After nasal allergen challenge, a rise in antigen-specific serum IgE levels was observed, but not all individuals showed this response (1078). The magnitude of the allergen-specific IgE response to nasal challenge appeared to be greater than the response to seasonal exposure. Moreover, the application of a diesel exhaust particulate into the nose induces a local production of IgE measured in nasal secretions (609). These data suggest that IgE can be pro-

duced locally into the nasal mucosa. Nasal allergen provocation has demonstrated that allergen-induced rhinitis is associated with an increase in local IL-4 mRNA, IgE heavy chain (Cε) and IgE heavy chain promoter (Iε) RNA and that pre-treatment with intranasal glucocorticosteroids inhibits the increase in these transcripts (1079). IgE class switching occurs locally within the nasal mucosa of subjects with seasonal allergic rhinitis but not in patients receiving intranasal glucocorticosteroid treatment (1080). In patients with perennial allergic rhinitis, IgE heavy chain (Cε) expression was detected and its levels were upregulated under natural allergen exposure (1081). Nasal epithelial B-cells are able to produce IgE and mRNA for IgE (609, 1082). Plasma cells in the nasal mucosa have been shown to produce allergen-specific IgE (1083, 1084). The maturation of IgE-expressing B-cells (activated or memory) to IgE producing plasma cells takes place in the nose (1084). Many of the cytokines produced by T-cells and mast cells after allergen provocation such as IL-4, IL-6 and IL-13 are B-cell proliferating factors (707, 748, 757, 1058, 1075). The mast cell/basophilic induction and stimulation on B-cell IgE production indicate that immunoglobulin switching, previously thought to take place only in lymph node germinal centres, may also occur in peripheral organs such as the nose. However, it is not clear which impact this mast cell/B-cell interaction has on the amount of IgE production. Local IgE synthesis may explain why some "atopic" patients develop rhinitis whereas others have either no clinical manifestations or develop atopic disease elsewhere (787).

4-4-3- Systemic IgE immune response

Allergic diseases can affect the nose, lung, eye, skin and gastrointestinal tract, concurrently or subsequently, during the course of a patient's life span. Atopic dermatitis and food allergy often precede ocular and respiratory manifestations induced by inhalant allergens. Moreover, allergen challenge of a sensitised target organ is associated with allergic changes at the level of other target organs. It has been observed that patients with asthma also present symptom-free inflammation of the salivary glands and bowel (1085, 1086). Patients with allergic rhinitis present minimal inflammation of the bronchi without clinical manifestations (1087). After allergen challenge, GM-CSF may play a role *in vivo* to increase the production of eosinophilic progenitors in allergic airway disease (730).

Bone marrow actively participates in the production of IgE-receptor positive inflammatory cells such as eosinophils, basophils and mast cells, which are actively recruited to tissues in atopic individuals. Increases in bone marrow inflammatory cell progenitors are associated with allergen-induced airway hyperresponsiveness and inflammation in asthmatics (729) and animals (1088). There appears to be a critical involvement of bone marrow in the development of eosinophilic airway inflammation (1089, 1090) suggesting that asthma and rhinitis represent a systemic disease (729).

Inhaled glucocorticosteroids were shown to reduce the baseline but not the allergen-induced increase in bone marrow inflammatory cell progenitors of asthmatic subjects (1091).

4-4-4- IgE receptors

Ishizaka and Tomioka (1092) were the first to describe the high affinity IgE receptor on mast cells (FcεRI). They found that these cells were able to degranulate after allergen stimulation. Degranulation induces the release of histamine whereas activation of the cells causes leukotriene and cytokine release.

4-4-4-1- The high affinity receptor for IgE (FcεRI)

The structure of FcεRI has been extensively studied (1093-1095). IgE binds to mast cells and basophils by its Fc fragment to FcεRI, which is a tetrameric receptor. The ligand-binding and signal transduction functions of this receptor are carried out by distinct sub-units. The extracellular portion of FcεRI contains the entire IgE-binding site. The distribution of FcεRI was initially restricted to mast cells and basophils, but it has been shown to be present on:
- Langerhans cells (1096, 1097),
- platelets (1098, 1099),
- activated eosinophils (752),
- monocytes from asthmatics (1100),
- bronchial epithelial cells from asthmatics (832).

However, the expression is about 10 to 100 folds lower on these cells than in mast cells. Moreover, these cells usually express a trimer and not the tetramer as seen in mast cells. It is believed that this structure serves the antigen presenting cell function by specifically targeting the antigen-IgE-FcεRI complexes to the intracellular antigen presenting compartment. This APC function is even more effective in dendritic cells. The APC function has also been described in mast cells (1101).

Interestingly, in atopic patients, there is an increased expression of FcεRI on basophils, eosinophils monocytes and dendritic cells compared to non-atopic subjects (1100, 1102, 1103). This may be due to elevated IgE levels (1104, 1105) which were recently shown to upregulate FcεRI (1106-1108). Th2-type cytokines such as IL-4 can also upregulate FcεRI on mast cells (1109).

In patients with allergic rhinitis, enhanced expression of FcεRI has been observed on:
- mast cells,
- eosinophils,
- macrophages and dendritic cells (707, 1110).

The increased expression of FcεRI on the mast cells of patients with allergic rhinitis has been associated with a greater binding to IgE molecules and an increased release of histamine and cytokines (714). Only few nasal eosinophils were shown to bear FcεRI in allergic rhinitis patients (1111). The activation of mast cells and basophils occurs within seconds after allergen challenge and results from the binding of IgE molecules bound on FcεRI with allergen. Histamine is released immediately whereas arachidonic acid metabolites are released within minutes

and cytokines later (2-4 hr) (1112). Mast cells isolated from nasal tissues of patients with allergic rhinitis release histamine, cytokines and Cys-LT. The activation of other cell types through the FcεRI is able to induce the release of eicosanoids (832) and cytokines (1099).

4-4-4-2- The low affinity receptor for IgE (FcεRII, CD23)

The low affinity IgE receptor FcεRII was characterised as a B-cell receptor for IgE. It is known to play an important role in the humoral responses acting in antigen-presentation to T-cells and in the adhesion of B-cells to each other. It is found on various cells such as:
- B-cells,
- macrophages (1113),
- eosinophils (753, 1114),
- natural killer cells,
- T-cells,
- Langerhans cells (1115),
- epithelial cells of bone marrow and thymus (1116),
- bronchial epithelial cells from asthmatics (833).

There are two forms of FcεRII, differing only by their N terminal amino acids. FcεRIIα is a developmentally regulated gene expressed only in antigen-activated B-cells before their differentiation into immunoglobulin-secreting plasma cells. It is present as an antigen IgE-FcεRIIα complex and presents antigen very effectively to T-cells. FcεRIIβ is inducible on all cell types, in particular by IL-4.

FcεRII is strongly expressed in tonsils and lymph nodes and it appears to play an important role in the maturation of B-cells.

4-5- FROM NASAL CHALLENGE TO CHRONIC RHINITIS

The mechanisms of allergic rhinitis have been clarified by using nasal challenge with allergen or pro-inflammatory mediators and by measuring cells and mediators released during the early and late-phase allergic reaction. However, the priming effect of the nasal mucosa is of importance as a single challenge does not perfectly mimic the ongoing allergic reactions induced by repeated allergen exposure. In intermittent and persistent allergic rhinitis, the same cells and mediators are important but non-specific nasal hyperreactivity develops (Figure 12).

4-5-1- Nasal challenge: early and late-phase reactions

Nasal challenge studies have improved our knowledge of the mechanisms of allergic rhinitis over the past ten years. The elegant studies by Naclerio *et al.* (642) using nasal allergen challenge followed by the measurement of cells and mediators in the nasal fluid have made it easier to analyse the events occurring during allergic reaction.

4-5-1-1- The early-phase reaction

Patients present symptoms within minutes of a nasal challenge with pollen grains. These are characterised mainly by rhinorrhea, obstruction, sneezing and occasionally pruritus (711).

4-5-1-1-1- Release of vaso-active mediators

Pathological studies have shown that mast cells are activated after allergen challenge (660) and the measurement of mediators in nasal secretions has shown that several mast cell derived mediators are released. These include:
- histamine (642, 711, 934),
- PGD_2 (642, 711, 905),
- CysLT, (712, 932, 934, 1117-1119)
- tryptase (713, 1120).

When individual patients are challenged, there is a great heterogeneity in the release of mediators and/or in the symptoms induced. This suggests that the mediators liberated (or the levels released) vary from subject to subject. Moreover, histamine release is not always correlated with the occurrence of symptoms (642, 711, 1118, 1121) except possibly sneezing (1122). A better correlation is often found between the release of lipid mediators and symptoms (642, 711, 1118). CysLTs may be of interest as their release appears to be prolonged and they induce sustained nasal obstruction.

4-5-1-1-2- Plasma exudation

During the early-phase reaction, nasal mucosal blood flow decreases (646) and plasma exudation is a major feature observed and related to both nasal hypersecretion and congestion. The exudation process is a non-injurious, fully reversible process of an almost unfiltered bulk blood flow of different sized proteins (1123). The plasma exudate provides a wide range of inflammatory enzymes including kinins (945, 946, 1124-1126), vascular-derived mediators, albumin (1123), immunoglobulins, plasma-derived histamine, pro-inflammatory mediators and activated complement fractions (1127) which can all be found in nasal fluids. Kinins and related compounds may play a role (947, 952, 1128, 1129).

4-5-1-1-3- Activation of epithelial cells

Epithelial cells are activated rapidly after allergen challenge as shown by an increased expression of adhesion molecules (1024). However, it is not clear whether this activation is direct or whether it is induced by mast cell-derived mediators such as histamine (833, 836). The activation of epithelial cells may be of importance in rhinitis but further elucidation is required (1035) (Figure 14).

4-5-1-1-4- Neuropeptides

Pruritus and sneezing are major symptoms caused by the histamine-induced activation of nerve endings located in epithelial tight junctions. Glandular secretion is directly stimulated by α-adrenergic and cholinergic agonists (682, 877). Although the release of substance P by an axon reflex has yet to be demonstrated in humans, it is likely that a cholinergic reflex occurs and that this may lead to hypersecretion (1130).

4-5-1-1-5- Release of chemotactic factors

During the immediate-phase reaction, a range of chemotactic factors (cytokines and mediators such as LTB4 (932, 1131)) and PAF (1132, 1133) are released by mast cells and epithelial cells. This can lead to a more complex ongoing inflammatory response. A mixed inflammatory infiltrate is observed shortly after the onset of the reaction (1134).
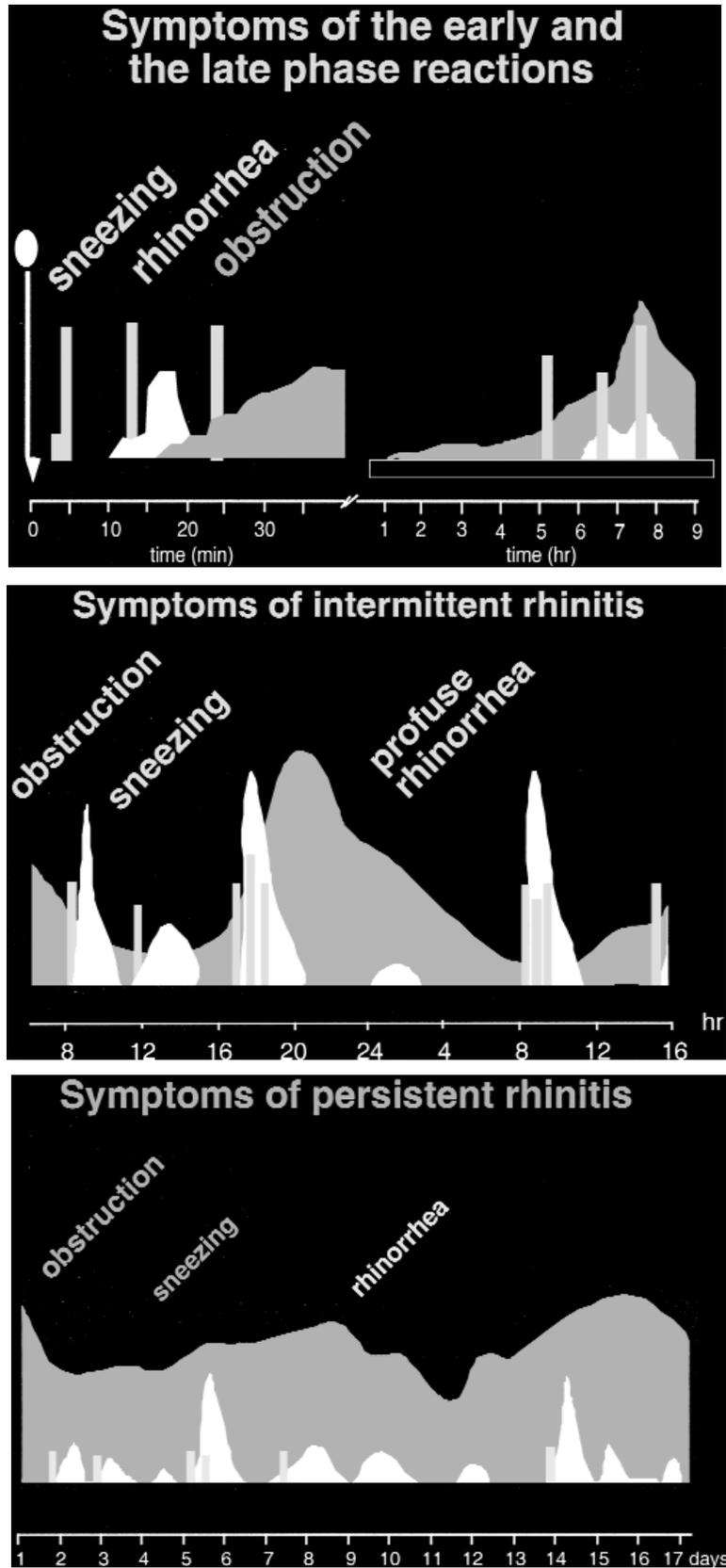
FIGURE 12: Symptoms induced by allergen challenge (early and late-phase reaction) and of intermittent and persistent rhinitis.
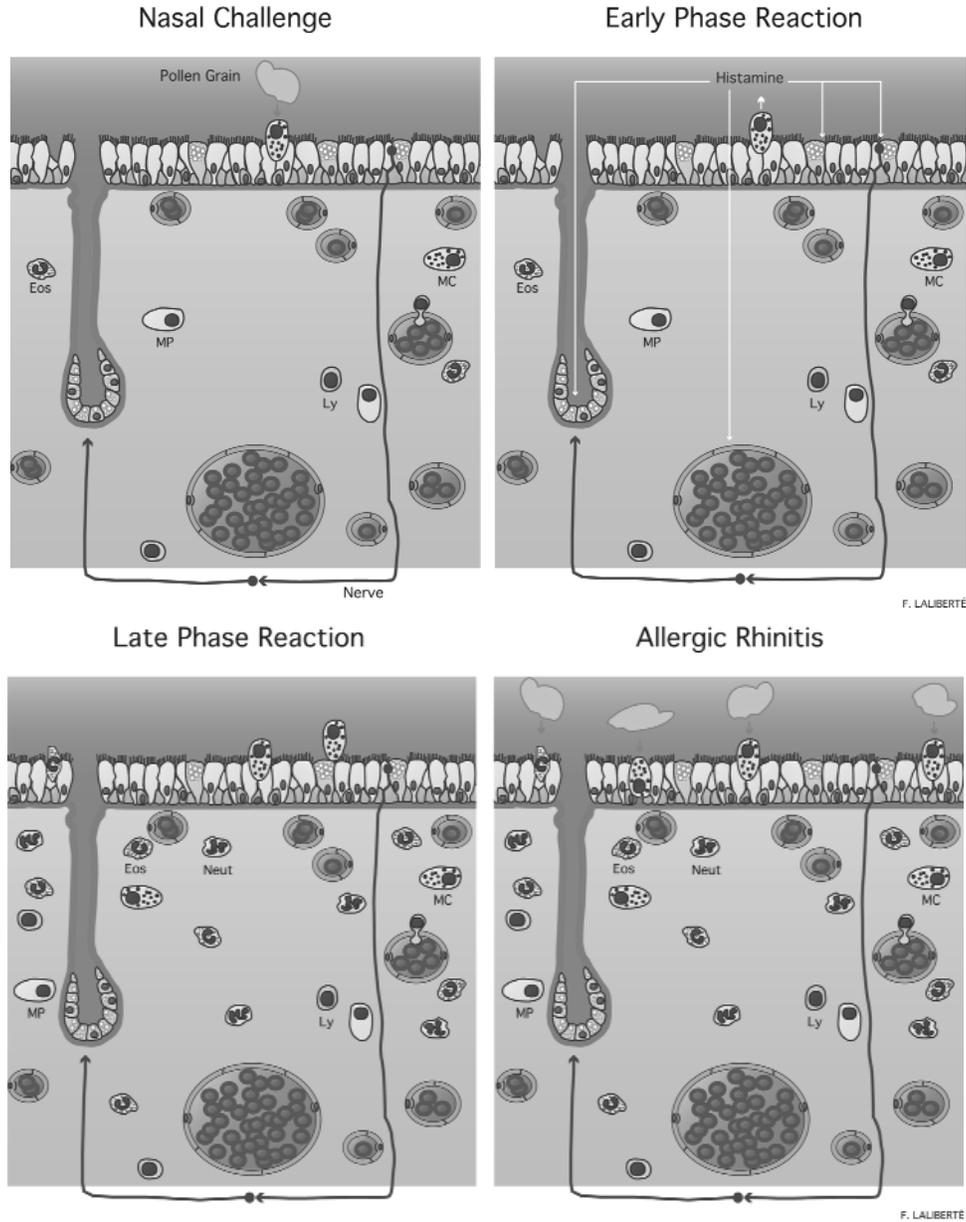
FIGURE 13: Mechanisms of allergic rhinitis.

4-5-1-2- Late-phase reaction

4-5-1-2-1- Cell activation and release of pro-inflammatory mediators

After a single allergen challenge, approximately 30 to 40% of patients develop a late- phase reaction (LPR) (starting 4 to 5 hours and peaking 6 to 12 hours after the challenge) which is manifested in the form of nasal obstruction and, to a lesser extent, rhinorrhea and sneezing (723). The LPR is characterised by the appearance of inflammatory cells at the site of the allergic reaction (1117):

• Neutrophils. The role of neutrophils in the late-phase reaction remains to be clarified. These cells are usually found in increased numbers when lavages are carried out 3 to 8 hours after challenge but they are present in patients with and without a late-phase reaction.
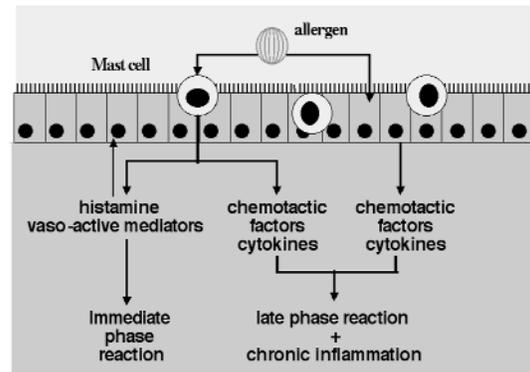
FIGURE 14: Activation of epithelial cells.

The presence of neutrophils is not discriminative (641, 1135, 1136).

- Eosinophils which release proteins (ECP, MBP) (641, 1135, 1137-1139). There is a time relationship between the increase in eosinophils and levels of ECP or MBP and the development of symptoms of a LPR after allergen challenge (1140). The magnitude of the nasal blockage is related to the number of cells, particularly eosinophils, during the late-phase reaction (1141).
- Basophils (but apparently not mast cells) (1142, 1143),
- CD4+ T-cells and CD25+ (interleukin 2 receptor bearing) cells (756).
- In some but not all studies, macrophages have been found in increased numbers (790).

Among the mediators recovered in nasal fluid, we find:
- histamine,
- CysLT,
- eosinophil-derived mediators (ECP, MBP)
- and kinins (723).
- It was thought that PGD_2 was not released during the late-phase reaction but recent studies have shown that, in at least some patients, there is a significant release of this mediator.

4-5-1-2-2- Cytokines, chemokines and the late-phase reaction

The regulation of the late-phase reaction is becoming better understood. It is now clear that cytokines and chemokines, more than any pro-inflammatory mediators, are involved in the recruitment, activation and perpetuation of cells in the inflammatory infiltrate.

Eosinophil (IL-5, GM-CSF, eotaxin, RANTES (757, 968, 979, 1003, 1144)) and neutrophil chemoattractants (IL-8) (748) are released during the LPR. There was a close correlation between "Th2-type" cytokine mRNA expression, particularly IL-5, and the number of activated (EG2+) eosinophils. This suggests that CD4+ T-cell recruitment and activation and the release of Th2-type cytokines *in vivo* contribute to the development of late nasal responses and are associated with tissue eosinophilia. GM-CSF appears to be of importance in the recruitment (and possibly survival) of eosinophils during the LPR (1145). However, the picture of cytokine and chemokine release is more complex than previously thought. The increase in IL-4, IL-10 and IL-13 mRNA levels (981) in the nasal mucosa after nasal allergen provocation was also upregulated. IL-16 is a potent chemoattractant for CD4+ cells *in vitro* and may play a significant role in recruiting CD4+ cells in the LPR (1146). Moreover, the nasal administration of rIL-5 into the nasal mucosa of patients allergic to *Cryptomeria japonica* pollen induced an accumulation and degranulation of eosinophils together with the development of nasal hyperreactivity to histamine (1147).

The precise cell origin of these cytokines and chemokines is yet to be determined, although initial data suggested the principal cellular provenance (at least at mRNA level) to be T-lymphocytes (1148), the contribution from mast cells appearing to be important (702, 985, 1148). RANTES may be mainly released by macrophages in the nasal mucosa (1149).

4-5-1-2-3- Recruitment of inflammatory cells and adhesion molecules

The accumulation of inflammatory cells in the nasal mucosa is characteristic of the LPR. The tissue eosinophilia may involve both the recruitment of mature eosinophils and the proliferation of their progenitors. A key factor for the influx of cells into the inflamed nasal tissues is the passage of blood cells through the endothelium to the submucosa (Figure 10). Nasal challenge with allergen upregulates the expression of vascular endothelial adhesion molecules in mucosal biopsies (1022) on epithelial cells (1026). It also induces the release of sICAM-1 into nasal secretions (1031).

4-5-1-2-4- Survival of inflammatory cells

The survival of inflammatory cells at the site of the allergic reaction depends on the fate they undergo in cell death during the evolution of airway inflammation. Although several studies have been carried out in asthma, less is known in rhinitis.

4-5-2- The priming effect

Nasal challenge with pollen grains differs from the natural course of the disease during the pollen season as, in the latter case, patients are exposed for days or weeks to allergens leading to significant inflammation of the nasal mucosa and non-specific nasal hyperreactivity. Moreover, during a single nasal challenge with pollen, the number of grains required to induce symptoms is far greater than that inhaled during the pollen season (642, 711). In 1968, Connell (8, 1150) suggested that nasal challenge with allergen was able to prime the mucosa. When he performed serial nasal provocations, he observed that the number of pollen grains required to elicit a positive nasal challenge was reduced by 10- to 100-fold when a second challenge was repeated the following day. He called this effect "priming". Conversely, this priming effect disappeared when patients were challenged at weekly intervals.

The mechanism behind this important finding was poorly understood at the time but is now thought to be due to the influx of eosinophils and metachromatic cells attracted to the mucosa by the first challenge (1151), this inflammation subsiding after a week or so. It is also possible that inflammatory cells are primed by cytokines or mediators as has been shown *in vitro* for basophils (1152) and eosinophils (1153). The priming effect can be mimicked using challenge with very low repeated doses of allergen. In such a challenge, changes in eosinophil mediator release in nasal lavage can be seen despite no, or minimal, clinical symptoms (1154). Histamine releasing factors (HRFs) are released into nasal secretions but they are present both in normal subjects and in patients with chronic rhinitis. However, these HRFs have been shown to be more potent on autologous basophils of

rhinitic patients than on those of control subjects (1155) and glucocorticosteroids reduce such HRF activity (1156). Other mechanisms may also explain the priming effect. The effects on nasal microvascular blood flow can be detected by means of laser Doppler flowmetry. In a study, patients reacted to the birch pollen provocation with an increase in blood flow. This increase was greater after the pollen season than before when the same pollen doses were used, indicating a priming phenomenon of the resistance vessels (1157).

The priming effect on the nasal mucosa explains the importance of the tree pollen season in patients allergic to tree and grass pollens (1158). The tree pollen season shortly precedes the grass pollen season. When tree pollen counts are high, the nasal mucosa is primed and patients develop symptoms, not only during the tree pollen season but also with very small amounts of grass pollens, e.g. very soon after the tree pollen season has ended. On the other hand, when tree pollen counts are low, patients sensitised to grass pollens only or polysensitised patients start to present symptoms only several days following the onset of the grass pollen season as there is no priming of the nasal mucosa.

4-5-3- Minimal persistent inflammation

The concept of "minimal persistent inflammation" is a new but important hypothesis that was recently proposed by Ciprandi *et al.* (9) and confirmed in perennial (9, 759) and seasonal allergy (1159). In patients with perennial allergic rhinitis, the allergen exposure varies within the year and there are periods in which there is little exposure. This is the case in the Mediterranean area for house dust mites during the summer, or when allergen avoidance is effective. However, these patients, even though they are symptom free, still present inflammation of the nose.

4-5-4- Persistent inflammation

4-5-4-1- Seasonal allergic rhinitis
4-5-4-1-1- Inflammatory cells
- Studies of cells infiltrating the nasal mucosa during the pollen season show that there is an increase in the number of various inflammatory cells and that this is correlated with both the severity of symptoms (641, 1160-1162) and nasal non-specific hyperreactivity (869, 871).
- Eosinophils are almost always found in the mucosa between non-desquamated epithelial cells as well as in the submucosa (661, 1160-1162). This tissue eosinophilia may result from increased eosinophil chemotaxis, vascular adhesion, increased bone marrow production of eosinophils or prolonged survival of eosinophils in tissues in relation to the release of cytokines and growth factors (973, 980, 984).
- Mast cells are present in increased numbers in the epithelium and the submucosa but they are often degranulated (660, 661, 699, 1163-1165).
- Neutrophils are also often observed in seasonal allergic rhinitis (1166), but the significance of the presence of these cells is still under scrutiny.

- CD4+ T-cells increase in number during the pollen season.
- Moreover, in allergic patients, there is an increase in Langerhans-like cells (CD1+) during the season (793).

4-5-4-1-2- Epithelial cells
The importance of epithelial cells in allergic rhinitis has often been discussed.
- By contradistinction to asthma, the epithelial layer is not shed even though numerous activated eosinophils are found among epithelial cells (1167).
- In seasonal allergic rhinitis, epithelial cells bear ICAM-1 molecules (817).
- Moreover, although hyper-permeability of the mucosa is thought to be a characteristic of rhinitis, an inverse finding was observed using the mucosal absorption of chromium-51 labelled EDTA suggesting that the airway epithelial barrier, which is subject to prolonged eosinophilic inflammation, may rather increase its functional tightness (1168).
- However, it is likely that epithelial cells are activated in seasonal allergic rhinitis.

4-5-4-1-3- Pro-inflammatory mediators
A range of mediators are released in nasal secretions during the pollen season (1169). These include:
- Cys-LT (1117, 1170),
- ECP (1171),
- histamine, whose levels are inconstantly increased when compared with pre-season levels (880, 1172). However, it has been shown that tissue histamine levels are correlated with symptoms during the pollen season (1173).
- Tryptase, whose levels were found not to increase (1172).

4-5-4-1-4- Cytokines and chemokines
- During the pollen season, IL-1ß, IL-18, but also IL-1rα and sIL-1RII, are upregulated during pollen exposure, and there was a significant correlation between these factors (Bachert, unpublished data).
- In patients allergic to pollens, there is an increased number of cells expressing Th2 cytokines during the pollen season (968, 972, 980-982).
- Eotaxin mRNA was found upregulated in nasal tissues from patients with allergic rhinitis (1003, 1004).
- IL-8 levels seem to be unchanged or even decreased during the season in allergic rhinitics (973, 1011).
- MCP-1 levels increase during the pollen season.

4-5-4-1-5- Edema
The airway mucosa responds to inflammatory provocations with bulk exudation of plasma into the airway tissue (vascular exudation) and lumen (mucosal exudation). The process of mucosal exudation of plasma is a prominent feature of airway inflammation and has been demonstrated in rhinitis (1123). The plasma exudation response also represents a first-line defence, allowing potent plasma proteins to appear on the airway mucosa and act as a barrier towards undue luminal material (656).

4-5-4-1-6- Neuropeptides
The role of neuropeptides is unclear:
- Substance P and vasoactive intestinal peptide have been shown to be released into nasal secretions during the pollen season (1174).
- Moreover, alterations of adrenoceptors and muscarinic acetylcholine receptors (1175, 1176) have been observed in patients with allergic rhinitis.
- Atopic subjects present an increased cholinergic hyperresponsiveness during the pollen season (1177) suggesting that inflammatory changes occurring in the mucosa increase its sensitivity to neuropeptides.

4-5-4-2- Perennial allergic rhinitis
4-5-4-2-1- Inflammatory cells
- Nasal eosinophilia is not a permanent feature of this disease (83, 759, 1178-1180) even in patients with allergic rhinitis. In a study examining the importance of eosinophils in perennial rhinitis, it was observed that eosinophils were often present in the nasal secretions of allergic, symptomatic patients (759).
- Neutrophils are present in non-infectious perennial rhinitis and a study performed by Knani *et al.* showed that neutrophil levels were increased in the non-allergic group (759).
- Epithelial mast cells are increased in numbers in the nasal mucosa of patients with allergic (1181) and non-allergic perennial rhinitis (1182). However, other studies did not show the increase in mast cells in non-allergic patients (1183).
- Perennial allergic rhinitis is characterised by a selective increase in CD4$^+$ memory T-cells (774, 777), as well as in CD3$^+$4$^-$8$^-$ double-negative T-cells, B-cells and γ/δT-cells in the nasal mucosa (774). The increase in CD4$^+$ memory T-cells in the allergic nasal epithelium may have critical implications in the pathogenesis of perennial allergic rhinitis.

4-5-4-2-2- Epithelial cells
- The importance of epithelial cells in allergic rhinitis has often been discussed but studies on the integrity of the nasal epithelium and the thickness of the basement membrane in patients with perennial rhinitis have not demonstrated any changes which are significantly different from control subjects (1184).
- Goblet cell numbers do not appear to be significantly different in perennial rhinitis subjects when compared to control subjects (653).

4-5-4-2-3- Pro-inflammatory mediators
- No increase in histamine release was demonstrated (1185).
- Eosinophil-derived mediators were recovered from nasal lavages of patients with perennial rhinitis (759).
- CysLTs are also released (759).
- Myeloperoxidase is released by activated neutrophils and increased levels of this mediator have been found in the nasal secretions of many patients suffering from allergic and non-allergic rhinitis (759).

4-5-4-2-4- Cytokines
- An imbalance in local T-cell cytokine production in favour of enhanced IL-5 and reduced IL-2 expression is observed in the nasal mucosa of patients with perennial allergic rhinitis (777).
- IL-5 is increased in nasal lavages carried out in patients with house dust mite-induced rhinitis, and the levels of this cytokine are decreased by intranasal glucocorticosteroids (1186).
- An increase in expression of IL-4 and IL-5 mRNA in the nasal mucosa of patients with perennial allergic rhinitis is observed during natural allergen exposure (986).
- IL-13 gene expression was detected in the epithelial compartment of the nasal mucosa of most patients with allergic perennial rhinitis but was undetected in normal volunteers and non-allergic patients with perennial rhinitis (776). ICAM-1 expression is significantly increased in the epithelium of patients with perennial rhinitis (1187).
- The immunolocalisation of cytokines in the nasal mucosa of patients with perennial rhinitis showed that both mast cells (988) and T-cells (775) were able to release IL-5. However, the precise importance of these two cell populations is still unclear.

4-5-4-2-5- Adhesion molecules
A few studies have been performed to investigate the origin of cells present in the inflammatory infiltrate. It has been observed that the expression of adhesion molecules is increased on the vascular endothelium of biopsies from patients with chronic rhinitis (843, 1188). In the study of Saito *et al.*, the increased expression of ICAM-1 in the mucosa was associated with an infiltration of activated lymphocytes. Other pro-inflammatory mediators may be involved but further experiments are required for their characterisation (1189).

4-6- ASPIRIN INDUCED RHINITIS

Inflammatory cell populations and cytokine mRNA expression were studied in the nasal mucosa of aspirin-sensitive rhinitis subjects (1190). In comparison to normal subjects, there was an increase in eosinophils, mast cells and activated T-cells. Marked increases were observed in the numbers of IL-5 mRNA$^+$ cells in aspirin-sensitive patients, whereas lower numbers of IL-4 mRNA$^+$ cells were observed. No differences were observed for either IL-2 or IFN-γ. The predominance of macrophages and the disproportionate increase in IL-5 compared to IL-4 mRNA expression suggests that factors other than "allergic" mechanisms may be important in this disease. A similar increase in IL-5 and over expression of LTC$_4$ synthase was reported in the bronchi of patients with aspirin-induced asthma (919, 920).

Activated eosinophils can be detected in nasal polyps of aspirin-induced asthmatics (1191-1193).

4-7- NASAL HYPERREACTIVITY

Non-specific nasal hyperreactivity is an important feature of allergic and non-allergic rhinitis (1194). It can be defined as an increased nasal response to a normal stimulus resulting in sneezing, nasal congestion and secretion, either as a single symptom or in various combinations.

This phenomenon can be observed after nasal stimulation (1195) such as:
- heating of the nasal mucosa (1196),
- challenge of the nose with histamine (1197-1201) or methacholine (1202). Although histamine and methacholine are the most widely used non-specific provocation tests (871, 1194, 1198, 1199), they are not validated in patients with non-allergic, non-infectious rhinitis.
- cold air. In patients with non-allergic, non-infectious rhinitis, intranasal cold dry air results in an increased mucus production and nasal blockage in a dose-dependent manner. It has proved to be a reliable method for the measurement of non-specific nasal hyperreactivity in these patients (1203).
- acrolein (1204),
- capsaicin (950),
- strong odours (1205),
- distilled water (1206).

Nasal hyperreactivity can also occur after non-nasal stimulation like for example:
- change of posture (1207),
- change in body temperature (1195),
- exercise (1208),
- consumption of hot drinks (soup) (1209).

Several hypotheses have been proposed to explain the mechanisms of nasal hyperreactivity in allergic and non-allergic rhinitis (675). They include:
- damage to the epithelial barrier,
- increased sensitivity of irritant receptors in the mucosa (1210, 1211),
- change in nerve transmission in periphery or in CNS (1212),
- release of pro-inflammatory mediators (1213),
- changes in receptor sensitivity of target cells or metabolism
- and/or influx of inflammatory cells (1214). The late-phase reaction following allergen challenge may be involved in the development or aggravation of nasal non-specific hyperreactivity (871, 1213, 1215, 1216).

4-8- NON-SPECIFIC TRIGGERS

Patients suffering from allergic rhinitis are variably exposed to diverse inciters, which modulate inflammation (Figure 15).
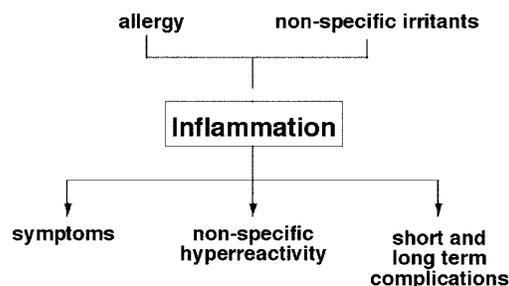
FIGURE 15: Inflammation in allergic rhinitis.

In normal subjects and patients with allergic rhinitis, indoor and outdoor pollutants induce symptoms of rhinitis (see chapters 2-1-3-7 and 3-2).

Tobacco smoking or passive smoking can, in some patients, induce a nasal reaction interfering with allergens and thereby participating in the symptomatology of rhinitis (1217) (see chapter 3-2).

Viral infections are known to induce the activation of various cell types including nasal epithelial cells (1218) and the release of various cytokines (972, 1219, 1220).

Cold air can induce an inflammatory response with the activation of mast cells (1221, 1222) and the occurrence of a late-phase reaction (1223).

5- Non-infectious, non-allergic rhinitis

Stricto sensu "rhinitis" means inflammation of the nasal mucous membrane. However, markers of inflammation are not examined in daily clinical work. Therefore, the term rhinitis is used for a disease of the nasal mucosa, which results in nasal itching, sneezing, rhinorrhea and nasal blockage.

The disease is "non-allergic" when allergy has not been proven by proper allergy examination (history, skin prick testing, measurement of serum specific IgE antibodies).

Rhinitis is called "non-infectious" when the nasal discharge is clear and watery, and not purulent. The detection of micro organisms (viruses, bacteria, fungi) is not used in clinical work and therefore it can not form a basis for the diagnosis.

"Non-allergic, non-infectious rhinitis" does not usually have a well-defined season and the disease is often called "perennial non-allergic rhinitis", although symptoms tend to be worst in the cold winter months. Formerly, the term "vasomotor rhinitis" was often used, but this implies that the underlying cause is a vascular and/or neurological dysfunction of the mucosa, and there are no sound data to support this notion. Therefore, the term "idiopathic rhinitis" is more correct for the disease of unknown aetiology.

5-1- PREVALENCE AND NATURAL HISTORY

It is estimated that 2-4% of the general population suffers from a chronic nasal disease with daily symptoms and a need for medication. The figures are uncertain because of the vague definition of the disease and the lack of studies.

Surprisingly, the U.S. National Health Interview Survey data of 1983-1985 placed "chronic sinusitis" (a term often used for nasal symptoms) first in rank among the most common chronic conditions, with a prevalence of 13.5%.

In contrast to allergic rhinitis, which usually makes its first appearance in children and youngsters, non-allergic, non-infectious rhinitis usually develops in middle-aged persons. Perhaps ageing-related changes of the nasal mucosa predispose for the development of this condition, isolated rhinorrhea in particular.

The course of the disease is capricious, but severe, persistent symptoms usually predict a long course. Thus, perennial non-allergic rhinitis does not have the same favourable natural course as seasonal allergic rhinitis.

5-2- PATHOPHYSIOLOGY

Non-allergic, non-infectious rhinitis is highly heterogeneous and mechanisms are often unclear.

5-2-1- Drug response and mediators

Our knowledge in this area is poor. The response to H1-antihistamines in patients who have sneezing as a predominant symptom points at histamine as an impor-

tant mediator, but H1-antihistamines are generally ineffective in most patients. Some effects of leukotriene receptor antagonists in aspirin-sensitive patients indicate that leukotrienes are of some significance in this subgroup. A response to glucocorticosteroids can be taken as proof of an inflammatory pathogenesis, but a subgroup of patients have neither signs of inflammation nor response to glucocorticosteroids. In patients with a non-eosinophilic disease, studies on nasal secretions and mucosal biopsies have failed to identify any differences between these patients and healthy controls, with respect to cellular or biochemical markers of inflammation. It appears therefore that in these individuals, the disorder is not of an inflammatory nature. If so, nasal hyperresponsiveness may have a totally different pathophysiological basis from that seen in chronic inflammatory disorders.

5-2-2- Nasal hyperreactivity

Nasal hyperreactivity is common in non-allergic, non-infectious rhinitis.

5-3- SYMPTOMS

A specific precipitating factor cannot be identified, but symptoms are often precipitated by non-specific stimuli such as smoke, strong odours, perfumes, alcoholic beverages, cold air and hot spicy food.

The symptoms are usually the same as in allergic rhinitis, but eye symptoms are less frequent and nasal blockage more prominent. From a clinical point of view, it can be practical to make a distinction between diseases based on the prominent nasal symptom, because this relates to response to pharmacotherapy.

5-3-1- Sneezers

The patient has the same symptoms as a patient with perennial allergic rhinitis and the symptoms usually respond to treatment with antihistamines and glucocorticosteroids.

5-3-2- Runners

Some patients, especially elderly gentlemen, suffer exclusively from watery rhinorrhea. They do not respond to treatment with antihistamines and glucocorticosteroids but they can be helped by an intranasal cholinoceptor antagonist (ipratropium bromide).

5-3-3- Blockers

These patients are made to feel uncomfortable by nasal stuffiness or congestion with reduced or abolished nasal breathing. The nasal mucosa is swollen due to vasodilatation, edema formation and/or hyperplasia. Anatomic abnormalities can contribute to the symptoms. These patients do not respond to H1-antihistamines but may or may not respond to glucocorticosteroids or to vasocon-

strictors, which initially may be most effective when given systemically for some days before intranasal treatment.

5-4- CAUSES AND CLASSIFICATION

The aetiology is unknown in most cases and the disease is therefore idiopathic. However, it is useful to analyse whether there can be causal or contributing factors.

5-4-1- Physiological symptoms

The nose serves as an efficient humidifier, heater and filter for inhaled air thereby protecting the lower airways. The nasal mucosa is constantly exposed to unconditioned and occasionally polluted inhaled air causing irritation, sneezing, reflex-mediated hypersecretion and nasal blockage. When the nasal mucosa is exposed to environmental challenges (cold air, polluted air), symptoms are a natural response. All subjects contract rhinorrhea from exposure to cold air and from eating hot spicy soup.

5-4-2- Aetiology of non-allergic, non-infectious rhinitis

There are a number of causes of non-allergic, non-infectious rhinitis (see chapter 1-6).

5-4-3- Inappropriate awareness of normal nasal symptoms

Occasional sneezing and rhinorrhea in the morning and upon exposure to cold and polluted air is considered to be a normal nasal response. Some persons consider even slight nasal symptoms to be abnormal and seek medical advice for that reason. Inquiry about the number of daily sneezes and nose blowings and about the hours with daily symptoms may help in making a distinction between a normal physiological response and a disease.

5-4-4- Anatomical abnormalities

Mild anatomical abnormalities are frequent. When nasal symptoms occur without a recent nasal trauma, an anatomical abnormality is usually not the aetiological factor, but it may contribute to the symptoms of a disease of the mucous membrane. Septal deviation is a well-known cause of nasal obstruction; it is often bilateral (S-shaped deviation). A septal deviation with a spur, resulting in contact between septal and lateral mucous membranes ('kissing mucous membranes'), causes irritation and induces reflexes and rhinitis symptoms. Other anatomical abnor-

malities, such as an air-filled middle turbinate, concha bullosa, can also cause nasal symptoms, especially blockage.

5-5- DIAGNOSIS

Although a diagnosis is based on the patient's symptoms, a diagnostic work up is required to differentiate this syndrome from perennial allergic rhinitis and to exclude differential diagnoses. Testing involves allergy testing, nasal endoscopy, preferably a nasal smear for eosinophils and, in selected cases, a CT-scan of nose and paranasal sinuses.

In the NARES syndrome, eosinophils can be found in the nasal mucosa and secretions (1224, 1225). It appears that nasal biopsy is superior to nasal smear for finding eosinophils (1226).

5-6- DIFFERENTIAL DIAGNOSIS

Other conditions may mimic some of the symptoms of non-allergic, non-infectious rhinitis.

Careful examination of a patient with non-allergic, non-infectious rhinitis is indicated in order to make the correct diagnosis and to exclude differential diagnoses and concurrent structural abnormalities.

Congenital choanal atresia can be a cause of unilateral obstruction, with discharge in an infant, but a foreign body is much more common at that age. Enlarged adenoids are a frequent cause of mouth breathing.

Unilateral symptoms, bleeding and pain are important warning signals of malignancy. Malignant tumours in the nose, paranasal sinuses or nasopharynx and Wegener's granulomatosis usually start with uncharacteristic symptoms. A first diagnosis of perennial rhinitis is not uncommon in these cases.

5-7- CONCLUSIONS

When allergy and infections have been excluded as the cause of rhinitis, a number of poorly defined nasal conditions of unknown aetiology and pathophysiology must be included in the differential diagnosis. These conditions are generally difficult to treat with the exception of aspirin-induced rhinitis, nasal polyposis and other rhinitis forms, which may respond to glucocorticosteroids. A diagnostic work up is required to differentiate this condition from perennial allergic rhinitis.

6- Co-morbidity and complications

Allergic inflammation does not necessarily limit itself to the nasal airway. Multiple co-morbidities have been associated with rhinitis. These include asthma, sinusitis and conjunctivitis.

6-1- ASTHMA

6-1-1- Introduction

The nasal and bronchial mucosa present similarities and most patients with asthma also have rhinitis (25, 28). Dysfunction of the upper and lower airways frequently coexists. Epidemiological, pathophysiological and clinical studies have strongly suggested a relationship between rhinitis and asthma. These data have lead to the concept that upper and lower airways may be considered as a unique entity influenced by a common, evolving inflammatory process, which may be sustained and amplified by interconnected mechanisms. Allergic rhinitis is correlated to, and constitutes a risk factor for, the occurrence of asthma (145). It has been proposed that the prevention or early treatment of allergic rhinitis may help to prevent the occurrence of asthma or the severity of bronchial symptoms. Therefore, when considering a diagnosis of rhinitis or asthma, an evaluation of both the lower and upper airways should be made. However, although the nasal and bronchial mucosa present similarities, there are also differences between rhinitis and asthma.

6-1-2- Epidemiology

6-1-2-1- Association between asthma and rhinitis

Epidemiological studies have consistently shown that asthma and rhinitis often co-exist in the same patients (6, 32, 145, 175, 187, 1227). In a study in which a poll base of 20,000 households were screened for symptoms of rhinitis, 16,786 responded (109). The point prevalence of perennial rhinitis (patients with at least 6 months of continuous symptoms) was 4.1% and the association of perennial rhinitis with a history of asthma was highly significant (13.4% in those with perennial rhinitis vs. 3.8% in those without; odds ratio 3.26). Asthma appears to be more often associated with perennial rhinitis than with seasonal rhinitis (30).

The majority of patients with asthma present seasonal or perennial allergic rhinitis symptoms (175). Rhinitis usually occurs in over 75% of patients with allergic asthma and in over 80% of patients with non-allergic asthma (6, 30). However, in many instances, symptoms predominate in one of the organs and may be hidden in the other. Data from Northern Sweden also demonstrate the association between asthma and allergic rhinitis. Results show that an adult with a family history of asthma or rhinitis has a risk of three to four-fold for developing asthma and of two to six-fold for developing rhinitis over an adult without a family history (95).

The age of onset of atopy may be an important confounding factor for the development of asthma and rhinitis or rhinitis alone. In an Australian study, it was found that atopy acquired before the age of 6 years is an important predictive factor for asthma continuing into late childhood whereas atopy acquired later was only strongly associated with seasonal allergic rhinitis (1228). Several surveys in children and adults have shown significantly lower prevalences of asthma and allergic diseases in Eastern Europe than in western countries. In former East Germany, tremendous changes towards western lifestyle have occurred since unification (189). In 1995-1996, 2,334 school children in Leipzig participated in a cross-sectional study that used the same methods as a previous survey done shortly after the fall of communism in 1991-1992 (218, 227). The prevalence of seasonal allergic rhinitis and atopic sensitisation increased significantly between 1991-1992 and 1995-1996. However, there was no significant change in the prevalence of asthma or bronchial hyperresponsiveness (189). These findings suggest important differences in the development of atopic disorders. Factors operating very early in life may be particularly important for the acquisition of childhood asthma and rhinitis, whereas the development of atopic sensitisation and seasonal allergic rhinitis may also be affected by environmental factors occurring beyond infancy.

6-1-2-2- Association between rhinitis and non-specific bronchial hyperreactivity

Many patients with allergic rhinitis have increased bronchial sensitivity to methacholine or histamine (1229, 1230).

Patients with seasonal allergic rhinitis develop seasonal bronchoconstriction unassociated with clinical bronchospasm (1231). Moreover, seasonal increases of carbachol, histamine or methacholine bronchial responsiveness and exercise-induced bronchoconstriction were commonly observed in patients allergic to grass or birch pollen (1232-1234). The reversal of bronchial hyperreactivity by intra nasal sodium cromoglycate (1235), nedocromil sodium (1236) or glucocorticosteroids (1237, 1238) suggests that bronchial inflammation is associated with nasal inflammation (1239).

In subjects with perennial allergic rhinitis, bronchial hyperreactivity appears to be more common and more severe than in patients with seasonal allergic rhinitis (1240, 1241). In an epidemiological study of the general population, it was confirmed that bronchial hyperreactivity was increased mainly in patients with perennial and seasonal rhinitis in comparison to those with seasonal rhinitis alone or healthy subjects (176).

In the NARES syndrome, 46% of patients with NARES but without histories of respiratory symptoms had a measurable bronchial hyperresponsiveness (85). In the same study, the presence of bronchial hyperrespon-

siveness was associated with an increased number of eosinophils in induced sputum but not with the inflammatory process in the nose.

Responsiveness of the bronchial mucosa in asthma patients is approximately 50 times that of normal (non-allergic or non-asthmatic) subjects, whereas that of the nasal mucosa in allergic rhinitis is only 2-8 times that of control subjects (1242, 1243). The inflammatory process involved in hyperresponsiveness is similar in both conditions, involving an increased infiltration of eosinophils and subsequent increased mediator release. The greater degree of bronchial hyperresponsiveness seen in asthma may be a consequence of the anatomical differences between the upper versus the lower airways.

6-1-3- The same triggers can cause rhinitis and asthma

Among the causative agents inducing asthma and rhinitis, some (e.g. allergens (6) and aspirin (1244, 1245)) are well known to affect both the nose and the bronchi (1246, 1247).

In the general population, allergy to house dust mite or animal dander is a risk factor for asthma and rhinitis whereas pollen allergy is a risk factor for rhinitis (1248-1251).

In aspirin sensitivity, after aspirin challenge, CysLTs are released into both nasal and bronchial secretions (148).

An interesting model for studying the relationship between rhinitis and asthma has been offered by occupational sensitisation. Subjects with occupational asthma may also report symptoms of rhinoconjunctivitis. In the case of low molecular weight agents, rhinitis is less pronounced. Rhinitis more often appears before asthma in the case of high molecular weight agents (561-563). In allergy to small mammals, rhinitis may be very severe but usually appears before asthma (1252). This highlights the importance of the cessation of allergen exposure in occupational allergic rhinitis in order to prevent asthma.

Thus, there is strong epidemiological evidence showing a close link between rhinitis and asthma, and suggesting a common genetic background for both these diseases. Some genes may be restricted to nasal symptoms. Some HLA-DR haplotypes distinguish subjects with asthma from those with rhinitis only in ragweed pollen allergy (301).

6-1-4- Natural history of the diseases

Studies have also identified a temporal relationship between the onset of rhinitis and asthma, with rhinitis frequently preceding the development of asthma. Allergic rhinitis developing in the first years of life is an early manifestation of an atopic predisposition, which may be triggered by early environmental exposures (145). Allergic rhinitis and positive allergy skin tests are significant risk factors for developing new asthma (275). A 10-year prognosis study for childhood allergic rhinitis was carried out and it was found that asthma or wheezing had developed in 19% of cases and was more common among those with perennial allergic rhinitis than among those with seasonal allergic rhinitis (276). Individuals with either of these diagnoses are about three times more likely to develop asthma than negative controls (275). However, upper and lower airway symptoms can also develop simultaneously in about 25 % of patients.

In aspirin-induced asthma, the clinical syndrome develops according to a pattern, characterised by a definite sequence of symptoms (31). Rhinitis is the first symptom of the disease and is usually related to a flu-like infection in the majority of patients. It appears on average at the age of 30, is characterised by discharge from the nose, often watery, nasal blockage, oral sneezing and less frequently by pain in paranasal sinuses. Rhinitis is perennial, difficult to treat and leads to a loss of smell in around 50% of the patients. In an average patient, the first symptoms of asthma appear two years after the onset of rhinitis. Intolerance to aspirin and other NSAID as well as nasal polyps become evident years later. In the majority of patients, aspirin intolerance, once developed, remains for the rest of their lives. Repeated aspirin challenges are, therefore, positive though some variability in intensity and spectrum of symptoms occurs. However, in an occasional patient, a positive aspirin challenge may became negative after a period of several years.

6-1-5- The mucosa of the airways

In normal subjects, the structure of the airway mucosa presents similarities between the nose and the bronchi. Both nasal and bronchial mucosa are characterised by a pseudostratified epithelium with columnar, ciliated cells resting on a basement membrane. Underneath the epithelium, in the submucosa, vessels and mucous glands are present with structural cells (fibroblasts), some inflammatory cells (essentially monocytic cells, lymphocytes and mast cells) (1253) and nerves.

There are also differences between the nose and the bronchi. In the nose, there is a large supply of subepithelial capillary, arterial system and venous cavernous sinusoids. The high degree of vascularisation is a key feature of the nasal mucosa and changes in the vasculature may lead to severe nasal obstruction (646)**.** On the other hand, smooth muscle is present from the trachea to the bronchioles explaining bronchoconstriction in asthma.

The nerves present in nasal mucosa include adrenergic and cholinergic nerves and nerves of the NANC (non-adrenergic non-cholinergic system) (675, 690, 966). Neurotransmitters and neuropeptides released within the autonomic nervous system exert homeostatic control of nasal secretion (by plasma extravasation) as well as of mucous and serous cell secretion. Sensory neuropeptides are present in human bronchial nerves beneath and within the epithelium, around blood vessels and submucosal glands and within the bronchial smooth muscle layer (1254, 1255). Cholinergic nerves are the predominant bronchoconstrictor pathway. On the other hand, there is no direct functional adrenergic supply to human airways.

The role of the NANC system is still poorly understood in asthma (1256) although it has been proposed that an imbalance between sensory neuropeptides may play a role in the mechanisms of asthma (676, 1257). Moreover, adrenergic control of the nose and bronchi differ since α-adrenergic agonists are effective nasal vasoconstrictors in rhinitis whereas ß2-adrenergic agonists are effective bronchodilators in asthma.

Nitric oxide (NO) is an intercellular transmitter, both in the central and peripheral nervous system. In addition to nerve cells, NO is also produced in the epithelial cells of various tissues and in the endothelium. NO is produced in large amounts in the noses of normal individuals. NO is an important mediator of the effector arm of the naso-nasal reflex that increases vascular permeability but is not involved in the sensory nerve afferent pathway (1258). NO appears to play a key role as a vasodilator, neurotransmitter and inflammatory mediator in the bronchi and is produced in increased amounts in asthma (1259). In healthy subjects, exhaled NO originates mainly from the upper airways with only a minor contribution from the lower airways (1260).

6-1-6- Relationships and differences between rhinitis and asthma

Recent progress achieved in the cellular and molecular biology of airway diseases has clearly shown that inflammation plays a critical role in the pathogenesis of asthma and rhinitis. A growing number of studies show that the inflammation of nasal and bronchial mucosa is sustained by a similar inflammatory infiltrate, which is represented by eosinophils, mast cells, T-lymphocytes and cells of the monocytic lineage (661, 1261-1263). The same pro-inflammatory mediators (histamine, CysLT), Th2 cytokines (IL-4, IL-5, IL-13 and GM-CSF) (661, 703, 965, 988, 1264), chemokines (RANTES and eotaxin (1003, 1265, 1266)) and adhesion molecules (814, 816, 818) appear to be involved in the nasal and bronchial inflammation of patients with rhinitis and asthma. However, differences may exist in the extent of the inflammatory indices, eosinophilic inflammation and epithelial shedding being more pronounced in the bronchi than in the nose of the same patients suffering from asthma and rhinitis (1184). Inflammatory cells assessed by sputum induction are present not only in the airways of patients with asthma but also in the airways of patients with seasonal allergic rhinitis, outside of season (1267).

Atopic patients without asthma present some degree of bronchial inflammation, in particular a few activated eosinophils (1087). An irregularly distributed subepithelial fibrosis of the bronchi is observed in subjects with allergic rhinitis (1268). It results from the deposition of type I and III collagens and fibronectin and suggests the presence of an active structural remodelling in the lower airways of allergic rhinitic subjects, similar in nature to that seen in asthma, although less marked. After bronchial segmental allergen challenge in non-asthmatic rhinitics, an early and late-phase reaction can be observed (1269) suggesting that the bronchial mucosa of

rhinitics is capable of being triggered by allergens. An increase in airways inflammation was found after segmental challenge in the same patients (1269).

It is well established that bronchial mucosal inflammation causes epithelium shedding, increased thickness of the reticular layer of the basement membrane and hypertrophy of smooth muscle cells (1270). On the other hand, in perennial rhinitis, epithelium is not usually shed (1167, 1226). In a biopsy study carried out in the nose and bronchi of the same asthmatic patients with rhinitis, it was shown that epithelium was not generally shed in the nose whereas shedding was observed in the bronchi (1184).

Airway remodelling exists microscopically in most if not all asthmatics (862) including bronchial wall thickening, deposition of collagen and proteins on the basement membrane, increase in smooth muscle mass and the release of fibrogenic growth factors. In allergic rhinitis, such a remodelling process is still under discussion and requires further studies. In a biopsy study carried out in the nose and bronchi of the same asthmatic patients with rhinitis, it was observed that the size of the reticular basement membrane was close to that in the nasal biopsies of normal subjects. (1184).

The early and late bronchial responses were compared in 123 patients with allergic rhinitis and mild asthma. In this study, the presence or the absence of asthma symptoms in allergic subjects was related to a quantitatively different airway responsiveness to allergen (1271).

Nasal and bronchial abnormalities observed in asthmatics therefore appear to present distinct entities, but inter-related conditions are not yet excluded. Comparative studies showing whether the release of inflammatory cytokines, chemokines and inflammatory mediators in the nose and the bronchi causes similar or different structural alterations of the mucosa remain to be fully evaluated (Figure 16).

6-1-7- Physiological relationships between rhinitis and asthma

The inflammatory reaction of the nose can cause a worsening of asthma by several different mechanisms (26). Although a nasal challenge with allergen does not induce airflow limitation of the lower airways, it may cause non-specific bronchial responsiveness (1272, 1273).

Several mechanisms have been proposed to link uncontrolled allergic rhinitis and the occurrence or worsening of asthma (1274):
- Nasal challenge induces the release of mediators, which can in turn cause a bronchoconstriction.
- The post-nasal mucous drip may induce contraction of the bronchial smooth muscle or inflammation of the lower airways. However, this mechanism may not be relevant in conscious human beings.
- Mouth breathing secondary to nasal obstruction is a common feature in asthmatics and may play a role in the severity of asthma.
- A putative reflex between the nose and the lungs has been proposed (1275) but has to be confirmed.
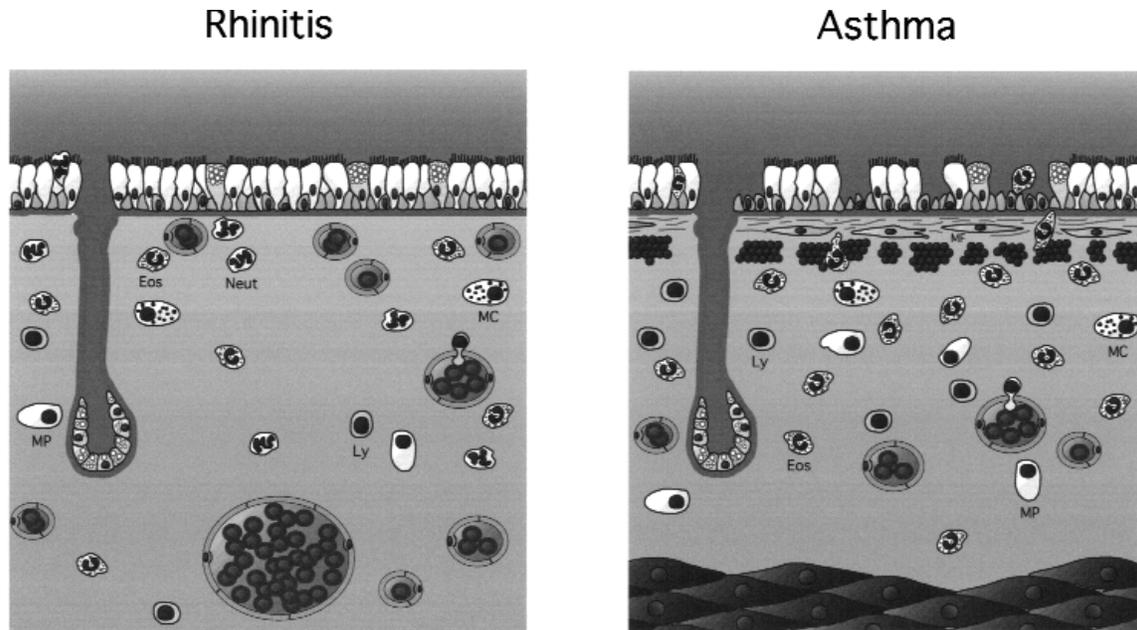
Rhinitis   Asthma

F. LALIBERTÉ

FIGURE 16: Similarities and differences between asthma and rhinitis. In rhinitis, there are numerous blood vessels explaining nasal obstruction. In asthma, there is smooth muscle explaining bronchial obstruction. *Eos*, Eosinophils; *Neut*, neutrophils; *MC*, mast cells; *Ly*, lymphocytes; *MP*, macrophages.

There are also close links between nasal infection by viruses and asthma exacerbations (1276). Rhinoviruses have been widely identified in nasal secretions during asthma exacerbations in both children and adults (1277, 1278). Nasal virus infections increase bronchial hyperreactivity in asthmatics (1279, 1280) and bronchial inflammation including eosinophilia (1281-1283).

6-1-8- Clinical relationships between rhinitis and asthma

Few studies have examined the chronology of symptoms during the pollen season. Usually, nasal symptoms occur early in the pollen season and reach a maximum with peak pollination or just after it. On the other hand, bronchial symptoms usually begin after the onset of the season, peak later than the peak pollen counts and persist for some time after (1284). In some patients, non-specific bronchial hyperreactivity may be prolonged for weeks (see chapter 6-1-2).

6-1-9- Costs

Asthma is a common and costly condition. Concomitant asthma and allergic rhinitis have been shown to increase the medication costs for people with asthma. A study has compared medical care costs of those with and without concomitant allergic rhinitis. Yearly medical care charges were on average 46% higher for those with asthma and concomitant allergic rhinitis than for persons with asthma alone, allowing for age and gender (32).

6-1-10- Conclusion

Upper and lower airways may be considered as a unique entity supporting the concept of a "united airways", but there are also differences which should be highlighted. Allergic rhinitis is correlated to, and constitutes a risk factor for, the occurrence or severity of asthma. The treatment of asthma and rhinitis presents similarities since the same drugs are effective in rhinitis and asthma (e.g. glucocorticosteroids) and differences since different drugs are effective in upper and lower airways (e.g. α- and ß-adrenergic agonists respectively). Moreover, some drugs are more effective in rhinitis than in asthma (e.g. H1-antihistamines). Finally, an optimal management of rhinitis may partly improve coexisting asthma.

6-2- CONJUNCTIVITIS

6-2-1- Prevalence of the association

Symptoms of "red eye" occur in a large proportion of patients with rhinitis. However, the prevalence of the association between rhinitis and conjunctivitis cannot easily be defined. Conjunctival symptoms are often considered to be of minor importance (1285) and possibly not spontaneously reported by patients with rhinitis and/or asthma in medical interviews or in questionnaire-based studies such as the ISAAC and the ECRHS (107, 150). Moreover, several signs of involvement of the external eye (Table 7) can be

TABLE 7: Symptoms and signs of allergic eye diseases

Symptoms	Signs
Seasonal and perennial allergic conjunctivitis	
Tearing	Mild hyperaemia
Burning	Mild edema
Mild itching	Mild papillary reaction (often absent)
Vernal keratoconjunctivitis	
Intense itching	Cobblestone papillae
	Intense hyperaemia
Tearing	Mucus discharge
Photophobia	Milky conjunctiva
Sensation of foreign body	Punctuate keratopathy
	Trantas dots
	Togby's ulcer
Atopic keratoconjunctivitis	
Itching	Hyperaemia
Burning	Eczematous lesions of eyelids
Tearing	Corneal ulcers
	Cataracts
	Pannus
	Keratoconus
	Retinal detachment
Contact lens conjunctivitis	
Itching	Giant papillae
Pain	Excessive mucus production
Sensation of foreign body	Corneal lesions
Lens intolerance	

documented only with an accurate eye examination, which was not part of the protocol in most studies of rhinitis patients. Accordingly, the association between rhinitis and conjunctivitis is underestimated in epidemiological studies.

A second even more relevant reason which makes several clinical studies on the prevalence of conjunctivitis in rhinitis patients of limited value is represented by the heterogeneity of the red eye syndrome, usually referred to as "conjunctivitis". In fact, a red eye can be caused by allergic and non-allergic agents. Moreover, allergic eye diseases represent a heterogeneous entity including different forms of conjunctivitis with different signs, symptoms, pathophysiology, degree of severity and response to treatment (1286-1288).

Allergic conjunctivitis is usually classified as acute, seasonal, perennial, vernal or atopic conjunctivitis. An immunological mechanism has also been postulated for conjunctival symptoms in contact lens wearers (Table 7).
- Acute allergic conjunctivitis (AAC) is an acute hypersensitivity reaction with hyperaemia and chemosis accompanied by intense tearing, itching and burning of the eye. This is caused by an accidental exposure to several substances such as gas and liquid "irritants" or animal danders.
- Seasonal allergic conjunctivitis (SAC) is the typical conjunctival reaction in seasonal allergic rhinitis rhinoconjunctivitis or following exposure to seasonal pollen allergens in sensitised subjects.
- Perennial allergic conjunctivitis (PAC) is a less intense but continuous conjunctival reaction related to exposure to perennial allergens such as house dust mites.

- Vernal conjunctivitis (VKC) is a severe bilateral eye condition in children, with frequent involvement of the cornea (vernal keratoconjunctivitis). It is characterised by conjunctival hypertrophy and mucus excess.
- Atopic conjunctivitis (AKC) is a keratoconjunctivitis associated with eczematous lesions of the lids and skin.
- Contact lens conjunctivitis (CLC) is a giant-papillary conjunctivitis observed in hard and soft contact lens wearers.

From surveys on a large number of patients with "allergic conjunctivitis" (1285), the prevalence of the association between rhinitis and "conjunctivitis" appears to be different depending on the type of allergic conjunctivitis. In 239 pollinosis patients studied in Italy, eye symptoms were almost always (95.2% of cases) associated with rhinitis or with asthma (28.7% of cases). Only 1.2% of patients had conjunctivitis and asthma but not rhinitis. The allergen responsible for sensitisation and symptoms was in these cases a perennial pollen (*Parietaria*).

The prevalence of rhinitis in patients with atopic and contact lens conjunctivitis is similar in allergic and non-allergic patients (1285).

It seems therefore that the association between rhinitis and conjunctivitis is a typical feature of patients with seasonal pollen allergy. More interestingly, it can also be speculated that the pathophysiology of the allergic patient is heterogeneous and that the type of disease association in a patient with rhinitis might help in better defining his/her clinical and pathophysiological phenotype.

6-2-2- Mechanisms

Two major mechanisms can be invoked for explaining the association between rhinitis and conjunctivitis:

• Naso-conjunctival reflexes, certainly possible from an anatomical point of view, seem to influence conjunctival symptoms in patients with rhinitis (and vice-versa). In fact, it is well appreciated that specific and non-specific challenge to the nose or to the eye is followed, respectively, by eye and nose symptoms associated with those at the level of the challenged organ. It is also well appreciated that in many forms of rhinoconjunctivitis, treatment of the nose also improves eye symptoms.

• A common pathophysiological background with contemporary involvement of the nose and the eye was suggested after the first description of hay fever. It was clearly documented for seasonal allergic rhinoconjunctivitis with the description of Type I hypersensitivity reactions. In IgE-mediated seasonal and perennial allergic conjunctivitis, mechanisms similar to those involved in seasonal and perennial allergic rhinitis do explain the pathophysiology of the disease and symptoms (1289-1291). Late-phase inflammatory events also occur in the eye after allergen challenge (1292). However, in normal conditions, they seem to play an important role only in subjects with a high degree of sensitisation and/or in those exposed to high allergen loads.

In vernal keratoconjunctivitis and allergic keratoconjunctivitis, there are elevated levels of total IgE in serum and a massive mast cell (1293) and eosinophil infiltration (1294-1296) of the conjunctiva. This is not necessarily associated with the detection of specific IgE antibodies. Accordingly, it has been suggested that a Th2-type allergic inflammation may be the major pathophysiological abnormality underlying symptoms and poor response to conventional anti-allergic treatments (1297). Corneal lesions and proliferative phenomena—never observed in seasonal and perennial allergic conjunctivitis—are present in vernal keratoconjunctivitis and allergic keratoconjunctivitis. Non-allergic rhinitis with eosinophilia is certainly more similar to vernal keratoconjunctivitis and allergic keratoconjunctivitis than to rhinoconjunctivitis.

Non-specific conjunctival hyperreactivity has been described in the eye after histamine (1298) and hyperosmolar challenge (1299). It is conceivable that, in analogy with vasomotor rhinitis, non-specific hyperreactivity represents a distinct pathophysiological abnormality, dependent on undefined tissue and neural mechanisms. This could possibly explain conjunctival symptoms in the absence of IgE antibodies and allergic inflammation, as in the case of some forms of acute and contact lens conjunctivitis.

6-2-3- Clinical aspects

• Eye examination should be part of the clinical assessment of allergic rhinitis.

• Conjunctival allergen provocation does not add relevant information to detect sensitisation or eye involvement in rhinitis patients (1300). However, it may be interesting to monitor interventions during clinical trials (1300-1308).

• Measurement of IgE and mediators in tears is mainly confined to research purposes.

• Conjunctival cytology may be important in categorising eye diseases.

• On the other hand, *in vivo* and *in vitro* tests for allergy diagnosis overlap between rhinitis and conjunctivitis. Interestingly enough, markers of eosinophilic inflammation—such as ECP or peripheral eosinophil cytofluorimetric profile—can be even more abnormal in some cases of allergic conjunctivitis than in cases of allergic rhinitis, in spite of the more limited extension of the involved mucosa (1309). Therefore, they should be considered as a marker of atopic status rather than as an index of the localisation and severity of target tissue involvement.

• Although some indirect benefits may result from topical treatment of rhinitis and conjunctivitis on the associated symptoms of the eye and nose respectively, the association between rhinitis and conjunctivitis should suggest the advantage of oral treatment which can benefit both diseases. In view of the severity of inflammation and corneal involvement, vernal keratoconjunctivitis or atopic conjunctivitis associated with rhinitis should be treated specifically.

6-3- SINUSITIS AND NASAL POLYPOSIS

6-3-1- Sinusitis

6-3-1-1- Relationship between allergy and sinusitis

The maxillary, anterior ethmoidal and frontal sinuses drain via the ostium of the maxillary sinuses and middle meatus, collectively known as the ostiomeatal complex. The posterior ethmoid drains in the upper meatus and the sphenoid in the spheno-ethmoidal recess. Swelling of the mucous membranes, whether due to allergy, infection or other causes, may obstruct the drainage and aeration of the sinuses and one might therefore expect allergy to increase the risk of developing acute and chronic sinusitis (1310, 1311).

Some studies suggested that rhinosinusitis is a common complication of allergic rhinitis (1312-1314). In one study, 43% of the cases of acute rhinosinusitis were seasonal, of which 25% were allergic (1315). Allergy was considered to be the cause of acute maxillary rhinosinusitis in 25% of young adults compared with 16.5% of healthy controls (1316). However, there is no evidence of change in ostial patency or of increase in the incidence of purulent rhinosinusitis during the pollen season (1317). This is present in similar proportions in patients with or without allergic rhinitis (1318).

Forty per cent of patients with chronic rhinosinusitis suffer from allergy, whereas in patients with bilateral maxillary rhinosinusitis, this increases to 80% (1317). Two studies (1319, 1320) however could find no significant difference on CT scans between allergic and non-allergic adults with chronic rhinosinusitis.

It has been suggested that allergens may enter the sinuses resulting in a similar allergic inflammation as in the nasal mucosa (1317). Experimentally, nasal instillation of allergens can produce mucosal oedema and sinus opacification (1321). However, using radio-labelled pollens, there is no evidence that allergens deposited in the nose can reach the sinus cavities (1322). Alternatively, it was proposed that allergens could reach the sinus mucosa through circulation after absorption through the skin, in the case of fungal allergens, or after absorption from food.

The pathology of sinusitis has been studied in recent years. Activated eosinophils are commonly found in biopsies taken from the sinuses of allergic and non-allergic patients (1323-1326). Other cells including mast cells, lymphocytes, macrophages and, to a lesser extent, neutrophils are increased, releasing pro-inflammatory mediators as well as cytokines and growth factors (1325, 1327). On the other hand, surprisingly, it was found that in patients suffering from perennial allergic rhinitis, ICAM-1 expression was low in the sinus mucosa when compared to the nasal mucosa (1187).

The analysis of the lavage fluid from patients with chronic rhinosinusitis reveals high concentrations of histamine, CysLT and PGD_2 in concentrations similar to those obtained after challenge with antigen in allergic rhinitis patients (1328). These high concentrations may indicate mast cell/basophil stimulation and contribute to the persistence of inflammation in chronic rhinosinusitis (1187).

In conclusion, although allergy may be expected to result in inflammation and swelling of the nasal mucosa, leading to obstruction of the sinuses and acting as a precursor for both acute and chronic rhinosinusitis, evidence is at present still inconclusive.

6-3-1-2- Relationship between asthma and sinusitis

For more than 70 years, the coexistence of asthma and paranasal rhinosinusitis has been noted in medical literature (1329-1331). In patients with chronic asthma, the associations of chronic rhinosinusitis with asthma and allergy appear to be restricted to the group with extensive disease (1332). Mucosal thickening in the nasal passages, sphenoidal, ethmoidal and frontal sinuses, but not the maxillary sinuses, is more common in patients with acute asthma than in control subjects (1333). Sinusitis may contribute to the severity of the bronchial symptoms (1334).

6-3-2- Nasal polyps

Polyps are smooth, grape-like structures, which arise from the inflamed mucosa lining the paranasal sinuses. These prolapse down into and may obstruct the nasal cavity. There are apparently two types of nasal polyps depending on the cells infiltrating the tissues. Nasal polyps occurring in association with cystic fibrosis may be neutrophilic in nature. However, in many other instances, such as polyps associated with asthma and particularly aspirin sensitive asthma (1335), infiltrating cells are eosinophils (1336-1338). Whilst the degree of cellular infiltration may vary, some patients with cystic fibrosis may also have allergic rhinitis and the distinction between neutrophilia and eosinophilia may not be so

clear-cut (1339, 1340). Differences in cell infiltration are related to the expression of adhesion molecules (845, 1341-1343) and reduced apoptosis (740).

6-3-2-1- Relationship between allergy and polyposis

For many years, an allergic aetiology has been presumed (1344) but never firmly demonstrated in nasal polyposis. The prevalence of nasal polyposis in allergic patients is rather low and usually under 5% (1345-1347). Wong and Dolovich (1348), in a series of 249 patients undergoing nasal polypectomy, found that 66% had at least one positive allergy skin prick test when tested with 14 inhalants and 5 food allergens. However, 74% had a positive skin test in a control group of patients undergoing non-polyp nasal surgery. It may be argued that:

- Skin tests may not identify all the allergens that could possibly play a role in nasal polyposis (1349).
- There may be a local production of IgE (1350, 1351). Perkins *et al.* however found no positive allergen-specific IgE by RAST in polyp fluid to any allergen not detected in serum, though in a smaller study with only 12 polyp patients, six had negative skin tests (1352).

Drake-Lee (1353) found no correlation between positive skin prick tests and the number of repeat polypectomies. Wong and Dolovich (1348), in a prospective study of 249 patients undergoing polypectomy, found no association between the number of polypectomies in patients with at least one positive allergy skin test. There was however an increased number of polypectomies in those with asthma and there was a positive association between the blood eosinophil count and the number of previous polypectomies.

6-3-2-2- Relationship between aspirin intolerance and polyposis

Aspirin intolerance is often observed in nasal polyposis (1354). Out of 500 patients registered at the European Network on Aspirin-Induced Asthma (AIANE), almost 80% suffered from the symptoms of rhinosinusitis and complained of nasal blockage accompanied by rhinorrhea (148). Loss of smell was present in 69% of these patients. Significant abnormalities in almost all paranasal sinuses were detected in 75% of the patients. Any combination of air-fluid levels, mucosal thickening or opacification were characteristic findings in one or more paranasal sinuses. Nasal polyps were diagnosed in 62% of AIANE patients, on average at the age of 33 years. The polyps had a tendency to recur and multiple polypectomies were common among AIANE patients (148).

6-3-2-3- Relationship between asthma and polyposis

Nasal polyposis is commonly found in association with lower tract respiratory disorders, such as asthma and non-specific bronchial hyperreactivity (1355). Patients with nasal polyps have a high incidence of bronchial hyperreactivity (1356, 1357)

Patients with nasal polyposis and asymptomatic bronchial hyperreactivity have an eosinophilic bronchial inflammation similar to that observed in asthmatic patients with nasal polyposis. On the other hand, patients with nasal polyposis without bronchial hyperreactivity do not

show eosinophilic lower airways inflammation (1358). The significance of asymptomatic bronchial hyperreactivity associated with nasal polyposis is unknown but it may therefore represent an indication of potential asthma. The clinical relevance of these results requires careful follow-up to determine whether eosinophilic inflammation in these patients precedes and is responsible for the development of obvious asthma.

The treatment of nasal polyposis and sinusitis may be involved in the control of asthma. It consists of medical and/or surgical management (1359-1361). Topical steroid therapy has a well established role in the management of nasal polyps, since it has proven efficacy on the symptoms and size of polyps and may help prevent the recurrence of nasal polyposis after surgery (1362-1367).

A study of 205 patients attempted to determine whether or not nasal and sinus surgery had a beneficial or deleterious effect upon the asthma of patients with nasal polyps and aspirin intolerance (1368). A classification system was devised to provide a means of determining the severity of asthma before and after surgery. These data indicate that surgery does improve the patient's asthma for relatively long periods of time. However, conflicting opinions exist concerning the evolution of asthma and asymptomatic bronchial hyperreactivity in patients with nasal polyposis (1368-1380). Some studies have even indicated that polypectomy and sinus surgery may induce a worsening of asthma severity (1381). In fact, few authors have evaluated the consequences of sinus surgery in nasal polyposis, relying on objective criteria such as lung volume measurements and the evaluation of non-specific bronchial hyperreactivity. There are no prospective studies published.

The initial response of nasal polyposis to glucocorticosteroids may be of importance in the relationships between asthma and nasal polyposis. In 23 intranasal glucocorticosteroid non-responders who underwent intranasal ethmoidectomy, Lamblin *et al.* (1358) reported an enhancement of non-specific bronchial hyperreactivity and a significant, but modest, decrease of FEV_1 over 12 months. No change was observed in 21 intranasal glucocorticosteroid responders. However, no change in pulmonary symptoms and asthma severity was observed. In a further study, the same group examined, over a 4-year period, the long-term changes of pulmonary function and bronchial hyperreactivity in 46 patients with nasal polyposis (1382). All patients were first of all treated with intranasal glucocorticosteroids for 6 weeks (beclomethasone 600 µg/day). Eighteen patients were successfully treated with intranasal glucocorticosteroids (intranasal glucocorticosteroid responders). Intranasal ethmoidectomy was performed in 28 patients who did not improve with intranasal glucocorticosteroids alone (intranasal glucocorticosteroid non-responders). Bronchial hyperreactivity did not significantly change over the 4-year follow-up period in the two groups. No change in pulmonary symptoms and/or asthma severity occurred, but non-reversible airflow obstruction appeared over a 4-year follow-up period in intranasal glucocorticosteroid non-responder patients requiring nasal surgery.

6-4- OTITIS MEDIA

6-4-1- Introduction

Otitis media is an inflammatory disease of the middle ear mucosa. The aetiology and pathogenesis of this disease are multifactorial and the exact mechanism is not fully understood. It is actually a spectrum of related disorders, such as Eustachian tube dysfunction, infection and mucosal inflammation induced by antigen-specific immune reactions.

Over the last decades, the aetiological relationship between rhinitis and otitis media, especially the role of allergy in otitis media with effusion (OME), has been the subject of much controversy. Uncontrolled studies reported the incidence of respiratory allergy in children with OME to range from 4% to over 90% (1383). This has resulted in confusion and misunderstanding of the relationship between these two diseases.

The nose and middle ears are situated in a system of contiguous organs. Both cavities are covered by respiratory mucosa and there is an anatomic continuation between these two cavities through the Eustachian tube. It is, however, not fully understood whether inflammation, infection or obstruction in the nose influence or promote otitis media. Many important questions still need to be firmly answered:
- whether the presence of allergic rhinitis predisposes an individual to the development of otitis,
- whether nasal dysfunction causes otitis to worsen,
- whether OME can be cured by treating the underlying nasal or sinus infection,
- whether the middle ear mucosa can be targeted directly by allergens.

To understand these entities better, it is important to know the pathophysiological mechanism by which allergy or other nasal pathologies influence middle ear disease. On the other hand, there is a need to perform longitudinal studies on these diseases with a comparable or standardised methodology. In this way, a more accurate assessment of the aetiological and pathophysiological relationship can be achieved between these two common diseases.

6-4-2- Definition and classification of otitis media

Otitis media is an inflammation of the middle ear without reference to aetiology or pathogenesis (1384). The various types of otitis media have been classified as:
- otitis media without effusion, e.g. present in the early stages of acute otitis media but may also be found in the stage of resolution of acute otitis media or may even be chronic,
- acute otitis media (AOM), e.g. acute suppurative or purulent otitis media,
- otitis media with effusion (OME), which can be serous, mucoid or purulent,
- atelectasis of the tympanic membrane.

6-4-3- Epidemiological relation between rhinitis and otitis media

Nasal and middle ear diseases are both common health problems and they may often occur at the same time. Allergic and non-allergic rhinitis is the most common chronic illness affecting children but peak prevalence is observed in adolescents and young adults. Infectious rhinitis, when compared to allergic rhinitis, is more common in infants and pre-school children and less common in school children and pre-adolescence (40).

Otitis media is the most common illness diagnosed during early childhood and accounts for 20-35% of paediatric office visits in the first 2 years of life (1385). This disease is uncommon but not rare in adults. In North America and Europe, patients over the age of 15 years constitute 10 to 15% of the AOM patients seen by primary care practitioners.

6-4-3-1 Infectious rhinitis and otitis media

Complications of infectious rhinitis are more commonly seen in children. Acute otitis media (AOM) is the most common complication. Most of the cases in children under 3 years are preceded or accompanied by viral rhinitis. In older children, viral infections are also common (1386, 1387). Respiratory syncytial virus is the principal virus which invades the middle ear during AOM (1388). In adults, acute sinusitis is a more frequent complication of the common cold than AOM.

The common cold is also a frequent cause of OME in children (1389, 1390). The highest prevalence of OME is seen 5 to 8 weeks after the last episode of a common cold. After this period, there is a progressive improvement of the middle ear status. The correlation between tympanometric findings and the annual frequency of a common cold is not as strong as that between the annual episodes of AOM and a common cold. This indicates that OME probably involves more factors in its pathophysiology than AOM and that the influence of a common cold on OME is indirect.

6-4-3-2- Allergy and otitis media with effusion

The role of allergy as an aetiological factor in the pathophysiology of OME is still controversial. In 1973, Miglets, reviewing 19 published papers, suggested that allergy was strongly associated with OME (1391). On the other hand, not everybody supported this concept (1392). The reasons for this controversy are probably the bias in the study design, especially in the selection of the study population. Up until 1975, there were no clinical studies available in which an unselected group of children was screened for both allergy and OME.

In 1975, Reisman and Bernstein (1393) published the first report on the relationship between allergy and OME using an unselected group of children from an otology practice. 23% of the children who were tested for OME had an atopic disease. This figure was only slightly higher than could be expected from a random examination of unselected children. These findings were confirmed by Ruokonen *et al.* (1394), while Kjellman *et al.* (1395) found that the incidence of atopic disease in OME was significantly higher than in an unselected control group. It is obvious that the incidence of allergy in children with OME is, at most, slightly greater than might be expected in the general population (1396). It is possible that children with atopic dermatitis present a higher prevalence of OME than non-atopic children (1397). In this large study, asthma and rhinitis were not predisposing factors for the development of OME. However, the number of OME episodes may be greater in atopic children than in non-atopic children (1398).

6-4-4- Potential interactions between rhinitis and otitis media

6-4-4-1- Eustachian tube dysfunction

The middle ear is naturally protected by the Eustachian tube from exogenous antigenic stimulation. A properly functioning Eustachian tube (ventilation, protection, drainage and clearance) is important in maintaining a normal middle ear. On the other hand, abnormal functioning of the Eustachian tube appears to be the most important aetiological factor in the pathogenesis of middle ear disease (1384). In addition to congenital or anatomical abnormalities of the Eustachian tube, mucosal inflammation caused by infection or by antigen-specific reaction is believed to be a common contributing factor to Eustachian tube dysfunction. Nasal obstruction may result in an initial positive nasopharyngeal air pressure followed by a negative phase of middle ear cavity. Under these conditions, viral and bacterial pathogens or possibly allergens may enter the middle ear via the Eustachian tube by aspiration, reflex or insufflation.

6-4-4-2- Infection

Pathogenic bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*) is found in the nasopharynx in 97% of patients with AOM, with organisms corresponding to those isolated from middle ear effusion in 69% (1399). The nasopharyngeal microorganisms may enter the middle ear through the Eustachian tube. This may be facilitated by nose-blowing, closed-nose swallowing (Toynbee manoeuvre) or by aspiration into the middle ear as a result of negative middle ear pressure. Anaerobic organisms may be present in otitis media.

It is still a controversial issue as to whether the indiscriminate use of antibiotics contributes to the problem by weakening children's immune systems or whether a more extensive use of antibiotics could help children avoid unnecessary surgery.

In many cases, especially in older children, chronic effusion may appear without any evidence of preceding AOM. It has been shown, however, that middle ear effusions are not sterile and that they contain the same spectrum of micro-organisms as found in acute effusions (1400). In these cases, the fluid is produced by the middle ear mucosa in response to sub-clinical antigenic stimulation rather than by an overt acute infectious process (1400).

6-4-4-3- Allergy and allergic inflammation

The relationship between allergy and otitis media, if any, is not fully understood. A question that has been under discussion for several decades is whether the mid-

dle ear can be considered as an allergic "shock organ". In mice, the middle ear is an immunologically potential organ, since it contains cells which can react to an immune stimulus (1401). Histologically, the nasal and middle ear cavities are covered by a similar respiratory mucosa, but there are fewer immunocompetent cells in the normal ear mucosa. Several cytokines, chemokines and growth factors are released in the exudate of otitis media in animals and in man (1402, 1403).

In some studies, it was found that many lymphocytes, plasma cells, macrophages, leukocytes and other inflammatory cells accumulated in inflamed middle ear mucosa, but that only a few mast cells are found in the normal middle ear mucosa (1404). In guinea pigs, in the tubotympanum, mast cells are mainly located in areas covered by ciliated and secretory epithelium. Small numbers of mast cells were found in foetal tubotympani that had received no antigenic stimuli (1405).

Mast cells and tryptase are present in a majority of chronic ear effusions (1406). This study suggests that middle ear mucosa may be able to mount an allergic response. However, the mechanism by which this allergen-specific immune reaction takes place remains to be clarified.

Intranasal allergen challenge in animals resulted in equivocal results. Miglets induced an acellular middle ear effusion by inoculating ragweed pollen into the Eustachian tube of sensitised monkeys whereas Doyle *et al.* failed to confirm this finding (1391, 1407). Nasal antigen challenge in guinea pigs induced an important infiltration of eosinophils, mast cells and edema in the mucous membrane lining the nose, nasopharynx and Eustachian tube near the pharyngeal orifice, but not in the rest of the Eustachian tube (1405).

In humans, the concept that the middle ear mucosa can act as an allergic "shock organ" is not generally accepted because in natural circumstances, the middle ear mucosa is not directly exposed to aeroallergens. However, some studies found that tubal dysfunction occured after intranasal challenge with allergen (1408-1410) and histamine (1411). During the ragweed pollen season, it was found that 60% of the 15 children followed developed Eustachian tube obstruction (1412). This was found to correlate with daily patient symptom-medication scores during pollen exposure.

A localised inflammatory process within the middle ear itself has been suggested to occur in man (1413, 1414). Hurst and Venge (1414) found abnormally elevated levels of ECP in the middle ear fluid in 87% of patients with OME.

In addition to IgE mediated mechanism, IgG was found to dominate acute otitis media with effusion, whereas IgA tends to be present in chronic but not in acute OME (1406). Bikhazi and Ryan (1415) have demonstrated, in both patients and experimental animals, that in chronic OME, IL-2+ and IL-4+ cells were less prevalent, but that IL-5+ cells were numerous. These findings support a model by which locally produced IL-2 and IL-4 augment IgG production in acute OME, whereas IL-5 contributes to increased IgA production in chronic OME.

6-4-4-4- The relationship between food allergy and OME

The relationship between food allergy and OME is not yet fully understood. It has been suggested that the food immune complexes, particularly with dairy products, may be an important factor, especially in the otitis-prone child less than 2 years of age (1396). Nsouli *et al.* (1416) suggested that food allergy should be considered in all paediatric patients with recurrent serous otitis media. However, it appears that food allergy is rarely associated with OME.

6-4-5- Conclusion

Rhinitis and otitis media are both common health problems and they may appear together in a patient. The pathogenic mechanisms of these diseases involve a spectrum of multifactorial elements such as bacteria, viruses and allergens. Acute bacterial or viral rhinitis is often associated with middle ear disease, particularly in young children. Eustachian tube dysfunction, however, is the most common aetiology of otitis media.

IgE-mediated allergic reactions are a very common cause of rhinitis, but represent only one aetiological factor for otitis media. Although there is a relationship between nasal allergic inflammation and otitis media caused by a dysfunction of the Eustachian tube, we should take into consideration the fact that there exists a difference in peak prevalence between these two diseases with respect to age distribution.

The middle ear mucosa itself is rarely a target tissue for allergic processes, although the biochemical mediators released during nasal allergic reactions most likely produce Eustachian tube edema and inflammation. Over a long period, this chronic inflammatory response, along with viral or bacterial infection, may produce middle ear effusion. On the other hand, in some patients with OME, atopy may be responsible for the recurrence and maintenance of middle ear disease.

7- Diagnosis and assessment of severity

The tests and procedures listed below represent the spectrum of investigations, which may be used in the diagnosis of allergic rhinitis. However, only a number of these are routinely available or applicable to each individual patient (Table 8).

7-1- HISTORY

Interviewing the patient with rhinitis is of importance in the diagnosis of rhinitis, co-morbidities and allergy. The interview begins with a thorough general medical history and should be followed by questions more specific to allergy including environmental and occupational information. It is also common to gather information on personal and familial history of patients with allergic disease. Nasal and pharyngeal pruritus, sneezing and associated conjunctivitis are more common in patients with allergic rhinitis than in those with non-allergic rhinitis.

7-1-1- Symptoms of rhinitis and complications

Clinical history is essential for an accurate diagnosis of rhinitis, assessment of severity and response to treatment. The patient should be allowed to give his/her account of the symptoms, followed by structured prompts/questions.

Although this sub-division may be too simple, patients with rhinitis are usually divided into "sneezers and runners" and "blockers" (Table 9). Those with allergic rhinitis are more commonly found in the "sneezer and runner" group (1). Rhinorrhea appears to be more common in seasonal allergic rhinitis whereas nasal obstruction is more common in perennial rhinitis (1417). Always ask the patient: "what is your main symptom?" This will often highlight the key problem and necessary treatment.

Sneezing and a blocked or runny nose, secondary to allergic rhinitis, are more intense during the morning in approximately 70% of sufferers (1418, 1419).

History should take into account some associated symptoms common in patients with rhinitis. They include:
• loss of smell (hyposmia or anosmia) (1420-1422),
• snoring, sleep problems (1423-1426),
• post nasal drip or chronic cough (1427, 1428), in particular if sinusitis is present,
• sedation, which may be caused by rhinitis (1429),
• questions on asthma and conjunctivitis (see chapter 7-3).

7-1-2- Other historical background

The history includes a full-length questionnaire:
• The frequency, severity, duration, persistence or intermittence and seasonality of symptoms should be determined.
• It is important to assess their impact on the patients' quality of life in terms of impairment of school/work performance, interference with leisure activities and any sleep disturbances.

TABLE 8: Diagnostic tests for allergic rhinitis

Routine tests
History
General ENT examination
Allergy tests
   - skin tests
   - serum specific IgE
Endoscopy
   - rigid
   - flexible
Nasal secretions
   - cytology
Nasal challenge
   - allergen
   - lysine aspirin
Radiology
   - CT-scan

Optional tests
Nasal biopsy
Nasal swab
   - bacteriology
Radiology, CT scans
   - MRI
Mucociliary function
   - nasal mucociliary clearance (NMCC)
   - ciliary beat frequency (CBF)
   - electron microscopy
Nasal airway assessment
   - nasal inspiratory peak flow (NIPF)
   - rhinomanometry (anterior and posterior)
   - acoustic rhinometry
Olfaction
Nitric oxide measurement

Testing for co-morbidities
   - asthma
   - conjunctivitis
   - otitis media
   - pharyngitis

• Potential allergic triggers should be documented including exposure in the home, workplace and school. Any hobbies which may provoke symptoms should also be noted. Patients with inhalant allergies may exhibit cross-reactivity with certain foods (see chapter 3-1-5).
• Patients with rhinitis, whatever the cause, may develop "nasal hyperreactivity" with symptoms following exposure to irritants (strong odours, cold air, pollutants, tobacco smoke, perfumes, deodorants, etc.) (see chapters 3-2 and 4-7). The typical features of allergic versus non-allergic (irritant) induced triggers may differ. However, these are frequently not clear-cut since in persistent rhinitis, chronic symptoms may be present without a clear relation to allergen exposure being apparent.

TABLE 9: Clinical differences between rhinitis patients	
"sneezers and runners"	"blockers"
- sneezing	- little or no sneezing
- watery mucus (running nose)	- thick nasal mucus (catarrh)
- anterior (+ posterior) rhinorrhea	- more often posterior rhinorrhea
- itchy nose	- no itch
- nasal blockage variable	- nasal blockage often severe
- diurnal rhythm (worse during day and improving during night)	- constant day and night but may be worse at night
- often associated conjunctivitis	

- An occupational history should be obtained (see chapter 3-1-6). Symptoms may occur at work or in the evening following work, with improvement during the weekends and holidays.
- The effects of previous allergen avoidance measures should be noted, bearing in mind that up to 3-6 months of vigorous cleaning may be needed to eradicate mites, cat dander and other relevant allergens from the home (see chapter 8-1).
- Similarly, the response to pharmacological treatment and previous immunotherapy should be recorded in terms of improvement and side effects.
- Compliance with treatment and patients' fears about treatment should be explored, particularly if the response to treatment has been below that expected.

A diagnostic approach is summarised as follows. In the majority of patients, a careful study of history, an examination and a limited number of skin tests is all that is required to confirm/exclude an allergic aetiology and the relevant allergen exposure. When there is discordance between history and skin prick tests, further tests including provocation tests or a therapeutic trial of allergen avoidance may be indicated.

7-2- EXAMINATION OF THE NOSE

7-2-1- Methods

In patients with mild intermittent allergic rhinitis, a nasal examination is optimal. All patients with persistent allergic rhinitis need to undergo a nasal examination.

Nasal examination should describe:
- the anatomical situation in the nose (e.g. the septum, the size of the inferior turbinate and if possible the structures in the middle meatus),
- the colour of the mucosa,
- the amount and aspect of the mucus.

Anterior rhinoscopy, using a speculum and mirror, gives information which is sometimes limited, but it remains an appropriate method for studying the major modifications observed in most cases of allergic rhinitis.

Nasal endoscopy can find nasal and sinus pathology that might easily be missed with routine speculum and nasopharyngeal examination (1430). ENT examination in the clinic is now considerably facilitated by the use of rigid Hopkins rods or flexible fibre-optic endoscopes (1431).

The administration of intranasal anaesthesia is recommended at initial assessment. Specific attention is paid to abnormality within the middle meatus and nasopharynx.

7-2-2- Findings

In allergic rhinitis, there does not appear to be an increase in the number or severity of anatomic abnormalities in comparison to normal subjects.

In allergic rhinitis, during allergen exposure:
- Bilateral but not always symmetrical swelling can be observed. This is usually localised to the inferior turbinate which appears oedematous, swollen and covered with watery secretions.
- Eventually, the mucosa of the middle meatus may be seen and, more rarely, micropolyps or edema may be observed in this area.
- Sometimes, these abnormalities are only localised in the posterior part of the inferior turbinate and require examination with an endoscope (1432).
- On the other hand, a major edema of the nasal mucosa (inferior turbinate) may make it impossible to study the nose.
- With regard to colour, changes are frequently reported from the purplish mucosa to a more common pale mucosa.
- An increase in vascularity is commonly seen.

If there is no allergen exposure, the nasal mucosa may be totally normal. However, chronic edema and/or viscous secretions may occur in patients who have suffered several years of rhinitis.

7-3- ALLERGY DIAGNOSIS

7-3-1- Methods

The diagnosis of allergic rhinitis is based on the coordination between a typical history of allergic symptoms and diagnostic tests. IgE is the major isotype of anaphylactic antibodies, and although theoretically IgG4 can also be a reagin, its clinical importance is not significant. Thus *in vivo* and *in vitro* tests used in the diagnosis of allergic diseases are directed towards the detection of free or cell-bound IgE (figure 17). The diagnosis of allergy has been improved by allergen standardisation providing satisfactory extracts for both *in vivo* and *in vitro* tests for most inhalant allergens.
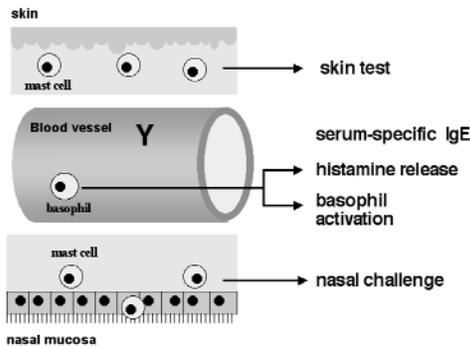
FIGURE 17: Diagnosis of IgE-mediated allergy.

7-3-1-2- Skin tests

Immediate hypersensitivity skin tests are widely used to demonstrate an IgE-mediated allergic reaction of the skin and represent a major diagnostic tool in the field of allergy. If properly performed, they yield useful confirmatory evidence for a diagnosis of specific allergy. As there are many complexities for their performance and interpretation, it is recommended that they should be carried out by trained health professionals (1433). Delayed hypersensitivity tests provide little information.

7-3-1-2-1- Methods

- Skin testing methods

Several methods of skin testing are available.

Scratch tests should not be used any longer because of poor reproducibility and possible systemic reactions.

Prick and puncture tests (SPT)

- are usually recommended for the diagnosis of immediate type allergy.
- There is a high degree of correlation between symptoms and provocative challenges.
- The modified skin prick test introduced by Pepys (1434) is the current reference method although the variability of this test has been shown to be greater than that of the intradermal test.
- Puncture tests with various devices (1435-1444) were introduced to decrease the variability of skin prick tests. Opinions concerning these so-called standardised methods vary according to the skill, experience and preference of the investigator as well as the aims of using skin tests. With a trained investigator, they are highly reproducible (1442, 1445).
- Skin prick tests should be 2 cm apart.
- In some instances (e.g. weak allergen solution), intradermal skin tests may be employed for allergy diagnosis.
- Although they are more sensitive than prick tests,
- they may induce some false positive reactions,
- they correlate less well with symptoms (1446)
- and they are somewhat less safe to perform since systemic reactions can rarely occur (1447). Particular care should be taken in patients treated with ß-blocking agents which may increase the risk of systemic reactions.

- As a general rule, the starting dose of intracutaneous extract solutions in patients with a preceding negative prick test should range between 100 and 1,000 fold dilutions of the concentrated extract used for prick-puncture tests (1449).
- It does not seem that intradermal skin tests are required for the diagnosis of inhalant allergy when standardised extracts are available (1433, 1450, 1451).

The European Academy of Allergology and Clinical Immunology (1452) and the US Joint Council of Allergy Asthma and Immunology (1449, 1453) therefore recommend skin prick-puncture tests as a major test for the diagnosis of IgE-mediated allergic diseases and for research purposes.

- Negative and positive control solutions

Because of interpatient variability in cutaneous reactivity, it is necessary to include negative and positive controls in every skin test study. The negative control solutions are the diluents used to preserve the allergen vaccines. The rare dermographic patient will give wheal-and-erythema reactions to the negative control. The negative control will also detect traumatic reactivity induced by the skin test device (with a wheal which may approach a diameter of 3 mm with some devices) and/or the technique of the tester (1449). Any reaction at the negative control test sites will hinder interpretation of the allergen sites (1449).

Positive control solutions are used to:

- detect suppression by medications or disease,
- detect the exceptional patients who are poorly reactive to histamine,
- determine variations in technician performance.

The usual positive control for prick-puncture testing is histamine dihydrochloride, used at a concentration of 5.43 mmol/L (or 2.7 mg/mL, equivalent to 1 mg/mL of histamine base) (1454). Wheal diameters with this preparation range from 2 to 7 mm. However, a 10-fold greater concentration is more appropriate (1455), with a mean wheal size ranging between 5 and 8 mm. For the intradermal test, the concentration routinely used is 0.0543 mmol/L. The mean wheal size elicited ranges from 10 to 12 mm. Mast cell secretagogues such as codeine phosphate 2.5% (1439) or 9% may also be used (1456).

- Grading of skin tests and criteria of positivity

Skin tests should be read at the peak of their reaction by measuring (in mm) the wheal and the flare approximately 15 minutes after the performance of the tests. Late-phase reactions are not recorded because their exact significance is not known (1449, 1452). Some scoring systems have been proposed and may be used in daily practice.

In the US, for example, for skin prick tests: neg=0 reaction, 1+=1 mm wheal above saline control; 2+=1-3 mm wheal above saline control; 3+ (the first point we consider a positive reaction) = 3-5 mm wheal above saline control plus an accompanying flare; 4+>5 mm wheal above saline control, plus an accompanying flare.

For prick tests, when the control site is completely

TABLE 10: Inhibitory effects of treatments on IgE-mediated allergic reactions

Drugs	Suppression		
	Degree	Duration	Clinical significance
H1-antihistamines			
astemizole*	++++	30-60 days	yes
azelastine oral	++++	3-10 days	yes
cetirizine	++++	3-10 days	yes
chlorpheniramine	++	1-3 days	yes
clemastine	+++	1-10 days	yes
ebastine	++++	3-10 days	yes
fexofenadine	++++	3-10 days	yes
hydroxyzine	++++	1-10 days	yes
ketotifen	++++	3-10 days	yes
loratadine	++++	3-10 days	yes
mequitazine	++++	3-10 days	yes
mizolastine	++++	3-10 days	yes
oxatomide	++++	3-10 days	yes
terfenadine*	++++	3-10 days	yes
H2-antihistamines	0 to +		no
imipramines	++++	>10 days	yes
phenothiazines	++	?	yes
corticosteroids			
oral/IM short term	0		unlikely
IM long term	possible		unlikely
intranasal	0		no
intra-bronchial	0		no
topical skin	0 to ++		yes
theophylline	0 to +		no
chromones	0		
ß2-agonists			
inhaled	0 to +		no
systemic	0 to ++		no
dopamine	+		no
clonidine	++		
specific immunotherapy	0 to ++		no

negative, small wheals of a mean diameter greater than or equal to 3 mm of the negative control represent a positive immunological response (1434, 1457), but these reactions do not imply the presence of a clinically relevant allergy (1433).

7-3-1-2-2- Factors affecting skin testing

Skin reaction is dependent on a number of variables that may alter the performance of skin tests (Table 10).

- The quality of the allergen extract (vaccine) is of importance. When possible, allergens that are standardised by using biological methods and that are labelled in biological units should be used (1449, 1452) (see chapter 8-3-3). Recombinant allergens can also be used accurately (1458).
- Age is known to affect the size of skin tests (1459) but positive skin prick tests can be found early in infancy (1460, 1461). In old age, the size of skin tests is decreased (1462).
- Seasonal variations related to specific IgE antibody synthesis have been demonstrated in pollen allergy (1463). The skin sensitivity increases after the pollen

season and then declines until the next season. This effect has some importance in patients with a low sensitivity (1464) and/or in patients sensitised to allergens such as cypress pollen (403).

- Drugs affect skin tests and it is always necessary to ask patients about the drugs they have taken. Some drugs such as astemizole (no longer available in many countries) can depress or abolish responses to skin tests for a period of up to 6 weeks (Table 10) (for review see 1433, 1465). Patients with skin disease may not be tested because of dermographism (urticaria) or widespread skin lesions.

7-3-1-2-3- Interpretation of skin tests

Carefully performed and correctly interpreted, skin tests with high quality allergen vaccines and a battery that includes all relevant allergens of the patient's geographic area are a simple, painless and highly efficient method. Therefore, skin testing represents one of the primary tools for allergy diagnosis by the trained physician.

Both false-positive and false-negative skin tests may occur because of improper technique or material. False-positive skin tests may result from dermographism or may be caused by "irritant" reactions or a non-specific enhancement from a nearby strong reaction (1466).

False-negative skin tests can be caused by:

- extracts of poor initial potency or subsequent loss of potency (1446),
- drugs modulating the allergic reaction,
- diseases attenuating the skin response,
- a decreased reactivity of the skin in infants and elderly patients,
- improper technique (no or weak puncture).

The use of positive control solutions may overcome some of the false-negative results because reactions will be either decreased or abolished in patients with slightly reactive skin.

The occurrence of positive responses to skin tests does not necessarily imply that the patient's symptoms are due to an IgE mediated allergy, since skin prick tests are positive in 15-35% of symptom free individuals depending on the allergen and the area (for review see 1433). The presence of positive skin tests in asymptomatic subjects may predict the onset of allergic symptoms (273, 1467), especially if the allergen load is high. The optimal cut-off values for clinically relevant skin prick test results have been reported for *Dermatophagoides pteronyssinus* (1468, 1469) but more data are needed.

7-3-1-2-4- Clinical value of skin tests

Even after false-positive and false-negative tests have been eliminated, the proper interpretation of results requires a thorough knowledge of the history and physical findings. A positive skin test alone does not confirm a definite clinical reactivity to an allergen.

- With inhalant allergens, skin test responses represent one of the first-line diagnostic methods and when they correlate with the clinical history, *in vitro* tests may not be required (1449, 1452). It has recently been shown that, in general practice, common nasal aller-

gies can be diagnosed efficiently with the aid of simple diagnostic criteria using either skin prick tests or serum specific IgE (RAST) (1470).

- For foods, particular caution should be taken since very few extracts are standardised and results of skin tests may be negative in truly allergic patients. Extracts made from fruits and vegetables are usually of poor quality since the allergens are rapidly destroyed. Skin tests with fresh foods are more accurate (80, 1471).
- For occupational rhinitis, skin tests are often unreliable in detection except in the case of high molecular weight compounds such as latex or grain dust.

7-3-1-3- IgE

The discovery of IgE in 1967 was a major advance in the understanding and diagnosis of allergic diseases (1472, 1473).

7-3-1-3-1- Serum total IgE

Serum total IgE is measured using radio- or enzyme-immuno assays (1474-1478).

In normal subjects, levels of IgE increase from birth (0-1 KU/l) to adolescence and then decrease slowly and reach a plateau after the age of 20-30 years. In adults, levels of over 100-150 KU/l are considered to be above normal. Allergic and parasitic diseases as well as many other conditions (including racial factors) increase the levels of total IgE in serum. Thus, the measurement of total serum IgE is barely predictive for allergy screening in rhinitis and should no longer be used as a diagnostic tool (2).

7-3-1-3-2- Serum specific IgE

In contrast to the low predictive value of total serum IgE measurements in the diagnosis of immediate type allergy, the measurement of allergen-specific IgE in serum is of importance.

- Methods

The first technique used to accurately measure serum specific IgE was the RAST (radioallergosorbent test) (1479-1481). New techniques are now available using either radio- or enzyme-labelled anti-IgE (1482-1493). The different reagents are critical for an appropriate assay (1494). Another technology is based upon sticks used as a matrix (1495). Results are expressed in terms of total radioactive counts bound (cpm), arbitrary units (RAST class, PRU/ml) or units of IgE (IU/ml, KU/l).

- Factors affecting the measurement of serum specific IgE

Many factors can affect the measurement of IgE. The quality of reagents used (allergens, anti-IgE antibodies) is of importance.

- IgE antibody assays need to be sensitive and specific to make quantitative measurements over as wide a range as possible (1496).
- A high capacity solid phase provides a large excess of allergen that maximises the binding of IgE antibody (1494).
- The anti-IgE preparations applied must be Fcε-specific and are preferably combinations of monoclonal antibodies with specificities against more than one

epitope on the Fc fragment and with complementary dose-response characteristics (1494).

- Calibrators should be traceable to the WHO International Reference Preparation for human IgE, 75/502 (1494).
- As for skin tests, the quality of allergens is of critical importance and, when possible, only standardised extracts should be used. Standardisation of the allergen source material in combination with adequate reagent design provides precise and reproducible data increasing the accuracy and efficiency of allergy diagnostic testing (1485). However, using molecular biology, it is possible to obtain large quantities of major allergens for many species. Recombinant Bet v I produced in bacterial expression systems allows accurate *in vitro* diagnosis of birch pollen allergy in over 95% of birch pollen allergic patients (534). Other studies have found similar values for recombinant allergens (1497). Thus, single recombinant allergen or a combination of a few major recombinant allergens can substitute the crude extract for *in vitro* diagnostic purposes (1498). Another possibility is to add some relevant recombinant allergens to an allergen extract.
- It also seems that *in vitro* diagnostics for pollen allergy can be simplified using cross-reactivities. Current diagnostic extracts for grass pollen allergy are usually composed of mixtures of pollen from different grass species. Their complex composition hampers accurate standardisation. It was recently shown that the use of one grass species is sufficient for the *in vitro* diagnosis of grass pollen allergy. Purified natural Lol p 1 and Lol p 5 detect over 90% of grass-positive patients. Around 80% of the IgE response to grass pollen is directed to these major allergens (1499). Reliable *in vitro* diagnosis is possible with a single Betulaceae tree pollen extract (birch or alder). The same is true for purified natural Bet v 1, Bet v 2 (1500) and profilin.
- Specific IgE measurements are not influenced by drugs or skin diseases.

- Significance of measurement of serum allergen specific IgE

- Several studies have shown that with the use of standardised allergen vaccines, serum specific IgE results correlate closely to those of skin tests and nasal challenges.
- As in skin tests, the presence or absence of specific IgE in the serum does not preclude symptoms, and some symptom-free subjects have serum specific IgE.
- Although a low specific IgE titre may not be clinically relevant, the titre of serum specific IgE is usually unrelated with symptoms. This is because the severity of symptoms depends not only on IgE antibodies but also on the releasability of mediators, the response of the target organ to mediators and non-specific hypersensitivity.
- When using single allergen tests, the cost of serum specific IgE measurement is high and only a selected list of allergens can usually be tested.

7-3-1-3-3- Screening tests using serum specific IgE

Some methods use either a mixture of several allergens in a single assay (1501-1504) or test several differ-

ent allergens during a single assay. These tests can therefore be used by specialised doctors and non-allergists as screening tests for the diagnosis of allergic diseases.

The clinical relevance of these tests has been extensively studied and it has been shown that their efficiency (specificity and sensitivity) in allergy diagnosis is often over 85% (1501). However, using these tests, the patient is defined only as allergic or non-allergic and more extensive investigations for rhinitis are needed if the test is positive.

7-3-1-4- Other tests

7-3-1-4-1- IgG and IgG4

The measurement of allergen-specific IgG or IgG4 antibodies in serum has no value in the diagnosis of allergic rhinitis.

7-3-1-4-2- Peripheral blood activation markers

Blood basophils of allergic patients can degranulate and release mediators (histamine and CysLT) when stimulated by specific allergen. The assay of mediators (e.g. histamine release or CysLT release) or the microscopic examination of cells (e.g. basophil degranulation test) can be performed. In the early 1980s, the basophil degranulation test was proposed but never fully validated (1505, 1506). New basophil activation tests are based upon the expression of CD63 (gp53) (1507, 1508) or CD45 (1509) in the presence of allergens or non-specific stimuli. In this test, CD63 or CD45 are measured using cytofluorimetry. These tests may be of interest in some difficult cases such as cypress pollen allergy (1510) but they require sophisticated equipment (cytofluorimetry) and further evaluation.

New tests based on CysLT release after allergen challenge may be interesting if they correlate closely with the clinical sensitivity of the patients, but further studies are required (1511-1513).

7-3-1-4-3- Nasal specific IgE

It has been proposed that some patients may have a local IgE immune response without any systemic release of IgE (1514), e.g. negative skin tests and serum specific IgE. Based on current data, the concept of local allergic reaction in the nose without systemic IgE release is not supported (1515) and the measurement of IgE in nasal secretions cannot be routinely proposed (1516, 1517).

7-3-1-4-4- Mediators released during allergic reactions

The measurement of mediators released in peripheral blood, nasal secretions or urine during allergic reaction was made possible by the development of highly specific and sensitive immunoassays for the titration of histamine, PGD_2, CysLTs, kinins and ECP. Mediators can be measured at baseline or after allergen challenge and provide important research tools, but do not apply to the routine diagnosis of allergy. Nasal microsuction has been used by several investigators (1172, 1518, 1519). The major advantage of this technique is that it permits a quantitative measurement of the mediators in nasal secretions. It is possible to obtain nasal secretions with a precise and minimally diluted volume.

7-3-1-4-5- Cytology and histology

Techniques for obtaining specimens include blown secretions, scraping, lavage and biopsy. Proper assessment of these specimens by trained personnel is required. The use of nasal cytology to evaluate the cell pattern may be attempted but clinical interest is usually weak (1520). However, nasal cytology to evaluate mucosal cellular patterns can be valuable in (1521):

- distinguishing inflammatory from non-inflammatory rhinopathies,
- distinguishing between allergic, non-allergic and infectious rhinitis,
- distinguishing between viral and bacterial infections,
- following the course of rhinitis and
- following the response to treatment.
- Morphological changes in the nasal mucosa may reflect reactions that are also occurring in other areas of the airway.

7-3-1-4-6- Measurement of nitric oxide in exhaled air

Measures of the concentration of NO in nasal air usually reveal higher mean levels in patients with allergic rhinitis as compared to those without rhinitis and also possibly to those with non-allergic rhinitis. However, substantial overlap exists between groups (1522) and the measurement of NO cannot be used as a diagnostic measure for allergic rhinitis (see chapter 4-3-2). Nitric oxide levels are low where there is severe nasal obstruction such as polyps.

In primary ciliary dyskinesia, very low levels of NO are seen – this may prove to be of diagnostic help.

7-3-1-5- Nasal challenge

Nasal challenge tests are used in research and to a lesser extent in clinical practice. They are however important in the diagnosis of occupational rhinitis.

Recommendation on and critical analysis of nasal provocations and methods to measure the effects of such tests have already been published (1523, 1524) (Table 11). Recently, a subcommittee of the "International Committee on Objective Assessment of the Nasal Airways" has put forward guidelines for nasal provocation tests concerning indications, techniques and evaluation of the tests (1525).

7-3-1-5-1- Nasal challenge with allergen

Different methods for the provocation and measurement of nasal responses have been used in recent years. Each technique has its own advantages and restrictions. For clinical purposes, techniques for qualitative measurements may be appropriate, but for experimental research, quantitative measurements with high reproducibility are essential (1526) (Table 12).

7-3-1-5-1-1- Provoking agent

Allergens are usually given as an aqueous solution, but although the solution is easy to administer into nostrils, this form of challenge has many defects:

- Allergen extracts (vaccines) are not always standardised. Only standardised allergen vaccines should be used when available.
- Allergen vaccines may not represent the native allergen and the amount of allergen insufflated is far greater than that entering the nose during natural allergen exposure.

TABLE 11: Indications for nasal challenge tests

1- Allergen provocations:
 • When discrepancies between history of allergic rhinitis and tests or between tests are present (e.g. in cases of diagnostic doubt).
 • For diagnosis of occupational allergic rhinitis.
 • Before immunotherapy for allergic rhinitis. Although it is still not very common to use nasal provocation before starting immunotherapy, it has been considered that a laborious long-lasting therapy is justified by a proper diagnosis. This holds true particularly in the case of perennial allergic rhinitis.
 • For research.
2- Lysine-aspirin: Nasal provocation is recommended as a substitute for oral provocation in aspirin intolerance. Whenever such a nasal provocation is negative, an oral test is still required.
3- To test non-specific hyperreactivity:
 Nasal provocation with non-specific stimuli (histamine, methacholine, cold dry air, etc.) is not relevant for daily clinical practice and diagnosis but can be used in research.

Data from (1525)

TABLE 12: Recommendations for the performance of nasal challenge tests

1- Provoking agent
 • use solutions at room temperature
 • standardised extracts
 • isotonic solutions buffered to a pH of about 7
 • use control solutions
2- Deposition into the nose
 • meter-dose pump spray
 • paper disks
3- Assessment of the nasal response: symptom scores are combined with objective measures
 • counting sneezes or attacks of sneezes
 • measuring volume or weight of nasal secretion
 • changes of nasal patency, airflow or airflow resistance
4- Methods to evaluate nasal patency, airflow and airflow resistance.
 The most important techniques are:
 • rhinomanometry
 • acoustic rhinometry
 • rhinostereometry
 • nasal inspiratory or expiratory peak flow
 Less common methods are:
 • head-out body plethysmography
 • oscillometry

Data from (1525)

• The potency of an aqueous extract often decreases rapidly and it is advised, at least for research projects, to use standardised and lyophilised extracts of the same batch freshly reconstituted on the day of the test.
• Preservatives such as glycerol, benzalkonium chloride or phenol can induce non-specific nasal reactions.
• Temperature, pH and osmolarity of the solution should be checked carefully.

Allergens can also be administered in the form of a powder (1527), as a solution adsorbed on a paper disk or in the form of pollen grains mixed with lactose in capsules (642, 711).

7-3-1-5-1-2- Deposition in the nose

Aqueous allergen vaccines can be delivered from atomisers and an exact dose can be applied. Other investigators use a pipette and allergens are deposited under rhinoscopy. When using any of these methods, care should be taken to avoid non-specific responses, and for all experiments, the diluent of the allergen extract must be administered before the allergen, to test for the non-specific response. Small paper disks can be directly applied to the nostrils and allergen powders or pollen grains can be insufflated easily with Spinhalers or derived devices.

Other methods are of interest. In the Vienna Challenge Chamber (1528, 1529) or the environmental exposure unit (1530-1533), patients are challenged under controlled conditions with purified airborne grass pollen. However, these conditions are only used for large clinical trials and have no value in the diagnosis of allergic rhinitis.

7-3-1-5-1-3- Assessment of the response

• Different methods have been used to assess the response to allergen. None of these are fully accepted by all investigators.

• Symptoms produced after a challenge can be recorded. Sneezing, rhinorrhea and nasal blockage are easy to assess and yield valuable information. However, patients can react with different symptoms on different test days and it is preferable to use a combination of symptoms (711).
• The importance of nasal obstruction is one of the cardinal symptoms in allergic rhinitis and the major symptom of the late-phase reaction following allergen challenge. The objective measurement of this symptom is therefore of the greatest importance (1534). However, physiological fluctuations in nasal resistance may interfere with nasal monitoring in the nasal provocation test (1535).

Several committees were formed for the objective assessment of the nasal airway and of advocated rhinomanometry as a reliable method for measuring nasal obstruction (1523, 1524, 1534, 1536, 1537). The following techniques may be used:

• Until now, rhinomanometry is the best evaluated and standardised technique. Active anterior rhinomanometry was recommended by an international committee in 1984 (1523). With active anterior rhinomanometry, unilateral measurements can be done, this in contrast to active posterior rhinomanometry. Passive anterior rhinomanometry was introduced by Clement *et al.* in 1981 (1538) as a suitable technique for measuring nasal resistance after nasal challenge, but it is more difficult to use than anterior rhinomanometry.
• Acoustic rhinometry (1539-1541), characterised by a

low coefficient of variation, has been used in nasal challenge tests with bradykinin, histamine and allergen. However, acoustic rhinometry does have limitations and pitfalls. The value of acoustic rhinometry to evaluate nasal responses after provocation in routine clinical work is not yet established.

- Rhinostereometry (1542) can be used to record changes in the thickness of the nasal mucosa. With a microscope, 0.2 mm changes in the thickness of the nasal mucosa can be recorded in test subjects fixed to the apparatus using an individually made plastic splint adapted to the teeth. Rhinostereometry is however a time-consuming method. It seems useful for comparisons between well-defined groups of subjects and patients and between the same subjects or patients at different occasions. It may be combined with laser Doppler flowmetry (1543).

- Nasal peak flow appears to correlate very well with rhinomanometry (1544-1548). Peak inspiratory nasal flow (NPIF) and peak expiratory flow (NPEF) (rate), especially the former, may be recommended for the long-term control of pharmacological or immunological treatment of different types of rhinitis.

- Other methods such as rhinostereometry and whole body plethysmography have been proposed (1549) but they are not yet fully assessed.

Comparisons between methods are also available. In order to find the most sensitive method, assessments were made by means of symptom score, acoustic rhinometry, nasal peak expiratory and inspiratory flow (NPEF and NPIF) and rhinomanometry during histamine challenge (1550). There was no difference in the mucosal reactivity between patients and controls regardless of the method used, but NPIF and NPEF were more sensitive to mucosal changes than the other methods studied (1551). Compared to rhinomanometry by body plethysmography (1552), acoustic rhinometry is less complicated, more quickly performed and more comfortable for subjects.

7-3-1-5-1-4- Measurement of mediators and cells during challenge

Allergen-specific nasal challenge is a valid and reliable tool for studying the pathophysiological mechanisms involved in allergic inflammation. Nasal challenge induces an immediate and late clinical response in allergic subjects with the release of pro-inflammatory mediators which may be studied (see chapters 4-5-1 and 4-5-2).

Nasal biopsies may also be obtained (see chapters 4-5-1 and 4-5-2). They have been used in many drug trials (1553).

7-3-1-5-1-5- Factors affecting nasal challenge

As in other *in vivo* tests, the major factors affecting nasal challenges are the quality of the allergens used as well as the drugs taken by the patient. Moreover, other factors are more specific to nasal challenge, including technical problems already discussed and inflammation of the nasal mucosa.

Sodium cromoglycate and usual anti-H1-histamines should be withdrawn 48 hours before the test, nasal beclomethasone 3 to 6 days before, ketotifen and imipramines 2 weeks before and astemizole at least 1 month before. Nasal vasoconstrictors may not modify nasal challenges. Specific immunotherapy decreases the sensitivity of the nose to allergens.

The nasal mucosa may be altered by several factors and the response to allergen may be largely affected.

- It has been shown that an allergic reaction significantly increases the reactivity of the nose because of the priming effect initially described by Connell (1150).

- Viral infections induce the release of histamine, pro-inflammatory mediators and cytokines in nasal secretions (1220). Nasal challenges should thus be performed at least 2 to 4 weeks after any allergic or infectious episode.

- Finally, the nasal cycle (647) should be taken into consideration when rhinomanometry is used.

7-3-1-5-2- Nasal challenge with non-specific agents

Non-specific nasal hyperreactivity is commonly observed in patients with allergic rhinitis (869, 1198) (see chapter 4-7). Challenges with methacholine or histamine have been widely carried out. Methacholine and histamine both induce a dose-dependent increase in secretion weights on the challenge site, whereas histamine alone induced a contra lateral reflex. Repeated stimulation with histamine, but not methacholine, resulted in tachyphylaxis (1554).

7-3-1-5-3- Challenge with occupational agents

The diagnosis of occupational rhinitis is often complex and requires nasal provocation tests with the relevant occupational agent (1555-1557). The challenge can be carried out in the form of natural exposure, especially if the relevant allergen is unavailable. As an example, this has been done for laboratory animal allergy in a vivarium during cage cleaning (high-allergen challenge), quiet sitting (low-allergen challenge) or in a remote location (sham challenge)(1558).

7-3-1-5-4- Aspirin-induced rhinitis and asthma

While a patient's clinical history might raise suspicion of aspirin-induced rhinitis and asthma, the diagnosis can be established with certainty only by aspirin challenge. There are three types of provocation tests, depending on the route of administration:

- Oral challenge (1247, 1559). Oral challenge tests are most commonly performed. They consist of the administration of increasing doses of aspirin (the starting dose is 1-20 mg) and placebo, according to a single-blind procedure. Careful monitoring of clinical symptoms, pulmonary function tests and parameters reflecting nasal patency for 6 hours after administration of the drug. The reaction is considered positive if a decrease in $FEV_1 > 15\text{-}20\%$ of baseline occurs ($PD_{15}FEV_1$, $PD_{20}FEV_1$), accompanied by symptoms of asthma, rhinitis and/or conjunctivitis. In most patients, the threshold dose evoking positive reactions varies between 40 and 100 mg of aspirin. Adverse symptoms are relieved by inhalation of a ß2-agonist. If necessary, a glucocorticosteroid can be administered. Since severe reactions may occur, oral aspirin chal-

lenge should be performed in a setting where emergency medical treatment is readily accessible.

- Inhaled challenge (1560). In inhalation challenge tests, nebulised aspirin (1561) or L-lysine aspirin (1560, 1562) have been used. The increase in L-lysine aspirin dosage is achieved every 30-45 minutes and the test can be completed in one morning. It is therefore faster than oral challenge which often takes 2-3 days, but the symptoms provoked are usually restricted to the bronchopulmonary tract, and not all patients with aspirin-induced asthma react to L-lysine aspirin.

- Nasal challenge (1563). Nasal provocation testing is an attractive research model and may also be used as a diagnostic procedure on an out-patient basis in patients with unstable asthma. A simple, safe and quick test for the diagnosis of aspirin-induced asthma has been described (1563). It may be a method of choice to confirm intolerance to aspirin manifested only by symptoms from the upper respiratory tract. Negative results do not exclude possible intolerance to aspirin. Patients suspected of the intolerance, with negative nasal tests, should undergo bronchial or oral challenge tests with aspirin.

Aspirin intolerance is usually long-lasting and although the threshold dose inducing a positive challenge may vary with time in individual patients, there is usually no need to perform serial aspirin challenges when the diagnosis is made.

7-3-2- Interpretation of tests and recommendations

7-3-2-1- Correlation between tests

Skin tests represent the primary diagnostic tools used for immediate-type hypersensitivity. Comparisons between the measurement of specific IgE and skin tests depend on the quality and standardisation of the allergens used in both types of tests and, to a lesser extent, on the method of skin testing used. The worst correlations have been obtained with house dust, mould, food extracts and unstandardised dander extracts. There are good correlations between a strongly positive response to a skin test and the detection of serum specific IgE and between a negative response to a prick test and the lack of detection of serum specific IgE, whereas small wheals induced by prick tests and positive results of intradermal tests with concentrated extracts are less frequently associated with the detection of serum specific IgE (113). Positive responses to skin tests and serum-specific IgE can be found in totally symptom-free subjects with a similar prevalence.

Correlations between responses to skin tests and serum specific IgE with nasal challenges are less consistent because of the non-specific hyperreactivity. Poor correlations are observed with unstandardised extracts, weak positive responses to skin tests and serum specific IgE results or when there is a discrepancy between the clinical history and skin tests.

There is usually a lack of correlation between titres of serum allergen-specific IgE and symptoms in untreated patients with seasonal allergic rhinitis (1564).

7-3-2-2- Diagnosis of inhalant allergy

The diagnosis of allergy is based on the correlation between the clinical history and diagnostic tests for allergy. It is not possible to diagnose allergy based solely on responses to skin tests, *in vitro* tests or even challenges. For these reasons, patients may benefit more from skin testing by specially trained health professionals. In some countries, general practitioners perform skin prick tests. Studies in Holland and the UK found that common nasal allergies can be diagnosed with a very high certainty using simple diagnostic criteria (1470, 1565). Factors affecting tests should always be checked before investigations since drug therapy may modify results of *in vivo* tests for days or even weeks.

7-3-2-3- Diagnosis of food allergy

Food allergy is rarely the cause of isolated rhinitis symptoms. While allergic reactions to foods are usually due to IgE-mediated hypersensitivity reactions, a number of immune mechanisms may contribute to adverse reactions to foods that have an immunological basis. Tests for IgE antibodies include both skin prick tests and the measurement of serum allergen-specific IgE antibodies. The diagnosis of food allergy is compounded, however, because allergen vaccines and test reagents currently available are not standardised and their stability is poorly determined (1566). The presence of food-specific IgE in serum or a positive skin test to a foodstuff does not always correlate with a food allergy since many patients outgrow their allergy with age (1567, 1568) and not all patients with food-specific IgE have a clinical sensitivity. In many instances, the diagnosis has to be confirmed by a double-blind food challenge that should be carried out under precisely specified conditions (1569, 1570) and by trained staff who have the competence to manage anaphylactic reactions. As for other forms of allergy, unproven and controversial techniques such as cytotoxic tests, VEGA testing or sublingual provocation tests have no proven value.

7-3-2-4- Diagnosis of occupational allergy

Occupational rhinitis must be more precisely confirmed than allergic rhinitis of other aetiology. In practice (1571), interviews concerning the causal relation, frequency, latent period and atopic disposition often provide suggestions but sometimes give unreliable evidence for the basis by which to diagnose occupational nasal allergy. Therefore, examinations such as skin tests, nasal provocation tests (1555-1557) and determination of the IgE antibody level are necessary to confirm the causality between the disease and the work exposure (1572).

7-4- OTHER ENT DIAGNOSIS

7-4-1- Bacteriology

Routine swabs taken blindly from the nose and nostril are not diagnostically helpful. This may not be the case if the swabs are taken endoscopically.

7-4-2- Imaging

7-4-2-1- Plain sinus radiographs

Plain sinus radiographs are not indicated in the diagnosis of allergic rhinitis or sinusitis.

7-4-2-2- Computerised tomography (CT)

CT has become the principal radiological investigation for major sino-nasal disorder but is of limited use in the diagnosis of allergic rhinitis (1320, 1573). CT scans can be carried out after receiving specialist advice:

- to eliminate other conditions (1574, 1575),
- to exclude chronic sinusitis,
- to eliminate complications from rhinitis,
- in patients who do not respond to treatment,
- in patients with unilateral rhinitis.

7-4-2-3- Magnetic resonance imaging (MRI)

Magnetic resonance imaging (1576) is rarely indicated as a diagnostic tool. However, there are circumstances where MRI is useful, in particular in fungal sinusitis.

7-4-3- Mucociliary function

Tests for mucociliary clearance (1577) or ciliary beat frequency (1578) have little relevance in the diagnosis of allergic rhinitis, but are relevant in the differential diagnosis of chronic rhinorrhea in children.

7-4-4- Nasal airway assessment

Nasal inspiratory or expiratory peak flow, rhinomanometry or acoustic rhinometry may be used (see chapter 7-1-1-5-1-3).

7-4-5- Olfaction

Although olfaction is often impaired in allergic rhinitis and methods for assessing olfaction are available (1579), these are not generally used for the diagnosis of allergic rhinitis.

7-5- DIAGNOSIS OF ASTHMA

The diagnosis of asthma may be difficult due to the transient nature of the disease and the reversibility of the airflow obstruction spontaneously or after treatment. Key indicators for diagnosing asthma are presented in Table 13 (36).

7-5-1- History and measurement of symptoms

The diagnosis of asthma is largely made on the basis of a history of paroxysmal attacks of breathlessness commonly associated with a tightness of the chest and wheezing. These are worse particularly at night and in the early hours of the morning. However, in themselves, these common symptoms are not diagnostic. Table 14 highlights questions for considering a diagnosis of asthma.

What is important is a history of recurrent exacerbations (or attacks) often provoked by factors such as allergens, irritants, exercise and virus infections. Under some circumstances, especially in patients with very responsive airways, asthma triggers may produce profound bronchoconstriction that rapidly gives rise to a life-threatening exacerbation.

Other useful clinical markers of asthma are the relief of symptoms either spontaneously or more specifically by means of a bronchodilator and anti-inflammatory treatment.

The seasonal variability of symptoms and a positive

TABLE 13: Key Indicators for Diagnosing Asthma*

Consider asthma if any of the indicators are present:

Wheezing - high-pitched whistling sounds when breathing out - especially in children. (A normal chest examination does not exclude asthma.)

History of any of the following:
  - Cough, worse particularly at night
  - Recurrent wheezing
  - Recurrent difficult breathing
  - Recurrent chest tightness.

  Note:
  Eczema, hay fever or a family history of asthma or atopic diseases are often associated with asthma, but they are not key indicators.

Symptoms occur or worsen at night, awakening the patient.

Symptoms occur or worsen in the presence of:
  - Exercise
  - Viral infection (common cold)
  - Animals with fur
  - Domestic dust mites (in mattresses, pillows, upholstered furniture, carpets)
  - Smoke (tobacco, wood)
  - Pollen
  - Changes in temperature
  - Strong emotional expression (laughing or crying hard)
  - Aerosol chemicals
  - Drugs (aspirin, beta blockers).

Reversible and variable airflow limitation as measured by using a peak expiratory flow (PEF) meter or FEV_1 in any of the following ways:
  - PEF or FEV_1 increases more than 12% 15 to 20 minutes after inhalation of a short-acting ß2-agonist, or
  - PEF or FEV_1 varies more than 20% from morning measurement upon arising to measurement 12 hours later in patients taking a bronchodilator (more than 10% in patients who are not taking a bronchodilator), or
  - PEF or FEV1 decreases more than 15 % after 6 minutes of running or exercise.

* Pocket guide for asthma management and prevention, based on data from (36)

TABLE 14: Questions to Consider in the Diagnosis of Asthma

Has the patient had an attack or recurrent attacks of wheezing?

Does the patient have a troublesome cough at night?

Does the patient cough or wheeze after exercise?

Does the patient cough, wheeze or experience chest tightness after exposure to airborne allergens or pollutants?

From (36)

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family history of asthma and atopic disease are also helpful diagnostic guides.

Symptom measures have been used for epidemiological studies or clinical trials and are reviewed by O'Connor and Weiss (1580).

TABLE 15: Advantages, disadvantages and applicable setting for pulmonary function tests to measure asthma outcomes

Table available in print only

7-5-2- Physical examination

Because asthma symptoms are variable throughout the day, the physical examination of the respiratory system may appear normal.

Clinical signs of dyspnea, airflow limitation (wheezing which is an important symptom but is not pathognomonic of asthma) and hyperinflation are likely to be present when patients are examined during symptomatic periods.

Some patients may have a normal chest auscultation but a significant airflow obstruction when measured objectively. Conversely, wheezing may be absent in very severe asthma exacerbations.

7-5-3- Measurement of lung function

Patients with asthma frequently have difficulty in recognising their symptoms and a poor perception of the severity (1581), especially if their condition is severe and long-standing (1582). Assessment by physicians of symptoms such as dyspnea and wheezing may also be inaccurate. The reversibility of airflow obstruction after inhalation of bronchodilators should therefore be measured using lung function tests (36).

7-5-3-1- Recording airflow obstruction
A wide range of different methods to assess the level of airflow limitation exists, but two methods have found widespread acceptance for patients over 5 years of age (36):
- forced expiratory volume in 1 second (FEV_1) (and its accompanying forced vital capacity - FVC) (1583, 1584),
- peak expiratory flow (PEF) (1585) which can be measured serially (at home) over a period of several days (1586).

Table 15 gives the advantages and drawbacks of these two methods.

These two methods (FEV_1 and PEF) involve a forced expiration from total lung capacity but they are not strictly equivalent when expressed as a percentage of predicted values (1587-1590). Moreover, FEV_1 is more reproducible and is a more accurate estimate of airflow limitation. However, PEF is the only method which can be used for bi-daily measurements of lung function. Because diseases other than those causing airflow limitation may result in a reduced FEV_1, a useful assessment of airflow limitation can be obtained as the ratio of FEV_1 to FVC. In healthy adults, this ratio is usually over 75% and in healthy children over 85%.

7-5-3-2- Assessing the reversibility of airflow obstruction
The reversible airflow obstruction of asthma needs to be distinguished from the irreversible obstruction of chronic bronchitis and emphysema (1591). It is usually carried out using inhaled ß2-agonists, and responses to bronchodilators are easy to assess (1592). An improvement of the FEV_1 of over 12% from baseline and 200 ml of absolute value after inhalation of a short acting bronchodilator is considered to be significant (1593). However, in some asthmatics, vigorous treatment (including a trial of oral glucocorticosteroids) may be needed to appreciate the reversibility of airflow obstruction (1594). It should be remembered that some patients with COPD may have reversible airflow obstruction during glucocorticosteroid treatment (1595).

7-5-3-3- Assessing the diurnal variation of airflow obstruction
A characteristic feature of asthma is a cyclical variation in the degree of airflow obstruction throughout the day. The lowest PEF occurs in the morning. Many asthmatics usually show a difference of at least 15% between morning and evening PEF (diurnal variability). Current asthma guidelines recommend that diurnal variability of the PEFR (1596) should be calculated when diagnosing asthma and assessing its severity (36, 1597). A diurnal variability in PEF of more than 20% is diagnostic of asthma (36, 1597). Diurnal variability of PEF has been used as a marker of air-

way responsiveness, particularly in studies (1598-1600), and as an outcome measure in clinical asthma trials (1601). However, there are problems associated with its use (1602).

7-5-3-4- Non-specific challenge testing

Airway responsiveness to methacholine, other non-sensitising stimuli or exercise may be used clinically to aid in the initial diagnosis of asthma, especially if baseline spirometry is normal and no reversibility can be demonstrated (1584). The methods for performing these tests are standardised but differences exist between countries (1603). However, asthma is not the only disease with non-specific bronchial hyperreactivity, and patients with allergic rhinitis and without clinical asthma may have an increased non-specific bronchial hyperreactivity (see chapter 6-1-2). Asthma severity categories partly based on $PD_{20}FEV_1$ histamine or methacholine have been suggested (1604).

7-5-4- Special considerations in difficult groups

- Young children whose primary symptom is a cough or who wheeze with respiratory infections are often misdiagnosed as having bronchitis or pneumonia (including acute respiratory infection) and thus ineffectively treated with antibiotics or cough suppressants. Treatment with asthma medication can be beneficial and diagnostic.
- Many infants and young children who wheeze with viral respiratory infections may not develop asthma that persists through childhood (1605). However, they may benefit from asthma medication for their wheezing episodes. There is no certain way to predict which children will have persistent asthma, but allergy, a family history of allergy or asthma and perinatal exposure to passive smoke and allergens are more strongly associated with continuing asthma.
- Asthma should be considered if the patient's colds repeatedly "go to the chest" or take more than 10 days to clear up, or if the patient improves when asthma medication is given.
- Tobacco smokers and elderly patients who suffer from COPD frequently have symptoms similar to asthma. Yet they may also have concurrent asthma and thus benefit from treatment. Improvement in PEF after asthma treatment is of importance for the diagnosis of asthma.
- Subjects who are exposed to inhalant chemicals or allergens in the workplace can develop asthma and may be misdiagnosed as having chronic bronchitis or chronic obstructive pulmonary disease. Early recognition (PEF measurements at work and home), strict avoidance of further exposure and early treatment are essential.
- Asthma attacks may be difficult to diagnose. For example, acute shortness of breath, chest tightness and wheezing can also be caused by croup, bronchitis, heart failure and vocal chord dysfunction. Using spirometry, establishing the reversibility of symptoms with a bronchodilator and assessing the history of the attack (e.g. whether it was related to exposures that commonly make asthma worse) aid the diagnosis. A chest x-ray can help rule out infection, large airway lesions, congestive heart failure or aspiration of a foreign object.

7-6- ASSESSMENT OF SEVERITY OF RHINITIS

For asthma, there are objective measures of severity such as pulmonary function tests and well-defined criteria for symptom severity (36). For atopic dermatitis, there are clinical scores of severity such as SCORAD (1606). However, for rhinitis, there is no accepted measure of nasal obstruction. The nasal inspiratory peak flow (NIPF) has been extensively studied but results are not consistent among the different studies (1544-1548). Moreover, the correlation between the objective measurement of nasal resistance and subjective reports of nasal airflow sensation is usually poor.

Visual analogue scales are often used to assess the severity of diseases with a subjective involvement such as pain (1607, 1608). They have been used to establish an effective treatment in patients with rhinitis (1609-1611). Over the past few decades, there has been some controversy over the relationship between subjective assessment and objective measurement of nasal airway obstruction. VAS measurements generally followed trends in nasal airway resistance either after challenge with histamine (1612) or capasaicin (1613) or during treatment with a nasal vasoconstrictor (1610, 1611). However, the studies differ in some respect. VAS results and rhinomanometry correlated better when unilateral nasal obstruction was evaluated compared to total nasal evaluation. When rhinomanometric data were divided into four clinically relevant grades of obstruction (very patent, normal, obstructed and very obstructed) and the quartiles of the VAS results were compared to these, the agreement was good or fairly good in 75-85% of the cases (1614). In another study (1615), the patient's own overall rating registered on a visual analogue scale was compared with a summed symptom score calculated from ratings of sneezing, rhinorrhea and congestion. A significant correlation, but not complete correspondence, was found in patients with untreated rhinitis during the birch pollen season and after challenges with birch pollen or histamine. Comparisons between the overall rating and scores for individual symptoms gave lower degrees of correlation or non-significant correlations. In children, VAS correlated with patients' nasal stuffiness scores but not with anterior nasal airflow (1616).

8- Management

The management of allergic rhinitis includes allergen avoidance, medication (pharmacological treatment), immunotherapy and education. Surgery may be used as an adjunctive intervention.

It is recommended to propose a strategy combining the treatment of both the upper and lower airway disease in terms of efficacy and safety.

8-1- ALLERGEN AVOIDANCE

A wide range of allergens have been associated with allergic rhinitis, of which house dust mite is clearly the most important and most investigated (1617, 1618). Most studies have however dealt with asthma symptoms and very few have studied rhinitis symptoms. The effectiveness of allergen avoidance in the treatment of asthma was first suggested by studies in which patients were removed from their homes into the low house dust mite level of high dry altitude (1619, 1620). However, the real challenge is to create a low allergen environment in patients' homes and, unfortunately, the majority of single interventions have failed to achieve a sufficient reduction in allergen load to lead to a clinical improvement. Indeed, a meta-analysis of appropriately controlled house mite avoidance trials suggested that this approach was doomed to failure in the treatment of asthma (1621), suggesting that a single intervention may be insufficient. However, this attempt at meta-analysis raised several problems (1622, 1623) and grouped any attempts at house dust mite avoidance together as if they were one treatment. As it is clear that some approaches are far more efficacious than others, this was probably an inappropriate methodology. If assessment was made only on trials which demonstrated a decrease in allergen load, then a different outcome may have become apparent. Certainly, virtually all asthma and rhinitis guidelines (1, 36) now suggest that allergen avoidance, including house mites, should be an integral part of a management strategy.

8-1-1- House dust mites

There have been several reviews on the effects of house mite avoidance in asthma (335, 1617).
- The single most effective strategy for mite reduction and control of the disease has involved bed-covering systems, which separate the mite and its allergen from the allergic individual. Provided the mattress, pillow and duvet are sealed in a mite allergen impermeable encasing, a reduction in allergen exposure can be achieved (1624) and this can be associated with an improvement in the condition (1625). However, these measures achieve only modest improvements compared with those achieved by transporting sensitive subjects to high altitudes where allergen exposure is virtually non-existent (1619, 1620). Mite allergen can accumulate on blankets, and bed linen and blankets should be washed regularly (once a week) in hot water (over 55°C) to ensure the destruction of the mites (1626). The same effect may be obtained by drying laundry in the sun, but no data are available to support this assumption. Washing laundry in cold water reduces allergen levels, but most mites survive (1627).
- Carpets are an important microhabitat for mite colonisation and a possible source of allergen from which the bed can be re-infested (1628). Ideally, the carpet should be removed and replaced by vinyl or polished wooden floor boards. If it is impossible to remove the carpet, it can be completely covered by polyethylene sheeting, taped to the skirting board or replaced regularly, since mites grow better on old carpets (1629). Steam cleaning (1630), liquid nitrogen or acaricides (1631) may help to reduce mite numbers in carpets.
- Curtains should be washable at 55°C. Children's soft toys can be a potent source of domestic mite allergen and should either be removed, washed in hot water or frozen once a week.
- Attempts to develop acaricide sprays which will both kill and denature allergens have demonstrated some effect in reducing mite numbers and allergen levels (1632). The clinical efficacy has been equivocal in asthma and many studies showed no effect (1625).
- High efficiency particulate air (HEPA) vacuum cleaners can reduce allergen load but again no trials have demonstrated that this will improve symptoms (1633, 1634). However, vacuum cleaners with inadequate exhaust filtration may increase airborne allergen levels during use (1635).
- High levels of humidity in the home are essential for mite population growth, and reducing humidity may be an effective control method. However, effective ventilation systems have achieved clinical efficacy in countries where the number of mites is usually low (1636), while no benefits were demonstrated in places with an elevated mite infestation (1637, 1638). Moreover, it has been shown that ventilation systems can appreciably reduce the allergen load but not sufficiently to reduce the symptoms of asthmatic children (1639).

On the other hand, very few studies have been reported on allergen avoidance in rhinitis. Three studies have evaluated the effect of acaricidal treatment with benzyl benzoate in perennial allergic rhinitis (1640-1642). All reported symptomatic improvement. Two were uncontrolled open studies while one was a double-blind, placebo-controlled parallel design involving 20 patients and lasting 12 months. Treatment was applied for six months to mattresses, upholstery, soft toys and carpeting in all rooms and accompanied by a programme of intensive vacuuming. Rhinitis symptom scores were significantly reduced in the active group compared to the control. However, when considering the physicians' evaluation of treatment efficacy and the changes in medication, there

was no significant difference between the two groups over the study period (1641, 1643). There is one report of benefit in house dust mite sensitive perennial rhinitis patients with the introduction of house dust mite impermeable, water-vapour permeable bedding covers for mattresses, duvets and pillows. This was assessed in a double-blind, placebo-controlled, parallel group trial design, but is only available as an abstract.

Avoidance measures ideally include (Table 16):

TABLE 16: Measures for reducing house dust mite allergen exposure

Essential
  Encase mattress, pillow and quilt in impermeable covers
  Wash all bedding weekly in a hot cycle (55-60°C)
Optimal
  Replace carpets with linoleum or wooden flooring
  If carpets cannot be removed, treat with acaricides and/or
    tannic acid *
  Minimise upholstered furniture/replace with leather furniture
  Keep dust accumulating objects in closed cupboards
  Use a vacuum cleaner with integral HEPA filter and double
    thickness bags
  Replace curtains with blinds or easily washable (hot cycle)
    curtains
  Hot wash/freeze soft toys

* Acaricides may induce adverse reactions in asthmatics.

It is likely that no single intervention will achieve sufficient benefits to be cost-effective. However, combined strategies in large groups of patients are urgently required (1644).

8-1-2- Cats and dogs

Cat and dog allergy is also of major importance in many countries. The allergens are not the dander itself but are contained in the saliva and in sebaceous secretions, which can flake off in small particles and remain airborne for considerable periods of time. This results in an ubiquitous allergen that can be found in many environments outside the home (443), even in cat-free buildings (1645) and schools (441, 442). It makes avoidance much more difficult, though there is little doubt in most people's minds that avoidance in the home can achieve improvement. The difficulty is that there are little published controlled study data to substantiate this assertion in the management of asthma. The only effective measure for avoiding animal dander allergens in the home is to remove the pet (cat, dog) and to carefully vacuum clean all carpets, mattresses and upholstered furniture. Although frequent washing of cats reduces allergen (1646), clinical studies have not shown clear benefit from this procedure when carried out once a week (1647). There is only one trial of domestic pet removal/allergen avoidance in rhinitis. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy did not find a significant effect on rhinitis (1648).

Clearly there are a number of other domestic pets that have the potential to produce allergic reactions. However, probably because of their relatively restricted location within homes, the effect of avoidance measures has not been tested.

8-1-3- Cockroaches

Cockroach infestation is an important cause of allergic sensitisation, particularly in inner city sub-standard apartment complexes (504). Approaches to the elimination of cockroaches are based on (i) eliminating suitable environments (by restricting havens through caulking and sealing cracks in the plaster work and flooring, controlling damp and availability of food), (ii) restricting access (by sealing entry sources such as around paperwork and doors) and (iii) using chemical control (abamectin) and traps. Two studies lasting between 8 and 12 months have shown that cockroach extermination by professionals is feasible in inner-city homes but that standard house-cleaning procedures are only partially effective in removing residual allergen (1649, 1650). In apartment blocks, however, it may be difficult to prevent re-infestation from neighbouring apartments.

Moreover, there have been no studies to evaluate the effect of cockroach eradication on rhinitis.

8-1-4- Outdoor allergens

Outdoor allergens, such as pollens and fungal spores, are difficult to avoid. Sometimes they will accumulate inside homes and it would seem prudent for sufferers with pollen allergy to seal their houses by day and to open windows only at night when the pollen count is low. The avoidance of pollen is often impossible due to their ubiquitous nature. Ventilation systems can be equipped with appropriate filters to avoid drawing pollen allergens into the house and the car. Protective face masks and eye glasses may be helpful.

8-1-5- Indoor moulds

Indoor moulds are frequently involved in inducing nasal and bronchial symptoms, and reducing these allergens appears to be prudent. The fight against moulds inside the home calls for hygiene measures and those subjects allergic to these spores must regularly inspect the humid areas of their house, as well as the aeration and heating ducts. However, although anecdotal reports have been presented, there are no controlled studies showing that these measures are effective in benefiting allergic patients.

8-1-6- Occupational agents

A large number of substances have been identified as occupational allergens and as risk factors that can cause rhinitis and asthma. Levels above which the sensitisation occurs frequently have been proposed for many chemicals (for review see 1252). However, once a patient has been sensitised, the level of sensitivity necessary to induce symptoms may be extremely low and the symptoms may become increasingly severe. Attempts to

reduce occupational exposure have been successful, especially in industrial settings. Some potent sensitisers, such as soya castor beans or some proteolytic enzymes used for detergents (511), have been replaced by less allergenic or sensitising substances. Moreover, the levels of sensitivity have been reduced in the workplace to avoid sensitisation (577). It is also important to considere co-morbidities since rhinitis often appears before occupational asthma. The early identification of occupational sensitisers and the removal of sensitised patients from any further exposure are important aspects of the management of occupational rhinitis.

Prevention of latex allergy is essential. Symptoms and presence of latex-specific IgE antibodies in subjects are significantly associated with measurable levels of latex aeroallergens. A latex aeroallergen level of 0.6 ng/m^3 is a critical threshold for workers who are sensitised to natural rubber latex (1651). A reduction in latex allergen content can be achieved using powder-free gloves and several methods can also reduce the allergenicity of latex itself (1652-1654). When airborne latex allergen is undetectable, asthma symptoms improve and asthma medications are reduced (549, 1655), but the impact on nasal symptoms still has to be demonstrated. The use of powder-free gloves may enable sensitised patients to continue working in their trained profession and may prevent measurable airborne latex exposure, but affected patients still need to avoid direct latex contact (1656). A glove selection programme utilising only powder-free and hypoallergenic gloves should be attempted in hospitals (1657, 1658) and dental schools (1659).

8-1-7- Food allergens

There is some dispute about the relative importance of food allergy in relation to allergic rhinitis. However, it certainly can occur (1660). Milk allergy is the most commonly described association with allergic rhinitis. Nevertheless, many other foods are likely to be involved. To what extent dietary avoidance achieves improvement has, again, not been adequately tested in controlled trials (1661).

8-1-8- Conclusion

Total allergen avoidance appears to be effective (patients are symptom-free out of the pollen season or away from occupational exposure). However, patients are often sensitised to many allergens and the degree of exposure varies within indoor and outdoor environments. Moreover, the magnitude of the reduction of allergen load needed to reduce symptoms is still unclear. On the other hand, allergen exposure leads to symptoms. Thus, avoidance measures are still recommended but more research is strongly needed.

8-2- MEDICATION

Medication has no long-lasting effect when stopped. Therefore, in persistent disease, whether administered topically or orally, maintenance treatment is required. No tachyphylaxis usually occurs during long-term treatment.

8-2-1- Routes of administration

Medications used for rhinitis are most commonly administered intranasally or orally. In exceptional circumstances, they may be administered intramuscularly. Rhinitis is confined to the nose, which is a small organ. The surface area of the nasal mucous membrane is only 300 cm^2. With an average thickness of the nasal mucosa of 3 mm, the volume of the diseased tissue in rhinitis is 100 cm^3 and the weight 100 gr. This is about 0.1% of the total body mass.

8-2-1-1- Advantages of intranasal administration
The major advantages of delivering drugs directly to the nose are:
- high concentrations can be delivered directly into the target organ so that systemic effects are avoided or minimised,
- some of the drugs (e.g. cromones) used for the treatment of rhinitis can be administered only via intranasal route because they are not adequately absorbed when given orally,
- some drugs have systemic effects when administered orally (e.g. glucocorticosteroids and atropine derivatives),
- the onset of action of an intranasal drug is usually faster than that of an oral one (e.g. vasoconstrictors and possibly H1-antihistamines).

8-2-1-2- Problems of intranasal administration
However, there are some problems related to intranasal medication:
- Many patients with allergic rhinitis present also with conjunctivitis and/or asthma. Thus, there is a need for multiple administrations in target organs. The rationale for an effective oral drug without side effects is that one administration should reach all the target organs.
- Studies have shown that the intranasal distribution of intranasal medication is not optimal. Only 20% of a pressurised aerosol and 50% of a watery spray/powder inhaler will reach the target, e.g. the ciliated mucous membrane. In addition, there is no reason to believe that intranasal medication will reach the ostiomeatal complex, which is of decisive importance for the development of pathology in the paranasal sinuses and nasal polyps. Furthermore, intranasal medication will not reach inflammation in the paranasal sinuses.
- An irritant or cilia toxic effect from added preservatives may be observed with intranasal drugs. It is necessary to add a preservative to an aqueous nasal spray, which may cause immediate nasal irritation. This symptom is, in part, a sign of rhinitis-induced hyperresponsiveness, and it will diminish with time when an intranasal glucocorticosteroid is used. However, the commonly used anti-microbial preservative, benzalkonium chloride, is cytotoxic and *in vitro* studies have shown that it damages ciliary motility and may exacerbate symptoms of rhinitis (1662-1664). The clinical significance of this adverse effect, however, is unlikely since it is not seen in studies performed *in vivo*.

- Other local side effects are medication-dependent. Intranasal glucocorticosteroids may cause nose bleeding and, in rare cases, the development of a septal perforation. The prolonged use of an intranasal vasoconstrictor involves a risk of the development of rhinitis medicamentosa, not seen with oral treatment. The use of intranasal ipratropium bromide can cause an unpleasant feeling of nasal dryness and produce blood tinged mucus.
- Intranasal medication cannot be given when the nose or nostril is completely blocked. The effect of partial nasal blockage has not been investigated. However, one study has shown that pre-treatment with systemic glucocorticosteroids, which will open a blocked nose in perennial rhinitis, can significantly increase the subsequent responsiveness to an intranasal glucocorticosteroid.
- Patients' compliance may be greater with oral than topical drugs, especially if multiple target organs are to be treated. Probably, the education of the advantages of topical treatment may improve compliance.

8-2-2- Oral H1-antihistamines

Antihistamines, or H1-blockers or H1-antihistamines, were discovered by Bovet and Staub at the Institut Pasteur in 1937 (1665). Although the compound was too weak and too toxic for clinical use, its discovery induced an enormous amount of research and led to the development of phenbenzamine (antegan®) in 1942 which was the first H1-antihistamine used in the treatment of allergic diseases (1666). Within a few years, other H1-antihistamines were made available and are still in use today: pyrilamine maleate (1667), diphenhydramine (1668) and tripelennamine (1669). First-generation H1-antihistamines (e.g. chlorpheniramine, diphenhydramine, prometazine and triprolidine) have an overall unfavourable risk/benefit ratio, since they show poor selectivity and remarkable sedative and anticholinergic effects. Therefore, where possible, these drugs are no longer prescribed for the treatment of allergic rhinitis (1, 3).

Over the last 15 years, pharmacological research has produced several compounds with higher potency, a longer duration of action and minimal sedative effects. These are the so-called new or second-generation H1-antihistamines, as opposed to the older or classic H1-antihistamines.

This class of drugs has recently been the focus of considerable medical scientific interest, both for their multiple anti-allergic properties and because of reports concerning rare but possible severe cardiotoxic effects with two molecules (astemizole and terfenadine). However, a group of molecules with favourable efficacy and safety is now available.

8-2-2-1- Mechanisms of action and rationale
8-2-2-1-1- H1-blocking effect

Although a number of mediators are involved in the pathophysiology of allergic symptoms, histamine still remains the main one. The pathogenic role of histamine has been experimentally demonstrated *in vivo* either after specific nasal challenge or under natural allergen exposure (642, 660, 1670). Histamine acts in the nose predominantly via H1-receptors, whereas the role of H2-receptors has not been fully clarified (1671-1673).

The human histamine H1-receptor gene, an intron-lacking gene, was isolated with bovine H1-receptor cDNA (1674) used as a probe (1675). H1-histamine stimulation reproduces any of the classical symptoms of rhinitis e.g. sneezing, itching and rhinorrhea and therefore these symptoms can be well controlled by administering H1-antihistamines (for review on clinical efficacy see 1676-1681). On the other hand, nasal blockage, which usually predominates in persistent allergic rhinitis, is sustained by a chronic inflammatory process and by numerous mediators, thus it responds only partially to H1-antihistamines.

H1-antihistamines act by binding to H1-histamine receptors. However, unlike histamine, the binding of the antagonists to the receptors does not elicit a tissue response.

The molecular study of the H1-receptor will make it possible to better identify new molecules. With cloning of the genes encoding the histamine H1-receptor, a new area of histamine research has become reality. Finally, it seems feasible to study the target of the therapeutically important classes of H1-antihistamines. Expression of the genes in mammalian cells allows detailed investigations of the various signal transduction routes of the histamine H1-receptor (1682). Moreover, using molecular biological techniques, it is now possible to investigate ligand receptor interaction at the molecular level (1683, 1684). These methods can be combined with a three-dimensional model of the histamine H1-receptor (1685, 1686). Studies with mutant H1-receptors have shown that H1-antihistamines bind to specific amino acid residues in the trans-membrane domains 3 and 5 and on Lys(200), and that they act as a specific anchor point for these "second-generation" H(1) antagonists. It is expected that these new developments will provide much fundamental knowledge on the ligand interaction with the H1-receptor.

8-2-2-1-2- Anti-allergic effects

Histamine is not the only mediator released during allergic reactions. The rank order of relative H1 antagonism by H1-antihistamines was studied by Simons *et al.* using skin tests with histamine and single doses of H1-antihistamines. The order from the most effective to the least effective was found to be: cetirizine, 10 mg; terfenadine, 120 mg; terfenadine, 60 mg; loratadine, 10 mg; astemizole, 10 mg; chlorpheniramine, 4 mg and placebo (1687). Other studies confirmed such ranking order (1688). However, when these drugs are compared in placebo-controlled clinical trials, it is usually impossible to differentiate their clinical efficacy in the treatment of nasal, ocular or skin symptoms (1689-1697). Skin test reactivity does not correlate with symptoms during nasal challenge (1698) or during the pollen season (1699). This suggests that these drugs are clinically active by possessing other properties besides H1 blocking activity, or alternatively that an incomplete H1 blockage is sufficient for clinical efficacy. Moreover, the blockage of the

release of histamine by a synthesis inhibitor was unable to significantly suppress symptoms during nasal challenge (1700).

Thus, it appears that drugs reducing the symptoms of the allergic reaction may have additive properties to H1 blockage. Over the past 15 years, it has become clear that most classical and new-generation H1-antihistamines had such anti-allergic properties besides H1 blockage (1701). These properties differ depending on the molecule and the cells used (1702-1706). *In vitro*, high concentrations of H1-antihistamines are able to block mediator release from basophils and human mast cells (1707-1711) by mechanisms which are not yet completely understood (1712).

These anti-allergic effects can also be seen *in vivo* in skin, nasal, lung and ocular challenge studies. Using nasal challenge with allergen, it has been observed that azatadine, loratadine and terfenadine reduce histamine, PGD_2 and kinin release during challenge (1713-1716). Cetirizine was found to reduce tryptase levels in nasal secretions (1717). Azelastine (1718) and cetirizine (1716) decreased CysLT release. On the other hand, the effects of ketotifen were rather disappointing in this particular model since mediator release was not blocked as expected (1719). Ebastine reduced cytokine production (1702). Cetirizine, at least in some studies in the skin, reduced eosinophil chemotaxis after allergen challenge (1720-1724) but no effect of cetirizine was found on eosinophils after allergen bronchial (1725) or nasal challenge (1215). Moreover, terfenadine, cetirizine and loratadine decrease the expression of ICAM-1 in cells from conjunctival or nasal secretions during allergen challenge (1024, 1726-1729) or natural allergen exposure such as pollens (1027, 1028, 1031, 1730-1732) or mites (1733).

The extent of these anti-allergic effects are not completely understood, yet these studies have led to the concept of anti-allergic drugs with H1-blocking properties (1701, 1734). However, it would be premature to attempt to reclassify the H1-antihistamines according to their anti-allergic properties because these properties have not been fully investigated and their relative contribution to the overall therapeutic effectiveness of each H1-antihistamine is unknown (1735).

Due to their variable H1-blocking activity, their anti-allergic effects and, possibly, their differences in lipophilicity and tissue deposition, the various H1-antihistamines are not equally effective on skin, nose, eye or lung symptoms. Moreover, it appears that not all H1-antihistamines have similar effects in patients and thus non-responders with one drug may respond favourably to another drug (1736).

8-2-2-2- Clinical and pharmacological effects

The newer H1-antihistamines are generally less likely to cause sedation, and most of them, due to their pharmacodynamic properties, can be administered OD (1465, 1737).

The new H1-antihistamines are highly selective to the H1-receptors and are therefore effective in reducing itching, sneezing and watery rhinorrhea (for review on clinical efficacy see 1676-1681). However, they are less effective on nasal obstruction (1738). It is important to note that when administered orally, an H1-antihistamine exerts its effects also on non-nasal symptoms such as conjunctivitis, which is often present in rhinitics. It has been shown that long-term continuous treatment with H1-antihistamines is more advantageous and effective than an "on demand" regimen (1739). Moreover, long-term treatment may also improve lower respiratory symptoms in children (1740). In infants with house dust mite or grass pollen sensitisation, but not in those with cat sensitisation, long-term treatment may exert a prophylactic effect (1741) on asthma onset.

Most of the new H1-antihistamines have a fast onset of action (1-2 hours) and their effects last for up to 24 hours except in the case of acrivastine, which needs multiple daily doses.

All the newer H1-antihistamines (except for cetirizine and fexofenadine) undergo hepatic metabolism via the cytochrome P450 system and most of them are transformed into active metabolites. Cytochrome P4503A (CYP3A) has an important involvement in the metabolism of many chemically diverse drugs administered to humans (1742, 1743). Moreover, its localisation in high amounts both in the small intestinal epithelium and liver makes it a major contributor to pre-systemic elimination following oral drug administration. Drug interactions involving enzyme inhibition or induction are common following the co-administration of two or more CYP3A substrates (1744). Cetirizine, which is the active metabolite of hydroxyzine, and fexofenadine, which is the active metabolite of terfenadine, are in turn poorly metabolised. Mizolastine is active *per se*. It is partly metabolised by cytochrome P450 and predominantly glucuronidated in the liver.

8-2-2-3- Side effects of H1-antihistamines

8-2-2-3-1- Central nervous system side effects

The most troublesome side effect of older H1-antihistamines is sedation. This can be defined as a global impairment of psychomotor performance and, subjectively, as a proclivity to fall asleep. Sedation, however, is often an important consequence of rhinitis itself (17).

Histamine is considered to be both a local hormone and a neurotransmitter in the central nervous system (CNS) (1745). It is synthesised by neurons and mast cells. The three types of receptors are present in the CNS but differ in their localisation, biochemical machinery, function and affinity for histamine. H1-receptors may be visualised by autoradiography and are widespread throughout the CNS. The physiological roles of H1-receptors in the CNS need better understanding, but it is well known that H1-antihistamines induce several effects.

- The most common side effect of classical H1-antihistamines is sedation. Sedation, ranging from mild drowsiness to deep sleep, can occur frequently, even at the usual therapeutic doses.
- CNS depression. Symptoms of CNS depression are disturbed coordination, dizziness, lassitude and inability to concentrate (1746, 1747).
- CNS stimulation.

Many factors have been involved in the CNS side effects of H1-antihistamines and can be attributed:

- to the poor selectivity to H1-receptors,

- to the capacity of crossing the blood-brain barrier (1748). This latter concept involves a number of different factors including lipophophilicity (1749, 1750), ionisation, binding to serum proteins and presence of active transportation. Non-sedative H1-antihistamines do not cross this barrier because of their decreased lipophilicity.
- Moreover, there is a highly significant correlation between the sedation caused by H1-antihistamines and the level of their binding on brain receptors (1751). Non-sedative H1-antihistamines may have a reduced affinity for CNS histamine receptors (1752, 1753).

The new generation compounds are mostly devoid of CNS side effects (1754). The absence of a sedating effect at therapeutic doses has been demonstrated for most of the new compounds (1755) by means of specific psychomotor tests (for review see 1756-1760). CNS side effects are potentiated by alcohol in classical H1-antihistamines (1761), but not in new-generation compounds (1762-1764).

Elderly patients present a greater risk for central nervous system side effects and old-generation antihistamines should not be used (1765).

8-2-2-3-2- Cardiac side effects

Over the last ten years, arrhythmogenic action and fatalities have been described for terfenadine and astemizole (1755, 1766, 1767). However, this is not a class effect and is only associated with terfenadine and astemizole, which have been withdrawn in several countries due to these side effects. This effect is a quinidine-like action that involves an abnormal prolongation of the QT interval (1768), possibly leading to torsade de pointes, ventricular tachycardia, atrioventricular block and cardiac arrest (1769-1802).

The cardiac action potential is generated by the transmembrane movement of several ion currents including Na^+, Ca^{2+} and K^{+0}. Disturbances in any of these ionic movements, in particular the potassium ions, may cause dysrhythmias (1803). The molecular mechanism sustaining the cardiotoxic action of H1-antihistamines appears to be the blockage of some potassium channels on ventricular myocytes, namely IKr and IK1, which are responsible for the inward rectifier current (1804-1806). The proclivity to block ion channels depends upon the molecular structure of the drug and it is maximal for terfenadine and astemizole. The blockage of these channels may occur and become clinically significant in the case of an abnormal plasma concentration of the drug due to an overdose or an impaired metabolism.

The risks of non-sedating H1-antihistamines were reviewed in the WHO adverse drug reaction database. It was suggested that cardiac side effects might be seen with many of these H1-antihistamines (1807). However, this report was based on crude adverse event reporting that contained inherent flaws and biases (1808). Therefore, concerns raised by this report cannot be confirmed.

There is a dose-dependent effect on cardiac toxicity. This is relevant for drugs metabolised by the P450 cytochrome since the concomitant administration of compounds which compete with the enzyme (macrolides, azolic antifungals) may reduce the metabolism of the H1-antihistamine and increase its plasma concentration. Loratadine (1809-1811) and ebastine (1812, 1813), although metabolised in the liver, do not appear to possess the intrinsic capacity to block ion channels. Strong experimental support is still missing for ebastine. On the other hand, cetirizine (1814), fexofenadine (1815, 1816) and mizolastine (1817) are poorly metabolised. Moreover, in healthy volunteers, there is no evidence of an effect of mizolastine (up to 40 mg - four times the therapeutic dose) on ventricular re-polarisation (1818).

8-2-2-3-3- Carcinogenic effects

Over the past 60 years, there has been no clinical evidence of suspected or actual carcinogenicity of commercial H1-antihistamines. A carcinogenic potential of loratadine hydroxyzine and astemizole was reported in a single study on mice (1819), but these results were not confirmed. Moreover, the results obtained in rodents are not immediately transferable to humans because of the different experimental conditions and the different cellular metabolic systems (1820, 1821). Cetirizine was found to have some clastogenic and aneugenic potential using CREST and FISH assays (1822), but these effects were shown at high doses and do not appear to be clinically relevant. Therefore, to date, there is no evidence of carcinogenicity or tumour promotion in humans taking H1-antihistamines (1823).

8-2-2-3-4- Other side effects

Most, if not all, classical H1-antihistamines possess pharmacological effects that are not related to H1-blockage.

- Many H1-antihistamines block cholinergic muscarinic receptors in a dose-dependent manner (1824). Due to the anticholinergic effect, the older compounds often cause a dry mouth, tachycardia and urine voiding.
- Cyproheptadine and ketotifen may cause appetite stimulation and consequent weight gain. This side effect does not appear to be a clinical problem with other newer compounds (1825, 1826). Weight gain can be observed with astemizole (1827).
- Certain H1-antihistamines, particularly promethazine, possess α-adrenergic receptor blocking properties. Others increase adrenergic effects by a cocaine-like effect, which decreases the re-uptake of the transmitter. Other H1-antihistamines possess anti-serotonine (1828) or anti-dopamine effects (phenothiazines) (1829).
- Several but not all H1-antihistamines are analgesic agents and some are also analgesic adjuvants. Effectiveness is reported in diphenhydramine, hydroxyzine, orphenadrine, pyrilamine, phenyltoloxamine, promethazine, methdilazine and tripelennamine.
- Gastrointestinal disturbances include nausea, vomiting, diarrhoea, loss of appetite and epigastric distress and are observed more frequently with some members of the ethylenediamine class.

> **TABLE 17:** Properties of H1-antihistamines
>
> Several properties should be met by the new-generation H1-antihistamines:
> - **pharmacological properties:**
>   - potent and non-competitive H1-receptor blockage,
>   - additive anti-allergic activities,
>   - no interference of activity by foods,
> - **side effects:**
>   - no sedation,
>   - no anticholinergic effect,
>   - no weight gain,
>   - knowledge and prevention of cardiac side effects,
> - **pharmacokinetics:**
>   - rapid onset of action,
>   - long duration of action, at least 24 hr,
>   - administration once a day,
>   - no development of tachyphylaxis (1830, 1831).

8-2-2-4- Molecules used

8-2-2-4-1- Acrivastine

Acrivastine is a side-chain-reduced metabolite of the H1-antihistamine triprolidine (1832, 1833).

- It is a short-acting histamine H1-receptor antagonist. Its effects usually last for about 4 to 6 hours.
- Double-blind, placebo-controlled clinical trial results have shown acrivastine (usually 8 mg, three times daily) to be an effective H1-antihistamine in the treatment of seasonal allergic rhinitis (1834, 1835).
- Acrivastine was found to cause less drowsiness than clemastine (1836), but it has some sedative effects (1757, 1837, 1838) and CNS interactions with alcohol have been observed (1839).

8-2-2-4-2- Astemizole

- Astemizole is a long-acting H1-antihistamine
- with no anticholinergic effects (1840-1842).
- Double-blind, placebo-controlled clinical trial results have shown that astemizole 10 mg OD is effective in the treatment of seasonal
- or perennial allergic rhinitis (1843-1850).
- Astemizole is effective in allergic conjunctivitis.
- In comparison to other H1-antihistamines, astemizole may not be as effective for the treatment of acute allergic symptoms because of its delayed onset of action (1532, 1851, 1852).
- Astemizole is non-sedating.
- Increased appetite and weight gain may occur (1827).
- Astemizole is metabolised by the liver cytochrome P450 and drug interactions with other compounds of the same metabolism have been observed.
- Cardiac side effects in the form of torsade-de-pointes are unusual (1744, 1767, 1791, 1794, 1795, 1806, 1827, 1853-1860). These are concentration-dependent, implying that the dosage of astemizole should not be increased above the stipulated level. Drug interactions (e.g. macrolide antibiotics and azolic antifungals) should be carefully avoided. Also, patients with underlying hepatic or cardiac disease should not take this agent.

- Due to its cardiac side effects, astemizole has been withdrawn from the market in most countries. Where possible, H1-antihistamines with the least potential for cardiac side effects should be used.

8-2-2-4-3- Azelastine

- Azelastine has H1-antihistamine activity.
- *In vitro,* it inhibits mediator release from mast cells and from cells relevant to the allergic inflammation following antigen and non-antigen stimuli (1863-1870). *In vivo*, in humans, some studies have confirmed anti-allergic effects (1718).
- Double-blind, placebo-controlled clinical trial results have shown that orally administered azelastine in doses of up to 4 mg/day significantly relieved symptoms in patients with seasonal (1871) or
- perennial allergic rhinitis (1872).
- In addition, azelastine, administered as an intranasal or intra-ocular formulation, was effective in alleviating symptoms of seasonal and perennial allergic rhinitis and conjunctivitis (see chapter 8-2-3).
- Azelastine was also tested as an anti asthmatic agent (1873-1877) but its indications need further studies in order to be fully appreciated. The drug is able to reduce allergen challenge-induced bronchoconstriction (1878, 1879) and non-specific bronchial hyperreactivity (1880). In most countries, azelastine is not approved for asthma.
- Azelastine is often well tolerated but, when administered orally, the most common adverse effects are an altered taste perception and drowsiness (1867). Administered intranasally, azelastine does not induce sedation at doses used in Europe (0.56 mg). However, it has a reported incidence of sedation (slightly greater than placebo) at doses used in the US (1.12 mg). Some patients present taste perversion.

8-2-2-4-4- Cetirizine

- Cetirizine is a piperazine derivative and carboxylated metabolite of hydroxyzine.
- It is a long-acting histamine H1-receptor antagonist. Cetirizine has a potent H1 blocking activity on skin tests (1687, 1688, 1881-1884) and nasal challenge (1885, 1886). In these models, cetirizine was found to be the most potent drug. However, most of these studies were carried out using single doses of H1-antihistamine and the differential effect between cetirizine and other H1-antihistamines was reduced using multiple doses (1887). The clinical relevance of skin tests or nasal challenge is not fully understood.
- There is no anti-cholinergic effect (1888).
- Some anti-allergic properties have been observed *in vivo* in man (see chapter 8-2-2-2).
- Double-blind, placebo-controlled clinical trial results indicate that cetirizine 10 mg OD is an effective treatment for seasonal allergic rhinitis,
- or perennial allergic rhinitis (1889-1899).
- Cetrizine is also effective in the treatment of allergic conjunctivitis (1900, 1901).

- In perennial allergic rhinitis patients, cetrizine was found to significantly improve quality of life (1899).
- Cetirizine was found to be effective in children in double-blind, placebo-controlled studies (1893, 1896, 1897, 1902, 1903).
- Continuous treatment reduces clinical and inflammatory variables more than symptomatic treatment given prn (1739).
- In asthma, cetirizine may improve symptoms during the pollen season (1904-1906) but more data are needed. Studies during allergen bronchial challenge are not all positive (1907). Cetirizine can induce a bronchodilatation (1908, 1909). However, there is no indication for cetirizine in asthma (1910-1912).
- In the ETAC® (Early Treatment of the Atopic Child) trial (1741), a multi-country, double-blind, randomised, placebo-controlled trial, 817 infants were treated for 18 months with either cetirizine (0.25 mg/kg BID) or placebo. Cetirizine halved the number of patients developing asthma in the subgroups sensitised to grass pollen or to house dust mite (20% of the study population).
- Using the subjective assessment of CNS function reported during drug trials, cetirizine is associated with a significantly lower incidence of sedation than hydroxyzine (1913, 1914). In these trials, cetirizine did not appear to be more sedating than placebo or other H1-antihistamines. However, in three double-blind, placebo-controlled studies (1889, 1892, 1894), cetirizine had a reported incidence of sedation greater than placebo. For driving performance, cetirizine did not differentiate from placebo and there were no significant additive effects of alcohol in most (1764, 1915, 1916) but not all studies (1917). Divergent results were obtained for vigilance (1918, 1919). When assessed objectively in pharmacodynamic comparisons, cetirizine was rarely more sedating than placebo or other second-generation H1-antihistamines (1676, 1758, 1913, 1920-1926).
- The long-term safety of cetirizine in infants has been largely demonstrated (1927).
- Cetirizine is not metabolised in the liver.
- No cardiac side effects have been reported (1814).

8-2-2-4-5- Ebastine
- Ebastine is a piperidine derivative (1678, 1928, 1929).
- Ebastine and its active metabolite carebastine are highly potent selective H1-receptor antagonists (1688, 1930-1932).
- Ebastine is devoid of any other noticeable receptor binding and has no anti-cholinergic effects.
- Some anti-allergic properties have been observed *in vivo* in man (see chapter 8-2-2-2).
- Double-blind, placebo-controlled clinical trial results have shown that, administered at doses of 10 mg OD, ebastine was found to be effective in seasonal
- or perennial allergic rhinitis (1933-1937).
- However, a dose of 20 mg OD was found to be more effective and a dual dosage has been suggested: 10 mg OD for mild rhinitis and 20 mg OD for severe seasonal (1938) and perennial rhinitis (1937, 1939).
- Ebastine is effective in allergic conjunctivitis.

- Ebastine is effective and safe in children.
- Ebastine has not been tested in asthma using double-blind, placebo-controlled studies.
- Ebastine does not induce sedation in clinical trials. The results suggest that ebastine in doses of up to 30 mg may be relatively safe for use by those who drive motor vehicles while receiving this medication (1940). Ebastine has no interaction with alcohol (1941). Objective measures of sedation did not show alterations in psychomotor performance and autonomic responses (1942, 1943).
- Ebastine interacts with cytochrome P450 (1744).
- Ebastine does not appear to possess cardiovascular side effects at recommended doses of 10 or 20 mg (1812, 1813, 1944-1946).

8-2-2-4-6- Emedastine
Emedastine is an H1-antihistamine (1947, 1948) for intra-ocular use (1949, 1950). It has been tested using conjunctival challenge (1951). There is, however, no controlled clinical study available on Medline.

8-2-2-4-7- Epinastine
Epinastine is an H1-antihistamine widely studied *in vitro* and in animals (1688, 1952-1962). There is, however, no controlled clinical study on Medline.

Epinastine seems to be non-sedating (1959). It is very poorly metabolised compared to terfenadine in human liver microsomes and does not inhibit CYP3A4 activity *in vitro* (1963). Cardiotoxic activity has been tested *in vitro* and *in vivo* in animals only and epinastine was not shown to have adverse effects (1964-1966).

8-2-2-4-8- Fexofenadine
Fexofenadine is the pharmacologically active metabolite of terfenadine (1967).
- It is a potent H1-antihistamine in skin test models (1677, 1968, 1969).
- It does not have anti-cholinergic properties.
- Its pharmacokinetics have been studied in adults and children (1970) and support OD dosing.
- Some anti-allergic properties have been observed *in vivo* in man (see chapter 8-2-2-2).
- Fexofenadine was found to reduce symptoms from nasal challenge with allergen (1971).
- Double-blind, placebo-controlled clinical trial results have shown that fexofenadine 120 or 180 mg OD controlled symptoms in patients with seasonal allergic rhinitis as effectively as cetirizine. Other double-blind clinical trials showed that fexofenadine 40 to 240 mg BID was significantly more effective than placebo (1816, 1894, 1972, 1973).
- Fexofenadine is also effective in allergic conjunctivitis.
- Compared with placebo, once-daily fexofenadine (120 or 180 mg) significantly improved patient-reported quality of life and reduced performance impairment in work and daily activities due to seasonal allergic rhinitis symptoms (1974).
- Fexofenadine is non-sedating (1816, 1894, 1972, 1973) and does not impair driving performance. It does not potentiate alcohol sedative effects (1975).
- Fexofenadine is not metabolised by the liver.

- Relative to placebo, fexofenadine did not affect mean QTc in patients who were given dosages of up to 480 mg/day for 2 weeks or in volunteers who received up to 800 mg/day for 6 days or 240 mg/day for 12 months. Although a letter reported some prolongation of QTc in one patient (1976), further assessment in this patient did not support fexofenadine as a cause (1977) and it appears that fexofenadine is not cardiotoxic (1815, 1978). Thus, this report did not lead to any change in the labelling of the drug.

8-2-2-4-9- Levocabastine

Levocabastine is a cyclohexylpiperidine derivative shown to possess long-lasting H1 antagonism and anti-allergic properties in animals (1979). It has only been developed for nasal and ocular administration due to its sedative effects.

In controlled trials, levocabastine was effective and well tolerated in the treatment of allergic rhinitis and allergic conjunctivitis (see chapter 8-2-3).

8-2-2-4-10- Loratadine
- Loratadine is a piperidine derivative.
- Loratadine is a long-acting H1-antihistamine (1753, 1980, 1981).
- No tachyphylaxis was observed over a 12-week treatment period (1831).
- No anti-cholinergic effect has been reported.
- Some anti-allergic properties have been observed *in vivo* in man (see chapter 8-2-2-2).
- Double-blind, placebo-controlled clinical trial results have shown that loratadine (10 mg OD) is an effective H1-antihistamine in seasonal allergic rhinitis (1689, 1691-1693, 1699, 1982-1985)
- or perennial allergic rhinitis (1690, 1986).
- Loratadine was also shown to be effective in the treatment of allergic conjunctivitis (1691, 1692, 1986).
- Loratadine significantly reduces skin tests to histamine, but its clinical efficacy was not correlated with skin test reactivity to histamine (1699, 1887).
- Prophylactic loratadine therapy was studied and was shown to be effective in suppressing symptoms of seasonal allergic rhinitis and in providing patients with symptom-free days throughout the pollen season (1987).
- Loratadine was also found to have an adjunct effect in the treatment of acute sinusitis (1988).
- No sedative effect or impairment of cognitive function or psychomotor performance have been observed with loratadine at the recommended 10 mg dose (1989-1994).
- Loratadine was found to be safe in children as young as 2 years of age.
- Loratadine is metabolised in the liver by cytochrome P450.
- No cardiac side effects have been reported in clinical studies with loratadine (1744, 1767, 1806, 1827, 1854, 1995, 1996). A report on one clinical case described a cardiac arrhythmia in a patient receiving loratadine (1997) but the causal relationship with the drug was unclear (1998). Thus, this report did not lead to any change in the labelling of the drug.

8-2-2-4-11- Mequitazine

Mequitazine is an oral H1-antihistamine with mild anti-cholinergic properties. It was found to be effective in seasonal (1691, 1999) and perennial allergic rhinitis (2000). Some sedative effects have been observed although psychomotor tests have not provided objective confirmation (2001, 2002).

Mequitazine has also been used as an intra-ocular drug in the treatment of allergic conjunctivitis and has been found effective in a challenge model (2003).

8-2-2-4-12- Mizolastine
- Mizolastine is a long-acting H1-antihistamine (1818, 2004)
- without anti-cholinergic effects (2005, 2006).
- Mizolastine has demonstrated anti-allergic effects in animals (2007-2009) and healthy volunteers and anti-inflammatory activity in animal models.
- No tachyphylaxis occurred throughout a prolonged treatment with mizolastine (2010).
- Double-blind trials have shown mizolastine to be significantly more effective than placebo and as effective as other second-generation antihistamine agents, such as loratadine or cetirizine, in the management of patients with seasonal allergic rhinitis (1679, 2011, 2012)
- or perennial (2013, 2014) allergic rhinitis. It has some effect on nasal blockage (2014).
- In conjunctivitis, mizolastine was found to be effective (1679, 2011, 2012).
- Available data also suggest that the prophylactic administration of mizolastine is significantly more effective than placebo and as effective as prophylactic terfenadine in delaying the onset of symptoms of seasonal allergic rhinitis (2011).
- Mizolastine 10 mg/day is generally well tolerated, with common adverse events. Sedation has been reported to be similar to the effect induced by placebo. Tests of psychomotor function in volunteers (2015) or animals (1916, 2016, 2017) revealed no impairment.
- Mizolastine is partly metabolised by cytochrome P450.
- In volunteers and patients, the incidence of prolonged QTc interval was similar in mizolastine and placebo treated subjects (1818, 1996).
- Nonetheless, mizolastine is contraindicated in those with cardiac disease or hepatic impairment or in those receiving erythromycin, ketoconazole or class I or III anti-arrhythmic agents.

8-2-2-4-13- Terfenadine
- Terfenadine is a selective histamine H1-receptor antagonist (2018)
- which is devoid of CNS and anticholinergic activity (1681, 2019).
- Some anti-allergic properties have been observed *in vivo* in man (see chapter 8-2-2-2).
- Double-blind, placebo-controlled clinical trial results have shown that terfenadine at a dose of 60 mg administered BID is effective in patients with seasonal allergic rhinitis (1689, 1692, 1892, 1984, 1985, 2020-2022).

- Terfenadine 60 mg BID is effective in perennial rhinitis (1690).
- The drug has been approved at an OD dose of 120 mg on the basis of equivalence in comparative (not placebo-controlled) trials (2023).
- Terfenadine was also found to be effective in allergic conjunctivitis (1689, 1692, 1984, 1985, 2021)
- and in children with allergic rhinitis in autumn (2024).
- Terfenadine, when administered at the onset and during the season, is more effective than when administered during the season (2025).
- Terfenadine is non-sedating (2021) and neither impairs psychomotor performance nor adversely affects subjective feelings, nor enhances the depressant effects of concomitantly administered alcohol or benzodiazepines (1681, 1763).
- Terfenadine is metabolised in the liver by cytochrome P450, and interactions with ketoconazole, itroconazole or erythromycin have been identified (1789).
- Cardiac side effects including torsade de pointes are unusual (1744, 1766-1768, 1791, 1806, 1812, 1814, 1818, 1827, 1854, 1858-1862, 2026-2034) and are concentration-dependent. This implies that the dosage of terfenadine should not be increased and that drug interactions should be carefully avoided.
- Due to its cardiac side effects, terfenadine has been withdrawn from most countries (2035). Where possible, H1-antihistamines with the least potential for cardiac side effects should be used.

8-2-2-4-14- Ketotifen

Ketotifen is an H1-antihistamine with *in vitro* anti-allergic properties. *In vivo*, in humans, such properties have not been confirmed (1719).

Ketotifen has shown efficacy in patients with allergic rhinitis (2036, 2037).

Sedation can be troublesome in older children and adults, usually for the initial 2 weeks of treatment. Weight gain is another notable side effect (2038).

In Japan, ketotifen is also used topically.

8-2-2-4-15- Oxatomide

Oxatomide is an orally active H1-histamine receptor antagonist which also inhibits mediator release (2039). Oxatomide has been found to be more effective than placebo in the treatment of allergic rhinitis (2040, 2041). Sedation is a common side effect, as is weight gain (2042, 2043).

8-2-2-4-16- Other molecules

Non-sedating first-generation antihistamines (e.g. brompheniramine, clemastine, chlorpheniramine) will not be reviewed in this document since the risk/benefit ratio is not as favourable as for the newer molecules. There are several other molecules which have not been fully tested in clinical trials by use of double-blind, placebo-controlled designs, which have yet to be reviewed (1529, 2044).

8-2-2-5- The future of H1-antihistamines

With the cloning of the gene encoding the histamine H1-receptor, a new area of histamine research has become reality. Finally, it seems feasible to study the target of the therapeutically important classes of H1-antihistamine. Expression of the genes in mammalian cells allows detailed investigations of the various signal transduction routes of the histamine H1-receptor (1682). Moreover, using molecular biological techniques, it is now possible to investigate ligand receptor interaction at the molecular level. It is expected that these new developments will provide much fundamental knowledge on the ligand interaction with the H1-receptor (2045).

8-2-2-6- Recommendations

Old-generation H1 antihistamines are effective (1871, 1983, 1986, 2046, 2047) and may be the only molecules available in some developing countries. But because of their more favourable risk/benefit ratio and enhanced pharmacokinetics (1, 3, 1746, 1747, 1751, 1756, 1757, 1758), new H1-antihistamines should be considered as a first-choice treatment for allergic rhinitis when they are available and affordable. However, in some countries, not all molecules are available and the choice may be restricted. The anti-allergic activities exerted by some drugs would suggest that long-term use is preferable to an "on demand" regimen, especially in persistent disease. In perennial allergic rhinitis, when obstruction is the predominant symptom, intranasal glucocorticosteroids should either be added to a H1-antihistamine or used as a first choice drug.

8-2-3- Topical H1-antihistamines

8-2-3-1- Rationale

The major advantage of delivering drugs directly into the nose is that high concentrations can be delivered more effectively into the target organ and systemic side effects are avoided or minimised.

8-2-3-2- Efficacy

8-2-3-2-1- Nasal administration

At least two intranasal H1-antihistamines are commercially available for the treatment of allergic rhinitis: azelastine (1867, 2048) and levocabastine (1979, 2049). These two drugs are effective and highly specific H1-receptor antagonists.

- Azelastine and levocabastine nasal sprays offer prompt relief for itching and sneezing (2050) and, when used BID regularly, they can also prevent the onset of symptoms.
- These drugs are effective during nasal challenge with allergen or histamine (1717, 1718, 2051-2062) and in park studies (2056).
- In double-blind, placebo-controlled studies, intranasal azelastine and levocabastine were shown to be effective in seasonal allergic rhinitis (2055, 2057-2066) ,
- or perennial allergic rhinitis (2067-2069).
- Azelastine was also found to be effective in children (2055, 2058, 2070).
- It was found in one study that long-term continuous treatment with azelastine was more effective than an "on demand" treatment regimen.
- Intranasal azelastine is more rapidly effective than beclomethasone dipropionate but in the long term, its

effects are less potent (2059). It was observed in some studies that azelastine was effective on nasal obstruction but, apparently, to a lesser extent than intranasal glucocorticosteroids (2071). Intranasal fluticasone was found to be significantly more effective than levocabastine in the treatment of seasonal allergic rhinitis (2072, 2073). The therapeutic benefits of intranasal fluticasone were also reflected by the decrease in nasal inflammatory cells (2072).

8-2-3-2-1- Ocular administration

- Azelastine and levocabastine have both been developed as eye drops for the intra-ocular treatment of allergic conjunctivitis.
- In double-blind, placebo-controlled studies, these drugs were found to be effective in seasonal symptoms (2074-2083) and during ocular provocation tests (2084).
- They demonstrate a similar efficacy profile to oral H1-antihistamines with the advantage of a significantly faster onset of action on both nasal and ocular symptoms.
- Topical treatment is, however, specific to the site of administration.
- Usually, intra-ocular levocabastine was found to be superior to cromoglycate in the treatment of allergic conjunctivitis (2079, 2085).
- Naphazoline/antazoline eye drops are also available for the treatment of allergic conjunctivitis but apparently no double-blind, placebo-controlled study has been carried out (1303).

8-2-3-3- Safety

In general, neither azelastine nor levocabastine, when topically administered at the recommended dose, show any significant sedative effect (2079, 2081, 2086, 2087) (see chapter 8-2-2-4-3).

One specific side effect, a short lasting perversion of taste, has been described for azelastine.

8-2-3-4- Recommendations

Topical H1-antihistamines have a rapid onset of action (less than 15 minutes) at low drug dosage, but they act only on the treated organ. Topical H1-antihistamines usually require bi-daily (BID) administrations to maintain a satisfactory clinical effect. Their use may therefore be recommended for mild organ-limited disease, as an "on demand" medication in conjuction with a continuous one (2088).

8-2-4- Topical glucocorticosteroids

Early attempts to use glucocorticosteroids like hydrocortisone or dexamethasone topically in the airways failed because they were either ineffective or had substantial systemic effects. The situation changed when beclomethasone dipropionate was introduced as an aerosol in 1972 (2089). Beclomethasone dipropionate separates anti-inflammatory and unwanted systemic activities by its high affinity for the glucocorticoid receptor. Moreover, the portion swallowed after inhalation/intranasal use (80-90% of the inhaled dose) is subjected to first-pass deactivation in the liver before reaching the systemic circulation. In 1973, beclomethasone dipropionate was introduced as a nasal

spray for seasonal allergic rhinitis (2090). Subsequently, other new intranasal glucocorticosteroids have been developed. They include budesonide, flunisolide, fluticasone propionate, mometasone furoate and triamcinolone acetonide (the commercial availability of these products depends upon the country).

Glucocorticosteroids are currently the most potent medication available for the treatment of allergic and non-allergic rhinitis. The effect of intranasal glucocorticosteroids is based on local activity. Oral administration of the equivalent amount of drug produces no benefit (2091-2093). The introduction of intranasal glucocorticosteroids is one of the best examples of how the therapeutic index of a medication can be dramatically improved when it is administered topically. Initially reserved as a second-line agent, the role of intranasal glucocorticosteroids is now changing. In three international reports on the management of rhinitis, intranasal glucocorticosteroids were considered as a first-line therapy for adults in moderate to severe cases of seasonal and perennial allergic rhinitis (1-3).

8-2-4-1- Mechanisms of action and rationale

The symptomatology of allergic rhinitis is currently considered to be caused mainly by the accumulation and activation of infiltrating cells, which release mediators and cytokines and result in allergic inflammation. Glucocorticosteroids can suppress many stages of the allergic inflammatory process. This may explain their potent effect on allergic symptomatology. Symptomatology of allergic inflammation is the consequence of mechanisms of priming to allergen and hyperreactivity. For this reason, it may be preferable to begin local glucocorticosteroid treatment before the onset of symptoms (2094). Also, the treatment appears to be more effective when given continuously (2095).

The rationale for using intranasal glucocorticosteroids in the treatment of allergic rhinitis is that high drug concentrations can be achieved at receptor sites in the nasal mucosa, with a minimal risk of systemic adverse effects.

8-2-4-1-1- Molecular effects

The effect of glucocorticosteroids is caused by binding to a single glucocorticoid receptor (GR), which is predominantly localised to the cytoplasm of target cells. After the binding of the glucocorticoid, the complex moves to the nuclear compartment. The GR is expressed in high density in airway epithelium (2096). Glucocorticosteroids produce their effect on inflammatory cells by activating GR to increase or inhibit gene transcription through a process known as transactivation and transrepression respectively (2097).

Transactivation is mediated by the binding of the hormone-activated GR to a DNA sequence called glucocorticoid response element (GRE) (2098). Genes involved in the control of neoglucogenesis, arterial pressure and intraocular tension contain GRE (2099-2101). Thus, transactivation may account for some GC unwanted effects (diabetes, arterial hypertension, hydrosodic retention, hypokaliaemia, glaucoma). On the other hand, transactivation may also result in a therapeutic benefit in

asthma since GC induces gene expression of the β2-adrenergic receptor (2102).

Transrepression is mediated by inhibitory protein-protein interactions between the hormone-activated GR and transcription factors like AP-1 and NF-κB (2103). AP-1 is a dimer made of peptides belonging to the c-Fos and c-Jun families (2104) whereas NF-κB is a dimer composed of proteins related to p65 (2105). Functional NF-κB response elements (NF-κBRE) and TRE are present in many genes encoding pro-inflammatory mediators and cytokines (2103, 2105). Nur77 homodimers potently activate transcription upon interaction with a novel palindromic response element, the NurRE, and may be involved in HPA axis regulation (2106). The convergence of positive signals mediated by Nur77 (and also probably by related family members) and of negative signals exerted by GR appears to be a general mechanism for the control of transcription, since it is active in both endocrine and lymphoid cells (2107). Expression of the signal transducer and activator of transcription factor 6 (STAT6) is increased in the nasal mucosa of atopic allergic rhinitics. This is reduced by intranasal glucocorticosteroids (2108).

8-2-4-1-2- Anti-inflammatory effects on cells
Glucocorticosteroids can suppress many stages of the inflammatory process. This may explain their strong effect on allergic symptomatology. Many cells and cytokines playing an active role in allergic inflammation in the nose are influenced by intranasal glucocorticosteroid treatment. However, the extent to which cells and cytokines are reduced differs (760).

• Antigen-presenting (Langerhans) cells are highly sensitive to treatment with intranasal glucocorticosteroids (809, 2109). Moreover, glucocorticosteroids also inhibit the uptake and/or processing but not the presentation of antigen by airway Langerhans cells (2110). The significant reduction of Langerhans cells by local glucocorticosteroid therapy could be an explanation for the subsequent reduction of secondary inflammatory response and symptomatology in allergic disease.

• Eosinophils and eosinophil products are also significantly reduced by intranasal glucocorticosteroids (701, 1186, 2111-2117). Even when the allergen stimulus is large, as in allergen provocation studies, or when the local glucocorticosteroid dose is relatively low, the decrease in cells is substantial (760). The reduction in eosinophil numbers tends to be more pronounced in the epithelium than in the *lamina propria*. It has been suggested that intranasal glucocorticosteroids may not only diminish airway eosinophilic infiltration but also decrease eosinophil survival (2112, 2118).

• The influx of basophils and mast cells in the epithelial layers of the nasal mucosa is reduced by intranasal glucocorticosteroids (1142, 2119-2121). Mast cells in the *lamina propria* are only reduced when differences are pronounced either by using a large allergen stimulus or high dose treatment (758, 2111).

• Intranasal glucocorticosteroids reduce T-cells and their subclasses in the epithelium, even in perennial allergic rhinitis (809). In the *lamina propria*, a decrease in T-cells is found only after a large stimulus (2111) or a high-dose treatment (758). T-cell function is also influenced by intranasal glucocorticosteroids (see chapter 8-2-4-1-3).

• Some cells, such as macrophages (791) and neutrophils, do not seem to be influenced. This may explain why intranasal glucocorticosteroids have no adverse effect on the immune response to bacterial infections.

8-2-4-1-3- Anti-inflammatory effects on cytokines
The effects of intranasal glucocorticosteroids on cytokines from the Th2 subgroup have been thoroughly described. Most of the studies have been done in allergen challenge studies. Glucocorticosteroids reduce the levels of mRNA and protein for IL-3, IL-4, IL-5 and IL-13 and their receptors (760, 981, 984, 987, 1186, 2113, 2122). However, some degree of variability has been observed and controversies remain in the literature. The effect of intranasal glucocorticosteroid treatment for other cytokines is not yet fully elucidated. Fluticasone dipropionate has been shown to inhibit the increase in ε germ-line gene transcripts (787, 1080), in CD3+ and in major basic protein (MBP+) cells expressing GM-CSF mRNA. However, increase was not inhibited in macrophages expressing GM-CSF (1145), RANTES, IFN-γ, TNF-α mRNA expressing cells and monocyte chemotactic proteins (1014, 2123). It is not clear whether intranasal glucocorticosteroids have a specific effect on cytokines in the Th2 group. The direct effect of glucocorticosteroids could be explained by the presence or absence of Glucocorticoid Response Element (GRE) in the promoter region of cytokines (2124).

8-2-4-1-4- Other effects of intranasal glucocorticosteroids
Glucocorticosteroids may also reduce the release of preformed and newly generated mediators, such as histamine (2125), tryptase, prostanoids (2126) and leukotrienes (2127). However, this action may be partly due to the reduction of inflammatory cells in the nasal mucosa.

Fluticasone has long-term effects on the nasal response to histamine in perennial allergic rhinitis. Part of this effect is claimed to be vascular (2128).

Intranasal glucocorticosteroids can also act on IgE production. During the pollen season, there is usually an increase in serum and nasal allergen-specific IgE (1077). Intranasal glucocorticosteroids inhibit seasonal increases in ragweed-specific IgE antibodies (2129).

8-2-4-2- Clinical and pharmacological effects
The marked efficacy of intranasal glucocorticosteroids for treating allergic rhinitis is indisputable.

A regular prophylactic use of intranasal glucocorticosteroids is effective in reducing nasal blockage, rhinorrhea, sneezing and nasal itching in adults and children.

In seasonal and perennial allergic rhinitis, intranasal glucocorticosteroids control nasal symptoms in the majority of patients and a meta-analysis has shown that

in rhinitis, intranasal glucocorticosteroids are equally or more effective than oral H1-antihistamines (1738).

Extensive reviews of the clinical studies are available for beclomethasone dipropionate (2130, 2131), budesonide (2132), fluticasone propionate (2133), mometasone furoate (2134, 2135) and triamcinolone acetonide (2136), all agreeing on the clinical efficacy of these compounds. Intranasal glucocorticosteroids are more effective than oral H1-antihistamines (2137-2139), intranasal H1-antihistamines (2140) and intranasal cromoglycate (2141, 2142). The effect of intranasal glucocorticosteroids on nasal blockage and their anti-inflammatory properties favours them to other treatments. This is the case especially in persistent allergic rhinitis, when obstruction is the main symptom and in long-lasting disease (3). They have a slower onset of action than H1-antihistamines, usually less than 12 hours, and maximum efficacy develops over days and weeks (2143-2145). When the nose is extremely congested, intranasal glucocorticosteroids may not be evenly distributed to the mucosa and it may be advisable to administer an intranasal decongestant (e.g. xylomethazoline) or systemic glucocorticosteroids (for no more than a week) to permit improved penetration (3). Intranasal glucocorticosteroids should be given regularly (2095) and in severe cases probably commenced before the beginning of the pollen season for maximal effect (3). An OD medication is usually sufficient in most cases and has good patient compliance (2116, 2146, 2147). BID medication may be necessary in severe cases and during exacerbations. The dose response curve of intranasal glucocorticosteroids is very shallow, and so reducing the dose as much as possible is advisable (2148).

Intranasal glucocorticosteroids were traditionally delivered as freon-propelled aerosols from pressurised canisters. However, since the pressurised aerosols containing CFCs are to be banished, many of the molecules are nowadays administered by mechanical aqueous pump sprays or as dry powder. Delivery systems are equally effective and safe, thus the patient can choose which formulation is personally preferred.

8-2-4-3- Side effects of intranasal glucocorticosteroids

8-2-4-3-1- Local side effects

The current intranasal preparations are well tolerated and can be used on a long-term basis without atrophy of the mucosa (2145). Intranasal glucocorticosteroids may occasionally cause local side effects like crusting, dryness and minor epistaxis but these side effects are mild and often transient (2145, 2147, 2149-2151). Changing to another compound or delivery system sometimes eliminates the side effects. Septal perforations due to a prolonged use of intranasal glucocorticosteroids are rare (2152, 2153). The risk of perforation is greatest during the first 12 months of treatment and the majority of cases involves young women (2153). The direction of the spray (towards the septum) could have an influence and patients should always be advised to aim away from the septum.

8-2-4-3-2- Effects on hypothalamic-pituitary-adrenal axis

Systemic absorption may occur following inhaled and intranasal administration of glucocorticosteroids, but the dose at which clinically relevant side effects occur is controversial (2154, 2155). Patients receiving only intranasal glucocorticosteroids appear to be at a very low risk of developing hypothalamic-pituitary-adrenal (HPA) axis suppression because of the limited systemic drug availability and the low doses required (2156, 2157). Studies have shown that intranasal glucocorticosteroids have no effect on the HPA axis (2135, 2158-2160), except for dexamethasone spray and betamethasone drops, which can rarely provoke systemic effects (2161-2165). The newer nasal glucocorticosteroids, fluticasone propionate, budesonide, triamcinolone acetonide and mometasone furoate, usually show no effect on the HPA axis (2134, 2166-2173).

In one study, the addition of intranasal glucocorticosteroids to intra-bronchial ones did not appear to increase HPA axis suppression (2174). However, more studies are needed to fully appreciate the effect of combined intranasal and intra-bronchial glucocorticosteroids. Moreover, HPA axis suppression does not take into account all potential systemic effects of these drugs.

8-2-4-3-3- Other systemic side effects

One study describes an effect on children's growth due to beclomethasone (2175). In view of recent concerns (FDA, MCA), more data are required on the safety of intranasal glucocorticosteroids in young children (2155). The labelling of all intranasal glucocorticosteroids has therefore been modified in the USA and growth concerns have been indicated. Other side effects such as skin thinning, increased cataract formation, glaucoma, metabolic changes and behavioural abnormalities may be observed with inhaled (bronchial route) glucocorticosteroids. However, they do not appear to be present in patients receiving only intranasal glucocorticosteroids (2154).

8-2-4-3-4- Other side effects

Contact allergic reactions of the skin and mucosa to intranasal glucocorticosteroids are rare but have been described (2176, 2177). In one study, central serous chorioretinopathy in 4 patients was apparently related to the use of intranasal glucocorticosteroid nasal sprays (2178).

8-2-4-3-5- Pregnancy

There are no documented studies concerning intranasal glucocorticosteroids (e.g. budesonide, fluticasone propionate, mometasone) during pregnancy. However, inhaled glucocorticosteroids (e.g. beclomethasone or budesonide (2179)) have not been incriminated as teratogens and are commonly used by pregnant women who have asthma. Although the choice of agents should partly be based on evidence of foetal safety, the issue of maternal health also needs to be considered to provide optimal management.

8-2-4-4- Molecules used

8-2-4-4-1- Beclomethasone dipropionate

- Beclomethasone dipropionate was the first glucocorticosteroid used intranasally for rhinitis (2090).

- It is available as a metered-dose pressurised aerosol and as an aqueous spray.
- The recommended starting dose is 200 μg daily for adults and 100 μg daily for children.
- Double-blind, placebo-controlled studies have shown that it is an effective treatment for seasonal allergic rhinitis (2090, 2130, 2144, 2180, 2181),
- or perennial allergic rhinitis (2182-2184) in adults,
- as well as for non-allergic rhinitis (2185, 2186).
- It is also effective in children with allergic rhinitis (2187, 2188).
- Beclomethasone dipropionate is equally as effective as flunisolide in seasonal and perennial allergic rhinitis (2184, 2189-2192). It has been shown to be more effective than cromoglycate (1284, 2193), terfenadine (2194, 2195) and astemizole except for eye symptoms (2137, 2196, 2197). It has been shown, however, that adding loratadine to intranasal beclomethasone dipropionate improves moderate severe seasonal allergic rhinitis (2198).
- Intranasal beclomethasone was not found to have an effect on the HPA axis at a dose of 336 μg daily (2157) but reduced urinary cortisol at 800 μg daily (2199).
- An effect on one year's growth has been found in one study (2175). In this study, carried out over one year, it was found that intranasal beclomethasone reduced growth by 1 cm in 6-9 year old children receiving standard therapy and these effects were apparent one month after starting the drugs.
- Other systemic adverse effects have not been reported.

8-2-4-4-2- Budesonide
- Intranasal budesonide is available as a metered-dose pressurised aerosol, as an aqueous spray or as dry powder (2132).
- The recommended starting dose is 64 to 256 μg daily for adults and 64 to 128 μg daily for children over 6 years of age.
- Double-blind, placebo-controlled studies have shown that it is an effective intranasal glucocorticosteroid in seasonal allergic rhinitis in adults (2146, 2200-2208),
- in perennial allergic rhinitis (2148, 2209-2211)
- or in non-allergic rhinitis (2148, 2212-2214).
- In children, it is effective in seasonal allergic rhinitis (2215-2218)
- and in perennial rhinitis (2210).
- A prophylactic effect was also demonstrated when budesonide was given prior to the onset of the pollen season (2219).
- Budesonide is effective in patients with nasal polyposis, improving global symptoms (2220-2222), reducing nasal obstruction (2221) and improving sense of smell (2222).
- In controlled clinical trials, budesonide has been shown to be more effective than beclomethasone in perennial non-allergic (2223) rhinitis and equally as effective compared to fluticasone (2151, 2224) and mometasone (2135). One study shows a faster onset of budesonide than fluticasone (2225). Budesonide was found to be more effective than nasal azelastine (2071) or oral H1-antihistamines (2226).

- Intranasal budesonide was not found to have an effect on the HPA axis at a dose of 200 μg daily (2170, 2171) but reduced urinary cortisol in another study (2199).
- An effect on long-term growth has not been observed.
- Other systemic effects have not been reported.
- The long-term safety of budesonide was observed (2227).

8-2-4-4-3- Flunisolide
- Flunisolide is administered at a dose of 200 μg daily for adults.
- Double-blind, placebo-controlled studies have shown that it is an effective intranasal glucocorticosteroid in seasonal (1284, 2228, 2229)
- or perennial allergic rhinitis (2230) in adults
- and in non-allergic rhinitis (2184, 2231-2233).
- Flunisolide was found to be effective in children (2234, 2235) over the age of 4 years.
- In controlled clinical trials, flunisolide has been shown to be equally as effective as beclomethasone dipropionate (1284, 2189, 2191, 2192) and budesonide (2236), and more effective than terfenadine (2237, 2238) or cromoglycate (1284, 2235).
- Effect on the HPA axis has not been reported.
- Effect on growth has not been reported.
- Other systemic effects have not been reported.
- The excipients polyethylene glycol and polypropylene glycol can cause transient local irritation.

8-2-4-4-4- Triamcinolone acetonide
- Triamcinolone acetonide is available as an aerosol or as an aqueous metered-dose pump spray with a recommended starting dose of 220 μg.
- Double-blind, placebo-controlled studies have shown that it is an effective intranasal glucocorticosteroid in seasonal (2160, 2239-2243)
- and perennial allergic rhinitis (2244-2246) in adults.
- Triamcinolone acetonide was found to be effective in children with allergic rhinitis (2247, 2248) within the first day of administration.
- In controlled studies, OD intranasal triamcinolone acetonide (220 μg per day) was equally as effective as beclomethasone (84 to 168 μg BID), fluticasone (200 μg OD (2249)) or flunisolide (100 μg BID) (2136). Furthermore, triamcinolone acetonide aerosol (220 μg OD) was significantly more effective than loratadine, clemastine and astemizole (2250-2252) and was equally as effective in reducing the associated ocular symptoms.
- Intranasal triamcinolone acetonide does not suppress hypothalamic-pituitary-adrenal axis function at therapeutic dosages (2159, 2160, 2170, 2171), even in children (2158).
- Long-term safety of intranasal triamcinolone has been tested over 12 months (2253, 2254).

8-2-4-4-5- Fluticasone propionate
- Intranasal glucocorticosteroid fluticasone propionate (2166) is administered as an aqueous nasal spray with

a recommended starting dose of 200 μg OD for adults and 100 μg OD for children.

- Double-blind, placebo-controlled studies have shown that it is an effective intranasal glucocorticosteroid in seasonal and perennial allergic rhinitis (2109, 2116, 2120, 2145, 2255-61),
- Fluticasone propionate is effective in children of 4 years and above with seasonal allergic rhinitis (2169, 2262, 2263).
- Fluticasone propionate is effective in children of 5 years and above with perennial allergic rhinitis (2264, 2265).
- In adults with non-allergic, non-infectious perennial rhinitis, fluticasone was clinically effective in one study (2258) but not in another one (89).
- In controlled clinical trials, fluticasone propionate has been shown to be as effective as beclomethasone dipropionate (2261, 2266), budesonide (2151, 2224), mometasone (2134, 2135, 2267) and triamcinolone acetonide (2249). It is also effective in nasal polyposis (1365, 1367, 2268). OD fluticasone propionate is more effective than terfenadine (2138, 2269, 2270), loratadine (2271-2273) and intranasal levocabastine (2072, 2073) for the treatment of seasonal and perennial allergic rhinitis. Moreover, the use of fluticasone propionate was more effective than cromoglycate in the prevention of pollen rhinitis symptoms (2141).
- Intranasal fluticasone was not found to have an effect on the HPA axis at a dose of 200 μg daily (2092, 2168), even in children (2169).
- Fluticasone propionate has been shown to be safe also after long-term use (one year) in perennial allergic rhinitis (2145, 2274). After one year of treatment, fluticasone was shown to reduce inflammatory cells and to have long-term clinical effects (2167). Fluticasone has long-term effects on the nasal response to histamine in perennial allergic rhinitis and part of this effect is likely to be vascular (2128).
- Treatment with fluticasone propionate partially prevents the increase in bronchial responsiveness observed during the pollen season (2275).

8-2-4-4-6- Mometasone furoate

- Mometasone furoate is administered as an aqueous nasal spray with a recommended starting dose of 200 μg daily for adults and for children over 12 years of age. It is approved from the age of 3 years at a dose of 100 μg daily (2134, 2135).
- Double-blind, placebo-controlled studies have shown that it is an effective intranasal glucocorticosteroid in seasonal (2150, 2276, 2277)
- and perennial allergic rhinitis (2267) in adults.
- It is effective in children (2278).
- Although comparative studies with other intranasal glucocorticosteroids have to be made, one study has shown that mometasone furoate has a rapid onset of action (2143).
- In controlled studies, mometasone furoate was as effective as beclomethasone dipropionate (2147), flu-

ticasone propionate (2267) and budesonide (2135) and more effective than loratadine in the treatment of seasonal allergic rhinitis (2134).

- Intranasal mometasone furoate was not found to have an effect on the HPA axis at a dose of 200 μg daily (2135, 2171).
- In a one year study in children, treatment with mometasone furoate 100 μg daily did not show growth retardation or suppression of the HPA axis (2279).
- Long-term administration of mometasone furoate is not associated with adverse tissue changes in the nasal mucosa of patients with perennial rhinitis (2280).

8-2-4-4-7- Other molecules

The new intranasal steroid ciclesonide was recently found to be effective in the treatment of allergic rhinitis (2281).

8-2-4-5- The future of nasal glucocorticosteroid treatment

Although modern intranasal glucocorticosteroids have all aimed at a high local anti-inflammatory effect combined with a low systemic bioavailability, it has not been possible to remove all metabolic effects and totally isolate desired anti-inflammatory properties. Although the systemic effects of intranasal glucocorticosteroids are probably not clinically relevant for adult patients with rhinitis alone, children and patients also having asthma (and requiring inhaled glucocorticosteroids) should use the lowest possible doses. They may need drugs with an equally or more potent local anti-inflammatory activity and with even less systemic activity.

8-2-4-6- Recommendations

A recent meta-analysis has demonstrated that intranasal glucocorticosteroids are more efficacious in reducing the symptoms of allergic rhinitis than antihistamines. The advantage was most obvious for nasal blockage (1738). However, in clinical practice, compliance, drug preference, drug availability and potential side effects should be considered.

Because intranasal glucocorticosteroids are more effective in moderate to severe rhinitis and can suppress many stages of the allergic inflammatory disease, the therapeutic risk/benefit ratio has to be considered. Generally, the groups of patients with persistent allergic rhinitis who usually suffer from nasal blockage are better managed with intranasal glucocorticosteroids. When symptoms are mild or only intermittent, an H1-antihistamine is a good choice. The balance between intranasal glucocorticosteroids and H1-antihistamines has to be individualised.

In conclusion, intranasal glucocorticosteroids should be regarded as a highly effective first-line treatment for patients suffering from allergic and non-allergic rhinitis with moderate to severe and/or persistent symptoms. Even though intranasal glucocorticosteroids may be less effective in non-allergic rhinitis, they are worth trying.

8-2-5- Systemic glucocorticosteroids

8-2-5-1- Rationale

Glucocorticosteroids are sometimes prescribed orally

or as an intramuscular depot preparation in clinical practice. There are relatively little scientific data available to support this practice. There is a lack of comparative studies on the preferred dose, the route of administration and the dose response relationship. There are typical regimens of glucocorticosteroids given orally (e.g. prednisolone, starting dose 20-40 mg/day) or as a depot-injection (e.g. methylprednisolone 40-80 mg/injection) (2282).

8-2-5-2- Efficacy and safety

Systemic glucocorticosteroids exert their action on a broad spectrum of inflammatory phenomena and are effective on most symptoms of rhinitis, especially on obstruction (2283, 2284) and loss of smell. No information is available on the efficacy and safety of the repeated administration of depot glucocorticosteroids. The only controlled comparison between oral and injected glucocorticosteroids in rhinitis showed a therapeutic index in favour of the depot-injection (2285). Nevertheless, there are arguments in favour of oral administration (2284). Oral administration is cheap and the dosage can be adjusted to the changing need for treatment. Moreover, it must be remembered that an injection of 80 mg of methylprednisolone corresponds to 100 mg of prednisolone and that continuous release during the day will suppress the HPA axis moreso than a single oral dose given in the morning for a period of three weeks. Depot injections have also been shown to cause local tissue atrophy.

The intranasal administration of depot injections into swollen nasal turbinates and polyps should be avoided, since serious adverse events (blindness) have been reported.

Since the risk of adverse effects from systemic glucocorticosteroids largely depends upon the duration of treatment, only infrequent short-term courses should be prescribed in rhinitis.

8-2-5-3- Contraindications

Contraindications to systemic glucocorticosteroids are glaucoma, herpes keratitis, diabetes mellitus, psychological instability, osteoporosis, severe hypertension, tuberculosis and other chronic infections.

8-2-5-4- Recommendations

Systemic glucocorticosteroids are never the first line of treatment for allergic rhinitis. They can be used as a last resort of treatment when other treatments are ineffective. Oral glucocorticosteroids have the advantage over depot injections that treatment adjustments can follow the pollen count. Systemic glucocorticosteroids, in contrast to intranasal treatment, reach all parts of the nose and the paranasal sinuses, therefore short courses in patients with severe perennial rhinitis or nasal polyposis can be helpful.

Systemic glucocorticosteroids should be avoided in children, pregnant women and patients with known contraindications.

8-2-6- Chromones

8-2-6-1- Rationale

The chromones used in the treatment of allergic diseases are disodium cromoglycate (cromolyn, DSCG) and sodium nedocromil. They still have an unclear mode of action *in vitro* (2286):

- The action of these drugs is linked to the cell wall of the mast cell (2287, 2288) and/or to the intracellular events that follow the allergen binding to IgE (2289).
- Disodium cromoglycate inhibits nasal connective tissue mast cells (2290). However, most nasal basophils resemble blood basophils and DSCG does not inhibit the de-granulation of these cells (2291).
- A blockage of the Cl⁻ channels on the mast cell membrane, a phosphodiesterase inhibition or a blockage of oxidative phosphorylation have been suggested as a mechanism (2292-2294).
- Disodium cromoglycate was also shown to inhibit IL-4 induced IgE synthesis (2295).
- Nedocromil sodium has been shown *in vitro* to inhibit the activation of neutrophils, eosinophils, monocytes, macrophages and mast cells (2296-2301).
- A "local anaesthetic" effect has also been hypothesised as an inhibitory effect on sensory neural stimulation (2302).

In vivo human studies have been performed. Nasal challenge studies suggest an inhibition of nasal mast cells by nedocromil sodium (2303). Disodium cromoglycate reduces mucosal eosinophil numbers in nasal scrapings from patients with seasonal allergic rhinitis (2304).

In regards to pharmacokinetics, DSCG or nedocromil are virtually not absorbed through mucosal surfaces. Furthermore, the swallowed portion is poorly absorbed from the gastrointestinal tract and is excreted in the faeces.

8-2-6-2- Efficacy and safety

8-2-6-2-1- Nasal administration

- In double-blind, placebo-controlled trials, DSCG 4 times daily has been shown to be effective in the treatment or prophylaxis of seasonal allergic rhinitis in some (1284, 2305-2311) but not all studies (2312, 2313).
- Intranasal DSCG was effective in double-blind, placebo-controlled trials in perennial allergic rhinitis in adults in some (2314-2317) but not all studies (2318).
- The symptoms of sneezing, rhinorrhea and nasal itching are usually better controlled than nasal obstruction (2304).
- Disodium cromoglycate is usually ineffective in non-allergic, non-infectious rhinitis (88).
- Although one study (not placebo-controlled) showed an equivalent efficacy of DSCG versus terfenadine (2304), DSCG is usually less effective than oral or intranasal antihistamines or intranasal glucocorticosteroids in adults (1284, 2061, 2064, 2141, 2235, 2315) and children (2142).
- Nedocromil sodium administered BID is more effective than placebo in the treatment of seasonal allergic rhinitis (1366, 2319-2322).
- In children, the efficacy of nedocromil was also demonstrated (2323).
- The combined therapy of nedocromil and astemizole appeared more effective than the H1-antihistamine alone (2324).

- It was interesting to note that the efficacy of nedocromil was rapid (2321).
- Both DSCG and sodium nedocromil are safe and almost totally devoid of side effects, but occasional minor local side effects have been reported.

8-2-6-2-2- Ocular administration

Both DSCG and nedocromil are available in the form of ocular formulations.

- Disodium cromoglycate was found to be effective in most (2325-2330) but not all studies (2331).
- Disodium cromoglycate is usually less effective than ocular formulations of H1-antihistamines (2079, 2081, 2085, 2332).
- Disodium cromoglycate may be administered as single dose units (2333) and this formulation is very convenient for patients with intermittent symptoms.
- Disodium cromoglycate eye drops are also effective in vernal keratoconjunctivitis but the efficacy is modest (2334).
- Ocular DSCG needs a four times daily administration.
- Regular administration appears to be more effective than a prn schedule (2335).
- Nedocromil sodium administered BID was found to be safe and effective in seasonal allergic conjunctivitis (2336-2341)
- and also in vernal keratoconjunctivitis (2342-2344).
- Efficacy was also found in the treatment of seasonal allergic conjunctivitis in children (2345).
- The comparison between intranasal levocabastine and nedocromil sodium was only carried out in a challenge model (2346). No randomised controlled study during the pollen season has been carried out.
- Both DSCG and nedocromil sodium are safe.

8-2-6-3- Recommendations

- In placebo-controlled trials, DSCG 4 times daily has been shown to be effective in allergic rhinitis and conjunctivitis, although less effective than H1-antihistamines or intranasal glucocorticosteroids.
- Nedocromil sodium has also been shown to be effective in allergic rhinitis and conjunctivitis and has the advantage of a BID dosing regimen.
- In adults, chromones are not a major therapeutic option in the treatment of allergic rhinitis, although they maintain a valued place for the treatment of allergic conjunctivitis.
- In children and pregnant women, chromones can be recommended in view of their excellent safety profile.

8-2-6-4- NAAGA

A gel formulation of the anti-allergic compound N-acetyl-aspartyl glutamic acid (NAAGA), a C3 convertase inhibitor, reduces cellular recruitment and mediator release during the late allergen-induced nasal reaction (2347). In a double-blind, placebo-controlled study, NAAGA was found to be effective in seasonal allergic rhinitis (2348). It was found to be slightly more effective than DSCG, but was less well tolerated. It may have some efficacy on nasal obstruction (2349).

8-2-7- Decongestants

8-2-7-1- Mechanism of action and rationale

Decongestant (vasoconstrictor) drugs cause vasoconstriction by their action on α-adrenergic receptors (2350). Decongestants available for clinical use include:
- α1-adrenergic agonists (e.g. phenylephrine) (2351, 2352),
- α2-adrenergic agonists (e.g. oxymetazoline, xylometazoline, naphazoline) (2351, 2353-2357),
- noradrenaline releasers (e.g. ephedrine, pseudoephedrine, amphetamines) (2358),
- drugs preventing the re-uptake of noradrenaline (e.g. cocaine, tricyclic antidepressants, phenylpropanolamine) (2359).

These may be administered intranasally or orally.

8-2-7-2- Efficacy

8-2-7-2-1- Intranasal decongestants

- In the short term, they are very effective in the treatment of nasal obstruction for both allergic and non-allergic rhinitis patients (2351, 2352).
- However, they do not improve nasal itching, sneezing or rhinorrhea.
- They can also be used for prophylaxis before air travel to lessen the likelihood of nasal, middle ear or sinus problems and to improve nasal patency prior to the administration of other intranasal medications.
- Following intranasal administration, local vasoconstriction occurs within 10 minutes, irrespective of the drug used.
- The effect lasts for less than 1 hour for epinephrine.
- The long-lasting effect of oxymetazoline (up to 8-12 hours) and xylometazoline may be explained by their slow mucosal clearance due to a decreased mucosal blood flow (2354).

8-2-7-2-2- Oral decongestants

- Oral vasoconstrictors such as ephedrine, phenylephrine, phenylpropanolamine and especially pseudoephedrine are commonly used oral nasal decongestants (2360-2362).
- They can be prescribed for both short and long-term use, although they are usually prescribed short-term to give fast acting relief.
- Generally, they have a weaker effect on obstruction than the intranasal decongestants, but they do not cause rebound vasodilatation.
- Vasoconstrictor agents do not improve other symptoms of rhinitis.
- Following oral administration, nasal decongestion occurs within 30 minutes and persists for up to 6 hours with liquid or regular tablet preparations. It persists for up to 8-24 hours with sustained release formulations.
- Phenylephrine is probably the least effective because of extensive first-pass metabolism (2363).
- Oral decongestants are used in the treatment of allergic rhinitis (2364) and viral upper respiratory tract infections (2365-2367). They are also used to treat conditions such as sinusitis and otitis.

8-2-7-3- Safety

8-2-7-3-1- Nasal side effects

- Nasal burning, stinging, dryness or mucosal ulcerations and even septal perforations may occur after the use of intranasal decongestants.
- Most of the studies with intranasal decongestants show that short-term courses of treatment do not lead to functional or morphological alterations. Decreasing responsiveness (tolerance) and rebound congestion characterised by chronic swelling rarely occur when these agents are prescribed for less than 10 days or so.
- A prolonged use (>10 days) of intranasal vasoconstrictors may lead to tachyphylaxis, a rebound swelling of the nasal mucosa and to "drug induced rhinitis" (rhinitis medicamentosa) (2368, 2369). With modern vasoconstrictors such as oxy- and xylometazoline, the risk of developing rhinitis medicamentosa has been considered to be small (2370). However, recent studies have shown that the over use of these drugs may result in rebound congestion, nasal hyperreactivity, tolerance and histological changes of the nasal mucosa (66, 67). Controversy still exists about the treatment of rhinitis medicamentosa and treatment has rarely been objectively evaluated. Fluticasone propionate is more effective and has a faster onset of action than placebo in the treatment of rhinitis medicamentosa (2371). An adequate treatment of these patients consists of a combination of vasoconstrictor withdrawal and intranasal glucocorticosteroid to alleviate the withdrawal process.
- Moreover, benzlakonium chloride, which is often used as a preservative, induces intranasal side effects (1662).

8-2-7-3-2- Systemic side effects

- Systemic side effects are not uncommon with these oral drugs and include irritability, dizziness, headaches, tremor and insomnia.
- Tachycardia (2372), especially in susceptible subjects such as pregnant women (2373), and hypertension (2374, 2375) may occur, as well as some less common effects such as visual hallucinations (2376).
- Most of these side effects are dose-dependent. Therefore, care should be exercised when giving the drugs to patients with cardiovascular diseases such as hypertension and myocardial ischaemia due to the systemic vasoconstrictor effects.
- Patients with glaucoma or hyperthyroidism and elderly men with urinary retention due to prostate enlargement are also at risk with oral sympathomimetic decongestants.
- These agents should also be used with caution in pregnant women, as the medication will be transferred to the foetus via the systemic circulation.

8-2-7-4- Recommendations

- In general, because of the risk of rhinitis medicamentosa, the use of intranasal decongestants should be limited to a duration of less than 10 days (2377).

- Short courses of intranasal decongestants can be useful to promptly reduce severe nasal blockage while co-administering other drugs.
- Decongestants should be used with care in children under one year of age because of the narrow range between therapeutic and toxic doses (40).
- Furthermore, it is advised not to prescribe pseudoephedrine to patients over 60 years of age, to pregnant women (2378) and, in general, to patients suffering from hypertension, cardiopathy, hyperthyroidism, prostatic hypertrophy, glaucoma and psychiatric disorders as well as to those taking β-blockers or monooxidase amine (MAO) inhibitors.

8-2-7-5- Combinations of oral antihistamines and decongestants

- In many countries, combinations of oral antihistamines and decongestants are commonly prescribed. The aims of these combinations are also to improve nasal obstruction which changes minimally when using H1-antihistamines alone.
- However, the pharmacokinetics of the two drugs in the combination are not similar and these drugs are often administered BID.
- The combination bears all the side effects of H1-antihistamines and vasoconstrictors, and food intake may alter the pharmacokinetics (2379).
- Although major H1-antihistamines (clemastine (2380), acrivastine (2381, 2382), cetirizine (2383, 2384), fexofenadine (2385), loratadine (2386-2391) and terfenadine (2392)) are marketed with pseudoephedrine. However, only a limited number of double-blind, placebo-controlled studies document the clinically relevant superiority of the combination over H1 antihistamines alone.
- There is, however, a study in asthma showing that the combination is more effective than antihistamines in controlling bronchial symptoms (2393).
- There are many OTC drugs combining sedative oral antihistamines with vasoconstrictors. Even though some studies have shown their effectiveness (2394), these should no longer be used since sedation is not usually reduced by stimulation from vasoconstrictors, and the duration of action of antihistamines is usually short.

8-2-8- Topical anti-cholinergics

8-2-8-1- Mechanism of action

Parasympathetic fibres originate in the superior salivatory nucleus of the brainstem and relay in the sphenopalatine ganglion before distributing to the nasal glands and blood vessels (2395, 2396). Parasympathetic stimulation causes a watery secretion, mediated by the classical autonomic transmitter acetylcholine, and a vasodilatation of blood vessels serving the glands. The muscarinic receptors of the sero-mucinous glands can be blocked by the anticholinergic drug ipratropium bromide (2397, 2398), which is commercially available in several countries as a nasal spray (pressurised aerosol or aqueous

pump spray). The recommended daily dose ranges between 120 and 320 µg given in 3 to 6 administrations (2399, 2400).

8-2-8-2- Efficacy
- Intranasally applied atropine was shown to reduce rhinorrhea in patients with rhinitis (2401).
- Ipratropium bromide, a quaternary derivative of isopropyl noratropine, is poorly absorbed by the nasal mucosa because of a low lipid solubility and it does not cross the blood-brain barrier (2398). Ipratropium can be used as a isotonic aqueous nasal spray pump (2402, 2403).
- Randomised controlled trials have shown that ipratropium bromide is effective in controlling watery nasal discharge, but it does not affect sneezing or nasal obstruction in perennial allergic and non-allergic (vasomotor) rhinitis (2400, 2402-2410).
- It is also effective in the common cold (2411), in gustatory rhinitis
- and rhinitis in elderly people (2412).
- A single dose of 42 µg per nostril reduces the secretion for 3 hours due to methacholine stimulation. 168 µg doubles the effect (48% reduction) and its duration in perennial non-allergic rhinitics (2408, 2413).
- The onset of action is fast (15 to 30 minutes), but maximal improvement of symptoms is generally noted several hours after the first treatment.
- No tolerance develops in clinical effects (2414).
- Combination therapy has also been studied in patients with allergic or non-allergic perennial rhinitis. The combination of an ipratropium bromide nasal spray with terfenadine is more effective than terfenadine alone for the treatment of rhinorrhea (2415). The combined use of ipratropium bromide nasal spray (0.03%) with beclomethasone dipropionate nasal spray is more effective than either active agent for the treatment of rhinorrhea (2416).

8-2-8-3- Safety
- Topical side effects, due to the anti-cholinergic action, are uncommon and usually dose-dependant in their severity. Nasal dryness, irritation and burning are the most prominent effects, followed by a stuffy nose, dry mouth and headache (2399, 2407, 2414). Olfaction, ciliary beat frequency and the clinical appearance of the nasal mucosa are not affected, even with long-term use.
- The systemic bioavailability of intranasal ipratropium is about 10% and systemic side effects are rare (2399, 2407, 2417), but they can occur with doses higher than 400 µg/day (2417).

8-2-8-4- Recommendations
- Studies performed in perennial allergic rhinitis demonstrated that ipratropium bromide only improves nasal hyper-secretion.
- No data are available for seasonal rhinitis.
- Since patients with perennial rhinitis usually suffer also from nasal congestion, itching and sneezing, other drugs are preferable as first-line agents to ipratropium in the vast majority of cases of allergic rhinitis.
- However, the ipratropium bromide nasal spray alone should be considered in patients for whom rhinorrhea is the primary symptom.
- Its use in combination with an intranasal glucocorticosteroid or an H1-antihistamine may be considered in patients where rhinorrhea is the predominant symptom, or in patients with rhinorrhea who are not fully responsive to other therapies.
- Moreover, ipratropium may be used in patients with or without allergic rhinitis who suffer from rhinorrhea when in contact with cold air.
- In elderly patients, ipratropium may be of interest in the treatment of isolated rhinorrhea.

8-2-9- Anti-leukotrienes

CysLTs appear to be important mediators of nasal allergic reactions, and their insufflation into the nose induces nasal obstruction. Drugs acting against CysLT may therefore be important in the treatment of allergic rhinitis either alone or combined with H1-antihistamines since these drugs are poorly effective in nasal obstruction (2418). However, the data available do not allow any firm conclusions.

Zileuton, a 5-LO inhibitor, was found to reduce nasal obstruction (2419). The efficacy of single oral doses of the CysLT-receptor antagonist, zafirlukast, was tested in subjects with acute seasonal allergic rhinitis during a two-day study in a park exposure (2420). Nasal congestion improved more than sneezing and rhinorrhea. In another study, 33 patients with seasonal allergic rhinitis were enrolled in a randomised double-blind study to treatments with oral zafirlukast (20 mg twice a day), intranasal beclomethasone dipropionate (200 µg twice a day) or placebo (2421). Patients receiving treatment with zafirlukast had degrees of nasal symptoms similar to those in the placebo group, whereas the beclomethasone group had significantly less symptoms compared with both treatments. The numbers of activated eosinophils in the nasal tissue increased significantly during the pollen season in both the zafirlukast and the placebo groups, but not in the beclomethasone group. These results were obtained with a limited number of patients and do not support the clinical efficacy of regular treatment with an oral antileukotriene in seasonal allergic rhinitis. More data are needed.

In seasonal allergic rhinitis, the combination of a CysLT receptor antagonist, montelukast and loratadine showed that symptoms of rhinitis and conjunctivitis were more effectively treated with the combination of these drugs as opposed to any one of them alone or with the placebo (2422).

It is believed that anti-leukotriene drugs will adopt a prominent role in the treatment of aspirin-sensitive rhinitis and asthma. The evidence is still preliminary. In the first controlled study published so far, the 5-LO inhibitor Zileuton notably diminished nasal dysfunction in these patients (2423). It also caused a remarkable return of sense of smell, less rhinorrhea and higher nasal inspiratory flows.

8-2-10- Oral anti-allergic drugs

In Japan and Eastern Asia, many so-called "oral anti-allergic" drugs such as pemirolast are used in the treatment of allergic rhinitis. These drugs display anti-allergic properties in vitro and in animal models by blocking the release of mediators. The efficacy of these drugs has rarely been tested using double-blind, placebo-controlled studies. One pilot study, carried out on a small number of patients, showed that pemirolast was effective in the treatment of seasonal allergic rhinitis (2424).

8-2-11- Treatments with a lack of demonstrable efficacy

The use of alternative medicine for the treatment of asthma in adults and children is common and increasing (2425). There is an urgent need for large, randomised and controlled clinical trials for alternative therapies of allergic disease and rhinitis. Scientific and clinical supports of these therapies are lacking (2426).

8-2-11-1- Homeopathy

The preparation of homeopathic drugs is based on potentiation. In a controlled randomised double-blind trial with 164 patients, the effectiveness of homeopathically prepared *Galphimia* dilution 10^{-6} and a placebo was investigated for the therapy of pollinosis. The average duration of treatment was about 5 weeks. No statistical significant improvement was achieved with homeopathy (2427). In a double-blind (not placebo-controlled) study, intranasal preparations of *Luffa operculata*, *Galphimia glauca*, histamine and sulfur were found to have a similar effect as intranasal DSCG (2428). However, in this study, pollen counts were not recorded, making it difficult to interpret the data.

In two other studies, homeopathic dilutions of house dust mite or grass pollen extract were administered and there was a significant improvement in placebo (2429, 2430). However, the methodology of these studies raises some concern and no firm conclusions regarding the results can be reached.

8-2-11-2- Acupuncture

Acupuncture has been proposed in some studies (2431-2434) but the only study attempting to validate this method in asthma suggested that there was no benefit from the treatment (2435).

8-2-11-3- Chiropractic

Chiropractic medicine is used in certain countries for the treatment of rhinosinusitis (2436), but there is no study in Medline to support its use.

8-2-11-4- Traditional medicine and phytotherapy

The use of herbal medicine, often from Chinese origin, is widespread and growing (2437). Many herbal medicines have a significant pharmacological activity and thus potential adverse effects and drug interactions (2438-2440). Traditional medicine is used in many patients to treat the symptoms of allergic and non-allergic rhinitis. Most of the studies are uncontrolled and no data are reported in the Medline from controlled studies. Mao-bushi-saishin-to, a Chinese blended medicine, was examined in a controlled (but not-placebo) study and found to reduce nasal obstruction in patients with Japanese cedar pollen allergy (2441).

Ayurvedic medicine is used (2442) to treat asthma and rhinitis (2443, 2444). There is, however, no controlled clinical study reported in Medline to support its use in rhinitis.

8-2-11-5- Other alternative therapies

A large number of alternative therapies are offered including balneology, Kneipp therapy, microbiological therapy, fasting, excretion therapy, different oxygen therapies, hydro-colon, urine therapy, own-blood therapy, Bach therapy, orthomolecular therapy, order therapy, environmental medicine, anthroposophy, neural therapy, electroaccupuncture according to Voll and similar therapies, nasal reflex therapy, reflex-zone massage, manual therapy, massage, lymph drainage, aromatherapy, thermotherapy, bioresonance, kinesiology, hopi candles and dietetics (2445). However, none of these therapies have been appropriately scientifically and clinically tested and some may even be dangerous.

The so-called bioresonance therapy or biophysical information therapy claims to improve the condition of patients with atopic disease. However, a conventional, double-blind, placebo-controlled study in hospitalised children with atopic dermatitis did not find this treatment to be effective (2446). No controlled studies have been carried out in rhinitis.

8-2-11-6- Yoga

Yoga may improve breathing but even in asthma, no clear efficacy was demonstrated (2447). In allergic rhinitis, there is no controlled study supporting its use.

8-2-11-7- Recommendations

None of the methods used in alternative medicine can be supported scientifically to be clinically effective. The public should be warned against methods of diagnosis and treatment which may be costly and which have not been validated (2448). Properly designed randomised clinical trials are required to assess the value of these forms of treatment.

8-2-12- Antibiotics

In non-complicated rhinitis, antibiotics are not a recommended treatment.

8-2-13- Nasal douching

Nasal douching with a traditional alkaline nasal douche or a sterile sea water spray was shown to improve symptoms of rhinitis (2449).

8-2-14- Surgical treatment of rhinitis

As surgery cannot contribute to the treatment of allergic disease itself, it should only be used in certain conditions such as turbinate hypertrophy, cartilaginous or bony obstruction of the nasal airways or secondary and independent sinus disease. In patients who suffer from perennial allergic or non-allergic rhinitis for many years, a severe drug-resistant hypertrophy of the inferior turbinates may develop, which leads to constant nasal

obstruction and watery secretion due to an increase in glandular structures. The surgical reduction of the inferior turbinate body and mucosal surface, which should always be limited, can reduce nasal obstruction and secretion (2450). Endoscopically controlled minimal-invasive techniques for the sinuses and the turbinates have replaced former procedures in most countries, and a range of new tools and instruments has been created to allow for more precise and less traumatic surgery. Laser surgery (2451) may also be used. Vidian neurectomy is not indicated for rhinitis because of the side effects (2452) and the availability of medical treatment (954). The indication for nasal and sinus surgery should always be based on the insufficient effect of adequate drug treatment and the functional and clinical relevance of the anatomical variation or disease.

Indications for surgical intervention are:
- drug-resistant inferior turbinate hypertrophy,
- anatomical variations of the septum with functional relevance,
- anatomical variations of the bony pyramid with functional/aesthetic relevance,
- secondary or independently developing chronic sinusitis (2453, 2454),
- different forms of nasal unilateral polyposis (choanal polyp, solitary polyp, allergic fungal sinusitis) or therapy-resistant bilateral nasal polyposis (1361, 2455),
- fungal sinus disease (mycetoma, invasive forms) or other pathologies unrelated to allergy (cerebro-spinal fluid leak, inverted papilloma, benign and malignant tumours, Wegener's disease, etc.).

8-2-15- Aspirin intolerance

8-2-15-1- Avoidance of aspirin and other NSAID

In order to prevent life-threatening reactions, patients with aspirin-intolerant rhinitis/asthma should avoid aspirin, all products containing aspirin and other analgesics that inhibit COX (938, 2456, 2457) (Table 6). The education of physicians and patients regarding this matter is extremely important. The patient should obtain a list of drugs that are contraindicated, preferably with both the generic and trade names. If necessary, these patients can take acetaminophen or paracetamol; it is safer not to exceed a dose of 1000 mg (2458). Sodium salicylate, benzydamine (2459), azapropazone (2460) and dextropropoxyphene can be administered.

The use of nimesulide, a COX-2 inhibitor, was studied in patients with aspirin and non-steroidal anti-inflammatory drug intolerance and it was found that this COX-2 inhibitor induced less reactions than aspirin itself (2461).

In patients with aspirin-sensitive eosinophilic rhinitis, intranasal fluticasone is a powerful and effective treatment (2462).

8-2-15-2- Induction of aspirin tolerance

In aspirin-intolerant patients suffering from rhinosinusitis and asthma, a state of aspirin tolerance can be induced and maintained by aspirin desensitisation. Small incremental oral doses of aspirin are ingested over the course of 2 to 3 days until 400 to 650 mg of aspirin is tol-

erated. Aspirin can then be administered daily, with doses of 80 to 325 mg used to maintain desensitisation. After each dose of aspirin, there is a refractory period of 2 to 5 days, during which aspirin and other COX inhibitors can be taken with impunity. However, stopping the treatment for longer may be dangerous since new administrations of aspirin or another NSAID can induce symptoms as severe as before tolerance. This is important for patients with aspirin intolerance who have degenerative joint diseases, rheumatic diseases and headaches, and as a preventive measure for the treatment of vascular diseases (2463).

Bronchial and nasal routes have also been used in aspirin desensitisation (2464).

The clinical benefits of aspirin tolerance on asthma and rhinitis are not clear. Most studies did not show a long-term improvement. During the state of aspirin desensitisation, if the aspirin dose is increased to 650 mg BID and is taken continuously, some patients may experience an improvement in their chronic respiratory symptoms and signs, especially in the nose (148, 2463, 2464). The ideal candidate for this treatment may be a patient with aspirin-induced asthma who has just completed sinus/polyp surgery. Aspirin desensitisation treatment was shown to delay the recurrence of nasal polyp formation by an average of 6 years.

The mechanism of aspirin desensitisation in patients with aspirin-induced asthma is only partially understood. It may lead to a reduction of airway responsiveness to LTE_4 because of the down regulation of CysLT receptors, which reduces receptor responsiveness to the same burden of CysLT. At acute desensitisation, urinary LT levels are the same as baseline levels and are therefore clearly available for the stimulation of CysLT receptors. Patients maintained for months in a state of aspirin desensitisation still respond to oral aspirin challenge with a rise in LTE_4 urinary excretion, although the responses were blunted when compared with the original aspirin challenges and the patients were all asymptomatic.

8-3- ALLERGEN SPECIFIC IMMUNOTHERAPY: THERAPEUTIC VACCINES FOR ALLERGIC DISEASES

8-3-1- Introduction

Allergen specific immunotherapy is the practice of administering gradually increasing quantities of an allergen vaccine to an allergic subject in order to ameliorate symptoms associated with subsequent exposure to the causative allergen. Allergen immunotherapy was introduced in 1911 by Noon and Freeman to treat "pollinosis" or allergic rhinitis (1301). There is good evidence that immunotherapy using inhalant allergens to treat seasonal or perennial allergic rhinitis and asthma is clinically effective.

Guidelines and indications for specific immunotherapy with inhalant allergens have been published over the past years by WHO (2465, 2466), the European Academy of Allergy and Clinical Immunology (EAACI) (2467-2469), the International Consensus Report on Asthma (35), the

Global Strategy for Asthma Management and Prevention (36), the International Consensus Report on Rhinitis (1), the British Society for Allergy and Clinical Immunology (2470), the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) (2471). These reports provide guidelines for a better understanding of the use of allergen specific immunotherapy.

Vaccines are utilised in medicine as immune modifiers, as is allergen specific immunotherapy. Knowledge gained from studies of allergic mechanisms, such as the importance of Th1 and Th2 cells, cytokine regulation of the immune responses and specific inhibition or ablation of pathogenic immune responses by means of tolerance induction, may be applicable to a variety of allergic and other immunological diseases. This is especially true for autoimmune diseases such as juvenile diabetes mellitus and multiple sclerosis. Thus, the concepts utilised and the scientific data which support the use of allergen immunotherapy to treat allergic diseases are now being scientifically applied to other immunological diseases. The recent WHO position paper has therefore been entitled "Allergen Immunotherapy, Therapeutic Vaccines for Allergic Diseases" to indicate that vaccines (allergen extracts) which modify or down regulate the immune response for allergic diseases are part of this broad based category of therapies developed to treat other immunological diseases (2466).

8-3-2- Treatment strategy

The treatment strategy of allergic rhinitis implies symptom reduction by drugs and attempts to interfere in the inflammatory cascade by anti-inflammatory drugs or specific immunotherapy. The relative advantage of these two different interventions is unknown, but theoretically, combining interventions at different levels should improve the clinical outcome. Allergen avoidance is always the first-line treatment and, although not completely effective (1621), it may reduce the need for further intervention. Drug treatment is often the next logical step for reducing disease severity. However, in patients with a constant need for pharmacotherapy, the advantages of instituting specific immunotherapy early in the evolution of the disease (e.g. while the severity of the disease is still modest and at a time when the possibility to prevent deterioration into asthma is at its highest) should be seriously considered (2466, 2469, 2472). Immunotherapy can significantly reduce the severity of allergic disease and the need for anti-allergic drugs, consequently improving the quality of life for allergic patients (2473).

A significant proportion of rhinitis patients have minimal persistent inflammation during allergen exposure in the lower airways (9). This inflammation is often underdiagnosed and therefore inadequately treated. Specific immunotherapy might, as the only treatment, improve inflammation independently of the shock organ. Allergen induced IgE-mediated inflammation should therefore be seen as a multi-organ disease and specific immunotherapy should be based on the allergen sensitisation rather than on the specific disease (2466).

In many patients, drug treatment insufficiently controls symptoms, and patient satisfaction is poor (2474). Moreover, some patients experience side effects from drugs. Specific immunotherapy was shown to improve symptoms and decrease the medication needs of patients with severe rhinoconjunctivitis (2475).

The advantages of combining allergen avoidance, specific immunotherapy and drug treatment require further investigations.

8-3-3- Allergen standardisation

The quality of the allergen vaccine is critical for both diagnosis and treatment. Where possible, standardised vaccines of known potency and shelf-life should be used (2476). The most common vaccines used in clinical allergy practice are now available as standardised products or are pending standardisation. However, there are many vaccines currently being marketed (many of which are only used occasionally) and it is neither feasible nor economically possible to standardise all of them. The measurement of major allergens for standardisation is now a realistic and desirable goal (2466, 2477). Several allergen units are used. Among them are the following:

- IU (international unit),
- AU (allergy unit),
- BAU (biological allergy unit),
- BU (biological unit),
- IR (index of reactivity),
- TU (therapeutic unit).

In the European Pharmacopeia, allergen preparations for specific immunotherapy include (2476):

- unmodified vaccines,
- vaccines modified chemically (e.g. formaldehyde allergoids),
- vaccines modified by adsorption onto different carriers (so-called depot-vaccines).

Modified and depot vaccines have been developed to make specific immunotherapy more effective and to reduce the risk of side effects.

Allergen vaccines should be marketed only if their potency, composition and stability have been documented as:

- vaccines from a single source material,
- mixtures of related, cross-reacting allergen vaccines such as grass pollen vaccines, deciduous tree pollen vaccines, related ragweed pollen vaccines and related mite vaccines
- mixtures of other allergen vaccines provided that stability data (2478) and data on clinical efficacy are available. Where mixtures are marketed, the relative amounts of each component of the mixture should be indicated on the label.

8-3-4- Mechanisms

Specific immunotherapy is specific to the antigen administered (2479). The mechanisms of specific immunotherapy are complex (2480, 2481) and may dif-

fer depending on the allergen (venoms or inhalant allergens) and the route of immunisation.

- Early studies focused on immunoglobulin levels (IgE, IgG and IgG subclasses) (2482, 2483) and, in particular, on the so-called "blocking" IgG (2484). It seems however that clinical benefit is not associated with immunoglobulin levels (2485). It is however possible that the binding capacity of immunoglobulins is modified during specific immunotherapy. Data are lacking to confirm this hypothesis.
- Newer studies suggest that specific immunotherapy acts by modifying T-cell responses either by immune deviation (increase in Th0/Th1), by T-cell anergy (decrease in Th2/Th0) or, more likely, by both (2486-2489). The role of IL-10 may be of importance (2490).
- Systemic and local increases in $CD8^+$ cells have also been observed (2491).
- Specific immunotherapy also reduces inflammatory cell recruitment and activation as well as mediator secretion (2492-2495).
- The mechanisms of local immunotherapy are still unclear, but a systemic effect is likely since serum immunoglobulin changes can be seen. The role of this form of treatment on the Th1/Th2 cytokine network needs further studies (2496).

8-3-5- Clinical efficacy

8-3-5-1- Subcutaneous immunotherapy

Immunotherapy dosing raises contrasting efficacy and safety issues. Low dose specific immunotherapy is ineffective (2497, 2498) and high doses of allergen vaccine may induce a high and unacceptable rate of systemic reactions (2499). It has been proposed that optimal doses of vaccines be provided either in biological units or in the weight of major allergens present (2466). The optimal dose is defined as the dose of allergen vaccine, which induces a clinically relevant effect in the majority of patients without causing unacceptable side effects (2500). Doses of 5 to 20 μg of the major allergen are optimal for most allergen vaccines (for review see 2466). The majority of patients with allergic disease can tolerate this target dose without difficulty. However, in selected individuals who have experienced reactions during their build up treatment phase, a lower maintenance dose may be necessary. As with any therapeutic approach, the risk-benefit ratio must be carefully considered to determine whether specific immunotherapy should be continued.

The efficacy of subcutaneous specific immunotherapy has been documented in most double-blind, placebo-controlled studies published in allergic rhinitis (and usually also conjunctivitis) when induced by:

- birch and Betulaceae pollen (2495, 2501),
- grass pollen (2475, 2485, 2493, 2502-2514),
- ragweed pollen (2479, 2499, 2515-2523),
- *Parietaria* pollen (2524-2527),
- a few other pollen species (2528, 2529),
- house dust-mite (2530-2535),
- cat. Many studies found that bronchial symptoms improve during cat specific immunotherapy (2536-2541), but nasal symptoms were not monitored.

Because cat specific immunotherapy is effective for asthma, it is likely that it is also effective for rhinitis.
- The mould *Alternaria* (1609). There is no study for *Cladosporium* immunotherapy for rhinitis.
- Specific immunotherapy with house dust, *Candida albicans*, bacterial vaccines (2542) or other undefined allergens is ineffective and not recommended (for review see 2466).

In 43 placebo-controlled, double-blind studies, subcutaneous specific immunotherapy was compared with placebo treatment. Immunotherapy resulted in a mean reduction in symptoms of 45%, compared with placebo. This is equivalent to, or even better than, the efficacy obtained with most drugs (2543). A recent meta-analysis using the Cochrane collaboration method showed that specific immunotherapy is effective in treating asthma (2544).

8-3-5-2- Nasal immunotherapy

The efficacy of high allergen dose intranasal specific immunotherapy has been documented in most double-blind, placebo-controlled studies carried out in allergic rhinitis (and often also conjunctivitis) when induced by:
- birch and alder pollen (2545, 2546),
- grass pollen (2547-2550),
- ragweed pollen (2551-2556),
- *Parietaria* pollen (2557-2560)
- house dust mite (2561).
Lower doses are not effective.

8-3-5-3- Sublingual-swallow immunotherapy

Efficacy of high allergen dose sublingual-swallow specific immunotherapy (at least 50 to 100 times the cumulative dose of subcutaneous immunotherapy) has been documented in double-blind, placebo-controlled studies carried out in allergic rhinitis to
- birch pollen (2562),
- grass pollen (2563-2566),
- *Parietaria* pollen (2560, 2567-2569),
- house dust mite (2473, 2570-2572).
Lower doses are not effective.

In one study, sublingual-swallow specific immuno-therapy was found to be slightly less effective than subcutaneous specific immunotherapy, but still showed a clinically relevant efficacy (2570). However, new data are pending and no firm conclusion concerning the relative efficacy of both forms can be drawn before the results of these studies.

8-3-5-4- Oral immunotherapy

The efficacy of oral specific immunotherapy in rhinitis has been documented in some (2573) but not all double-blind, placebo-controlled studies (2574-2578).

8-3-6- Side effects

8-3-6-1- Subcutaneous immunotherapy

Subcutaneous specific immunotherapy can cause systemic allergic reactions. The risk of serious anaphylactic reactions is lower in rhinitis patients than in asthma patients (2466, 2579, 2580).

In a recent review (2543), approximately 20% of the studies on immunotherapy efficacy did not provide information about side effects. In about 20% of the studies, no systemic side effects were reported. In all the studies, the mean frequency of systemic side effects was 14%, with the majority being rather mild with few life-threatening reactions.

However, systemic reactions represent a general limitation in the use of specific immunotherapy. Therefore, such strategies have to be carried out by a specialist who is aware of the risks. Injections should be performed or supervised by physicians who are able to effectively treat systemic reactions (2466, 2468). Major side effects include severe asthma and anaphylaxis (2581, 2582). It is therefore important to minimise risks (Table 18).

8-3-6-2- Local immunotherapy

With intranasal specific immunotherapy, the only reported systemic side effect is asthma (probably caused by an incorrect administration of allergen vaccine).

In one study with sublingual specific immunotherapy, some serious systemic side effects (asthma, urticaria and gastrointestinal complaints) were observed in children (2572). However, in all other studies, only mild reactions were observed, even in children with asthma (2473, 2562-2571, 2583). A post-marketing surveillance of sublingual-swallow specific immunotherapy showed that this procedure appeared to be well tolerated in children (2584).

Since local specific immunotherapy is self-administered at home, patients should be informed of the potential risks of a systemic reaction and how to treat such a reaction should it occur (2466).

8-3-7- Immunotherapy alters the natural course of allergic disease and may prevent asthma

Although drugs are highly effective and usually well tolerated, they only represent symptomatic treatment. Specific immunotherapy is the only treatment that may alter the natural course of the disease (2466).

Long-term efficacy of specific immunotherapy after it has been stopped has been shown for sub-cutaneous specific immunotherapy (2585-2589). In one study (2589), under double-blind, placebo-controlled conditions, 3-4 years of grass pollen immunotherapy remained effective for at least 3 years after the discontinuation of the injections. In both the group that received maintenance immunotherapy and the group that discontinued immunotherapy, clinical improvement was accompanied by a notable decrease in the late skin test response to allergen challenge. The results confirm prolonged clinical benefit and provide evidence of decreased immunological reactivity for at least 3 years after the discontinuation of immunotherapy for pollen-induced seasonal allergic rhinitis. In the study concerning ragweed-sensitive patients by Naclerio *et al.* (2588), the discontinuation of immunotherapy was accompanied by a partial recrudescence of imme-

TABLE 18: Recommendations to minimise risk and improve efficacy of immunotherapy. From the International Consensus Report on Diagnosis and Management of Asthma

Specific immunotherapy needs to be prescribed by specialists and administered by physicians trained to manage systemic reactions if anaphylaxis occurs.

Patients with multiple sensitivities may not benefit from specific immunotherapy as much as patients with a single sensitivity. More data are necessary.

Patients with non-allergic triggers will not benefit from specific immunotherapy.

Specific immunotherapy is more effective in children and young adults than in later life.

It is essential, for safety reasons, that patients should be asymptomatic at the time of the injections because lethal adverse reactions are more often found in asthma patients with severe airways obstruction.

FEV_1 with pharmacological treatment should reach at least 70% of the predicted values, for both efficacy and safety reasons.

From (35)

diate allergen-induced responses, even though there was a continued suppression of symptoms. In a retrospective study of mite-sensitive children, immunotherapy, when continued for more than 3 years, was associated with a more prolonged remission of symptoms when compared to patients who had received immunotherapy for less than 3 years (2587). Long-term efficacy still has to be documented for local specific immunotherapy (2590).

Specific immunotherapy is used to improve the symptoms of allergic diseases but it may have a preventive efficacy. Allergic sensitisation usually begins early in life and symptoms often start within the first decade. It has been shown that specific immunotherapy is less effective in older patients than in children. In addition, inflammation and remodelling of the airways in asthma indicates a poor prognosis for effective treatment with specific immunotherapy (2591). Moreover, if specific immunotherapy is used as preventive treatment, it should be started as soon as allergy has been diagnosed (2472).

To determine whether specific immunotherapy with standardised allergen vaccines could prevent the development of new sensitisations over a 3 year follow-up survey, a prospective non-randomised study was carried out in a population of asthmatic children aged under 6 years whose only allergic sensitivity was to house dust mites (2592). In this study, 22 children who were monosensitised to house dust mites and who were receiving specific immunotherapy with standardised allergen vaccines were compared with 22 children of the same age who were monosensitised to house dust mites and who were taken as controls. Approximately 45% of the children receiving specific immunotherapy did not develop new sensitivities compared to none in the control group. This study suggested

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TABLE 19: Considerations for initiating immunotherapy. From the WHO Position Paper on Allergen Vaccines

1- Presence of a demonstrated IgE-mediated disease:
  - positive skin tests and/or serum specific IgE
2- Documentation that specific sensitivity is involved in symptoms:
  - exposure to the allergen(s) determined by allergy testing related to appearance of symptoms
  - if required, allergen challenge with the relevant allergen(s)
3- Characterisation of other triggers that may be involved in symptoms
4- Severity and duration of symptoms:
  - subjective symptoms
  - objective parameters e.g. work loss, school absenteeism
  - pulmonary function (underline: essential): exclude patients with severe asthma
  - monitoring of pulmonary function by peak flow
5- Response of symptoms to non-immunological treatment:
  - response to allergen avoidance
  - response to pharmacotherapy
6- Availability of standardised or high quality vaccines
7- Relative contraindications:
  - treatment with β-blocker
  - other immunological disease
  - inability of patients to comply
8- Sociological factors:
  - cost
  - occupation of candidate
  - impaired quality of life despite adequate pharmacological treatment
9- Objective evidence of efficacy of immunotherapy for the selected patient (availability of controlled clinical studies)

Adapted from Bousquet J, Lockey R, Malling H. WHO position paper. Allergen Immunotherapy: therapeutic vaccines for allergic diseases. Allergy 1998;53(suppl 54). With permission from Blackwell Science Ltd.

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that specific immunotherapy in patients monosensitised to house dust mites alters the natural course of allergy in preventing the development of new sensitisations.

When specific immunotherapy is introduced to patients with only allergic rhino-conjunctivitis, specific immunotherapy may stop the development of asthma. The early study of Johnstone and Dutton (2593) with several different allergens showed that 28% of children receiving specific immunotherapy developed asthma as compared to 78% of placebo-treated children. To answer the question "does specific allergen immunotherapy stop the development of asthma?", the Preventive Allergy Treatment (PAT) study has been started in children aged from 7 to 13 (2594, 2595). This study is performed as a multi-centre study in Austria, Denmark, Finland, Germany and Sweden. After two years of specific immunotherapy, a significantly greater number of children in the control group developed asthma as compared to the active specific immunotherapy group.

It is therefore proposed that specific immunotherapy should be started early in the disease process in order to modify the spontaneous long-term progress of the allergic inflammation and disease (1461, 2466, 2468).

8-3-8- Indications

8-3-8-1- General considerations

Double-blind, placebo-controlled studies have confirmed the efficacy of immunotherapy. Clinical efficacy does not necessarily mean clinical indication, especially since controlled trials of immunotherapy are optimally designed and may not always be applicable to daily medical practice. Safe and effective pharmacological treatment is also available for the treatment of allergic diseases. Thus, before starting immunotherapy, it is essential to appreciate the value of allergen avoidance, pharmacotherapy and immunotherapy. Certain factors must be considered before beginning immunotherapy (2466):

- demonstration that the disease is due to an IgE-mediated allergy (Table 19),
- determination of all the symptoms caused by the allergens,
- assessment of the allergen exposure and, before initiating immunotherapy, attempt at avoiding exposure to the allergen(s) which are causing the symptoms of the IgE-mediated reaction. However, most common aeroallergens cannot be completely avoided, and this is particularly true for patients allergic to house dust mites or to multiple allergens,
- potential severity of the disease to be treated,
- efficacy of available treatment modalities,
- patient's attitude to available treatment modalities,
- quality of allergen vaccines used for treatment. When possible, standardised allergens should be utilised,
- cost and duration of each form of treatment,
- risk incurred from the allergic diseases and the various forms of treatment.
- finally, assessment of the patient's attitude to treating symptoms versus trying to interfere with the pathophysiology of the disease, and discussion with the patient of treatment alternatives. The patient (and the parents in the case of children) should be carefully informed of the risk, duration and effectiveness of the treatment. Their co-operation and compliance are absolute requirements when considering specific immunotherapy (40, 2466, 2468).

The indications for specific immunotherapy in asthma and rhinitis have been separated in some guidelines and this artificial separation has led to unresolved questions (2596, 2597), possibly because the IgE-mediated reaction has not been considered as a multiple organ involvement. It is therefore important to consider specific immunotherapy based on the allergen sensitisation rather than on a particular disease manifestation (2466).

Young patients (children) respond better than adults, especially for asthma (2591). This is probably related to the duration of the disease, implying that attempts to interfere with the natural course of the disease should be introduced at a time where the patient has the capacity to respond positively. In this way, specific immunotherapy does not take the position of being an ultimate treat-

ment principle, but represents a supplement to drug treatment used in the early phase of the disease.

Some paediatricians recommend injection specific immunotherapy in children at 1-2 years of age, but it is desirable to evaluate more closely in controlled studies the benefits of specific immunotherapy in patients below 5 years of age. At the moment, it is not known whether specific immunotherapy should be administered to very young children. Usually it is started after the age of 5 years (1461, 2466, 2468).

8-3-8-2- Subcutaneous immunotherapy

Injection specific immunotherapy is indicated (2466):

- in carefully selected patients with rhinitis, conjunctivitis and/or asthma caused by pollen, house dust mite or cat allergy. Immunotherapy is indicated when asthma during the pollen season complicates rhinoconjunctivitis. British guidelines on immunotherapy state that patients with chronic asthma should not receive immunotherapy (2470), but this is the only country with such a recommendation.
- in patients in whom H1-antihistamines and intranasal pharmacotherapy insufficiently control symptoms,
- in patients who do not wish to be on pharmacotherapy,
- in patients in whom pharmacotherapy produces undesirable side effects,
- in patients who do not want to receive long-term pharmacological treatment.

8-3-8-3- Local immunotherapy

Local nasal and high dose sublingual-swallow specific immunotherapy may be indicated in (2466, 2469):

- carefully selected patients with rhinitis, conjunctivitis and/or asthma caused by pollen and mite allergy,
- patients insufficiently controlled by conventional pharmacotherapy,
- patients who have presented with systemic reactions during injection specific immunotherapy,
- patients showing poor compliance with or refusal to injections.

However, the dose of vaccine should be far higher than for subcutaneous immunotherapy and, at least for sublingual immunotherapy, the cumulative dose should be 100 times greater, or more.

In the WHO and EAACI position papers (2466, 2469), only four studies were available for sublingual immunotherapy, and due to the side effects reported in one paper, sublingual specific immunotherapy was not recommended in children. Several other papers have now been published and pharmacosurveillance data have shown that sublingual specific immunotherapy does not induce severe side effects in children. In this Position Paper, it is proposed that sublingual specific immunotherapy can be administered in children and adults.

8-3-9- Relative contraindications

Relative contraindications for immunotherapy include (2468):

- serious immunopathological and immunodeficiency diseases,
- malignancy,
- severe psychological disorders,
- treatment with β-blockers, even when administered topically,
- poor compliance,
- severe asthma uncontrolled by pharmacotherapy and/or patients with irreversible airways obstruction (FEV_1 is consistently under 70% of predicted values after adequate pharmacological treatment) (35),
- significant cardiovascular diseases which increase the risk of side effects from epinephrine,
- children under 5 years of age unless there are specific indications (35, 1461, 2466).

Pregnancy is not considered as a contraindication for the continuation of immunotherapy, but, in general, treatment should not be started during pregnancy.

8-3-10- Recommendations

- In order to make the patient as symptom-free as possible, immunotherapy is indicated as a supplement to allergen avoidance and as a drug treatment in patients with rhinitis predominantly induced by dominating allergens.
- Immunotherapy should be initiated early in the disease process to reduce the risk of side effects and to prevent the further development of severe disease. Arguments for specific immunotherapy are:
  - Insufficient response to conventional pharmacotherapy,
  - side effects from drugs
  - rejection of drug treatment.
- Injection (subcutaneous) specific immunotherapy may be used in severe or prolonged allergic rhinitis (eventually associated with asthma),
- Local (intranasal and sublingual-swallow) specific immunotherapy may be considered in selected patients with systemic side effects and with refusal to injection treatment.

8-4- FUTURE POTENTIAL TREATMENT MODALITIES

The management of allergic rhinitis can be divided into three basic approaches, namely allergen avoidance, pharmacotherapy (2598) and specific immunotherapy.

Health economics is becoming an increasing fundamental consideration for any novel approach. This has to take into account the disease burden, the cost, efficacy and side effect profile of current standard therapies and the impact and potential advantages of any development as well as the cost of its application. There are a variety of novel approaches currently under evaluation for the modification of allergic inflammation at differing stages of development. These range from their evaluation in *in vitro* cell systems and assessment in animal models to human clinical trial evaluation. The potential use of these

therapies would have to be considered against H1-antihistamines and intranasal glucocorticosteroids (the two main pharmacological therapies for allergic rhinitis), as well as on their profile against other co-existing allergic conditions such as asthma. Research in this area has been driven by a search for disease modifying therapies for asthma, a disease condition that would bear a higher therapeutic cost on account of its life-threatening nature and health care costs (indirect and direct). Thus, any future approaches to rhinitis management would have to be considered as to whether they would be utilised both for rhinitis and asthma or for rhinitis alone.

It is apparent from the review on allergen avoidance that little has been formally undertaken to assess the benefits of this in allergic rhinitis, particularly perennial allergic rhinitis associated with sensitisation to indoor allergens. The widespread benefit of such an approach is appealing and warrants the initial cost if proven to be helpful, whereas such an initiative purely for rhinitis may be considered uneconomic. On the other hand, in patients with rhinitis and asthma, such an approach is more economically sound.

8-4-1- Rhinitis with asthma

A high percentage of asthmatics have coincidental rhinitis and so treatment for asthma that is also beneficial for rhinitis would be applicable to many patients with asthma. Such approaches include humanised monoclonal antibodies against IgE.

8-4-1-1- Humanised monoclonal antibodies against IgE

Three companies, Genentech, Novartis Pharma AG and Tanox Biosystems, have focused their efforts towards the strategy of anti-IgE therapy, and monoclonal antibodies against human IgE have been raised (e.g. rhu-Mab-E25 and CGP 51901). However, only one of these mAbs is currently developed for the treatment of rhinitis and asthma.

A monoclonal antibody was raised against the $C\varepsilon3$ domain of IgE molecules (MAE11). This region of the IgE molecule is involved in the binding of IgE to its receptors ($Fc\varepsilon RI$). The complexing of free IgE with MAE11 prior to the linking with $Fc\varepsilon RI$ prevents cross-linking of receptors (via antigen). It also prevents activation of mast cells and basophils (2599). MAE11 binds only to free IgE and not to $Fc\varepsilon RI$ bound IgE. Thus, MAE11 does not activate cells bearing $Fc\varepsilon RI$. This characteristic is required in order to achieve a prolonged pharmacological effect without inducing anaphylaxis (2600). Hybridoma technology enables the creation of rodent monoclonal antibodies but these have limited clinical utility (2601). Humanised antibodies have improved pharmacokinetics, reduced immunogenicity and have already been used during clinical trials. MAE11 was therefore humanised and the best of several humanised variants, version 25 (Rhu-MAb-E25), was selected (2599). Based on previous studies, it appeared likely that $Fc\varepsilon RI$ expression on basophils and

mast cells is regulated by levels of circulating IgE antibodies. Treatment with the anti-IgE MAb decreased free IgE levels to 1% of pre-treatment levels and also resulted in a marked down-regulation of $Fc\varepsilon RI$ on basophils (2602). This effect is reversible *in vitro* and *in vivo* (2603).

Another chimeric anti-IgE antibody has been raised and was found to have similar properties in animals (2604, 2605).

A study was carried out using rhu-Mab-E25 mAb in the treatment of ragweed pollen induced rhinitis. The effect of the rhu-Mab-E25 mAb was small, probably because the dose infused was insufficient (2606). Only the patients with a dose of 300 mg of rhu-Mab-E25 every 4 weeks had a reduction of H1-antihistamine use which was over 60% greater than that of the placebo. Furthermore, symptoms were reduced by over 20%. Other data are therefore needed using the proper dose. The efficacy, pharmacodynamics and pharmacokinetics of CGP 51901 were evaluated for 153 patients with seasonal allergic rhinitis treated with placebo or with 15, 30 or 60 mg of CGP 51901 in six bi-weekly doses (2607). Clinical efficacy was demonstrated in this study, but the magnitude of the effect and the effectiveness of anti-IgE mAb in comparison to classical treatment have to be established.

Rhu-Mab-E25 mAb has been tested in asthma and proof of concept was found since rhu-Mab-E25 inhibited the late-phase allergic reaction following allergen bronchial challenge (2608-2610). Moreover, in moderate to severe asthma, a recent study confirmed that rhu-Mab-E25 mAb was able to reduce oral and inhaled corticosteroids and improve quality of life (2611).

The safety of any novel therapy for asthma and allergic diseases is critical since these diseases are rarely lethal. Short-term safety was examined in three studies. CGP 51901 was well tolerated and only one subject had a weak antibody response against the mAb (2612). Rhu-MAb-E25 has been administered to over 3,000 patients for periods of up to one year and no serious adverse event has occurred. Moreover, there was no development of antibodies against Rhu-MAb-E25. Another safety issue is the theoretical outcome of tissue damage resulting from increased serum concentrations of Rhu-MAb-E25/IgE immune complexes. This does not seem to occur in these studies.

8-4-1-2- Inhibition of eosinophilic inflammation

Many novel treatments for asthma are based on an inhibition of eosinophil development or tissue recruitment. Such approaches include:
- monoclonal antibodies against IL-5 (2613, 2614),
- soluble IL-4 receptors (2615),
- inhibitors of chemokines such as RANTES and eotaxin (2616, 2617),
- chemokine receptor inhibitors, in particular the CCR3 receptor, inhibitors of adhesion molecule activity, either as receptor antagonists or as soluble receptors,
- ligand inhibitors such as VLA-4 antagonists (2618). As VLA-4 is involved in basophil and T-lymphocyte

recruitment as well as in eosinophil recruitment, this may have a greater potential as oral therapy (2619).

Although allergic rhinitis is associated with tissue eosinophil recruitment, there is little evidence to link eosinophil recruitment and activation with clinical disease expression. This will be clarified only when specific inhibitors of eosinophil recruitment and activation are assessed, such as anti-IL-5. However, it is unlikely that such treatments will have a widespread effect for rhinitis.

8-4-1-3- Inhibition of allergic inflammation

The major effector cells for clinical symptom expression appear to be basophils and mast cells. The development of effective inhibitors of degranulation, such as ion channel inhibitors (2620) and specific adenosine receptor antagonists (2621), are under evaluation. The recruitment of these cells in addition to involving chemokines and leukocyte endothelial cell adhesion molecule upregulation involves cytokine release from mast cells and T-cells.

Different approaches to the inhibition of T-cell activation are under development. These include the modification of antigen presentation to inhibitors of the T-cell receptor and the modification of accessory molecule expression, such as with the CTLA4 fusion protein (2622, 2623). These have yet to be evaluated in rhinitis.

8-4-1-4- Specific immunotherapy

Approaches to immune modification by specific immunotherapy or developments from these approaches are also under consideration (2624). In addition to improved allergen vaccines, these include:
- recombinant allergens (2625, 2626),
- peptide vaccines (2627-2629),
- the use of IL-12 as an adjuvant with specific immunotherapy,
- bacterial or mycobacterial products to stimulate Th1 response (2630-2632)
- plasmid DNA encoding of antigen (2633-2635).

8-4-2- Allergic rhinitis alone

Once evaluated in persistent disease and if found to be effective, any of these approaches may be extended to seasonal allergic disease. Any treatment for allergic rhinitis alone will have to measure up to intranasal glucocorticosteroids or H1-antihistamines. New H1-antihistamines may be produced since the H1-receptor has recently been cloned and 3D structures have been deduced (1686).

Glucocorticosteroids are the most effective anti-inflammatory treatment for asthma and rhinitis but more effective or safer products are needed (2636). Dissociated glucocorticosteroids may be of interest (2637). There may well be differences in systemic bioavailability between different intranasal glucocorticosteroid preparations.

One area currently under evaluation is the role of leukotriene receptor antagonists, particularly in combination with H1-antihistamines. Such a combination would modify two major mediators of allergic disease. Clinical trial evaluations of such a combination are under way or planned.

Kinin antagonists are now available (2638) but their effect in rhinitis requires further study (2639, 2640).

A final area of unexplained potential that pharmacological intervention will help clarify is that of the role of neuropeptides such as substance P and CGRP (2641). The development of tachykinin antagonists will provide clarification in this respect when evaluated in the clinical disease situation. Intranasal capsaicin can stimulate sensory nerve fibres and may destroy cells of the c-afferent (2642) or deplete neuropeptides (81). Intranasal capsaicin was shown to be an effective treatment when used for up to 9 months in patients with non-allergic rhinitis (954, 1613).

Immunotherapy is of proven benefit in seasonal allergic disease. At present, this is moreso limited to more severe disease but, on account of its potential to modify disease expression, it is likely to be extended to the treatment of individuals with milder disease.

8-5- PRACTICAL GUIDELINES FOR THE TREATMENT OF ALLERGIC RHINITIS AND CO-MORBIDITIES

8-5-1- Development of guidelines

Clinicians can often find treatment recommendations in traditional narrative reviews or in the discussion sections of articles and meta-analyses. In traditional approaches where the collection and assessment of evidence remains unsystematic, all relevant options and outcomes may not be considered, and values remain implicit and provide recommendations of weak rigour (2643).

Increasing attention should be being paid to the methodology of guideline development and the validity of guideline recommendations. While an increasingly rigorous approach is taken to guideline development, it is important to re-emphasise the central role of guidelines themselves, which is to help clinicians make better decisions. These guidelines are based on the best available published data and were proposed using the opinions of experts based on clinical trials or mechanistic approaches. However, it seems that "evidence-based medicine" (EBM) will be included in the analysis of new guidelines.

"Evidence-based medicine" is an increasingly important concept which may become a new paradigm in medicine (2644). It is the ability to track down, critically appraise (for its validity and usefulness) and incorporate the information obtained from randomised trials in order to establish the clinical bases for diagnosis, prognosis and therapeutics (41). The increasing influence of EBM is due partly to the work of the Cochrane Collaboration. The importance of this collaboration needs to be stressed even though it has lead to some criticisms (2645-2648).

Evidence-based medicine is attractive in its simplicity and few would argue with the philosophical concept. The reality of its application in primary care may however be rather different. It may be difficult to interpret evidence when it is available and to apply this evidence during consultation. Systematic reviews, which neither consider all relevant options and outcomes nor make the prefer-

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TABLE 20: Classification schemes of statements of evidence

Category of evidence:

Ia: evidence for meta-analysis of randomised controlled trials

Ib: evidence from at least one randomised controlled trial

IIa: evidence from at least one controlled study without randomisation

IIb: evidence from at least one other type of quasi-experimental study

III: evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies

IV: evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Strength of recommendations:

A: directly based on category I evidence

B: directly based on category II evidence or extrapolated recommendation from category I evidence

C: directly based on category III evidence or extrapolated recommendation from category I or II evidence

D: directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

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ences underlying recommendations explicit, offer intermediate rigour recommendations (2643). Moreover, very few meta-analyses are available for the management of rhinitis (1738).

Despite wide promulgation, clinical practice guidelines have had a limited effect on changing physician behaviour (2649-2651). Little is known about the process and factors involved in changing physician practices in response to guidelines. Every effort should be made to improve the implementation of guidelines at the general care level.

The first point of contact for many patients presenting with allergy symptoms is the primary care physician. In the managed care system, this initial primary care visit is essential. Guidelines for the primary care physician in diagnosing and treating rhinitis as well as in referring patients to allergy specialists were described (2652).

8-5-2- Development of guidelines for rhinitis

The 1994 guidelines (1) follow a stepwise approach in the treatment of allergic and non-allergic rhinitis. This seems to be the most practical approach for the general practitioner as well as for the specialist.

In 1999, the EAACI proposed new guidelines (3) and, unlike the 1994 guidelines (1), not only mild and moderate cases are considered but also severe ones. These

guidelines are consequently also aimed at the general practitioner and the specialist. There are general remarks about "how to interpret" and "how to follow" the practical guidelines for the treatment of rhinitis.

In the present guidelines, the suggestions were made by a panel of experts and based on the literature data available as from December 1999. A full consensus was reached on all of the material presented in this position paper. The panel recognised that the suggestions it puts forward are valid for the majority of patients within a particular classification but that individual patient responses to a particular treatment may differ from the suggested therapy.

It is assumed that a correct diagnosis is achieved before treatment.

The statement of evidence for the development of these guidelines has followed WHO rules (Table 20) and is based on Shekelle *et al.* (2653).

The statements of evidence for the different treatment options of allergic rhinitis have been examined by the report panel (Tables 21 and 22). However, a slight modification has been proposed since:
- for most interventions, placebo-controlled studies are available,
- there is evidence that neither physician nor patient can easily distinguish between an effective and an ineffective procedure for allergic disease without performing a proper trial (2654). Although these considerations were issued for allergen specific immunotherapy, it seems that they also apply to other treatments of allergic rhinitis.

Thus, for double-blind studies with a placebo group, the level of evidence was classified as A, and as A* for double-blind studies without a placebo group.
- For each intervention, the highest level of evidence was set from Ia to IV depending on the available studies published in papers indexed in Medline and Embase according to the category of evidence presented in Table 20.
- In Table 21, only the highest level of evidence for each intervention was reported. Thus, many studies with a lower level of evidence have not been listed in the Table.
- In Table 21, the level of evidence was:
  - Ib DB-PC: level of evidence Ib using double-blind, placebo-controlled studies
  - Ib DB: level of evidence Ib using double-blind studies.
- The strength of recommendation from A to D was based on Table 20 with a slight modification (Table 22):
  - A: for meta-analyses (Ia) and for double-blind, placebo-controlled Ib studies
  - A*: for double-blind Ib studies.

8-5-2-1- Definition of terms
It is necessary to define "intermittent", "persistent", "mild" and also "moderate-severe" (Table 1).

TABLE 21: Level of evidence of different interventions in allergic rhinitis: Category of evidence

intervention	level of evidence	seasonal adults	seasonal children	perennial adults	perennial children
Allergen avoidance					
house dust mites	IV			1641, 1643,	
cats, dogs	IV			1648	
cockroaches	IV			1649, 1650.	
outdoor allergens	IV				
latex	IV			1651-55.	
H1-antihistamine					
oral	Ib, DB-PC	1679, 1689, 1691, 1692, 1693, 1699, 1816, 1834, 1835, 1843, 1844, 1847, 1848, 1871, 1889, 1890, 1892, 1894, 1904, 1933-35, 1972-74, 1982-85, 1987, 1999, 2011, 2012, 2020-22, 2024, 2025, 2036, 2037, 2040.	1893, 1902, 1903, 2024	1690, 1845, 1847, 1872, 1891, 1895, 1898, 1899, 1936, 1937, 1986, 2000, 2041.	1896, 1897
intranasal	Ib, DB-PC	2055, 2057-61, 2065, 2066, 2068, 2073.	2055, 2058-60.	2067, 2068.	2067, 2070.
intra-ocular	Ib, DB-PC	2074, 2075, 2080, 2081.	2075, 2076.		
Glucocorticosteroid	Ib, DB-PC	1284, 2090, 2120, 2143,	2169, 2187,	2116, 2120,	2210, 2248,
intranasal		2144, 2150, 2160, 2180, 2200-03, 2206-08, 2215, 2216, 2228, 2229, 2235, 2239-43, 2255, 2256, 2276, 2277.	2188, 2217, 2218, 2247, 2234, 2247, 2260, 2262, 2263	2145, 2147-48, 2209, 2211, 2244-46, 2261, 2267.	2264, 2265.
oral	Ib, DB-PC	2284			
IM	Ib, DB-PC	2282			
Chromone					
intranasal	Ib, DB-PC	1284, 1366, 2305-13, 2319-22, 2655.	2305, 2307-09, 2312, 2313, 2319-23, 2325	2314-18 2656-59.	
intra-ocular	Ib, DB-PC	2326-29, 2331, 2333 2336-41, 2660, 2661	2327, 2328, 2330 2336, 2337, 2340 2341, 2345, 2660	2329	
NAAGA intranasal	Ib, DB-PC	2348			
Decongestant					
intranasal	no data				
oral	no data				
Oral decongestant + H1-antihistamine	Ib, DB-PC	2380-82, 2386, 2388, 2389, 2391, 2393	2380, 2386, 2388, 2390	2384	
Anti-cholinergic intranasal	Ib, DB-PC			2410	2410
CysLT antagonist	Ib, DB-PC	2422			
CysLT antagonist + H1-antihistamine	Ib, DB-PC	2422			
Anti-allergic drugs	Ib, DB-PC	2424			
Homeopathy	Ib, DB	2428			
Acupuncture	no data				
Chiropractic medicine	no data				
Phytotherapy	no data				
Other alternative medicine	no data				
Antibiotics	no data				
Specific immunotherapy					
subcutaneous					
asthma	Ia	2544	2544	2544	2544
subcutaneous rhinitis + conjunctivitis	Ib, DB-PC	2475, 2479, 2485, 2493, 2495, 2499, 2501-29	2485, 2493 2501-04.	1609, 2530-35.	1609, 2533, 2664.
intranasal rhinitis + conjunctivitis	Ib, DB-PC	2545-59	2665	2561	
sublingual rhinitis + conjunctivitis	Ib, DB-PC	2560, 2562, 2563, 2566-69.	2563, 2566, 2583.	2571, 2572	

TABLE 22: Level of evidence of different interventions in allergic rhinitis: Strength of recommendation

intervention	seasonal adults	seasonal children	perennial adults	perennial children
Allergen avoidance				
house dust mites			D	D
cats, dogs			D	D
cockroaches			D	D
outdoor allergens	D	D		
latex			D	
H1-antihistamines				
oral	A	A	A	A
intranasal	A	A	A	A
intra-ocular	A	A		
Glucocorticosteroid				
intranasal	A	A	A	A
oral	A			
IM	A			
Chromones				
intranasal	A	A	A	
intra-ocular	A	A	A	
NAAGA intranasal (a)	A			
Decongestant				
intranasal				
oral				
Oral decongestant + H1-antihistamine	A	A	A	
Anti-cholinergic intranasal			A	A
CysLT antagonist	A			
CysLT antagonist + H1-antihistamine	A			
Anti-allergic drugs (a)	A			
Homeopathy (a)	A*			
Acupuncture				
Chiropractic medicine				
Phytotherapy				
Other alternative medicine				
Antibiotics				
Specific immunotherapy				
subcutaneous				
asthma	A	A	A	A
subcutaneous				
rhinitis + conjunctivitis	A	A	A	A
intranasal (b)				
rhinitis + conjunctivitis	A	A	A	
sublingual (b)				
rhinitis + conjunctivitis	A	A	A	

A: 1b DB-PC: level of evidence 1b with double-blind, placebo-controlled studies.
A*: 1b DB: level of evidence 1b with double-blind studies.
a: Based on a single study. More data are needed.
b: Recommendation only applied to high-dose vaccine.

8-5-2-2- Availability of treatment

The guidelines are made on the presumption that the suggested treatments are available and affordable to the patient. There is a list of essential drugs published by WHO. It is important that all the major drugs needed in the treatment of rhinitis should be available worldwide.

The guidelines do not take the cost of treatment into account. They are made on the presumption that all treatments are readily available and financially affordable to the patient (on health insurance).

8-5-3- The management of allergic rhinitis

8-5-3-1- Pharmacological management of rhinitis

8-5-3-1-1- Mild intermittent disease (conjunctivitis not considered)

Options (not in preferred order) are:
- oral or intranasal H1-antihistamines,
- intranasal decongestants (for less than 10 days and not to be repeated more than twice a month),
- oral decongestants (not usually recommended in children),

8-5-3-1-2- Moderate/severe intermittent disease (conjunctivitis not considered)
- Options (not in preferred order) are:
  - oral or intranasal H1-antihistamines,
  - oral H1-antihistamines and decongestants,
  - intranasal glucocorticosteroids. The efficacy of short and repetitive courses has not been demonstrated by published data.
  - (chromones).
- The intramuscular injection of glucocorticosteroids is not usually recommended due to the possible occurrence of systemic side effects.
- The intranasal injection of glucocorticosteroids is not usually recommended due to the possible occurrence of severe side effects.

8-5-3-1-3- Mild persistent disease (conjunctivitis not considered)
Options (not in preferred order) are:
  - oral or intranasal H1-antihistamines,
  - oral H1-antihistamines and decongestants,
  - intranasal glucocorticosteroids,
  - (chromones),
- The intramuscular injection of glucocorticosteroids is not usually recommended due to the possible occurrence of systemic side effects.
- The intranasal injection of glucocorticosteroids is not usually recommended due to the possible occurrence of severe side effects.
- A stepwise approach is proposed.
- The patient should be reassessed after 2 to 4 weeks:
  - The patient is symptom-free or has less symptoms: it is advised to continue the treatment. However, for intranasal glucocorticosteroids, the dose may be reduced (e.g. by half). In the case of perennial allergy, symptoms may reoccur and a long-term treatment may be needed. In the case of seasonal allergy, a shorter course of treatment is required depending on the pollen season.
  - The patient has persistent mild symptoms and he (she) is under H1-antihistamines or chromones: change to intranasal glucocorticosteroids.
  - The patient has moderate to severe symptoms: go to step up.

8-5-3-1-4- Moderate/severe persistent disease (conjunctivitis not considered)
1- A stepwise approach is proposed.
2- It is advised to use intranasal glucocorticosteroids as a first-line treatment.
3- If the nose is very blocked:
  - a short course (e.g. one to two weeks) of oral glucocorticosteroids may be added
  - alternatively, intranasal decongestants for less than 10 days.
4- The patient should be reassessed after 2 to 4 weeks:
  - If the patient does not improve:
    - consider reasons for failure to respond to intranasal glucocorticosteroids:
      - inadequate compliance,
      - patient (or doctor) misunderstanding the dose

and frequency of administration of the intranasal glucocorticosteroids,
  - nasal obstruction preventing drug delivery,
  - additional nasal pathology (e.g. nasal polyps, sinusitis) or nasal septal deviation,
  - heavy persistent allergen exposure (e.g. cat on the bed),
  - wrong diagnosis (see classification of rhinitis),
  - double the dose of intranasal glucocorticosteroids if the major symptom is blockage,
  - add:
    - H1-antihistamines if the major symptoms are sneezing, itching or rhinorrhea,
    - ipratropium bromide if the major symptom is rhinorrhea,
    - oral H1-antihistamine and decongestant.
- If the patient does improve, a step down approach should be used (mild persistent disease). However, the treatment should last for at least three months or for the duration of the pollen season. In the step down treatment, low dose intranasal glucocorticosteroids may be required as a maintenance treatment to control symptoms.
5- Referral to a specialist may be considered:
  - if the treatment is not fully effective,
  - if the duration of the treatment is over 3 months and is unsuccessful.

8-5-3-2- The management of conjunctivitis
1- If the patient suffers from conjunctivitis, the options (not in preferred order) are:
  - ocular H1-antihistamines,
  - ocular chromones,
  - saline,
  - oral H1-antihistamines.
2- Ocular glucocorticosteroids have been associated with serious short-term and long-term complications. Their administration is not recommended if an eye examination has not been carried out.

8-5-3-3- Preventive treatment
8-5-3-3-1- Avoidance of allergen and trigger factors
Although there is no definite demonstration that allergen avoidance measures are effective in the treatment of rhinitis, it is indicated when possible.
8-5-3-3-2- Allergen specific immunotherapy
Specific immunotherapy has a place in patients who have a demonstrable IgE mediated disease and who either have a long duration of symptoms or in whom pharmacotherapy is not effective or induces side effects.

8-5-4- Treatment of rhinitis and asthma
8-5-4-1- Allergen avoidance
Allergen avoidance is always indicated in the treatment of allergic rhinitis (1) and asthma (36). It seems that this form of treatment is effective for all allergic symptoms, but definite evidence in rhinitis is still lacking. In asthma, a controversial meta-analysis was published recently (1621) but allergen avoidance is still advocated (1622).

8-5-4-2- Specific immunotherapy

The indications of specific immunotherapy in allergic asthma and rhinitis have been separated in some guidelines (2466). This artificial separation has led to unresolved issues (2596, 2597) possibly because the allergen-induced IgE-mediated reaction has not been considered to be a multi-organ disease. It is therefore important to consider specific immunotherapy based on allergen sensitisation rather than on the disease itself since most patients with allergic asthma also present rhinitis or rhino-conjunctivitis (see chapter 6-3).

8-5-4-3- Topically administered drugs

Medications for asthma and rhinitis can be administered via local (intranasal, intra-ocular or inhaled (intra-bronchial)), oral or parenteral routes. There are advantages (and some drawbacks) when the drug is administered directly into the target organ (see chapter 8-2-1) (1, 36). Moreover, some drugs like cromoglycate or nedocromil are not absorbed when given orally and are only effective when administered locally. In patients suffering from asthma and rhinitis, the local administration of drugs should be both nasal and bronchial. This may decrease compliance to treatment which is low in asthma and rhinitis.

Glucocorticosteroids are the most effective drugs for the treatment of rhinitis and asthma when used topically in the nose and bronchi. At large doses of inhaled glucocorticosteroids, side effects have been reported (2172) whereas it appears that intranasal administration is safer (2171). One of the problems of dual administration is the possible addition of side effects. In one study, it was found that the addition of intranasal to inhaled formulations did not produce any further significant suppression of mean values. However, there were more individual abnormal cortisol values associated with the dual therapy (2174). More data are urgently needed.

The observation that the management of allergic rhinitis also relieves symptoms of asthma has heightened interest in the link between these diseases.

The intranasal treatment of rhinitis using glucocorticosteroids was found to improve asthma moderately in some, but not all, studies (2666). Symptoms (2275, 2667) and pulmonary function tests (2667) were improved and exercise-induced asthma (2668) or bronchial hyperresponsiveness (1272, 2275, 2669) were reduced. Nasal beclomethasone prevents the seasonal increase of bronchial responsiveness in patients with allergic rhinitis and asthma (2670). This treatment modality may have advantages over the ordinarily used intranasal and bronchial topical treatment in patients with both asthma and rhinitis, especially when conventional inhaled therapy is associated with side effects. These data suggest that treating nasal inflammation may help to control asthma. However, a number of aspects, such as the extent to which the pathophysiology of the two diseases overlaps and whether treating one will affect the other, still remain to be clarified.

Less is known about the effects on nasal disease by inhaled (intra-bronchial) treatment with glucocorticosteroids. A study examined effects on nasal allergic disease of inhaled budesonide (avoiding nasal deposition of the drug) in patients with seasonal allergic rhinitis but without asthma (2093). During the birch pollen season, budesonide reduced the seasonal eosinophilia both in the circulation and in the nose along with an attenuation of seasonal nasal symptoms. Nasal and systemic anti-eosinophil actions are produced at commonly employed dose levels of orally inhaled budesonide.

8-5-4-4- Orally administered drugs

On the other hand, drugs administered by oral route may have an effect on both nasal and bronchial symptoms.

Oral H1-antihistamines represent the first-line treatment of allergic rhinitis. However, although some studies have found a modest effect on asthma symptoms (1904), in most studies showing an effect in asthma, drugs were administered at a higher dose than the recommended one and, usually, pulmonary function tests and/or peak flow rates were unchanged (2671-2673). Thus, these drugs are not recommended for the treatment of asthma (for review see 36, 2674, 2675). However, a recent study has shown that loratadine plus pseudo-ephedrine improved nasal and asthma symptoms, pulmonary function and quality of life in patients with seasonal allergic rhinitis and concomitant mild asthma (2393). Azelastine 8 mg is marketed in some countries for asthma.

Leukotriene modifiers were shown to be effective in controlling the symptoms of mild to moderate asthma, and some limited studies have suggested that, in association with oral H1-antihistamines, they may be effective in the treatment of rhinitis. Anti-leukotrienes therefore have the potential to treat asthma and possibly rhinitis but more data are needed to fully evaluate their real effect. Moreover, the combination of anti-leukotriene and H1-antihistamine produces a predominant inhibition of allergen-induced early and late-phase airway obstruction in asthmatics (2676). This suggests an enhanced effect of anti-leukotrienes in asthma when associated with H1-antihistamines.

Theophylline was found to reduce nasal inflammation (2677). It has also been observed that theophylline can reduce bronchial hyperresponsiveness in patients with allergic rhinitis (1273) but there are no controlled data concerning the therapeutic effect of this drug on nasal symptoms.

Oral glucocorticosteroids are highly effective in the treatment of rhinitis and asthma but side effects are common after long-term use.

8-6- PAEDIATRIC ASPECTS

Allergic rhinitis is part of the "allergic march" during childhood (2678). Positive skin prick tests and specific IgE antibodies to food allergens are most prevalent during the first and second years of life. However, specific IgE and positive skin prick tests to inhalant allergens develop after the second year of life as do the symptoms of allergic asthma and allergic rhinoconjunctivitis (2679). Although pollen sensitisation may occur early in life (1618), seasonal allergic rhinitis is exceptional before two years of age. Allergic rhinitis is most prevalent during school age. In the worldwide ISAAC study,

the prevalence of allergic rhinitis varied in different parts of the world from 0.8% to 14.9% in the 6-7 year-olds and from 1.4% to 39.7% in the 13-14 year-olds (12). This coincides with age variation in the prevalence of positive skin prick tests to inhalant allergens (2679).

8-6-1- The development of sinus cavities in childhood

The four paired paranasal sinuses (ethmoid, maxillary, sphenoid and frontal) begin to develop during late fetal life and continue to develop for two decades after birth. They form as outgrowths or diverticula on the walls of the nasal cavities and become air-filled extensions of the nasal cavities in the adjacent bones. At birth, the ethmoid, maxillary and sphenoid sinuses are present. The frontal sinuses develop from the anterior ethmoid sinuses during early childhood and are not clinically important in young children.

8-6-2- Pharmacological treatment

The principles of the treatment are the same as in adults, but special care has to be taken to avoid the side effects which are typical in this age group (3, 40). Dosages have to be adapted and some special considerations have to be followed. On the one hand, caution is necessary because of the young age of the patient, but on the other hand, an early appropriate treatment may have not only therapeutic but also prophylactic capacities, as was shown recently (2680, 2681). Few drug treatments have been tested in children under the age of two years. Among the most important aspects to consider are the cognitive functions of pre-school and school children in relation to the general malaise caused by rhinitis and in relation to the antihistamine treatment (18).

Oral glucocorticosteroids and depot-preparation should be avoided in the treatment of rhinitis in young children. Intranasal glucocorticosteroids are the most effective treatment of allergic rhinoconjunctivitis but the fear of systemic side effects, albeit rare, should always be considered in children. Modern intranasal glucocorticosteroids are much less absorbed (bioavailability <30%) and the minimal dose needed to control symptoms should be used. Intranasal glucocorticosteroids with high bioavailability such as betamethasone should not be used in children (2163). One special concern is the effect upon growth and growth velocity. A recent study found no short-term effect from intranasal budesonide and mometasone furoate (2682). Treatment with inhaled glucocorticosteroids has been demonstrated to affect growth to a moderate degree in asthmatic children (2683-2685) and this has been shown for some but not all intranasal glucocorticosteroids (2175). Recently, it was shown that the intranasal glucocorticosteroids mometasone (2279) and fluticasone did not affect growth in children with allergic rhinoconjunctivitis. On the other hand, oral and depot glucocorticosteroid preparations have a clear effect on growth and growth velocity (2686).

The use of H1-antihistamines is important for the treatment of rhinitis in children. Classical oral H1-antihistamines have central side effects with sedation as the most common (2687). The response to different antihistamines may differ from patient to patient, but it has been demonstrated that children not responding to one antihistamine may respond to another (1736). Classical first-generation H1-antihistamines used in toxic doses affect the central anti-cholinergic syndrome, could induce life-threatening reactions in children (2688) and require treatment with physostigmine. These effects are not generally seen with the new low-sedating antihistamines, though they differ to some degree. Focus has been put upon the cognitive effect of classical antihistamines. Seasonal allergic rhinitis per se may affect learning ability and concentration (18). Treatment with classical antihistamines often had a further reducing effect upon cognitive function (1825). However, use of the newer H1-antihistamines counteracts the feeling of malaise caused by allergic rhinitis and may improve learning ability in allergic rhinitis (18). Interactions with the cytochrome P450 may reduce the metabolism of the H1-antihistamines metabolised in the liver. Macrolide antibiotics, commonly used in children, may have this effect.

The use of intranasal antihistamines like levocabastine, azelastine and antazoline has the benefit of almost no side effects. However, although there is a beneficial effect upon symptoms in the organ to which they are administered, they usually have little effect elsewhere. These drugs are useful in children with symptoms limited to the nose or the eyes (2061).

Disodium cromoglycate has been one of the common drugs used for allergic rhinoconjunctivitis in children. Both DSCG and nedocromil sodium were found more effective than placebo, but DSCG was found to be less effective than intranasal glucocorticosteroids or H1-antihistamines. It is important to note that in children, these drugs are free from side effects (2689). However, a dosage of 4-6 times a day is required for DSCG and compliance with treatment is often difficult. In randomised double blind trials, DSCG has been demonstrated to be less effective than both intranasal levocabastine and intranasal glucocorticosteroids.

Nasal saline drops or spray can help to clear the nose before eating or sleeping. The treatment of allergic rhinitis in small children under the age of 4 again depends on allergen avoidance, but DSCG and oral H1-antihistamines are also available for this age group. Mometasone furoate is available for children of 3 years and over. Fluticasone propionate is available for children of 4 years and over and other intranasal glucocorticosteroids may be used in children over the age of 5 years.

8-6-3- The relationship between rhinitis and asthma

Allergic rhinoconjunctivitis is often a precursor of bronchial asthma in children. Often, allergic rhinoconjunctivitis and asthma occur simultaneously in children. The treatment of allergic rhinoconjunctivitis with inhaled glucocorticosteroids may also improve asthma (25, 2690). It is not known whether an early anti-inflammatory treatment in allergic rhinitis may influ-

ence later development of bronchial asthma. However, 200 children with pollen allergy were treated for allergic rhinitis in an open trial of three years of specific immunotherapy or allergy vaccination. Preliminary results indicate that allergen vaccination with grass or tree pollen may reduce the development of asthma in children with allergic rhinitis (2595). Pharmacological treatment in sensitised, high-risk infants may also prevent asthma (1741, 2691) but more data are needed to fully appreciate this effect.

8-6-4- Sport and rhinitis

Children and adolescents are physically active and often participate in sporting events. Many elite athletes may suffer from allergic rhinoconjunctivitis. For children and adolescents active in sport, it is important to observe the doping rules set by the medical commission of the International Olympic Committee. It may indeed be a very serious event for an athlete to be suspected of doping, especially when the drug is taken without knowing the regulations. With particular relevance to allergic rhinitis, it is important to note that systemic nasal decongestants like pseudoephedrine or phenyl-propanolamine are considered to have a central stimulant effect and thus are not allowed for use in sport. These α-adrenergic agonists are often combined with H1-antihistamines and should be carefully avoided by athletes. Physicians treating children and adolescents should be aware of these regulations and of any changes in the regulations. For intranasal glucocorticosteroids, a certificate should be issued. However, regulations between countries are different.

8-7- PREGNANCY

8-7-1- General considerations

Rhinitis is often a problem during pregnancy since nasal obstruction may be aggravated by pregnancy itself (70, 72, 2692). Caution must be taken when administering medication to a pregnant woman, as most medications cross the placenta. The risk of malformation of the foetus represents a major fear. In studies concerning teratogenicity in animals, the apparent safety of medication in healthy adults or the chemical structure of a drug do not formally eliminate toxicity in a fœtus. Moreover, these limited studies have been done only on small groups without long-term analysis. Prescribing a drug to a pregnant woman, even a drug which has been on the market for a number of years, enlists the responsibility of the doctor. It is worth considering, therefore, the benefit/risk ratio, as much for the mother as for the fœtus. Generally, treatment does not cause any problem (74, 2378, 2693-2695). Moreover, there are differences in regulations between countries.

8-7-2- Specific considerations

With regard to anticholinergic agents, there is no existing teratogenicity in animals. Atropine passes through the placenta and can be prescribed to pregnant women. The prescription of its derivatives also seems to be without danger, but it is advisable, due to lack of extensive studies, to avoid these during the first trimester.

With regard to glucocorticoids, even though in animals they are all teratogenic (principally harelip but also cardiovascular malformations), no abnormality has been found in humans. The increased risk of growth retardation *in utero*, in the case of prolonged systemic corticotherapy, seems to be more related to a severe underlying maternal pathology than to the corticotherapy itself (2693). The risk described initially of adrenal insufficiency in newborns in the perinatal period has not been confirmed (2696). For example, in 36 pregnant asthmatic women treated with prednisone, Snyder *et al.* (2697) did not notice any pathological pregnancy or medical problem in the children born and observed during a two-year period. Inhaled glucocorticoids have not been incriminated as teratogens and are commonly used by pregnant asthmatic women (2378). Greenberger *et al.* (2698) did not find any materno-fœtal side effects in 40 pregnant asthmatic women who were treated with beclomethasone.

With regard to the cromones, no teratogenic effect has been found in animals. To this day, no side effect has been found in humans (2699), but there are no prospective studies available. Schatz and Zeiger (2693) propose the use of cromones as a first-line treatment for allergic rhinitis in pregnant women.

Second-generation antihistamines do not appear to be teratogenic in animal experimentation. Once more however, the absence of controlled trials in humans and the crossing of the placental barrier make the avoidance of their prescription necessary during pregnancy. Some first-generation antihistamines (e.g. brompheniramine, promethazine, diphenhydramine and hydroxyzine) were shown to be teratogenic in animals (2700, 2701). A prospective matched-case control study of hydroxyzine and cetirizine was carried out in pregnancy and no side effects were found (2702).

Concerning specific immunotherapy, Metzger *et al.* (2703) have proved its safety by a study in 121 pregnant women each receiving specific immunotherapy for allergic rhinitis. It is advisable, however, not to increase the dosage during pregnancy in order to avoid any possibility of an anaphylactic accident. It is also advisable not to begin specific immunotherapy for allergic rhinitis during pregnancy (2466).

8-8- THE ELDERLY

With aging, multiple physiological changes occur in the connective tissue and vasculature of the nose which may predispose or contribute to chronic rhinitis (2704). The accurate differentiation between allergic and non-allergic causes of rhinitis requires skin testing or *in vitro* measures of specific IgE. Empirical treatment with OTC first-generation H1-antihistamines and oral deconges-

tants frequently results in CNS, anticholinergic and cardiovascular adverse effects (2705). Thus, as recommended in general, it is important to use second-generation antihis-tamines. Intranasal therapies including DSCG, glucocorticosteroids and ipratropium bromide are all well tolerated with minimal adverse effects.

Patients with glaucoma or urinary retention should not use anti-cholinergics. The avoidance of allergens and/or irritants is an important adjunct in treating patients with allergic and vasomotor rhinitis. On the other hand, specific immunotherapy is not recommended in elderly patients (2706).

9 - Education

The education of the patient and /or the patient's care giver regarding the management of rhinitis is essential. Such education maximises compliance and the possibility of optimising treatment outcomes (37).

After the initiation of therapy, an appropriate follow-up for patients with rhinitis optimises the chances that a patient will benefit from the broad array of therapeutic approaches available, and that possible complications from rhinitis or its treatment are identified and addressed. At these visits, education and compliance are critical elements.

Maximum therapeutic responses require patients who are compliant with recommendations. Patient compliance with physicians' recommendations for therapy is more likely in patients who understand their disease, the various available treatment options and the likelihood of success of each possible treatment. This demands that the patient establishes a relationship of trust with, and confidence in, the physician. It is important to educate both the patient and relevant family members regarding the nature of the disease and available treatments. This should include general information regarding the symptoms, causes and mechanisms of rhinitis. In addition, education about means of avoidance, immunotherapy and drug therapy must be provided. It is vital that patients understand the potential side effects of therapy, especially drug side effects, in order to ensure that they do not abruptly discontinue beneficial therapy but rather communicate adverse events to their physician so they can deal with them in a manner best for the patient. It is also important to provide patients with education about the complications of rhinitis including sinusitis and otitis media, and about comorbid conditions such as nasal polyps. They should be aware of how such complications are recognised and how they are treated. Patients need to be aware of the potential negative impact of rhinitis on the quality of life and potential benefits of complying with therapeutic recommendations. Patients must also have realistic expectations for the results of therapy and should understand that complete cures do not usually occur in the treatment of any chronic disease, including rhinitis.

Compliance is enhanced when:
- a fewer number of daily doses is required;
- the patient schedules when doses are to be taken and selects an appropriate reminder mechanism, such as mealtimes, daily rituals, etc;
- there is a good doctor-patient relationship with a high level of physician trust;
- the patient has written instructions to follow;
- rhinitis medication is taken with the same dosing frequency as other medications;
- there is a well designed reminder chart for times of dosing interval.

10- Prevention of rhinitis

There is a general misconception that the same factors involved in the induction of allergy are also likely to incite disease once established. However, this is not necessarily the case. Thus, strategies for primary prevention or prophylaxis may be very different to those required for the management of established disease. Using the analogy of prophylaxis for tuberculosis, prevention can therefore be divided into primary, secondary and tertiary intervention:

- Primary prophylaxis will be employed on populations at a high risk of becoming sensitised in situations where there is no evidence of allergic sensitisation (2707).
- Secondary prophylaxis will be in individuals who show evidence of sensitisation to allergens but not yet any evidence of disease in the upper respiratory tract.
- Tertiary prophylaxis will be preventive strategies for the management of established allergic rhinitis. Most published work comes from tertiary prophylaxis.

A more complete description of preventive measures is reported in the WHO initiative "Prevention of allergy and asthma".

10-1- PRIMARY PREVENTION

It has been shown that the foetus is far from immunologically naive. Indeed, allergen specific cellular responses can be identified as early as 20-22 weeks of gestation. As pregnancy is a Th-2 (allergy biased) phenomenon modulating the mother's immune response to foeto-paternal antigens (2708), it is perhaps not surprising that a high percentage of newborns are not only sensitised to allergens to which their mothers have been exposed, but also have a Th-2 biased response (2709). To what extent this persists and evolves into allergic disease is probably influenced by postnatal experience, but it has raised the possibility of introducing primary prophylaxis during pregnancy in high risk families.

There is considerable concern that we do not have sufficient information on critical doses and on the timing of exposure that might be associated either with the development of sensitisation or of tolerance. Indeed, there is even limited evidence to suggest that high dose exposure will induce IgG antibody production in the mother and thereby reduce the possibility of allergy developing in the offspring. There is one remarkable study showing reduced allergy in the children of mothers who received specific immunotherapy during pregnancy (2710). Given these observations, the recommendation of allergen avoidance in pregnancy could conceivably increase rather than decrease the frequency of sensitivity and thereby the subsequent development of disease. At this stage, no recommendations should be made but further research is critically required.

10-2- SECONDARY PREVENTION

Much of the early efforts of allergen avoidance have focused on infant feeding and, in particular, an early avoidance of cow's milk protein and sometimes egg, fish and nuts. Most studies have commenced avoidance in the postnatal period and results have been variable with no clear-cut view emerging. The two studies that have had the longest follow-up have both identified a transient effect reducing food allergy and atopic dermatitis. However, continued follow-up has shown a diminishing effect on allergic manifestations in the respiratory tract, this effect eventually disappearing altogether (2711, 2712). The conclusion from one of these studies was that the effort was not justified by the outcome (2712). Furthermore, there is limited evidence that early dietary manipulation may be a risk for impaired growth. Therefore, great caution is required in employing such approaches (2713).

Aero-allergen avoidance has been largely promoted in order to avoid sensitisation as it has been clearly shown that there was a correlation between the level of allergen exposure in infants and sensitisation to allergens (366, 1618). However, recent studies suggest that, in contradistinction to what had previously been published, the avoidance of early cat exposure does not prevent allergy (2714, 2715) and that early contact with cats and dogs may prevent allergy more effectively than avoidance (217).

These controversial results have led to suggest that, in the future, secondary prophylaxis will be to redirect the new born infant's immune response into a Th-1 non-allergy immune response; this approach may be promising. This might be achieved by high exposure to relevant allergens as opposed to normal low dose exposure. It may be facilitated by the utilisation of fusion proteins combining allergen and cytokines such as IL-12 which will induce a Th-1 response (205). This idea has gained considerable credibility in relation to the so-called hygiene hypothesis which identified associations between early microbial experience and subsequent reduced allergic disease (2716).

10-3- TERTIARY PROPHYLAXIS

See chapter 8-1.

11- Quality of life

Quality of life (QOL) is a concept including a large set of physical and psychological characteristics assessing problems in the social context of lifestyle. Nowadays, it has been recognised that allergic rhinitis comprises more than the classical symptoms of sneezing, rhinorrhea and nasal obstruction. In the last decade, an increasing effort has been made to understand the socio-economic burden of rhinitis in terms of effects on health-related quality of life (HRQL) and health care costs. It has been acknowledged in several consensus reports that allergic rhinitis is associated with impairments in how patients function in day to day life at home, at work and in school (1, 2). With the introduction of a questionnaire designed to measure rhinitis associated impairments of quality of life (2717), it became clear that patients may be bothered by sleep disorders, emotional problems, impairment in activities and social functioning. Also, in general terms, patients with allergic rhinitis are impaired in physical and mental functioning including vitality and the perception of general health (16).

11-1- HEALTH RELATED QUALITY OF LIFE

11-1-1- Methods measuring HRQL

In rhinitis research, two types of HRQL measures have been used: generic and specific.

11-1-1-1- Generic questionnaires
Generic questionnaires measure physical, mental and psycho social functions in all health conditions irrespective of the underlying disease and can be used in the general population. These include the Sickness Impact Profile, the Nottingham Health Profile and the Medical Outcomes Survey Short Form 36 (SF 36). The SF36 has been used to characterise patients with perennial rhinitis (16, 109) and to evaluate the effects of a non-sedating H1-antihistamine on quality of life (1899). The advantage of generic instruments is that the burden of illness across different disorders and patient populations can be compared. The disadvantage however is that the instruments miss depth and may not be responsive enough to detect changes in general health states in spite of important changes in disease-related problems (2718).

11-1-1-2- Disease-specific questionnaires
Specific instruments have been designed by asking patients what kind of problems they experience from their disease. Both frequency and importance of impairments find expression in the questionnaires. These instruments have the advantage that they describe more accurately the disease-associated problems of the patients. Moreover, they seem to be more responsive to changes in HRQL than generic instruments.

Specific instruments for different age groups of patients with rhinitis have also been developed. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (2717)

and the Rhinitis Quality of Life Questionnaire (2719) have been tested in adult patients with seasonal allergic rhinitis and perennial allergic rhinitis respectively.

Taking into account that adolescents may experience different problems to adults, the Adolescent RQLQ questionnaire has been developed covering patients aged 12-17 years (2720). This questionnaire is a slightly modified version of the adult version, as problems in (school) work and the problem of generally not feeling well appeared to be more important in adolescents than in adults.

A Paediatric RQLQ Questionnaire has been developed for children aged 6-12 years (2721). This questionnaire differs from others, as children are less bothered by emotional problems and rhinitis interferes less with day to day life.

The RQLQ has been used in several trials focused on the effect of nasal glucocorticosteroids (2211, 2721-2723), H1-antihistamines (2724) and the combination of glucocorticosteroids and H1-antihistamines (2273) on rhinitis related QOL.

11-1-2- Relevance of HRQL measurement

Rhinitis related QOL appears to be moderately correlated to the more classical outcome variables used in clinical trials such as daily symptom scores and nasal hyperreactivity (2725). These observations are in line with the results of studies comparing disease-specific HRQL in asthmatics with asthma symptoms, peak flow and bronchial hyperresponsiveness (2726, 2727). It has been suggested that the classical outcome variables may only partially characterise the disease of the patient. From that point of view, it has been advocated to measure HRQL along with the conventional clinical indices (2728).

11-1-3- Impairment of HRQL in rhinitis and rhinitis co-morbidity

Using a generic questionnaire (SF-36) (2729), QOL was found to be significantly impaired in patients with moderate to severe perennial allergic rhinitis when compared to normal subjects (16). Using the same questionnaire, QOL was impaired, but to a lesser extent, in patients suffering from seasonal allergic rhinitis (2730), suggesting that a prolonged allergen exposure was impairing QOL more than a seasonal exposure. However, although QOL questionnaires are of great interest in assessing the overall effect of a disease on QOL in a group of individuals, unfortunately they do not appear to be sensitive enough to be used in individual patients.

It appears that the impairment in functioning of patients with moderate to severe perennial rhinitis (16) is comparable with the limitations perceived by asthmatic patients with a moderate to severe disease (2731). However, the extent to which asthma and rhinitis co-morbidities are associated in QOL remains to be elucidated.

Sinusitis is a common feature of rhinitis and, using the SF-36 and a sinusitis-specific QOL measure (the CSS: Chronic Sinusitis Survey), it has been shown that sinus surgery may improve the quality of life of sinusitis patients (2732, 2733). Recognising that rhinosinusitis is a disabling disease, other specific instruments such as the Rhinosinusitis Disability Index (RDI) (2734) and the 31-item Rhinosinusitis Outcome Measure (RSOM-31) (2735) have been introduced.

The impact on social life of recurrent ENT infections in children during the first 4 years of life is not easily captured. Indirect information can be obtained using specific questionnaires which measure parental quality of life (2736).

11-1-4- Evolution of HRQL during interventions

When using HRQL outcomes in clinical trials, the question arises as to whether a change in HRQL is clinically important. It has been shown that in QOL instruments which use a 7-point scale, the minimal important difference of quality of life score per item is very close to 0.5 (2737).

Generally, the effect on HRQL runs parallel with the effect on conventional medical outcome measures. However, in some studies, differences can be found. In a study evaluating the combined effect of glucocorticosteroids and H1-antihistamines, no differences were seen in terms of QOL between patients treated with H1-antihistamine and glucocorticosteroids versus glucocorticosteroids alone. However, for some patient-rated symptoms, the combination was found superior (2273). This might indicate that patients perceive differences in efficacy, not captured by conventional symptom scores. Patients with chronic conditions may adapt themselves to their disease. As the perception of patients is clearly important in the management of disease and patient compliance, the measurement of this "dimension" by HRQL questionnaires in clinical trials may be justified.

In the future, with more data available, it is possible that QOL measurements may represent a primary outcome measure for clinical trials.

11-2- LEARNING DISABILITY IN RHINITIS

If nasal symptoms are not well controlled in patients with allergic rhinitis, they may contribute to learning problems during school hours either by direct interference or by nocturnal sleep loss resulting in daytime fatigue (19, 1426). Seasonal allergic rhinitis may be associated with a reduced ability to learn. Treatment with sedating H1-antihistamines will aggravate these problems, whereas treatment with non-sedating H1-antihistamines will only partially reverse the limitations in learning (18, 2738). Recently, in an open single-blind study carried out over 6 months in 113 children with allergic perennial rhinitis and 33 children with non-allergic perennial rhinitis, it was shown that beclomethasone or ipratropium bromide diminished the interference of rhinorrhea in school attendance, in concentration on school work and in sleep (2739).

11-3- WORK IMPAIRMENT IN RHINITIS

Allergic rhinitis is a disease inducing work absenteeism and a reduction in work productivity. Moreover, using sedative H1-antihistamines, work productivity is reduced even further (20). In the U.S., allergic rhinitis results in approximately 811,000 missed work days, 824,000 missed school days and 4,230,000 reduced activity days per year (21).

These data indicate that allergic rhinitis may have an important impact on occupation and worker productivity. Patients are bothered by fatigue, poor performance and concentration at work, headaches and malaise. Conjunctivitis may impair vision and vision-related activities. Not only disease but also medication may influence work productivity. It has been estimated that 50% of the workers who treated their allergic rhinitis with first-generation sedating antihistamines functioned at only 75% of their total capacity for 14 days per year (2740). Patients taking these sedating antihistamines are more likely to sustain occupational injuries (odds ratio 1.5). The type of occupational injuries include fractures, dislocations, open wounds, superficial injuries and burns (2741). With the newer antihistamines, these problems have been significantly reduced (20).

Very little is known about the impact of allergic rhinitis on the career of patients. It is imaginable that patients will not change or lose jobs except in the case of occupational allergy. A five year health surveillance in milling, baking and other food manufacturing operations showed that 56% of the patients with a diagnosis of occupational rhinitis continued to do the same job, 13% were doing a different job in the same area and 31% were working elsewhere in the factory (2742).

11-4- HEALTH-RELATED QUALITY OF LIFE AND HEALTH CARE COSTS

The high prevalence of allergic rhinitis and the concern about health care costs justifies the increasing interest for cost-effectiveness studies. Not only the efficacy of treatment has to be demonstrated but also the cost-effectiveness (see chapter 12). In these studies, HRLQ measures have to be incorporated in order to make comparisons across patient populations and different disorders. It is however difficult to incorporate the generic SF-36 or disease specific HRQL scores into cost-effectiveness analyses. To that purpose, utilities such as the Standard Gamble, Feeling Thermometer have been developed measuring the value that patients themselves place on their own health status. Alternatively, some utilities measure the value that society places on various health states. Examples are the EuroQol and Multiattribute Health Utilities Index. An advantage of these utilities is their ability to produce quality-adjusted life years (QALYs). QALYs associated with different medical therapies can easily be incorporated into cost-effectiveness studies.

Utility instruments are mostly generic. A recent rhinitis specific utility – the Multiattribute Rhinitis Symptom

Utility Index - has been developed as a patient outcome for clinical trials and for cost-effectiveness studies comparing medical treatment for rhinitis (2743). More research is however needed to validate this instrument.

11-5- PERSPECTIVES FOR THE FUTURE: THE USE OF QUALITY OF LIFE INSTRUMENTS IN INDIVIDUAL PATIENTS

Rhinitis significantly impairs QOL when general or disease-specific questionnaires are used. The decrease in QOL seen in perennial rhinitis is comparable to that observed in patients with moderate to severe asthma and can affect sleep, work, education and social life. Quality of life measurements need to be taken into consideration in clinical trials and when treating patients.

Although studies have shown an impairment of QOL in rhinitis, these questionnaires are not currently applicable for use as a clinical tool in individual patients. Inclusion of these outcome measures in the evaluation and management of the individual patient should be the next step. Moreover, there is a need for a specific instrument measuring QOL in patients with both asthma and rhinitis and, if appropriate, this questionnaire may be used as a primary outcome variable in clinical trials. However, HRQL questionnaires are still being refined (2744) and the number of outcome measures — also in the field of nasal disease — is increasing. Some criticisms have been raised against the proliferation of instruments and the burgeoning theoretical literature devoted to the measurement of QOL (2745). Some methodological problems are not yet resolved (2727). Therefore, further research needs to be focused on the selection and "sharpening" of a limited number of patient-friendly instruments in order to better interpret the results of clinical trials and to better understand the patient with rhinitis.

12- The social economic impact of asthma and rhinitis

Asthma and rhinitis are chronic conditions with a substantial economic impact on the affected persons, their families, the health care systems and society as a whole. This burden is composed of direct expenditures generated within the health care system as well as indirect costs associated with the loss of economic productivity. Persons with asthma or rhinitis must cope with both the immediate and long-term impact of a condition that often affects daily functioning. They are frequently required to make choices on how to re-allocate their personal and family resources—originally dedicated to daily needs such as food, clothing and housing—to pay for medical care aimed at improving their condition. The economic burden of these conditions also affects the work place since symptoms often adversely affect work productivity.

World literature on the economic burden of asthma and rhinitis has only recently emerged and to date has focused primarily on asthma. However, the few individual studies examining the economic impact of rhinitis also provide compelling evidence of its substantial impact.

12-1- THE IMPACT OF ASTHMA AND RHINITIS

Asthma and allergic rhinitis are common health problems that cause major illness and disability worldwide. Studies such as the ISAAC (154) and the ECRHS (107) have demonstrated that asthma is a prevalent condition in most countries. These studies suggest that there are more than 150 million persons worldwide who are affected by asthma. Rhinitis is similarly seen as a worldwide condition with lifetime prevalence estimates of between 10 and 20% of the population in the US, UK, Germany, Switzerland and Finland (11, 261, 912, 2746).

The global burden of these conditions is reflected in the use of health care resources and loss of productivity due to illness-related disability. Costs of illness studies have begun to express these facts in economic terms.

12-2- UNDERSTANDING THE COSTS OF ILLNESS

The cost of illness study is the tool for understanding the economic burden of illness (2747). The cost of illness approach separates costs into those associated with medical care treatment for the illness (direct costs) and those resulting from non-medical losses as a consequence of the illness (indirect costs). Standard methods exist for placing an incremental economic value on direct medical care costs and indirect non-medical costs. Intangible costs, specifically those associated with the value of the psychosocial impacts of illness, have also been theorised.

However, to date, the methods for valuing intangible costs have not been fully developed. Costs of illness can be viewed from the perspective of the society, the health care system (organisations within a community that provide or finance care) and/or the individual. The literature contains studies of the costs of illness for both asthma and rhinitis.

12-3- THE COSTS OF ILLNESS FOR ASTHMA

There are at least seven recent international costs of illness studies for asthma (36, 2748-2755). Total costs of asthma vary notably, from a low of 433.5 million to a high of 6.4 billion annually in Canada and the United States respectively. The population would account for much of this variation. However, the cost per affected person also varies from less than $400 to more than $1,000 annually. Also, there is no consistent relationship between direct and indirect costs. An important finding in most of these cost of illness studies is that emergency care and hospitalisation—generally thought to be avoidable events—are a large cost component of care. However, it has recently been calculated that a significant increase in asthma prescribing costs is likely to be needed if an optimal control of asthma is to be achieved (2754).

The economic burden associated with asthma morbidity cannot be overstated. It is estimated that childhood asthma accounts for over seven million days restricted to bed and ten million days missed from school each year (2756). In Australia, children lose approximately one million school days each year due to asthma (2757). Asthma also affects family activities. Families with children who have asthma report that this illness influences a range of decisions concerning holidays, pets, furnishings, carpets, lifestyle and household spending (2758-2760). Also, these studies clearly indicate how morbidity associated with work loss due to the care of a child with asthma contributes to the economic burden of this condition. Work loss and decreased work productivity of adults with asthma is an equally big problem (2761).

Thus the many international studies of cost of illness for asthma have begun to depict a global picture of the economic burden of this disease. To date, information on the costs of illness is missing from many countries with sizeable populations, such as India, Indonesia and China. The costs of illness for asthma in these countries may be characteristically different than those of the US and Europe. One small study from the community of Transkei in South Africa suggests that expenditures per person affected with asthma may be as low as $10 US annually, which is far below that of other countries studied to date (36). The results from this study suggest the importance of understanding the costs of illness in non-industrialised countries.

12-4- THE COSTS OF ILLNESS FOR RHINITIS

The literature characterising the economic impact of persons with rhinitis is much more modest than that of asthma. There are currently three cost of illness studies examining the costs of allergic rhinitis (21, 2762, 2763). In 1994, there were an estimated 39 million persons in the US suffering with allergic rhinitis, accounting for an estimated 1.2 billion $ in total costs (21). It is interesting to note that only approximately five million of these persons sought medical treatment for this condition, and direct medical expenditures were estimated to account for 93% of their total costs (21). Much of the costs associated with rhinitis may be underestimated due to the frequent use of non-prescribed medications and the tendency to associate this condition with other conditions such as asthma (21).

A study of the direct medical costs of illness for US children with and without asthma revealed that children with asthma used substantially more medical care services (e.g. 3.1 times as many prescriptions, 1.9 times as many ambulatory care visits, 2.2 times as many emergency department visits) than children who did not have asthma. However, only 26 % of the difference in these costs was related to asthma-specific medical care. A large percentage of these additional costs was associated with other conditions, mainly upper airway illnesses such as rhinitis (2753).

All Japanese people belong to either government, union or community health insurances. Total medical expenditures can therefore be reported. In 1994, total costs for rhinitis were 1.15 Billion $ including direct and indirect costs as well as OTC costs. The average annual expenditure was 118 $ per patient (2764).

Rhinitis increases asthma costs. In one study, yearly medical care charges were on average 46% higher for those with asthma and concomitant allergic rhinitis than for those with asthma alone, accounting for age and sex (32).

12-5- SEARCHING FOR THE BEST ECONOMIC STRATEGIES FOR THE CARE OF PERSONS WITH ASTHMA AND RHINITIS

Resource constraints directly and indirectly affect all medical treatment decisions. Yet, presently, there is not enough information available to inform patients, health care providers and health care systems as to the relative impact of various alternative treatments on resources and costs of care. Costs of illness studies, such as those described above, provide information on the overall disease burden. However, other pharmacoeconomic methods can be used to improve the quality of medical and financial decision making by providing more specific data on the relationship between treatment decisions, health outcomes and costs.

For both asthma and rhinitis, there are many medical treatment alternatives, such as pharmaceuticals, allergen avoidance, desensitisation regimens and educational programs. Traditionally, medical decisions were primarily based on the evidence of clinical efficacy. Yet continually increasing cost constraints as well as increases in the number of similar alternative treatment options are making these decision processes more and more complex.

Sometimes, decisions as to which medical treatment or product to use are based on evidence from controlled clinical trials that focus on efficacy and safety as their specific aim. Efficacy is measured under tightly controlled research conditions. These studies often involve very select patient populations, making them efficient study designs but not very generalisable. Studies of clinical effectiveness have evolved in response to the need for more real world information about treatment alternatives and patient outcomes. Effectiveness refers to the impact of the intervention or technology under routine operating conditions administered to a more generalised patient population (2765, 2766). Improvements to the early studies of effectiveness have led to the "cost-effectiveness" study design. This type of study design provides information on the effectiveness of various interventions in relation to the efficiency of the consumption of economic resources (2767, 2768).

Cost-effectiveness studies link resource use (such as health care utilisation) with patient outcomes (via effectiveness measures). Results from this type of study design fall into one of four major categories. First is the unwanted outcome, where the new treatment is both less effective and more costly. Second, is a common scenario, where the new treatment is more effective but also more costly. Third, is an uncertain situation where the treatment is less effective but less costly. In the fourth, called the dominant or uncommon winning outcome, the new treatment is more effective and less costly.

The increasing worldwide sensitivity to costs of care in relation to improved health benefits has not gone unnoticed in the areas of asthma and rhinitis (36, 2769). While the cost-effectiveness literature has so far principally targeted asthma, well-designed pharmacoeconomic studies on the treatment of rhinitis are likely to be forthcoming. To date, there are no clear dominant cost-effective treatment strategies for either asthma or rhinitis. However, there are studies to suggest that the use of inhaled glucocorticosteroids for persons with persistent asthma are reasonably cost-effective in comparison to using only rescue beta-agonist therapy. Yet, even these studies reflect only Europe and the U.S. Health economic studies of asthma and rhinitis treatment do not exist for many of the countries that bear much of the global burden of these conditions.

12-6- POLICY IMPLICATIONS OF THE ECONOMIC BURDEN OF ASTHMA AND RHINITIS

Health care decision makers, such as health care providers and health planners, are constantly faced with establishing priorities for the allocation of limited health care resources, especially in developing countries. This prioritisation spans chronic conditions such as asthma and rhinitis, as well as communicable diseases, and must also consider needs for health promotion and disease prevention.

Therefore, in order to reduce the global burden of asthma and rhinitis, it will be necessary to first identify the degree of community-specific disease burden, and then establish credible justification for the re-allocation of health care resources. The costs and benefits of introducing new asthma and rhinitis management programs must be considered not only in regards to cultural appropriateness but also in light of the existing resources of each community. Finally, these decisions must be examined in relation to what the existing resources can purchase by way of other medical care and other non-medical goods (36).

Also, while much of the focus on establishing new treatment strategies must rest on the community's willingness to provide resources, in most if not all communities, some of the burden of care for both asthma and rhinitis falls upon the individuals and their families. Many persons with rhinitis in particular seek healing not from the health care practitioner but from other sources ranging from non-prescription medications and herbal remedies to non-allopathic care providers. The individual and their family are likely to carry much of the economic burden for this care. It is essential to further understand the value of such non-traditional approaches in comparison to allopathic care and its accompanying newer pharmacotherapeutic approaches.

12-7- CONCLUSIONS

Millions of persons suffer physical impairments, reductions in quality of life and economic consequences associated with asthma and rhinitis. Health economic studies have helped to characterise the costs of these diseases, but are limited to studying industrialised nations. There are even fewer comparative studies by which one can judge the most efficient ways of delivering health care for these conditions. With health care costs increasing world wide, there is an increasing need for more advanced health economic studies if improvements are to be made to lessen the social and economic impact of these conditions.

13- Unmet needs and research

13-1- EPIDEMIOLOGICAL EVIDENCE

There are many studies, which have shown that rhinitis and asthma often co-exist in the same patient. It seems that perennial rhinitis is more often associated with asthma than seasonal rhinitis.

Research needs:
- More epidemiological studies need to be carried out in order to better assess the prevalence of intermittent and persistent rhinitis as well as to better understand the cause of rhinitis.
- More epidemiological evidence is needed to link rhinitis, asthma, conjunctivitis and other allergic diseases.
- In these studies, the epidemiological definition of rhinitis should be refined.
- Objective measures for assessing nasal obstruction should be developed and applied to epidemiological studies.
- In these studies, the categorisation of rhinitis, as it has been proposed in this document, should be used.

13-2- SEVERITY OF RHINITIS ASSOCIATED WITH GREATER RISK FOR ASTHMA

Although this is a relevant question, no data are available. Thus, studies should be started to answer this question.

13-3- NATURAL HISTORY OF ASTHMA AND RHINITIS

The chronology of rhinitis and asthma is still under discussion. From the studies usually carried out, it appears that rhinitis often occurs before the onset of asthma and may therefore be a predictor of asthma. Confounding factors may be gender, allergen sensitisation or occupation.

Research needs:
More epidemiological evidence is needed to better understand the natural history of allergic rhinitis and asthma.

13-4- WHY RHINITIS AND/OR ASTHMA AND/OR ATOPIC DERMATITIS

In children with asthma, rhinitis is extremely common. However, more studies are required in children with rhinitis alone. It may be difficult to study children under the age of 4 years. In patients with allergic rhinitis alone, intra-bronchial allergen challenge induces a bronchial response.
- Distinct clinical genotype
Are there genes which differentiate rhinitis and asthma? There are genes which are important for bronchial hyper-reactivity but we do not know whether the susceptibility gene polymorphism differs between patients with rhinitis alone and asthma. However, the characterisation of the phenotype should be very precise in these genetic studies.

At present, response to anti-allergic/asthmatic treatment is very heterogeneous and may be due, at least partly, to genetic polymorphism. It should be checked whether genetic polymorphism differs in rhinitis and asthma.
- Environmental exposure (see "Prevention of allergy and asthma").

13-5- COMMON AND DIFFERENTIAL PATHOPHYSIOLOGICAL MECHANISMS IN UPPER AND LOWER AIRWAYS

Although many studies showed that the same pathology is present in the nose of rhinitis patients and the bronchi of asthmatics, more data are needed to confirm common mechanisms rather than causal association. Moreover, we should ask the following questions:
- Is there a common pathology ?
- What are the similarities and differences in pathophysiology?
- Are changes in the nose reflected by changes in the bronchi and vice-versa?

13-6- IS THERE REMODELLING OF THE NOSE?

Research is needed.

13-7- INFLUENCE OF SINUSITIS AND POLYPOSIS ON ASTHMA

Many papers have attempted to study the causal links between asthma, sinusitis and nasal polyposis. However, the methodology is extremely difficult and no firm conclusion could be drawn from these studies except in aspirin sensitivity. Carefully designed prospective studies are needed to better understand these important links.

13-8- INFLUENCE OF RHINITIS ON EXERCISE-INDUCED ASTHMA

The impact of rhinitis on exercise-induced asthma is supported by the influence of airway temperature in bronchial symptoms (2770, 2771) and the function of the nose in protecting the lower airways from cold and dry air challenge. However, more data are needed to fully appreciate the links.

13-9- CAN RHINITIS PREDICT ASTHMA EXACERBATIONS?

It has been widely reported that a flare of rhinitis may be a prodrome of subsequent asthma. Viral infections or allergen exposure can lead to rhinitis followed by asthma. However, we need more data :
- to assess the links between these exacerbations,

- to explain how this association may have an impact upon the management of asthma,
- to show that treatment of nasal inflammation subsequent to viral infection may prevent the development of bronchial symptoms.

13-10- TREATMENT OF AR INFLUENCES THE SEVERITY OF ESTABLISHED ASTHMA

Since most asthmatics have nasal symptoms, treatment of the patient requires targeting both sites. However, although many studies have been performed:
- it is not known if the treatment of one site significantly improves treatment requirements of the other site.
- it is not known whether intranasal and inhaled corticotherapy have an impact on safety.
- it is not known whether the doses of inhaled corticosteroids can be reduced if nasal corticosteroids are added. Such studies should be carefully designed since steroid tapering is very difficult to assess.
- the optimal way of treating patients with two concurrent diseases has not been studied.
- drugs administered by oral route can reach both sites and may be of interest. Studies are required.
- the impact of treating both sites on QOL should be tested.

- the impact of treating both sites on asthma exacerbations (or control) should be tested.

13-11- LONG-TERM VERSUS PRN TREATMENT

In asthma, it has convincingly been shown that long-term controller therapy is required to maintain control of the disease and prevent exacerbations.

However, in rhinitis, although a minimal persistent inflammation has been shown in the nasal mucosa of symptom-free patients allergic to house dust mites or pollens, the clinical relevance of these findings has to be better established. Thus, although it is recommended to continue the treatment of patients with controlled persistent rhinitis for some time, guidelines for the duration and cessation of treatment have to be developed and tested.

The relevance of "nasal minimal persistent inflammation" to the lower airway inflammation has to be considered.

13-12- TREATMENT OF AR IN CHILDHOOD PREVENTS DEVELOPMENT OF ASTHMA

See "Prevention of allergy and asthma" initiatives.

14- Recommendations for developing countries

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In developing countries, health care planners are faced with establishing priorities for the allocation of limited health care resources and infectious diseases, both of which remain a public health priority. When deciding on priorities for public health action, it is important to remember that, just as with clinical practice, public health practice needs to be evidence-based. Evidence for public health activities may differ somewhat from that needed for clinical practice and is required to be more extensive.

14-1- DECIDING ON PUBLIC HEALTH ACTION

The following components need to be addressed when considering public health action:

14-1-1- Efficacy

When considering an action (in this case, the management of allergies and asthma), it is necessary to determine whether or not the interventions being proposed have a scientific basis. In most cases, when it comes to treatment, this necessitates evidence of efficacy derived from clinical trials. The technical requirements of clinical trials are known—they should preferably be randomised, double-blind and controlled. In addition, it is important to determine that the population in which the clinical trial has been carried out is similar to the one in which the intervention is proposed. In clinical trials, it would be irresponsible to consider treatment interventions without a scientific base.

When considering intervention in terms of diagnosis, it is essential that the test characteristics of the diagnostic intervention should be satisfactorily evaluated. This refers to the sensitivity (the test's ability to identify a high proportion of those who have the disease) and the specificity (the test's ability to correctly identify a high proportion of those without the disease) of the test. In addition, the test must have a high degree of reliability (when it is performed repeatedly in a given situation, it should produce consistent results) and should be valid (a positive test should reflect the presence of the disease).

14-1-2- Effectiveness

Effectiveness, unlike efficacy, is the ability of the intervention to perform well in large populations. For example, it is necessary to demonstrate that when a large group of patients is treated (without the selection of 'eligible' subjects, as is often the case in clinical trials), the treatment actually produces results similar to those obtained in clinical trials. If a treatment is efficacious but difficult to take (for example, if it has associated adverse reactions), it will not be effective in the community because the patients will not take the medication.

Likewise with diagnostic interventions, it is necessary to demonstrate that they can be applied to a population and produce reasonable results. For this purpose, it is necessary to evaluate the predictive value of patients routinely presenting for diagnosis. The predictive value of a positive test is the probability that the individual with a positive test result actually has the disease. The predictive value of a negative test is the probability that an individual with a negative test does not have the disease. The value of these two parameters varies with the prevalence of the disease. Very frequently, tests with a high degree of sensitivity and specificity do not have a satisfactory predictive value when the disease is relatively rare.

14-1-3- Feasibility

The next requirement for evidence supporting a public health intervention is feasibility. Can the intervention actually be delivered to a high proportion of the patients who suffer from the disease?

This is an issue frequently overlooked by clinicians. Even when an intervention has a high degree of efficacy and effectiveness, if it cannot be delivered to a high proportion of those with (or at risk of) the disease, it is not a reasonable public health intervention. This is a major problem with many proposed activities. Feasibility may be jeopardised by a number of factors:
- the treatment may not be available or may be too expensive,
- there may be logistic difficulties in providing a regular supply,
- perhaps those suffering from the condition live far away from the health service.

Evaluating feasibility often necessitates a 'pilot project'. Interventions at the community level (public health interventions) should never be adopted as general policies if they have not been demonstrated to be feasible.

14-1-4- Cost Benefit

It is necessary that any intervention shown to be efficacious, effective and feasible should be made available. However, it is often forgotten that the resource base is finite and that there is always a competition for existing resources, necessitating setting priorities. Among the pieces of evidence necessary for setting priorities is demonstration of cost benefit. This allows comparison of yield of a variety of interventions. Those with the greatest yield for the amount invested will clearly have priority.

In addition to this evidence base, one must consider the process by which public health interventions are developed. There is a clear plan by which such actions should be initiated. When the problem is very large and

necessitates a response, there is often an insufficient evidence base. The following steps should therefore be taken to develop this base:

- given the existing knowledge, gain a consensus of experts on the best approach to take. Use this consensus to propose a standardised approach to the intervention.
- use this consensus to mount the process of creating evidence, namely clinical trials, followed by field trials, pilot projects and then economic evaluation.
- when a public health action is initiated, commence the activities in such a way that the necessary information for monitoring implementation and operations is built into the programme. This usually requires a standardised data collection procedure and a systematic evaluation.
- establish a period of operations after which a systematic and critical evaluation is carried out. The evaluation should take account of the information routinely collected in order to determine whether the established objectives are being met.
- revise the policy, based on the critical evaluation.
- repeat the whole procedure.

By systematically defining, adopting, evaluating and revising policy, it is possible to increase efficiency and cost benefit and to ensure that the application of the policy actually delivers the outcome it was designed to provide. Implementation of public health policy without a systematic approach frequently leads to failure and a waste of investment.

14-2- STANDARDISED MANAGEMENT FOR INDIVIDUAL PRACTICE

Allergic rhinitis may be considered as a public health problem in some developing countries and is becoming a public health problem in some low income countries. However, the prevalence of chronic rhinitis is already high in some developing countries and is frequently associated with asthma (154). These patients are often treated incorrectly by general practitioners prescribing antibiotics, and a lot of money is spent on inadequate care. For these reasons, a standardised management plan for allergic rhinitis should be proposed to practitioners to prescribe the most effective treatment affordable for patients living in developing countries.

14-2-1- Diagnosis

Diagnosis is easy when rhinitis is associated with other manifestations of the disease such as conjunctivitis, skin allergy and/or asthma. The diagnosis is more difficult when rhinitis is the only manifestation of the disease. In view of the frequency of asthma and rhinitis co-morbidity even in developing countries, when patients consult for chronic nasal symptoms, evaluate asthma symptoms and when they consult for asthma symptoms, it would be useful to evaluate nasal symptoms.

14-2-1-1- Questionnaire

When a patient consults for chronic or recurrent nasal symptoms, a standardised questionnaire might be a very good tool for the diagnosis of allergic rhinitis. This questionnaire must assess the major symptoms of rhinitis including sneezing, a runny nose and/or a blocked nose when the patient does not have a cold.

For the identification and evaluation of severity of the allergic rhinitis, a standardised questionnaire is proposed in Table 23. Some questions are from (or are adapted from) the standardised questionnaires used in two important epidemiological studies: the International Study of Asthma and Allergies in Childhood "ISAAC" (154) and the European Community Respiratory Health Survey "ECRHS" (107).

This standardised questionnaire, proposed as a tool for diagnosis, contains three parts:

- questions in the first part identify specific symptoms of allergic rhinitis, main trigger factors and family history of allergic disease;
- questions in the second part are used to establish the severity of the disease;
- questions in the third part identify seasonal and occupational allergic rhinitis:
  –pollen sensitisation: symptoms occur each year during the same season and are accompanied by itchy and watery eyes.
  –aspirin sensitisation: serious symptoms with nasal obstruction frequently associated with nasal polyps, also sensitisation to aspirin and/or non steroidal anti-inflammatory drugs (NSAIDs). These patients generally have allergic rhinitis associated with urticaria and severe asthma attacks after the ingestion of aspirin or other NSAIDs.
  –occupational: symptoms occur only at the workplace or at night after work. At the beginning of the disease, symptoms may disappear totally during the weekend and holidays and reappear at work. In most of these cases, allergic rhinitis is associated with asthma.

Finally, in most cases, a concise questionnaire is sufficient to identify allergic rhinitis, to determine co-morbidity with other manifestations of the disease, to classify the severity of symptoms and to suspect particular cases.

If possible, and depending on the development of services in the country, these particular cases suspected by general practitioners should be referred to specialists for confirmation of diagnosis and specific management.

A panel of specialists proposed a quantitative score (Annesi I, Didier A, Klosek M et al.). A diagnostic criteria score for allergic rhinitis (SFAR) was proposed: Development, hospital validation and population acceptability (submitted) for the diagnosis of allergic rhinitis. An evaluation of this score would be useful in clinical practice.

14-2-1-2- Examination

In severe cases, clinical examination may be performed by anterior rhinoscopy if a rhinoscope with a speculum is available. In the absence of adequate equipment, direct observation of the nostrils may reveal the principal signs of allergic rhinitis:

- signs of inflammation localised to the inferior turbinate which appears oedematous, red, swollen and covered with secretions.

TABLE 23: Standardised Questionnaire proposed for patients with chronic nasal symptoms. * Some questions are taken or adapted from the ISAAC and ECRHS standardised questionnaires.

Research for allergic rhinitis

1. In the past 12 months, have you had a problem with sneezing or a runny or blocked nose when you HAVE NOT had a cold or the flu?

2. If Yes: In the past 12 months, has this nose problem been accompanied by itchy, watery eyes?

3. In which of the past 12 months did this nose problem occur?

January	☐	May	☐	September	☐
February	☐	June	☐	October	☐
March	☐	July	☐	November	☐
April	☐	August	☐	December	☐

4. Do you think that trigger factors provoke or increase your nose problem? If Yes: what are they?

5. Have you ever had hay fever, asthma or a skin allergy?

6. Has a member of your family ever had asthma, or a skin or nasal allergy?

Determine severity for classification

1. In the past 12 months, how many times have these symptoms occurred?
   Less than 4 days a week or less than 4 weeks in the year?
   More than 4 days a week and for more than 4 weeks in the year?

2. In the past 12 months, have these nose problems been accompanied by sleep disturbance?

3. In the past 12 months, how much has this nose problem interfered with your daily activities, and/or school, and/or work, and/or leisure, and/or sport?

Not at all	☐
A little	☐
A moderate amount	☐
A lot	☐

Identification of seasonal and occupational allergic rhinitis

1. Do you experience these symptoms every year only during a particular season and always during the same season?
2. Do you experience these symptoms mainly during the working day? Do they disappear during the weekend and holidays?
3. Do you experience these symptoms after the ingestion of aspirin or other pain-killing tablets?

If Yes: Which tablets?

* When the patient has other chronic respiratory symptoms, another questionnaire to research asthma will be applied before. The IUATLD standardised questionnaire is proposed in the IUATLD Asthma Guide (6).

- polyps may be seen in some patients with partial obstruction of the nostrils, particularly for patients with sensitisation to aspirin.

14-2-1-3- Classification

Based on the severity of symptoms:

The classification of severity proposed for industrialised countries, based only on the severity of the symptoms, can easily be applied in developing countries (Table 23).

The three questions from the second part of the standardised questionnaire proposed in Table 23 are sufficient to establish the severity of allergic rhinitis and classify the disease.

Identification of seasonal and occupational rhinitis:

Three questions proposed in Table 23 may be helpful in particular cases of allergic rhinitis with specific sensitisation to pollen, aspirin and other NSAIDs, or to an occupational agent.

14-2-2- Management

14-2-2-1- Avoidance measures

Avoidance measures should be used for rhinitis whenever relevant. These include removing cats and reducing mite allergen by encasing mattresses and pillows in impermeable covers. However, some of these measures are difficult or impossible in poor socio-economic conditions.

TABLE 24: The price of principal drugs for Allergic Rhinitis. Price in France: Source: Vidal 1999

Brand name	DCI	Presentation	Price FF (French Francs)	Dose for adults	Price per day FF	Price per month US$ (US Dollars)
H1- Antihistamines: first generation with sedative effects						
Polaramine	Dexchlopheniramine maléate	Box of 30 tablets 30mg/tb	8.90	1 to 2 tb/d	0.29 - 0.58	1.3 -2.6
Dimegan	Brompherinamine	Box of 20 tablets 4mg/tb	19.70	4 to 6 tb/d	3.94	18
Zaditen	Ketotifen	Box of 30 tablets 2mg/tb	81.50	1tb/d	2.72	12.5
H1-Antihistaminies second generation with low or no sedative effects						
Zyrtec Virlix	Cetirizine Dichlorhydrate	Box of 15 tablets 10mg/tb	51	1tb/d	3.4	15.6
Clarityne	Loratadine	Box of 15 tablets 10mg/tb	46.5	1tb/d	3.1	14.25
Allergodil	Azelastine	Nasal solution 17ml	59	4p/d	1.97	9
Telfast	Fexofenadine	Box of 15 tb 120mg/tb or 180 mg/tb	49.90	1tb/d	3.33	15.3
Primalan	Mequitazine	Box of 14 tb 10mg/tb	50.7	1tb/d	3.62	16.6
Tinset	Oxatomide	Box of 30tb 30mg/tb	44.30	2tb/d	2.95	13.5
Other drugs						
Lomusol	Cromoglycate	Nasal solution 15ml	47.50	4 to 8 p/d	2 to 4	9 to 18
Beconase	Beclomethasone	Nasal solution 200 p 50µg/p	51.50	4 to 8 p/d	1 to 2	4.5 to 9

IDA Price 1999

Average cost of a month's treatment with drugs from IDA : only two drugs are available:

Dexchlorpheniramine : 0.25 US$ and Beclomethasone aerosol for inhalation: 5 US$

IDA Price 1999 was in Euro   In 1999: 1 EURO= 1. 0391 US$

Vidal Price 1999 was in FF   In 1999: 1 US$= 6.53 FF

In the case of occupational disease, it will be necessary to remove the patient from the exposure at work. But in many cases, the patient will not accept this decision because he will lose his job. The best solution when possible would be to remove the most dangerous agent, replacing it with another less potent one. This is possible in most cases and would provide a collective preventive solution for healthy workers. It would also maintain patients in their trained work.

14-2-2-2- Medications

Among the medications proposed for treatment, two are available in developing countries for the effective management of the majority of allergic rhinitis patients: chlorpheniramine (first generation oral H1-antihistamines) and nasal beclomethasone (intra-nasal corticosteroids).

The rationale for this choice of drugs for developing countries is based upon 4 points:

- **High level of efficacy**: Intra-nasal corticosteroids for rhinitis are probably the most cost-effective drugs as demonstrated for asthma, even in developing countries (2272).
- **Low cost drugs affordable for the majority of patients:** With chlorpheniramine which is sedating, it is possible to have monthly treatment for only 1 or 2 US $ (0.25 US $ if bought through IDA) and for 5 US $ with intra-nasal corticosteroids (Table 24).
- **Inclusion in the WHO essential list of drugs:** These two drugs are on the WHO essential list of drugs. It is a very important step for countries to include drugs in their national essential drugs list. However, non-sedative antihistamines should also be included.
- **Decrease of cost might be expected**: If demand increases, it may be possible to have these drugs at a lower price in the near future with the production of generics. The new oral H1-antihistamines are more effective with no sedative effect, but they are not recommended as first-line drugs in developing countries due to their high cost (9-20 US $ for one month's treatment). They are currently more expensive than intra-nasal corticosteroids. However, they should be used as first-line drugs if they are more affordable in the future.

14-2-2-3- Immunotherapy

Immunotherapy could be indicated in patients with allergic rhinitis according to the recommendations previously given (8-3-5-1). However, indications could be limited in developing countries for the following reasons:

- Many allergens in developing countries have not been identified,
- Rigorous and costly examinations are required to identify these cases,
- Specialists must prescribe allergen vaccines,
- Immunotherapy must be administered by doctors because of possible side effects,
- The cost of allergens and of personnel would be very high in some countries,
- Immunotherapy is not effective if low doses or poorly standardised allergen vaccines are used.

14-2-2-4- Stepwise treatment proposed
- **Mild intermittent rhinitis:** The oral H1-antihistamine chlorpheniramine will be prescribed on demand. The patient has to be aware of its sedative effects and should take the medication only in the evening although this may not prevent an antihistamine hangover. The new-generation oral H1-antihistamines without sedative effects will be better as a first line treatment, but only in the future when they are affordable for the patient.
- **Moderate/severe intermittent rhinitis:** Intra-nasal beclomethasone (300-400μg daily) will be prescribed. If needed, after a week of treatment, oral H1-antihistamines and/or oral corticosteroids will be added.
- **Mild persistent rhinitis:** Treatment with oral H1-antihistamines or a low dose (equivalent to beclomethasone 100-200 μg) of intra-nasal corticosteroids will be sufficient.
- Moderate-Severe persistent: A high dose of intra-nasal corticosteroids (equivalent to beclomethasone 300-400 μg) will be prescribed. If symptoms are severe, add chlorpheniramine and oral steroids at the beginning of the treatment.

The treatment of persistent rhinitis will be daily if symptoms are perennial but will be needed only during the season if symptoms are seasonal.

In the case of co-morbidity with asthma, asthma management is the priority. Asthma management for developing countries was proposed in the IUATLD Asthma Guide (2273). The affordability of inhaled steroids is very low in these countries (2274). If it is affordable for the patient to treat the two manifestations of the disease, it should be recommended to add the treatment of allergic rhinitis to the asthma management plan.

- **Management of particular cases:** In addition to the standardised treatment, and depending on the level of severity, other dispositions are necessary:
  - Occupational rhinitis: flooring, wood and iso-cyanates are frequent causes of occupational rhinitis and asthma, even in developing countries. In most cases, if the patient maintains exposure at work, a severe aggravation of the disease will occur, even with adequate treatment. If it is impossible to remove the agent from the workplace, it will be recommended to remove the patient from his/her job. In cases where the patient refuses, individual preventive measures will be proposed.
  - If these patients are all referred to specialised services, it will be useful to have a register of occupational allergic rhinitis and asthma. This register will serve as a very good tool for identifying specific exposed workplaces and for proposing collective measures of prevention: replacing one agent by another less toxic agent, using hoods over stoves, etc.

Rhinitis with sensitisation to aspirin and other NSAIDs:
  - The majority of these cases suffer severe asthma and require rigorous treatment and strict follow-up. As a severe accident may occur if these patients take aspirin or other NSAIDs, it is particularly important to give them the list of drugs that should be avoided. Paracetamol is well tolerated by the majority of patients.

14-3- CONCLUSION

A standardised management plan for allergic rhinitis may be proposed for developing countries. In the majority of cases, the diagnosis of allergic rhinitis may be carried out using a simple standardised questionnaire. Its management might be possible with only one or two drugs. In the case of co-morbidity with asthma, it is useful to add rhinitis treatment to asthma treatment.

A research programme will be necessary to determine the future need for public health action.

Appendix 1: Statements of evidence

A.- <u>Development Process (12 points):</u>

1.- Have you clearly defined the purpose of the guideline? (1 point)

[X]Yes

[ ]No

[ ]Can't Tell ("Can't tells" score 0 points)

> The present document is intended:
> - to update the state of art of allergic rhinitis,
> - to highlight the impact of allergic rhinitis on asthma,
> - to provide an evidence-based documented revision on diagnosis methods,
> - to provide an evidence-based revision on the treatments available,
> - and to propose a step-wise approach to the management of the disease.

2.- Have you clearly defined the usefulness of the guideline? (1 point)

[X]Yes

[ ]No

[ ]Can't Tell

The present document will improve the diagnosis and management of allergic rhinitis. It will also improve the recognition that asthma and rhinitis are common co-morbidities. Moreover, the improved management of allergic rhinitis is likely to be cost-effective.

3.- Have you clearly defined the scope of the guideline? (1 point)

[X]Yes

[ ]No

[ ]Can't Tell

The present document is intended for the specialist, the general practitioner and health providers.

4.- Have you included a specific and clear description of the process for the development of the guideline? (1 point)

[X]Yes

[ ]No

[ ]Can't Tell

(see 8-5)

5.- Does the development process of the guideline have a population-based focus? (1 point)

[X]Yes

[ ]No

[ ]Can't Tell

6.- Have you included a specific description of the literature review process and sources of evidence? (1 point)

[   ]Yes

[X]No

[   ]Can't Tell

In Medline, articles can be traced in two ways: by any word listed on the database, including words in the title, abstract, authors' names and the institution where the research was done; and by a restricted thesaurus of medical titles, known as medical subject heading (MeSH) terms (2775). Not all medical articles are indexed on Medline and some have been misclassified. Searching by textword can therefore supplement a search by MeSH (2776). In the present document, we used the search by words and MeSH.

In the present document, an extensive Medline search was carried out from 1966 to 31-12-1999 using PubMed® concerning the following items:
- rhinitis
- all treatment options (see 8-1, 8-2, 8-3, 8-4)
- all diagnosis options (see 7)
- for medications, the generic name of all known medications (for rhinitis) was used with the key words "placebo-controlled". When no placebo-controlled studies were available, we used the key words "controlled".

For treatment options, a search with EMBASE® (Excerpta Medica) was also carried out to find papers not referenced on Medline.

A search of randomised rhinitis trials was done using the Cochrane Library database (12-1999). The search included the Cochrane Database of Systematic Reviews (CDSR) and the Database of Reviews of Effectiveness (DARE).

The literature of each of the chapters was extensively reviewed by at least the chairmen and two members of the panel.

7.- Has the literature review process of your guideline been systematic and not biased? (2 points)

[X]Yes

[   ]No

[   ]Can't Tell

8- Have you considered economic information (cost-effectiveness, use of resources...) in the review process? (1 point)

[X]Yes

[   ]No

[   ]Can't Tell

In the guideline, a special section on cost-effectiveness has been included (chapter 12). However, in the recommendations, such an item was not possible due to the variable costs for medications in different parts of the world and the lack of some drugs in the essential drug list of WHO.

9.- Have you included the most updated and the highest quality available evidence? (3 points)

[X]Yes

[   ]No

[   ]Can't Tell

B.- *Quality of recommendations (8 points):*

10.- Have you developed valid recommendations (consistent with evidence findings)? (3 points)

[X]Yes

[   ]No

[   ]Can't Tell

    (see 8-5)

11.- Have you specified all important options and outcomes? (3 points)

[X]Yes

[   ]No

[   ]Can't Tell

    (see 8-5)

12.- Have you used an explicit and acceptable process to combine the relative value of different outcomes? (1 point)

[X]Yes

[   ]No

[   ]Can't Tell

    All diagnostic and therapeutic interventions have been reviewed and referenced. Moreover, double-blind, placebo controlled studies and double-blind studies have been clearly mentioned (see 8-5).

13.- Have you used a rational and acceptable approach to integrate economic and clinical data? (1 point)

[X]Yes

[   ]No

[   ]Can't Tell

    In the guideline, a special section on cost-effectiveness has been included (chapter 12). However, in the recommendations, it was not possible to add such an item due to the variable costs for health care and medications in different parts of the world.

C.- *Implementation and dissemination (2 points):*

14.-Is your guideline locally adaptable? (1 point)

[X]Yes

[   ]No

[   ]Can't Tell

15.- Does your guideline include effective strategies for the dissemination and implementation to its target audience? (1 point)

[X]Yes (in process)

[   ]No

[   ]Can't Tell

This will be done for the dissemination of the pocket guide.

D.- *Evaluation (3 points):*

16.- Does the guideline allow later review (methods, sources properly documented)? (2 point)

[X]Yes

[   ]No

[   ]Can't Tell

17.- Does your guideline define indicators to monitor its impact? (1 point)

[X]Yes (in process)

[   ]No

[   ]Can't Tell

Overall, is the guideline valid according to the principles in Annex 1?

[X]Yes, excellent, 20 points or more

[   ]Yes, satisfactory, 16 points or more

[   ]No, less than 16 points

[   ]Not acceptable, 16 points or more but contrary to WHO's principles (see Annex 1)

[   ]Can't Tell, lack of information to judge essential aspects (more than five can't tells and the rest of the answers yes)—Go back and check it again—

Internally for WHO-NCM, if we want to answer the question: *"Am I doing an evidence-based guideline or not?",* check questions 1, 2, 3, 6, 7, 9, 10, 11.

[X] If all answers are Yes: evidence-based guideline according to WHO-NCM criteria.

List of abbreviations

AA: arachidonic acid
AAAAI: American Academy of Allergy, Asthma and Immunology
AIANE: European Network on Aspirin-Induced Asthma
AOM: acute otitis media
APC: antigen presenting cell
AQLQ questionnaire: asthma quality of life questionnaire
ATS: American Thoracic Society
CCR: CC chemokine receptor
CD: cluster of differentiation
CD23 (FcεRII): low affinity receptor for IgE
CGRP: calcitonin gene-related peptide
CNS: central nervous system
COX: cyclooxygenase
Cys-LT: cysteinyl leukotrienes
CXCR: CXC chemokine receptor
DSCG: disodium cromoglycate
EAACI: European Academy of Allergy and Clinical Immunology
ECP: eosinophil cationic protein
FcεRI: high affinity receptor for IgE
FcεRII: low affinity receptor for IgE (CD23)
ECRHS: European Community Respiratory Health Survey
EDN: eosinophil derived neurotoxin
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
FLAP: 5-lipoxygenase (LO) activating protein
GM-CSF: granulocyte, monocyte colony stimulating factor
GR: glucocorticosteroid receptor
GRE: glucocorticosteroid receptor responsive element
HDM: house dust mite
HPA axis: hypothalamic-pituitary-adrenal axis
HETE: hydroxyeicosatetraenoic acid
HPETE: hydroperoxyeicosatetraenoic acid
HRQLQ: Health related quality of life
ICAM-1: intra-cellular adhesion molecule 1
IFN-γ: interferon-γ
IL-: interleukin-
ISAAC: International Study on Asthma and Allergy in Childhood
LFA-1: Leukocyte function antigen-1
LO: lipoxygenase
LPR: late-phase reaction
LTC_4: leukotriene C_4
LTD_4: leukotriene D_4
LX: lipoxin
mAb: monoclonal antibody
MBP: major basic protein
MIP-1: macrophage inhibitory protein

mRNA: messenger ribonucleic acid
NANC: non-adrenergic, non-cholinergic
NAR: nasal airway resistance
NARES: non-allergic rhinitis with eosinophilic syndrome
NF-κB: nuclear factor-κB
NGF: nerve growth factor
NHANES II: second National Health and Nutrition Examination Survey (U.S.A.)
NK: neurokinin (A or B)
NO: nitric oxide
NO_2: nitrogen dioxide
NPY: neuropeptide Y
OME: otitis media with effusion
$PD_{20}FEV1$: provocative dose inducing a decrease of 20% in FEV_1
PEF: peak expiratory flow
PEFR: peak expiratory flow rate
PGD_2: prostaglandin D_2
PLA_2: phospholipase A_2
OR: odds ratio
PDGF: platelet derived growth factor
PG: prostaglandin
PM10: particulate matter less than 10 μm
PRIST: paper radio-immunosorbent test
QOL: quality of life
QTc: QT interval
RAST: radio-allergo-sorbent test
RQLQ questionnaire: rhinoconjunctivitis quality of life questionnaire
Rhu-MAb-E25 mAb: monoclonal anti-IgE antibody
RSV: respiratory syncytial virus
SAPALDIA: Swiss Study on Air Pollution and Lung Diseases in Adults
SCARPOL: Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen
SCF: stem cell factor
SP: substance P
SRSA: slow reacting substance of anaphylaxis
SIT: specific immunotherapy
SO_2: sulfur dioxide
TNF-α: tumor necrosis factor-α
TGF-β: transforming growth factor β
TX: thromboxane
VCAM-1: vascular cellular adhesion molecule 1
VIP: vaso-intestinal peptide
VLA-4: very late antigen 4

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Notes

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