01

EARLY DETECTION AND MANAGEMENT OF ASTHMA – A CHALLENGE

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Asthma may be a mild episodic nuisance or a severe persistent disease. If asthma becomes manifest with severe attacks, the diagnosis is easy to make. However, it is usual that patients have symptoms compatible to asthma for months or even years before the right diagnosis. At that time the disease may already be in a persistent stage. Biopsy studies have shown that significant inflammation is present in early asthma, also in patients with only a short duration of symptoms, or with mild disease. But the relation of this inflammation to the disturbances of lung function, and specificly to increased bronchial responsiveness, is not straight forward. Transient eosinophilic inflammation of the bronchial mucosa may be quite common especially in atopic subjects, but it is far from always causing deterioration on lung function. It may be argued that the diagnosis is always late, if asthma with increased bronchial responsiveness is detected. Those subjects with disturbed lung function (real asthmatics), consist only a part of the population having the problem of recurring eosinophilic airway inflammation. The whole concept of asthma may face a new era, causing headache to epidemiologists but meaning good news to those who are at risk. The eosinophilic inflammation (bronchitis) is detected at earlier stages, and even before functional deterioration is observed. For early diagnosis new methods are emerging, and biochemical characterization of the bronchial inflammation from sputum, serum, urine samples or exhaled air may be on reach. A widened view of asthma, including also those with asthma-like symptoms, would improve early detection and guide to the right type of interventions. This should influence the outcome, and may even prevent the patient to have overt asthma. Today, most patients with prolonged mucus production and cough, but with normal lung function, are treated with antibiotics, and with everything else but adequate anti-inflammatory therapy. Inflammation is a response. What is the cause of the response leading to asthma, what is triggering it and how? These are the crucial questions, to which answers should be searched for especially in the affluent part of the world, where asthma and asthma-like symptoms are on clear increase.

02

GUIDED SELF MANAGEMENT OF ASTHMA

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Potentially preventable factors are common in asthma exacerbations and over 70% of admissions to hospital for acute asthma can be avoided with proper prior medical care. At least 40% of asthmatics do not react appropriately to increasing asthma symptoms and more than half of the patients admitted with acute asthma have had alarming asthma symptoms for one week prior to admission. In its study of deaths due to asthma in the early 1980s the British Thoracic Association recommended that patients should measure their own peak flow rates and treat deteriorating symptoms themselves. Guided asthma self management consists of efficient patient education and of symptom- and/or peak expiratory flow-based patient instructions in early asthma deteriorations. Several studies have shown that educational progrmmes of asthma both increase the patient's skill and improve the general outcome of asthma care. Although self management practices have been suggested in several asthma guidelines, somewhat conflicting results exits concerning the efficacy of this treatment. Some of the self management studies have been either uncontrolled or have relied on retrospective data analysis. In a recent study (BMJ 1996;312:748-52) we have compared the efficacy of guided self management of asthma with trational treatment. This one year trial of 115 patients with mild to moderately severe disease randomised half of the patients to a traditional asthma care and half to a self management programme consisting of education about asthma and daily peak flow readings.

The mean number of unscheduled visits to ambulatory care, days off work, and courses of antibiotics and prednisolone per patient were lower in the self-management group than in the traditionally treated group (0.5 v.s. 1.0, p=0.04; 2.8 v.s. 4.8, p=0.02; 0.4 v.s. 0.9, p=0.009 and 0.4 v.s. 1.0, p=0.006, respectively). In both groups hospitalisations due to asthma were rare and the spirometric values remained completely stable at the schedule visits. One year self management had a superior effec (8 quality of life points, 95% CI 2-15 points) on quality on life compared to traditional treatment. The self mangement was 4.5% more effective (p< 0.0001) than the trational treatment in terms of healthy days (defined as day without incidents caused by asthma). The direct health care costs were FIM 649 greater (p=0.05) in the self management group, mainly due to the greater costs of counselling. The self management, however, resulted in a 2.412 FIM savings (p=0.008) in indirect costs per patient and as a result the total costs of asthma (direct and indirect costs) were 1.762 FIM smaller (p=0.09) per patient treated during the one year study period.

Intervention thresholds of <85% of the optimal peak flow for doubling the dose of inhaled steroid for two weeks and of <70% of the optimal peak flow for starting a course of oral steroids for one week worked well and the adherence of patients to the self management instructions was better than generally expected.

There were four elements in our study: early treatment of deteriorating airway inflammation, peak expiratory flow measurements per se (changed lifestyle), patient education about asthma and possibly improved general compliance with treatment. It is not possible to say which of these is most important to the success of guided self management of asthma. Successful asthma self management requires a good patient-provider relationship and treatment organization. Flexible access to assessments when needed is fundamental. Self management mus not be implemented in such a way that the

; atient is left on his or her own after initiation of care. Education and changed attitudes – not only among patients – are the prerequisites for the implementation of asthma self management.

03

INHALATION DEVICES AND COMPLIANCE IN THERAPY

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Current guidelines for the management of asthma in both children and adults recommend that most asthma therapy should be given by the inhaled route. Reasons given include that a fast onset of action is obtained, the drug is delivered straight to the site of action, a smaller dose is required and there is reduced potential for systemic side effects.

In asthma, nebulisers are used chiefly for the delivery of large doses of bronchodilator drugs or for patients who cannot use other devices. Pressurised metered dose inhalers (PMDIs) are the most commonly used devices being quick to use, compact, portable, multi-dose and cheap. However, unless the breath actuated version is used inhalation technique is not easy. The PMDI with spacer has all the practical advantages of the PMDI and is not difficult to use but is bulky. Dry powder devices (DPIs) are generally easier to use than the conventional PMDI although there are differences between individual DPIs in their efficiency in achieving pulmonary deposition.

Clinicians are frequently encouraged to prescribe a specific therapy. Insufficient time may be spent considering an appropriate device for the patient which is often as important as the therapy to be prescribed. There are numerour devices on the market at present and choice should be made with care. 'Cheap' does not necessarily equal 'cost effective'.

To aid compliance health professionals should not only consider the treatment and device prescribed but should also explore the patient's health beliefs and attitude towards their condition.

Modern asthma management has demanded a new approach with emphasis on the importance of developing a special anticipatory and organisational long-term approach. Patient assessment, education and follow-up is a continuing process. To improve compliance it is important to make sure the patient knows that he or she is at risk and to give them reassurance that their treatment is both safe and effective.

Management plans must be tailored to meet individual patient needs and wherever possible should be practical and easy to maintain long term.

04

COST EFFECTIVENESS IN ASTHMA THERAPY

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It is now widely acknowledged that the pathology of asthma is predominantly an inflammatory process of the bronchial mucosa with smooth muscle contraction secondary to airway inflammation. The concept of airway inflammation in asthma and its control by anti-inflammatory therapy has provided more precise aims and the idea of long-term care for both adults and children. In general regular anti-inflammatory treatment reduces in tendency of the bronchi to respond to any endogeneous and exogeneous stimulus. A decreased bronchial hyperresponsiveness may help to diminish asthma exacerbations, nocturnal asthma, diurnal variations in lung fucnction, continuing symptoms and hospital admissions. Thus, an adequate managment of asthma may prevent long-term risk disease by that providing high cost effectiveness.
With respect to long-term effects of prologed treatment with steroids questions many raise whether physicians can be sure that this treatment in entirely free of any advers effect, in particularon asthma itself. In literatur, for example, a lack of imformation is found on which minimal dose of medication is required to contol asthma by that avoiding side effects and reduced cost effectiveness.
Our understanding of asthma and its therapy has grown significantly over the two last decades. However, there is evidence that asthma is not well controlled in many patients. Numerous specialists state that hospital admissions and visits to emergency departments may reflect failures of primary preventive care for asthma of out-patients. It is believed that specialist care allows greater cost effectiveness and the focusing of clinical expertise. However, in medical systems with tiered patient care the cooperation between specialists in out-patient clinics and general practitioners is needed. Yet, there are grap of communication between specialists who are well experienced in asthma disease and general practitioners less educated in asthma who see the patient not rarely at times of crisis. So, there may be a great deal of improvement necessary in the care of asthma by general practitioners. In the future it must be in primary care that the really important improvement must take place. It could improve cost effectiveness because it should be more effective in reducing loss of work and hospital admissions and should be probably administratively cheaper.
However, the most important task is patient education. Patients must learn what asthma is and what it means to be a chronic disease. Patients and their families may learn that they can manage asthma effectively and, in most cases, live active lives. They need to be able to follow instructions and comply with treatment recommendations, Although these aspects of patient education have recieved more attention, research suggests that many patients emerge from their contacts with physicians ill prepared to carry out treatment plans. Many findings underline that physicians need better education themselves in the key skills needed for asthma management.
The subject of cost effectiveness of modern asthma treatment is full of difficulties because the various factors underlying it differ from one country to another. The best to be done is to examine the broad picture and the various factors which can be modified.

05

GUT FUNCTION AND ATOPIC DERMATITIS

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The intestinal mucosa is an important organ of defence providing a barrier against the antigens encountered by the enteric route. Apart from the barrier function, the intestinal mucosa is efficient in assimilating antigens. Intestinal antigen handling determines subsequent immune response to the antigen.

To explore the intestine's barrier function and antigen transfer across the intestinal mucosa in patients with atopic dermatitis, the absorption and degradation of horseradish peroxidase (HRP, molecular weight 40 000) were studied in vitro in Ussing chambers. Eighteen biopsy samples of upper small intestinal mucosa from 14 patients (aged 0.5-8 years) with atopic dermatitis and 18 samples from 15 age-matched controls were examined. The mean (95 % confidence interval) absorption of intact HRP was significantly higher in children with atopic dermatitis than in controls: 242 (81-404) pmol . h^{-1} . cm^{-2} as against 23 (12-33); p=0.007. The absorption of degraded HRP was 972 (732-1213) pmol . h^{-1} . cm^{-2} in patients with atopic dermatitis and 672 (532-811) in controls; p=0.03.

To assess the mucosal effector responses induced by double-blind placebo-controlled cow milk challenge in infants with atopic dermatitis, the concentrations of tumour necrosis factor-α (TNF-α), eosinophil cationic protein (ECP) and α-1 antitrypsin in faeces as indicators of intestinal inflammation were determined. An increased α-1 antitrypsin concentration was detected in 43% of the infants positive as compared to 11% of those negative to challenge, p= 0.02. An elevated concentration of ECP in faeces was associated with immediate-type reactions to the cow milk challenge, while TNF-α in faeces was associated with delayed-type reactions to the challenge.

Impaired barrier function and defective handling of antigens in the epithelial cells may be an important pathogenetic mechanism in atopic dermatitis. Aberrant antigen transport in the gut may initiate and perpetuate inflammatory response to the most important source of allergens early in life, i.e. diet. These results suggests that the treatment of atopic dermatitis should counteract the mechanisms that enhance intestinal inflammation.

References

1. Majamaa H, Isolauri E. Evaluation of gut mucosal barrier: evidence for increased antigen transfer in children with atopic eczema. J Allergy Clin Immunol 1996, in press.

2. Majamaa H, Miettinen A, Laine S, Isolauri E. Intestinal inflammation in children with atopic eczema: faecal eosinophil cationic protein and tumor necrosis factor-α as noninvasive indicators of food allergy. Clin Exp Allergy 1996; 26: 181-7.

06

DIAGNOSTICS OF FOOD ALLERGY - NEW VISIONS

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The European Academy of Allergy and Clinical Immunology (EAACI) and the European Society of Pediatric Allergy and Clinical Immunology (ESPACI) have each published in 1995 a supplement of the present knowledge of adverse reactions to foods and their diagnostics. (1-2) EAACI has proposed a new classification of adverse food reactions into toxic and non-toxic reactions. Non-toxic reactions include non-immune mediated reactions, i.e. food intolerance, and immune mediated reactions, i.e. food allergy. Allergic reactions can be either IgE- or non-IgE-mediated. Double-blind, placebo-controlled food challenge (DBPCFC) is widely accepted as the most reliable method in the diagnosis of adverse reactions to foods. Demonstration of food-specific IgE antibodies either with RAST or skin tests refers to IgE-mediated food allergy. In infants under the age of 1 year the tests suggest a relevant food allergy, because at this age it is more difficult to detect specific IgE, and the secondary development of tolerance has hardly taken place yet.(3) In older children the relevance of RAST and skin test has to be confirmed by DBPLFC. In spite of the large amount of new knowledge on the field, the basic mechanisms of adverse reactions to foods are still poorly understood. The lack of standardized food antigens for the skin tests causes also difficulties. DBPCFC, with which all other tests are compared, is called the gold standard of diagnostics but remains itself unstandardized.(4) Especially delayed reactions in food allergy are poorly understood.

Confusion arises also from the fact that food allergy in infants, children and adults are being described simultaneously, although food allergy in infants is condidered the main cause of atopic eczema, while in older persons there are several pathogenetic mechanisms that may lead to the clinical picture. Allergy to basic foods like milk, egg, soy, cereals, fruits and vegetables is often discussed simultaneously, although the nutritional role of milk and apple, for instance, is strikingly diffferent in infants. Also allergy to milk, egg, etc. has a favourable prognosis during the first 2-3 years of life, whereas allergic reactions to fruits and vegetables in pollen-allergic people tend to be permanent.

Räsänen et al.(5) have studied the applicability of skin prick test (SPT), basophil histamine release test, patch test and lymphocyte proliferation test in atopic children with either immediate or delayed cutaneous symptoms upon oral challenge to cow's milk. They showed that tests and lymphocyte proliferation tests were more often positive in children exhibiting delayed type reactions, whereas SPT and basophil histamine release test were more often positive in children with immediate oral challenge reactions to cow's milk. Isolauri and Turjanmaa (6) confirmed this results in 183 patients with atopic eczema. Open and DBPCFC tests of one week's duration each to cow's milk were performed in all children (age 2-36 months), and both challenge types were positive in 54%. Immediate challenge reactions appeared within 60 min from the beginning of the challenge and delayed-type symptoms within 34 hours on averange. SPT was positive in 48% and patch test in 61% of milk challenge-positive children. In patients with negative oral challenge to cow's milk, SPT was positive in 16% and patch test in 18%. Sensitivity of SPT alone was 48% only, but with concomitant patch test it was a high as 86%. Acute reactions to oral milk challenge correlated well with positivity in SPT, whereas delayed reactions were more often seen in patients with positive patch tests. The patch test panel for food allergy testing in our clinic has included also lyophilized egg, soy, wheat, rye, barley and oats during the last two and a half years in the diagnosis of all

children under 2–3 years with atopic eczema or gastrointestinal symptoms. In SPT, ordinary flours have been used as test material. Positive SPT to wheat was found in 36% and patch test in 74% of 143 milk challenge–positive children. In 129 milk challenge–negative children, SPT to wheat was positive in 26% and patch test in 64%.(7) These results suggest that cereal allergy has been largely neglected. Similar results were published recently by Suomalainen et al.(8). We have found an extensive panel of skin tests to help select suitable diets for infants to get them symptomless for challenge tests.

Hannuksela (9) recommended division of food–allergic people into three different age groups according to the time of appearance of symptoms: 1) infants undet 1 year of age, 2) older children and 3) adults.

When symptoms appear for the first time during the first year of life, it is probable that the basic foods are responsible. When they appear at 1–2 year or later, chocolate, cocoa, citrus fruits, lemonades and candies often end to be responsible. In children and adults with birch pollen allergy, fruits and vegetables often cause symptoms decribed as oral allergy syndrome. Adults with atopic eczema are seldom suspected to being allergic to basic foods. This should, though, be the case when eczema is chronic and does not disappear even in summer. Milk, fish and cereal allergy may occur, but the diagnosis is difficul. DBPCFC should be done for one week each under otherwise constant conditions, but there are many practical problems with adults, the psychological aspects not being the least. Therefore food allergy in infancy should be properly diagnosed and treated by dietary means until tolerance has developed, hoping that later symptoms could be diminished.

The delayed–type allergy to foods may also be an IgE–mediated allergy, even in cases with low total IgE and no detectable specific IgE to foods. The reactions may occur via high–affinity IgE receptors expressed on Langerhans and dendritic cells leading to allergen–specific T cell responces capable of promoting IgE production and delayed–type hypersensitivity reactions.(10) If this is the case with atopic dermatitis, the definition of atopic eczema has to be rediscussed, maybe even delayed–type reactions should be classified as IgE–mediated reactions.

References

1. Allergy 1995:50 (suppl 20)
2. Pediatr Allergy Immunol 1995:6 (suppl 8)
3. Bock SA, Sampson HA, Food allergy in infancy. Pediatr Clin North Am 1994;41:5:1047–67.
4. Bock SA, Sampson HA, Atkins F, Zeiger RS, Lehrer S, Sachs M, Bush RK, Metcalfe DD. Double–blind, plasebo–controlled food challenge (DBPCFC) as an office procedure: A manual. J Allergy Clin Immunol 1988;82:986–97.
5. Räsänen l, Lehto M, Reunala T. Diagnostic value of skin and laboratory tests in cow's milk allergy/intolerance. Clin Exp Allergy 1992;22:385–90.
6. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. J Allergy Clin Immunol 1996;97:9–15.
7. Saavalainen L. Lehmänmaitoallergian kliininen kuva ja diagnostiikka (Clinical picture and diagnostics of cow's milk allergy). Advanced studies, Tampere University 1996.
8. Suomalainen H, Järvinen K–M, Sorva R, Saarinen M, Turpeinen M, Savilahti E, Juntunen–Backman K. The value of patch testing in the diagnosis of food allergy in infants (abstract). Pediatr Allergy Immunol 1995;6(suppl 8):71.
9. Hannuksela M. Suomen Lääkärilehti 1989;44:1108–10.
10. Maurer D, Ebner C, Reininger B, Fiebiger E, Kraft D, Kinet J–P, Stingl G. The high affinity IgE receptor (FceRI) mediates IgE–dependent allergen presentation. J Immunol 1995;154:6285–90.

07

ATOPY IN A SUBARCTIC AREA

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The frequencies of atopic diseases show wide variations in different parts of the world. Atopic diseases are undoubtedly hereditary, but environmental factors have been made responsible for the increase reported in various parts of the world during the last few decades. Studies on atopic diseases from the northern parts of the Nordic countries are limited. Our studies were initiated by an interest in knowing whether geographical, ethnic, environmental or other factors might interfere with the frequency of atopic diseases.

Atopic diseases were confirmed in 36% of 7-12 year old schoolchildren on the Varanger peninsula and the areas close to the Russian border, with 23% having atopic dermatitis (AD) and 18% mucous membrane atopy (MMA). A parental history of atopic diseases was reported by 37% of all children, occurring more frequently in mothers than in fathers. In families with no parental history of atopic diseases 41% of the children appeared to develop some kind of atopic disease; this increased to 63% with a single and to 75% with a double parental history. A strong cumulative effect was seen in cases with a parental history with identical symptoms in parents and children. Flexural lichenfied dermatitis was present in 88%, and 12% of the children had facial and extensor involvement with or without hand dermatitis. 64% of the children showed mild and 33% moderate symptoms; only 3% had severe symptoms confirmed by clinical examination.

Low levels of aerospores were found in homes and schools. Mould allergy is supposed to be a minor problem in this area. Domestic mites were found in some homes and there was a strong association between sensitization/atopy and the occurrence of domestic mites in mattress dust. Cat and dog allergens were found in large amounts and smoking was more common than in other parts of the country.

In a Lappish population in a nearby area atopic diseases were found to be less frequent in the same age groups, i.e. a total of 20%, of which 12% had AD and 11% MMA. The occurrence of indoor allergens is supposed to be very high in this ethnic group. On the other hand, the Lapps spend most of their time outdoors, which may contribute to the low frequency of air passage allergy symptoms among them. The latter results are in accordance with a previous study of a non-Lappish population of schoolchildren of the same age in a nearby area.

Various aspects of the occurrence/frequency of atopic diseases in subarctic areas will be discussed.

NATURAL RUBBER LATEX ALLERGENS

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Immediate hypersensitivity reactions to natural rubber latex (NRL) proteins have been increasingly recognized during the past 15 years. Currently, approximately 3% of hospital employees and 5–10% of physicians and nurses working in operation units are allergic to NRL. Manufactured NRL products, such as surgical and household gloves, catheters, condoms, baby pacifiers and toy balloons may contain allergenic proteins capable of eliciting type I allergic reactions. Recently, substantial progress has been made in the purification and molecular characterisation of several NRL allergens which has facilitated the assessment of their significance and given grounds for proper comparison of the results obtained by different researchers. In fresh NRL, the source material for manufactured products, over 200 different polypeptides have been demonstrated by 2-dimensional immunoblotting but only some 25% them bound IgE antibodies from latex-allergic patient sera and can be considered as allergens. NRL-allergic patients frequently have allergic symptoms from a variety of foods, like fruits and vegetables, but the molecular basis of these cross-allergies is currently poorly understood.

Rubber elongation factor (REF) was first suggested to be *the* major allergen (Hev b 1) in NRL and the only allergen present in one latex surgical glove[1] but more recent studies show that IgE-antibodies to highly purified REF, detected by immunoblotting and ELISA, are practically confined to the subgroup of patients with spina bifida[2]. A 20 kD NRL protein, previously shown to be the most important allergen for adult NRL-allergic patients, has been identified by amino acid sequencing as prohevein[3]. IgE antibodies to purified prohevein are found in 70–80% of NRL-allergic patients and prohevein elicits positive SPT reactions in most NRL-allergic patients and can thus be considered as a major NRL allergen. Attempts have also been made to localise IgE-binding epitopes of prohevein. Only a minority (15%) of patients with antiprohevein IgE antibodies had IgE against the prohevein C-domain whereas IgE antibodies to purified hevein, the 43 amino acid N-terminal fragment of provehein, were found in 56% of NRL-allergic patient sera[4]. In the same study Alenius et al. also showed that purified hevein elicited positive SPT reactions in all patients showing IgE to the N-terminus of prohevein and that IgE-binding peptides purified from a brand of highly allergenic NRL gloves could be identified by amino acid sequencing and mass spectrometry as hevein molecules. Recent results of another group[5] confirm the role of hevein as a major NRL allergen.

Adult NRL-allergic patients frequently recognise prohevein and hevein, whereas the majority of paediatric patients with spina bifida seem to react with REF and with a 27 kD protein showing partial homology to REF[6]. The amino acid sequences of tryptic peptides from the 27 kD protein and from a 23 kD protein described by Lu et al.[7] were in essence identical suggesting that these proteins are the same or they represent different isomers or modifications of the same protein.

A 36-kD NRL protein showed high homology to several plant endo-1,3-β-glucosidases and this protein bound IgE from 21% of NRL-allergic patient sera and was therefore considered a significant NRL allergen[3]. Beezhold et al.[8] reported that NRL protein bands with apparent MW of 46-kD and 110-kD had identical, previously unrecognised N-terminal amino acid sequences and that IgE antibodies from NRL-allergic patient sera bound frequently to the 46-kD sized protein. Hevamine, a 29.6 kD NRL protein, has turned out to be unimportant as a NRL allergen.

Information on molecularly characterised NRL allergens present in gloves or other manufactured products is limited. More than 70% of the IgE binding capacity of one highly allergenic glove was attributable to hevein[4], and REF has been issolated from a glove brand[1]. Monoclonal antibody against a 23 kD NRL protein[7] recognised epitopes of this allergen in certain glove brands and epitopes of a 27 kD allergen have likewise been detected in manufactured NRL products[9]. NRL allergens or their epitopes remaining in NRL products represent a group of protein/peptide molecules that are resistant to high temperatures and to a variety of chemicals used in the manufacturing processes. It can be thus anticipated that all significant NRL allergens extractable from manufactured products are remarkably stable molecules.

REFERENCES

1. Czuppon AB, Chen Z, Rennert S, Engelke T, Meyer HE, Heber M, Baur X. The rubber elongation factor of rubber trees (Hevea brasiliensis) is the major allergen in latex. J Allergy Clin Immunol 1993;92:690-7.
2. AleniusH, Kalkkinen N, Turjanmaa K, Mäkinen-Kiljunen S, Reunala T, Palosuo T. Significance of the rubber elongation factor as a latex allergen. Int Arch Allergy Immunol 1996;109:362-8.
3. Alenius H, Kalkkinen N, Lukka M, Reunala T, Turjanmaa K, Mäkinen-Kiljunen S, Yip E, Palosuo T. Prohevein from the rubber tree (Hevea brasiliensis) is a major latex allergen. Clin Exp Allergy 1995;25:659-65.
4. Alenius H, Kalkkinen N, Reunala T, Turjanmaa K, Palosuo T. The main IgE-binding epitope of a major latex allergen, prohevein, is present in it's n-terminal 43 amino acid fragment, hevein. J Immunol 1996;156:1618-25.
5. Chen Z, Posch A, Raulf-Heimsoth M, Baur X. Isolation and identification of hevein as a major IgE-binding polypeptide in latex from Hevea brasiliensis [Abstract]. J Allergy Clin Immunol 1996;97:428.

6. Alenius H, Kalkkinen N, Lukka M, Reunala T, Turjanmaa K, Mäkinen-Kiljunen S, Palosuo T. Purification and partial amino acid sequencing of a 27 kD natural rubber allergen recognized by latex allergic children with spina bifida. Int Arch Allergy Immunol 1994;106:258-62.
7. Lu L, Kurup V, Hoffman D, Kelly K, Murali P, Fink J. Characterization of a major latex allergen associated with hypersensitivity in spina bifida patients. J Immunol 1995;155:2721-8.
8. Beezhold D, Sussman G, Kostyal D, Chang N. Identification of a 46-kD latex protein allergen in health care workers. Clin Exp Immunol 1994;98:-408-13.
9. Palosuo T, Alenius H, Turjanmaa K, Mäkinen-Kiljunen S, Reunala T. Detection of antigenic epitopes of the 27 kD latex allergen in rubber products [Abstract]. J Allergy Clin Immunol 1994;93:181.

O10

COW DANDER ALLERGENS

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Cow dander-derived allergens are an important occupational cause of allergic asthma, skin disorders and allergic rhinitis among dairy farmers in Finland.

Cow dander contains several immune reactive components including two proteins of 20 kD and 22 kD which can be classified as major allergens. The most important of those is the 20 kD allergen (BDA20) which also appears in the urine, although in low quantities. More than 90% of the immunoblot-positive cattle tenders have specific IgE against BDA20[1]. Other important allergens of cow dander are the 11 kD and 24 kD proteins. About one third of cow-asthmatic farmers had specific IgE to them.

Our recent studies have allowed us to confirm the realtionship between BDA20 and Prahl's Bos d 2. In fact, the similar amino acid compositions of the two proteins had earlier pointed to this possibility but the final evidence was obtained from immunochemical studies with anti-Bos d 2 antiserum (made available to us by Dr. Hansen).

The spectrum of cow dander allergens is probably more complex than previously presumed. When we used more efficient analytical methods it turned out that there are two separate 22 kD allergens in the bovine dander. Moreover, the previously described 11 kD allergen seems to be a dimer in its native form[2].

An important goal of the allergen research is the purification of allergens for diagnostic and therapeutical purposes. Monoclonal antibodies with a high specificity offer an efficient tool for detecting the antigen. We utilized this property of our monoclonal antibodies for pyrifying the BDA20 from raw extract with immune affinity chromatography[3]. When an additional purification step was performed BDA20 was almost 100% pure. This preparation has been used successfully in skin tests, histamine release assays and in the measurements of cellular and humoral responses[4]. Anti-BDA20 monoclonal antibodies have also allowed us to develop a very sensitive and reliable immunometric ELISA[5]. We have applied it for measuring the concentrations of airborne BDA20 is dust samples collected from cowsheds. This method is also very suitable for estimating the BDA20 content of cow allergen extracts.

Modern methods of molecular biology have made possible a detailed analysis of primary structures of allergens. We created a cDNA library from bovine skin by isolating mRNA and synthesizing cDNA which was then cloned to a bacteriophage vector. The library was immunoscreened with cow-asthmatic patients' sera containing specific IgE. Positive plaques were picked, subclonal, and eventually the cDNA was cloned to a high-level expression vector for the production of recombinant allergens. Recombinant DNA technology has allowed us to establish the necleotide and corresponding amino acid sequences of three cow allergens: a protein related to oligomycin sensitivity-conferring protein of the mitochondrial adenosine trisphosphate synthase complex[6], BDA11 (which shows high homology to human psoriasin, a protein expressed in psoriasis)[7] and BDA20[8].

The analysis of the cDNA indicates that the bovine major allergen BDA20 comprises 172 amino acids, has a predicted molecular weight of 19.56 and pI of 4.48. Sequence homology searches in the EMBL and SWISS-PROT libraries revealed that BDA20 shows significant similarities with proteins belonging to the functional group named lipocalins, and we think that homology comparisons (amino acid homology of about 32%) warrant the admission of BDA20 to this functionally important family. Lipocalins are present in the various body fluids and secretions of several animal species. They act as carries of small hydrophobic molecules, such as retinoids and pheromones. Interestingly, the major mouse and rat are urinary allergens (α2-euglobulins) are lipocalins. This raises a question of possible common allergenic properties of lipocalins and allergens in general. The biological function of BDA20 in the bovine skin is not known.

The recombinant BDA20 appeart to be immunologically fully functional. An interesting finding was that the binding of monoclonal antibody or human IgE to BDA20 seems to be almost completely dependent on the conformation of the molecule. This was observed in experiments in which various segments were deleted either from the N- or C-terminal end of BDA20. After the modification of the molecule, antibody binding was practically lost. As expected, T-cell clones could be induced to proliferate with the fragments. We believe that this finding may have important consequences with regard to immunotherapy. It may become possible to alleviate allergy with highly defined preparations that lack the adverse property of inducing immediate hypersensitivity reactions.

References

1. Ylönen J, Mäntyjärvi R, Taivainen A, Virtanen T. Comparison of the antigenic and allergenic properties of three types of bovine epithelial material. Int Arch Allergy Immunol 1992;99:112-7.
2. Rautiainen J, Pentikäinen J, Rytkönen M, Linnala-Kankkunen A, Pelkonen J, Virtanen T, Mäntyjärvi R. Molecular analysis of allergenic proteins in bovine dander. Allergy (in press).
3. Ylönen J, Virtanen T, Horsmanheimo L, Parkkinen S, Pelkonen J, Mäntyjärvi R. Affinity purification of the major bovine allergen by a novel monoclonal antibody. J Allergy Clin Immunol 1994;93:851-8.
4. Virtanen T, Zeiler T, Rautiainen J, Taivainen A, Pentikäinen J, Rytkönen M, Parkkinen S, Pelkonen J, Mäntyjärvi R. Immune reactivy of cow-asthmatic dairy farmers to the major allergen of cow (BDA20) and to other cow-derived proteins. The use of purified BDA20 increases the performance of diagnostic tests in repiratory cow allergy. Clin Exp Allergy 1996;26:188-96.
5. Ylönen J, Virtanen T, Rytkönen M, Mäntyjärvi R. Quantification of a major bovine allergen by a two-site immunometric assay based on monoclonal antibodies. Allergy 1994;49:707-12.
6. Parkkinen S, Rytkönen M, Pentikäinen J, Virtanen T, Mäntyjärvi R. Homology of a bovine allergen and the oligomycin sensitivity-conferring protein of the mitochondrial adenosine triphosphane synthase complex. J Allergy Clin Immunol 1995;95:1255-60.
7. Rautiainen J, Rytkönen M, Parkkinen S, Pentikäinen J, Linnala-Kankkunen A, Virtanen T, Pelkonen J, Mäntyjärvi R. cDNA cloning and protein analysis of a bovine dermal allergen with homology to psoriasin. J Invest Dermatol 1995;105:-660-3.
8. Mäntyjärvi R, Parkkinen S, Rytkönen M, Pentikäinen J, Pelkonen J, Rautiainen J, Zeiler T, Virtanen T. cDNA cloning of the predominant allergen of bovine dander; a new member in the lipocalin family. J Allergy Clin Immunol (in press).

NOVEL ALLERGENS: YEASTS

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The yeats are some of the most fascinating allergens because of their biologic properties and the resulting multiple form of exposure. We ger exposed to yeasts by foods, such as bread (*Saccharomyces cerevisiae*), wine (*Saccharomyces ellipsoideus*) and beer (*Saccharomyces carlsbergensis*). We inhale several yeasts as aeroallergens (*Cryptococcus spp, Rhodotorula spp.*), especially in moist conditions, both indoor and outdoor. The most important way of exposure to yeasts is, however, by saprophytic growth on the skin (*Pityrosporum ovale/orbiculare*) and the mucous membranes (*Candida albicans*).

Because of the unusual way of exposure the clinical significance of yeast hypersensitivity remains disputed in several diseases. Most convincing evdence of true yeast hypersensitivity has been found studying the role of saprophytic yeasts in atopic dermatitis of the head neck and shoulder region. Consequently the allergenic compositions of the yeasts involved to any extent in this type of atopic dermatitis have been studied most throughly (*Pityrosporum ovale, Candida albicans* and *Saccharomyces cerevisiae*).

The first yeast to be characterized by IgE immunoblotting was *C.albicans* and by now the allergens of it have been characterized in six studies. In the studies with small population sizes (n<50) the main allergens vary. In the largest presented population of anti-*C.albicans* IgE positive individuals (n=105) the main allergen among altogether 44 IgE binding componenets is a 46 kD protein band followed by a 27 kD band. The 46 kD component of *C.albicnas* has been reconigzed as enolase enzyme. Another important antigen of *C.albicans* is mannan, a polysaccharide. Both enolase and mannan are also the most important allergens of baker's yeast. In fact, enolase of *S.cerevisiae* was the first yeast component to be recognized as a single allergen.

Yhe IgE immublotting profiles af allergens of *P.oribiculare* and *P.ovale*, different morphological forms of the yeast, differ. In the first presented analyses the major allergens of *P.ovale* were 25 kD and 9 kD bands and ones for *P.orbiculare* were 86, 76, 67, 28, 17, and 13 kD bands. Our own studies of *P.ovale* revealed the 9 kD, 96 kD and 20 kD bands to be the most important. We also found marked IgE reactivity to *P.ovale* mannan by use of chemically purified mannan and nitrocellulose RAST. The mannan stain could also be seen in IgE immunoblots as well.

Stability of the yeast allergens is extremely poor in storaged solution. Especially the enolases of *C.albicans* and *S.cerevisiae* are very labile allergens. The majority of the allergens of *C.albicans, P.ovale* and *S.cerevisiae* lose their IgE-binding capacity when storaged. On the contrary to proteins manna is a stable allergen. The maximum storage times at +6°C in 50% glycerol are six month for *C.albicans* and one month for *P.ovale* and *S.cerevisiae*. The baker's yeast allergens are labile in the gastrointestinal tract as well. In an *in vitro* analysis only mannan and a 10 kD allergen were stable after the gastric and duodenal conditions. These two allergens also appear to be thermostable.

The yeast allergens, despite of the great biological differences of yeasts, crossreact. The main crossreacting allergens are enolase and mannan. In IgE immunoblotting inhibition experiments the IgE antibodies against enolases of *C. albicans, C.utilis* and *S.cerevisiae* crossreact and so do the mannans of *C.albicans, P.ovale* and *S.cerevisiae*in RAST inhibition.

In recent years a great deal of information of yeast allergens has become available. This information helps us to understand the role of yeasts as sensitizers and allergens. In the coming years the analysis of the immunomodulating properties of yeast allergens on human immune responses will be the most challenging era of the yeast allergen research.

Further reading

Ito K, Ishiguro A, Kanbe T, Tanaka K, Torli S. Detection of IgE antibody against *Candida albicans* enolase and its cross-reactivity to *Saccharomyces cerevisiae* enolase. Clin Exp Allergy 1995;25:522-8.

Jensen-Jarolim E, Poulsen LK, With H, Kieffer M, Ottevangen V, Stahl-Skov P. Atomic dermatitis of the face, scalp and neck: type I reaction to the yeast Pityrosporum ovale? J Allergy Clin Immunol 1992;89:44-51.

Johansson S, Karlström K. IgE-binding components in Pityrosporum orbiculare indentified by an immunoblotting technique. Acta Derm Venereol 1991;71:11-6.

Kieffer M, Bergbrandt I-M, Faergeman J, Jemec GBE, Ottevange V, Svejgaard E, Skov PS. Immune reactions to *P.ovale* in adult patients with atopic dermatitis and seborrhoic dermatitis. JAAD 1990;22:739-49.

Kortekangas-Savolainen O, Kalimo K, Lammintausta K, Savolainen J. IgE binding components of baker's yeast recognized by immunoblotting ananlysis. Clin Exp Allergy 1993;23:179-84.

Kortekangas-Savolainen O, Savolainen J, Einarsson R. Gastrointestinal stability of Baker's yeast allergens studied by in vitro analysis. Clin Exp Allergy 1993;23:587-90.

Kortekangas-Savolainen O, Einarsson R. Thermal and storage stability of *Saccharomyces cerevisiae* (baker's yeast) allergens. Clin Exp Allergy 1994;24:257-62.

Nermes M, Savolainen J, Viander M, Lammintausta K, Kalimo K. Determination of IgE antibodies to Candida albicans mannan with nitrocellulose-RAST in patients with atopic disease. Clin Exp Allergy 1994;24:318-23.

Nermes M, Savolainen J, Kortekangas-Savolainen O. Nitrocellulose-RAST analysis of allergenic cross-reactivity of yeast. Int Arch Allergy Immunol 1995;106:118-23.

Savolainen J, Broberg A. Allergenic crossreactivity of *Pityrisporum ovale* and *Candida albicans*. Clin Exp Allergy 1992;22:469-74.

Savolainen J, Viander M, Einarsson R, Nieminen E, Koivikko. Stability of *Candida albicans* allergens during storage. Clin Exp Allergy 1992;22:991-5.

Savolainen J, Lammintausta K, Kalimo K, Viander M. *Candida albicans* and atopic dermatitis. Clin Exp Allergy 1993;23:332-9.

Savolainen J. A standardized densitometric immunoblotting analysis of *Candida albicans* allergens. Clin Exp Allergy 1995;25:357-63.

Savolainen J, Rantala A, Nermes M, Lehtonen L, Viander M. Elevated IgE responses to *Candida albicans* in postoperative disseminated candidiasis. Clin Exp Allergy 1996: in press.

012

MOSQUITO SALIVA ALLERGENS

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Most, if not all, people are sensitized to mosquito bites in the early childhood. Cutaneous symptoms include immediate wheals and delayed bite papules, which tend to be more severe at the onset of the mosquito season. Systemic Arthus-type symptoms may occur but, in contrast to bee and wasp stings anaphylactic mosquito-bite reactions are very rare (1). Mosquito-bite wheal is IgE antibody mediated. With a sensitive immunoblot assay we could show saliva-specific IgE antibodies in almost all subjects with immediate skin reactivity to Aedes mosquitoes (2). In addition, passive transfer experiments confirmed that saliva-specific IgE antibodies can cause mosquito-bite whealing *in vivo* (3).
When feeding female mosquitoes inject saliva into the skin. To characterize mosquito saliva antigens we immunized mice with the bites of *Aedes communis* (northern European species), *Aedes aegypti* (tropical and subtropical species) and *Anopheles stephensi* (Asian species). The main *A. communis* saliva antigens were 22-, 30-, and 36-kD, *A. aegypti* saliva antigens 31-, 36-, and 46-kD and *A. stephensi* saliva antigen 46-kD proteins. Most of the saliva antigens appeared to be species-specific and cross-reactivity was observed only between saliva proteins of *A. communis* and *A. punctor*, two taxonomically closely related species. Human IgE and IgG4 antibodies from mosquito-sensitive children bound to the same saliva proteins confirming that these are also allergenic in man. At present, the function of mosquito saliva allergens is unknown. We could show saliva allergens in the female but not in the male *A. communis* saliva suggesting that these proteins are involved in blood feeding. We have partially sequenced the 22-kD saliva allergen from *A. communis* but it showed no homology to any known proteins. A gene expressing the 36-kD protein from *A. aegypti* salivary glands has also been isolated but the function and allergenic properties of this protein is not known (4).
In conclusion, Aedes and Anopheles mosquito saliva contains several proteins which bind human IgE and IgG4 antibodies. In the future, isolation and production of saliva allergens may give tools for immune therapy in mosquito-bite allergy.

References

1. Reunala T, Brummer-Korvenkontio H, Palosuo T. Are we really allergic to mosquito bites? Ann Med 1994;26:301-6.
2. Brummer-Korvenkontio H, Lappalainen P, Reunala T, Palosuo T. Detection mosquito saliva-specific IgE-and IgG4-antibodies by immunoblotting. J Allergy Clin Immunol 1994;93:551-5.
3. Reunala T, Brummer-Korvenkontio H, Räsänen L et al. Passive transfer of cutaneous mosquito-bite hypersensitivity by IgE anti-saliva antibodies. J Allergy Clin Immunol 1994;94:902-6.
4. James AA, Blacmer K, Marinotti O et al. Isolation and characterization of the gene expressing the major salivar gland protein of the female mosquito, *Aedes aegypti*. Mol Biochem Parasitol 1991;44:245-54.

013

CONTACT ALLERGY TO TALL OIL ROSIN: RESULTS OF PATCH TESTING

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Aims: The major types of rosin (colophony) are gum rosin, wood rosin and tall oil rosin. Gum rosin and tall oil rosin are the two dominating rosin types today. Tall oil rosin is obtained as a by-product in the pulp industry. The aims of the study were to gather information on the sensitizing properties of tall oil rosin.
Methods: 99 patients who were patch tested to tall oil rosin (20% pet) during 1983-1994 were included in the study. All the patients were also tested to standard colophony (gum rosin) (20% pet), 71 were tested to abitol (10% pet), 51 to abietic acid (10% pet), and 21 patients to pine and spruce resins from living trees (20% pet)
Results: Twenty-four patients got an allergic test reaction to colophony and 14 patients to tall oil rosin. All the 14 patients with an allergic patch test to tall oil rosin were also positive to colophony, and 10 were positive to abietic acid (10 of 10 tested), 1 to abitol (1 of 10 tested) and 4 to the living tree resins (4 of 4 tested). The patients with an allergic patch test to colophony had the following allergic test reactions: 14 were allergic to tall oil rosin, 10 of 16 tested to abietic acid, 3 of 23 tested to abitol and all 6 tested to the tree resins.
Conclusion: Tall oil rosin contains the same allergenic compounds as gum rosin. The differences in the amounts of the allergens are probably responsible for the lower frequency of allergic reactions to tall oil rosin. The results support the view that skin contact to tall oil rosin may cause contact sensitization.

014

THE PROBLEMS OF OCCUPATIONAL ASTHMA AND ITS PREVENTION

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During last years the significant increase in incidence of allergic diseases including occupational asthma is notable. Long - term studies showed that occupational asthma is polyethiological disease. The ethiological factors are divided into three main groups: sensitizers, irritants and substances with mixed mode action. Among industrial workers chemical haptens are the most common cause of asthma. At the moment asthma is very common disease in Russia especially in workers of chemical, textile, mining industry and machine building. In light, food, microbiological industries and agriculture there is a lot of factors of plant and animal origin which can cause occupational asthma. They are different fibres of plants, molds and bacteria colonising them etc. The sensitising ability of industrial allergen, the power of action, duration of exposure, its physical and chemical properties and hereditary predisposition and immune status of organism play an important role in development of asthma. Many inhaled irritants are non-inflammatory triggers that increase bronchi sensitivity and reactivity that leads to impairment of primary defence mechanisms. A number of studies gave the possibility to elaborate the occupational asthma classification and solve some problems of its management and prevention.

015

RELATIONSHIPS BETWEEN CHEMICAL STRUCTURE AND SENSITISING POTENTIAL OF ORGANIC ACID ANHYDRIDES (OAAs) IN ANIMAL MODELS

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OAAs are reactive, industrial chemicals causing airway symptoms and the induction of specific IgE immuno-globulins in exposed workers. Studies of the effects of OAAs on man and guinea pigs (GPs) indicate that there are large differences in sensitising potential for different OAAs. Thus, the OAAs are excellent model compounds in animal experimental studies on chemical structures behind allergy. In a previous study, the IgE and IgG formation was studied in GPs after intradermal immunization with 13 different OAAs (Welinder et al. 1994).

In the present study, rats were immunized intradermally with 8 different OAAs in dioxane/paraffin oil. Blood was collected 4 weeks after immunisation and analysed by ELISA for specific IgE to rat serum albumin conjugates of the OAAs.

Phthalic anhydride, trimellitic anhydride, methylhexahydrophthalic anhydride tetrahydrophthalic anhydride, and methyltetrahydrophthalic anhydride all showed elevated specific titres in the rat as well as in the GP model, while succinic anhydride was negative in both. The introduction of methyl groups seems to enhance the formation of antibodies.

A reasonable agreement was found between the results of the GP and rat models. Also, the findings of the animal experiments are in agreement with findings from studies of exposed workers. Thus, the models may be useful for a better understanding of the sensitising potential of different OAAs and perhaps also other compounds.

016

ATOPIC DISEASES IN FARMER FAMILIES AND IN NON-FARMING POPULATION IN FINLAND

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Farmers and their families are exposed to several biological dusts including animal dander, pollen and molds. A random sample of farmer families and non-farming families in Kuopio county was selected for computer-assisted telephone interview (CATI). Altogether 772 adults were interviewed from 400 families (221 farmers and spouses, 551 adults in other non-farming families). The farmer families had 232 children and other families 646 children.

In adults, no significant differences were found in the prevalence of self reported asthma among farmers and their spouses (5 %) compared with non-farming population (4 %). The prevalences of allergic rhinitis were 27 % and 26 %, respectively. Also allergic conjunctivitis was as common in both groups. The life-time prevalence of atopic eczema was 17 % in farmers and 20 % in non-farming adults.
In children, the prevalence of asthma was lower in farmer families (1 %) than in the non-farming families (3 %). The prevalence of allergic rhinitis was also lower in children of farmer families (8 %) than in children in the non-farming families (13 %). Atopic eczema was also less common in farmer families than in non-farming families. We conclude that higher exposure to common allergens does not increase the risk of atopic diseases.

017

MOISTURE DAMAGE IN A SCHOOLBUILDING IN RELATION TO ALLERGIC SYMPTOMS AND SERUM IgE AMONG ELEMENTARY SCHOOLCHILDREN

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The purpose of this study was to assess the effect of microbial exposure due to moisture damage in a schoolbuilding on the respiratory symptoms and serum immunoglobulin E (IgE) levels of schoolchildren. The study group consisted of 367 children between the ages 7 and 10 years in a moisture-damaged school and 176 children of similar ages in a new building without any moisture problem. The IgE radioallergo-absorbent tests (RAST) were carried out with the Phadiatop cap FEIA (R) method on 81 randomly selected children from the moisture damaged-school and 50 unexposed controls.
The microbial analyses included the following molds: *Aspergillus fumingatus, Cladosporium herbarum, Penicillium notatum and Cephalosporium acremonium.*
The prevalence of respiratory symptoms was 1.5 times higher for the exposed children than for the controls; in addition they had two times more wheezing and 1.6 times more shortness of breath than the unexposed children, According to the questionnaire, 33.3% of the exposed children and 29.9% of the controls had had allergic symptoms earlier. Sixtythree percent of the exposed children had an elevated serum IgE level

(>0.4 kU/l) as compared with 33% of the controls. In the most contaminated classroom 84% of the children had an elevated IgE value.

Table: Serum IgE levels of the study population

RAST categories (kU/l)	< 0.4	0.4-0.7	>0.7-3.5	>3.5-17.5	>17.5
Exposed children	37.0%	12.4%	21.2%	7.2%	22.2%
Controls	66.7%	0	11.1%	7.6 %	15.6%

We conclude that moisture damage, and the microbial exposure associated with it, increases the risk of respiratory symptoms and elevated serum IgE among children attending moisture-ldamaged schools.

018

DOMESTIC AND OCCUPATIONAL LATEX ALLERGY – CONSECUTIVE CASES IN A PRIVATE ALLERGY WARD

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Background: In the last decade, latex has been focussed upon as a cause to severe IgE-mediated reactions in man, i.e. during dental, gynecologic or surgical exploration of patients with gloves or catheters made of latex rubber. Among risk groups for this allergy are newborns with defect neural crest closure, dental and hospital care personnel in frequent mucosal or skin contact with latex. Extracts of latex from the rubber tree contains IgE-binding proteins from 2,5 to 120 kD in molecular size. Reaginic allergy is demonstrated by aid of RAST test,skin prick test(SPT) and provocations. The latter must be made cautiously because of risk for anaphylaxis. The prevalence of reaginic latex allergy according to other studies is observed to be 7% in atopic patients tested with common airborne allergens, 3% in unselected healthy hospital care personnel and 5,6-7,4% in nurses working in operation rooms. Use of latex as material in furniture is increasing.
Issues: The relative importance of latex allergy in atopic patients and latex sources in domestic and occupational environments need further elucidation.
Patient material: Since October 1995 hitherto 62 consecutive patients with combinations of rhinitis, asthma, eczema and urticaria have been investigated.
Methods: SPT with 11 ALK allergens. S-total-IgE. RAST-test against latex, banana, avocado, chestnut and benjaminficus.
RAST-positive cases: SPT and nasal provocation with ALK Latex 1:2000-1:20.
Results:RAST-class: 0 1 2 3 4 5 6
No of cases: 44 3 6 5 2 1 1
In 11 cases, positive case histories in domestic or occupational environment are confirmed by positive RAST, SPT and provocations. Highest titers, class 3-6 are seen in broadly sensitized atopics with rhinitis, asthma and eczema. Allergy-provoking activities are:Wearing latex gloves, use of condoms, using beds with a latex mattress,work in and visit to factories using adhesive folie, working as a hair dresser, being patient or working in *dentist's or dental hygienist practices.*
Conclusions: Latex allergy may be more frequent than earlier supposed. Not only those with risk occupations or chronically ill patients who are repeatedly exposed to latex during diagnostic procedures should be investigated for latex allergy. Also broadly sensitized atopics and those with longlasting exposure should be examined for possible latex sensitization.

019

RUSSIAN PROJECT »IMPROVING THE QUALITY OF LIFE IN ASTHMA AND ALLERGY« 1996-1998

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Public Health Committee of the Mayor's Office of St. Petersburg, St. Petersburg State Scientific Centre of Pulmonology, St.Petersburg Asthma and Allergy Association are chief executive organisations of the Russian Project. At the moment 50 regions of Russia and Byelorussia Republic participate in the Project. The Project has the patronage of the WHO / Headquarters Geneva /, the IAC / Headquarters Toronto / and Ministry of Health of Russian Federation. The main directions of the activities within the framework of the Russian Project: implementation of the WHO and other international organisations recommendations on asthma and allergy in medical practice in Russia, training and education of general practitioners and patients in the aspects of practical approach to management and control of asthma and allergy, conduction of epidemiological studies on the prevalence of asthma and allergy in different regions of Russia, occupational asthma and allergy, family planning in asthma and allergy, publishing the journal "Asthma and Allergy", creation of National Asthma and Allergy Association and regional methodical and consulting Asthma - Centres.

020

TRENDS IN THE OCCURRENCE OF ASTHMA IN FINLAND

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Asthmatic patients who need regular or longstanding medication receive special reimbursement for antiasthmatic drugs in Finland. The diagnosis must be made by a specialist. All patients are registered by the Social Insurance Institution. This database provides nationwide information on the prevalence and incidence of persistent asthma.
The register included 150,000 patients at the end of 1995, i.e 2.9% of the total population, ranging from 2.5% to 4.1% in the 22 hospital districts. In 1986, the prevalence rate was 1,5%. The number has doubled among both genders since 1986, and the annual growth has been about 10%. The prevalence has in relative terms increased most among children, and their share of all patients has grown from 9% in 1986 to 14% in 1995. Prevalence rate among boys was 0.54% and among girls 0.29% in 1995. In the total population, the age-standardized rate was slightly higher among females (3.0%) than males (2.9%). Differences in the age-specific incidence rates increase the share of atopic asthma among patients.

021

RISK FACTORS FOR ASTHMA - Report from the Obstructive Lung Disease in Northern Sweden Study

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This paper presents data on risk factors for asthma based on two cross-sectional studies in the same population sample 6 years apart.
In 1986 a cross-sectional study of respiratory diseases was performed in the northernmost province of Sweden. The first part of the study was a postal questionnaire survey. Completed answers were given by 5,698 (86%) subjects out of 6,610. In 1992 the cohort was invited to a follow-up study, in which 87% (N=4,932) of the participants in the 1986 y study participated.
The cumulative incidence of asthma during the 6 y period was high, 3%, and was based on the question "Have you ever had asthma?" after exclusion of all subjects with asthma or suspected asthma in 1986. This indicates a mean annual incidence rate of asthma of 0,5/100/y. After family history of asthma (RR 4,0) both current and ex-smoking appeared to be important risk factors for asthma. Regarding smoking habits the highest incidence of asthma, 0,9/100/y, was seen in those who were smokers in 1986 but had stopped smoking in 1992. If the risk to develope asthma in never smokers without asthma heredity was 1 in a linear regression model, the risk for ever smokers without asthma heredity was 1,8, in never smokers but with asthma heredity 4,3 and in ever smokers with asthma heredity 6,7; the risk increases mainly additively. In multiple logistic regression models also farming and employed in forestry were risk factors, as well as manual workers in industry and female sex.

022

WHAT'S TAKING PLACE ON THE AIRWAY MUCOSA?

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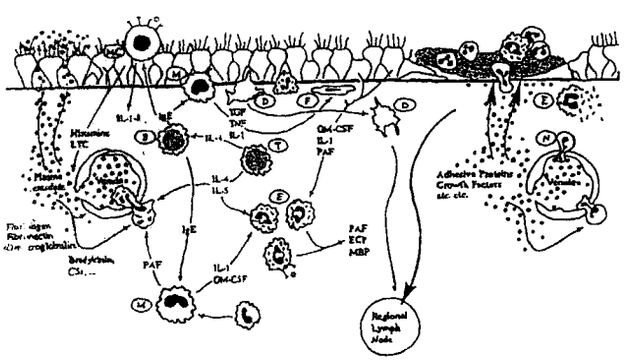
The profuse airway mucosal microcirculation has several important functions in health and disease. One of its major roles lies in the process of extravasation and mucosal exudation of bulk plasma. This response is produced by allergic reactions, infectious processes, occupational disease factors, inflammatory agents, and epithelial shedding. In contrast, simple neurogenic irritants and metacholine-type challenge are without exudative effects. The extravasated plasma harbours adhesive and leukocyte-activating proteins (such as fibrinogen and fibronectin), proteases, immunoglobulins, cytokines and cytokine-mudolating proteins, and an endless variety of biologically active peptides. The plasma exudate-derived dynamic molecular milieu of the inflamed airway mucosa may explain in part why any translation of in vitro cell data to in vivo function may be fraught with disaster.

New data on epithelial restitution, after shedding suggest a pramount role of plasma exudation in mucosal repair (as well as novel roles for both basal cells and ciliated cells). Shedding-like removal of the epithelial lining in a defined are promptly induces extravasation and luminal entry of bulk plasma. A plasma-derived gel thus covers the denuded but intact basement membrane until a new flat epithelium has been established. The gel is rich in fibronectin-fibrin and other repair-promoting plasma-derived agents. Contrasting current cell culture paradigms, reepithelialisation in vitro occurs both promptly and at exceedingly high speeds.

The epithelial restituton process involves several physiological responses (plasma extravasation, secretory effects), granulocyte responses (migration and activation of neutrophils and eosinophils), and remodelling effects (proliferation of fibroblasts and smooth muscle cells, thickening of reticular basement membrane, and growth of regional lymph nodes). Hence, shedding-restitution processes, as they evolve under in vivo conditions, evoke several disease-like effects encompassing airway and organ pathophysiology, leukoscyte pathology, and airway remodelling. - Propecting the epithelial lining from damage and shedding emerges as an increasingly important goal of the treatment of asthma and rhinitis.



In this complex scheme exudative inflammation goes on either with the epithelium intaact (left) or with shedding-restitution as a prominent feature (right). In both kinds of inflammatory conditions plasma-derived adhesive proteins and other plasma-derived effectors solutes contribute significantly to the molecular milieu of the lamina propria, the epithelium, and the mucosal surface. Note that the epithelial shedding-restitution process may be a driving force for asthma-like cellular pathology and exudative pathophysiology.

023

LIMITATIONS IN THE USE OF INHALED STEROID

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Inhaled corticosteroids (iGCS) have a favourable benefit to risk ration when assessing the ratio between topical airway activity and systemic (adverse) effects such as those on HPA-axis suppression and bone metabolism. Inhaled corticosteroid therapy clearly has a much better benefit to risk ratio than oral steroid therapy (1, 2). Although this favourable property of inhaled corticosteroids has been extensively highlighted, dose-dependent systemic effects do occur and some of these systemic effects may limit the use of inhaled steroids.

Corticosteroids, when sytemically available, produce a number of dose (concentration) dependent biological effects. The most important effects from a safety point of view are adrenal suppression, growth retardation and negative effects on: connective tissue, calcium- bone-, carbohydrate- and lipid metabolism. In addition to the systemic effects, local effects such as oral candidiasis, dysphonia, cough and throat irritation may occur when iGCS are used (3). The frequency of local effects vary in different studies because of the different criteria used for assessment. Based on controlled clinical trials and spontaneous adverse reaction reporting systems, regulatory agencies estimate the frequency of local adverse effects to about 5%.

Of the systemic effects, adrenal suppression and negative effects on bone metabolism are of a major safety concern.

Adrenal suppression

The magnitude of adrenal suppression is dertermined by the systemic availability (absorption) of the deposited dose in the lungs. Magnitude of deposition is in turn determined by the efficiency of the inhaler device (4). Although a significant part of the inhaled dose is deposited in the oroparynx, and subject to gastrointestinal absorption, the additional systemic load is small due to a very efficient first-pass metabolism of modern inhaled steroids (≥ 90% for budesonide and fluticasone). The lung is a hihgly efficient absorbing organ due to a large surface area and high perfusion.

Most clinical studies have utilised morning plasma cortisol as a direct marker for adrenal suppression. In these studies, significant suppression has been seen only with very high doses (3). It should be emphasised that morning cortisol is a relatively insensitive and highly variable marker for cortisol production since a single measurement does not reflect production rates and is subject to bias due to the cyclic nature of the cortisol production.

In recent year, studies utilising pharmacokinetic methodology reflecting cortisol production rates, have shown that inhaled corticosteroids suppress cortisol productions in a dose-dependent manner. Short term (≤ 7 days) studies in healthy volunteers (5, 6) as well as in asthmatic patients (7, 8) Show that cortisol production is significantly suppressed within the clinically recommended dose range. The systemic potency (degree of suppression) varies between steroids (and devices). Table 1 summarises recent results from short term comparative (budesonide [BUD] vs fluticasone propionate [FP] dose-response studies all showing FP to be 2-4 times more potent in suppressing plasma cortisol than BUD on a μg equivalent basis. The studies also illustrate the importance of the devide for the development of sytemic effects.

The clinical relevance of the observed adrenal suppression is nuclear. However, at high dose levels (> 1500 μg), FP induced an almost complete (> 80%) suppression of the HPA-axis

Reference	Study design	Daily dose (µg)	% suppression
5 / Grahnén	7 day b.i.d. parallell group (within-group cross-over) study 81 normals subjects (24 hr plasma AUC)	BUD-TBH: 200/500/1000/2000 FP-DH: 200/400/800/1600	BUD: 14/18/19/47 FP: 10/17/41/86 FP/BUD: 2/1
6 / Dogterom	4 day b.i.d. placebo controlled cross-over study 21 normal subjects (24 hr plasma AUC)	FP-MDI: 400/750/2000 BUD-MDI: 400/800/2000	BUD: 1/ 3 /27 FP: 2/39/84 FP/BUD: 4/1
7 / Clark	Single dose placebo controlled cross-over study 12 adult asthmatics (10 hr urine cortisol)	BUD-MDI: 400/1000/1600/2000 FP-MDI: 500/1000/1500/2000	BUD: 23/ns/49/46 FP: 59/ns/81/78 FP/BUD: 3/1
8 / Clark	Single dose placebo controlled cross-over study 10 asthmatic children (12 hr urine cortisol/crea)	BUD-MDI: 400/800/1250 FP-MDI: 400/800/1250 (large volume spacer)	BUD: 15/ 0/ 0 FP: 36/60/63 FP/BUD: 3/1

BUD=budesonide; FP=fluticasone propionate; TBH=Turbuhaler®; DH=Diskhaler®; MDI=metered dose inhaler; ns=not specified

where as for BUD, suppression reches only about half of that response. A pronounced systemic activity has the potential of giving rise to clinically significant adverse effects. Assuming that tachyphylaxis to the response does not occur, this different between the steroids may have clinical relevance with regards to the long-term safety in patients requiring high dose treatment. However, data on long term effects in asthmatic patients including the possible development of tachyphylaxis are lacking.

Bone metabolism and growth retardation

It is generally accepted that in doses below 800 µg/day iGCS are relatively free of bone metabolism effects. In contrast to oral steroids, osteoporosis has not been reported. Short term studies of surrogate markers for bone metabolism (osteocalcin, type I collagen carboxy terminal propeptide) have shown dose-dependent effect on these markers (9). There is considerable debate as to the clinical significance of these findings. Since controlled, prospective longitudal studies are lacking, the risk of developing osteoporosis (especially in patients with other risk factors) cannot be adequately assessed.

Short term, dose dependent, retardet growth in children treated with inhaled corticosteroids has been reported (3). However, studies indicate that growth retardation seems to be a clinical feature of the asthma disease itself and not specically related to the use of inhaled corticosteroids. A controlled prospective long term (up to 6 years) study in 216 asthmatic children revealed that budesonide in doses up to 400 µg/day did not adversely effect growth (10). Whether other more systemically potent corticosteroids lack negative effects on growth in unclear.

Summary

Inhaled steroids have a favourable benefit risk to ratio, with few adverse effects. However, it is important to realise that treatment with inhaled steroids is not solely topical. All inhaled steroids available on the market are efficiently absorbed from the lungs and systemic effects will manifest in a dose-dependent manner.

To minimize development of systemic adverse effects, selection of an optimal dose regimen in relation to the systemic potency of the steroid is essential. It should also be emphasised that an uncontrolled asthma carries a much larger risk to the individual patient than potential adverse effects induced by inhaled steroids.

References

1. Toogood JH, Baskerville J, Jennings B et al. Bioequivalent doses of budesonide and prednisone in moderate and sever asthma. J Allergy Clin Immunol 1989;84:-668-70.
2. English AP, Naete MS, Quint DJ et al. Biological activities of some corticosteroids used in asthma. Am J Respir Crit Care Med 1994;149(suppl):A212.
3. Barnes PJ, Pedersen S. Efficacy and safety inhaled corticosteroids in asthma. Am Rev Respir Dis 1993;148(suppl):s1-s26.
4. Lipworth BJ. New prespectives on inhaled drug delivery and systemic bioactivity. Thorax 1995;50:105-10.
5. Grahnén A, Brundin RM, Ling-Andersson A, Lönnebo A, Eckernäs SÅ. The systemic potency of fluticasone propionate from Diskhaler™ vs budesonide from Turbuhaler®. Am J Respir Crit Care Med 1996;in press.
6. Dogterom P, Oosterhuis B, Ebels JT, Jonkman JHG. Inhaled fluticasone propionate unduces greater cortisol suppression compared to budesonide. A dose reconse study using pressurized metered dose inhalers (pMDI's). Eur Respir J 1995;8(suppl 19):p303S.
7. Clark D, Grove A, Cargill RI, Coutie WJ, Lipworth BJ (1995). Increased adrenal suppression with fluticasone propionate(F) verus Budesonide(B) given by MDI in asthmatics. Eur Respir J 1995;8(suppl 19):p303S
8. Clark DJ, Clark RA, Lipworth BJ. Comparative systemic bioactivity inhaled budesonide and fluticasone propionate in asthmatic children. Thorax 1996;subbmitted for publication.
9. Grove A, McFarlane LC, Lipworth BJ. Effects of short term exposure to inhaled corticosteroids on novel biochemical markers for bone metabolism. Eur Respir J 1995;8(suppl 19):p303S.
10. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med 1994;88:373-81.

024

OPTIMISING DRUG DELIVERY

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In clinical practice today, the physician is confronted with many different inhaled formulations for the treatment of asthma, and must consider a number of inhaler aspects in order to make the right choice. As the amount of drug reaching the effector organ. in our case the lungs, determines the elicited effect (Borgström et al., Am J Respir Crit Care Med, 1996) lung deposition is one of the more important aspects when optimising drug delivery in asthma. A good inhaler thus should deliver a large dose to the lungs, with a concomitant low oropharyngeal deposition. Different inhalers show large variations in the degree of lung deposition and each combination of drug and device is a unique combination. Caution should be exercised when extrapolating the outcome of one combination from other combinations of drug and device. Lung deposition for dry powder inhalers (DPIs) ranges from 10 to 30 %, with Turbuhaler® at the upper end of the range and most other DPIs at around 10 %. pMDIs also vary in lung deposition; some pMDIs give 15-20% while others deliver 10-15% of the nominal dose to the lungs.

A high lung, and a low oropharyngeal, deposition optimises the balance between desired effects in the lung and undesired local or systemic side effects. This balance can be described by the L/T-ratio, where L denotes the local, desired availability of the given drug and T denotes the total systemic availability The L/T-ratio gives an index for comparison of different formulations of the same active drug. The best possible value is 1.0; a low L/T-ratio for an inhaler tells us that there is great potential for

improvement in inhaler design. Using the L/T-ratio concept, it has been shown that it is advantageous, with respect to the balance between desired and undesired effects, to change from pMDI to Turbuhaler. It has also been shown, when comparing e.g. salbutamol pMDI and salbutamol Rotahaler®/Diskhaler® that it is more advantageous to use the pMDI than the corresponding Rotahaler/Diskhaler formulations.

Variability in the dose reaching the effector site can be of concern as a large variability in availability at the effector site can have implications for the elicited response. *In vitro*, the dose variability is larger for Turbuhaler than for pMDI, whereas the reverse is true *in vivo* (Beckman et al., J Aer Med, 1996). Thus, in a clinical situation, the DPI gives a more reproducible dose in the lungs than does the pMDI. This is probably a class phenomenon for DPIs, as the generation and inhalation of drug aerosol for DPIs, such as Turbuhaler, Diskhaler, etc., is a continuous process. For pMDI formulations, generation and inhalation of the drug aerosol is a non-continuous process and thus more open to patient influence.

There are also other aspects to consider when choosing the optimal inhaler and the pros and cons of the different inhalers must obviously be considered when making the choice. Ultimately, however, it is the patient who makes the choice. If the patient is happy with the inhaler, he/she will use it; thus an increased compliance could be the best "inhaler improvement" in the foreseeable future.

025

CANDIDATE GENES IN ASTHMA

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Asthma is a chronic inflammatory disease of bronchial epithelium and submucosa. Like in other atopic diseases, inflammatory response is modified by T helper 2 cell mediated cytokines. Many of these cytokine genes (IL3, IL4, IL5, IL13, IL9, and GM-CSF) are clustered on chromosome 5q31-q33 together with multiple other immune response genes. All cytokines in the cluster are haematopoetic growth factors, IL5 specific for eosinophils. IL4 induces the proliferation of T cells and their further differentiation to T helper 2 cells. It is also essential for the induction of immunoglobulin E synthesis. Soluble IgE molecule is an important inducer of activation of several cell types through its high and low affinity receptor in allergic inflammation. The former receptor is expressed mainly by eosinophils and mast cells which cause epithelial damage, bronchus constriction, and oedema in asthma. The low affinity receptor is expressed by multiple immunologically active cells, including B lymphocytes. Sib-pair analysis in Amish families has demonstrated linkage between 5q31.1 and genetic control of serum IgE concentration. Among Dutch families ascertained through a parent with asthma, evidence for linkage of the IgE phenotype to 5q was also obtained by both sib-pair and lod score analyses. Thus, a large genomic region in chromosome 5 has been implicated in the control of IgE levels and bronchial hyperreactivity and may harbor genes predisposing to asthma. In complex traits, however, it is important to verify the results of linkage in independent populations by using additional methods. Family-based association studies especially in genetically homogeneous populations such as the Finns, should offer further advantages to refine the gene region involved. We analyzed 16 polymorphic markers from the gene region 5q31-q33 in 157 nuclear families ascertained through at least one proband with self-reported asthma. Ninety percent of the grandparents of the study families originated from eastern central part of Finland representing a genetically isolated population founded some 500 years ago by a relatively small number of settlers. Based on hospital documentation, two specialists in pulmonary medicine verified in each patient the criteria for asthma based on the recommendations of American Thoracic Society. Serum total IgE was determined by solid phase immunoassay. The physical map of the 5q31-q33 region was first refined and the marker set covered all the markers used in previous studies. Haselman-Elston analysis found no linkage between IgE levels and 5q31-q33 markers in 56 sib pairs and 52 cousin pairs, and statistically significant haplotype associations were found in 5q between neither serum IgE level nor asthma. The difference in reported results might be due to different genetic determinants in different populations or different gene-environment interactions.

026

ARE TWIN STUDIES STILL USEFUL FOR STUDYING THE ETIOLOGY OF ASTHMA

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The risk of developing asthma is determined by the joint action of genes and environment. Environmental factors that have been associated with increased risk include indoor and outdoor allergens, air pollutants and some viral infections. Quantitative variation in IgE is considered to be of importance in the determination of risk of astma, while other major risk factors may still be unknown.. Before engaging in the study of the genetic architecture of asthma, ie. to determine which genes are involved, their polymorphisms and the average effects associated with these alleles, it is useful to estimate the contribution of genetic and environmental factors in the etiology of asthma. The heritability of trait is a major determinant of the sample size necessary to detect individual disease loci. Also, the proper identification of the base population is a necessary prerequisite for drawing valid inferences.

The Finnish Twin Cohort (FTC) has been established in two stages, in 1974 and in 1987, to include >40,000 twin pairs. A population-based twin cohort permits independent ascertainment of twinship and disease status and allows comparison of incidence rates in twins of different types. This, in turn, enables more accurate estimates of the role of genetic influences on liability to disease. Large numbers are required to permit identification of sufficient and representative numbers of

exposure-discordant MZ pairs: Studies on the mortality of astma-discordant pairs indicate that the increased mortality associated with asthma appears to be independent of genetic factors. Thirdly, a large cohort permits assessment of age, gender and social environmental effects with statistical robustness; Data from the FTC show that heritability of liability to astma decreases with age being high in adolescents (see below) and less in middle-aged adults (Nieminen MM, Kaprio J, Koskenvuo M. A population-based study of bronchial asthma in adult twin pairs. Chest 1991;100:70-75.). Finally, information on the biological relatives of twins can be obtained, so that families-of-twins become the sampling units and the resolution of genetic and cultural transmission can be improved.

For example, Finnish twins, their siblings and parents from five consecutive birth cohorts (1975-1979) form the FinnTwin16 study sample. The twins are ascertained from the national population registry, which identifies nearly 100% of all living twins. Baseline questionnaires are mailed to the twins within 60 days of their 16th birthday; pairwise response rates ~ 85% across gender and zygosity, and 3 years of data-collection targeted 1858 families. Parents were sent their own questionnaires and also asked about health and development of the twins during childhood. A history of asthma and hayfever were asked of the twins and of their parents. Univariate analysis of the twin data indicated that over 60% of the variance in the liability to asthma could be attributed to genetic factors. Parental asthma increased the risk of asthma in the twins, but parental hayfever alone did not increase the risk of asthma in their children. Support: U.S.-PHS/AA-8315 & Academy of Finland.

027

GENETIC STUDIES IN AN ISOLATED POPULATION

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The study of genetic determinants in multifactorial diseases, such as atopy and asthma, is complicated by phenocopies, incomplete penetrance, variable expression, and locus and allelic heterogeneity, among other factors. To avoid problems caused by such heterogeneity, we are studying asthma in a genetically homogeneous population as a model for multifactorial diseases in general. Even though continuous population existed in Finland for thousands of years, vast regions in the east were settled only within the last 500 years. Migration created isolated, small but expanding breeding units that allowed for genetic drift to affect the frequencies of rare genes. Due to the short population history, original founding haplotypes have not been obscured by numerous successive recombinations, but linkage disequilibrium is commonly seen around rare founding genes in, e.g., monogenic diseases. Such observations have recently facilitated the positional cloning of genes for an inherited form of epilepsy and congenital chloride diarrhea. As reported in detail by T. Laitinen in this meeting, we used affected relative pair analysis and a family-based association strategy to study the chromosomal region 5q31-q33, previously implicated in the regulation of IgE and bronchial hyperreactivity. No linkage of serum IgE levels to 16 physically ordered genetic markers in 5q31-q33 was detected by the study of altogether 108 sib or cousin pairs, and no significant haplotype associations with high or low IgE levels or the asthma phenotype were detected in 157 nuclear families originating from a small geographical area. These results suggest that other genetic factors remain unidentified that affect IgE levels and transmit susceptibility to bronchial hyperresponsitivity in this subpopulation.

028

FUTURE IMPLICATIONS OF CURRENT ADVANCES IN THE GENETICS OF ASTHMA

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It has long been known that asthma runs in families but the genetic basis of this has, until recently, eluded definition. Debates over whether asthma is inherited as a recessive or dominant trait have long since passed with the recognition of the disease having a polygenic basis which accounts for up to 60% of the asthma phenotype. A single gene such as the polymorphism of the $Fc_{\epsilon}RI$-β chain, as proposed by the Oxford group, while seemingly attractive, has proven difficult to reproduce in different family studies. The IL-4 gene cluster comprising IL-4, -13, -5, -9 and GM-CSF encoded on the long arm of chromosome 5 ($5q_{31-33}$) may be considered in regulating IgE, mast cell, basophil and eosinophil responses. Four independent studies and one by our own group have shown either linkage or allelic association between polymorphic markers located in this region of the human genome and the occurrence of allergy and asthma. Other candidate loci for which some evidence for linkage has been found include the α chain of the T cell receptor (CD3), TNFα and the IL-5 receptor. Using anonymous markers in a random human genome search, at least ten "hot spots" have been located. With the recognition that early life events including nutrition, allergen and air pollutant exposure predispose to the later development of asthma and allied disorders provides an opportunity for using genetics to identify those who are at greatest risk of developing atopic disease and in whom early environmental and pharmacological primary prevention might be targeted. The next decade is likely to witness enormous advances in genetic and environmental influences on asthma towards the unified goal of prevention. To achieve this effectively co-operation and collaboration between those interested in genetics and those who believe that environmental factors take primacy in determining disease phenotype.

029

PRICK TESTS WITH FOOD ALLERGENS

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Both ordinary skin prick test (SPT) and its modifications like prick-prick test, scratch test and scratch patch test can be used to detect immediate allergy to foods. There is no age limit for prick testing. In fact, the younger the patient is, the more reliable the results are. In children under one year of age, a positive prick test usually means clinical food allergy. In most older children and adults, a positive test result is valid only for skin sensitivity, not for allergy to ingested foods. Commercial food allergens are reliable in detecting allergy to stable food proteins like milk, egg, fish and soy. SPT is the golden standard for testing them. The allergens in fruits and vegetables are so unstable that they should preferably be tested as such. The prick-prick method is the method of choice for them. The fruit or vegetable is pierced first with a prick test lancet and the skin immediately after that. Scratch test can also be used for testing fruits and vegetables, and also dry allergens, such as flours and powdered spices. In scratch patch test, the scratch is covered with an epicutaneous test chamber or just by a piece of tape for 15 - 20 minutes. It is somewhat more sensitive than scratch test but it is needed very seldom. In small children, the back skin is the most practical skin area for prick testing. In older children and adults, the volar aspects of the lower arms are used in most instances. The significance of positive prick tests should always be confirmed by peroral challenge tests.

030

PATCH TESTING WITH FOOD ALLERGENS

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Dermatologists use epicutaneous patch testing with chemicals (e.g. nickel) to diagnose allergic contact dermatitis. Recently, several investigators have performed patch testing with protein allergens in atopic dermatitis (AD). It is clinically well known that some patients with AD experience exacerbation of their skin lesions after contact with aeroallergens such as house dust mite and pollens. Aeroallergen patch tests have yielded positive results in 10%-40% of adult AD patients (1,2). Patch tests with food allergens have been studied in children with AD. The allergens are applied for 48 hours in aluminium chambers (Epitest Ltd, Tuusula, Finland) on clinically uninvolved skin. The test is read at 48 and 72 hours and grading is similar to the conventional contact allergy patch testing. Clear-cut positive reactions show erythema with oedema or eczema. Cow's milk powder, casein, β-lactoglobulin, cereal flours, eggwhite powder, etc. suspended in saline can be used as allergens and microcellulose as negative control. Positive patch tests to cow's milk have been found in 30%-60% of AD infants with cow's milk allergy (3,4). Interestingly, the highest frequency of positive patch tests (89%) has been found in those children who experience delayed symptoms after cow's milk challenge. Moreover, several of the patch test positive, cow's milk allergic children were negative in prick tests and/or RAST. Although false positive patch test results can occur, a parallel prick and patch testing with cow's milk had a diagnostic sensitivity of 0.78 in infants with acute-onset and 0.92 in the delayed-onset cow's milk allergic symptoms (4). Cereal allergic AD children can also show positive patch tests although the type I tests (prick, RAST) are negative (5). These results suggest that patch tests can significantly enhance the diagnostic accuracy of food allergy in children with AD. At present, the value of food allergen patch testing in adults has not been evaluated in larger studies. Much research is also needed to standardize the allergens and vehicles used in the "atopy patch testing", and to elucidate the pathomechanism of patch test reactions to foods and aeroallergens.

References

1. Reitamo S, Visa K, Kähönen K, Käyhkö K, Stubb S, Salo OP. Eczematous reactions in atopic patients caused by epicutaneous testing with inhalant allergens. Br J Dermatol 1098;114:303-9.
2. Darsow U, Vieluf D, Ring J. Atopy patch test with different vehicles and allergen concentrations: an approach to standardization. J Allergy Clin Immunol 1995;95:677-84.
3. Räsänen L, Lehto M, Reunala T. Diagnostic value of skin and laboratory tests in cow's milk allergy/intolerance. Clin Exp Allergy 1992;22:385-390.
4. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. J Allergy Clin Immunol 1996;97:9-15.
5. Räsänen L, Lehto M, Turjanmaa K, Savolainen J, Reunala T. Allergy to ingested cereals in atopic children. Allergy 1994;49:871-876.

031

CONTACT ALLERGY TO CHEMICALS IN ADOLESCENTS

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When contact dermatitis is suspected in children and adolescents, the clinical picture rarely helps in the differentiation between allergic and irritant contact dermatitis. The patient must be subjected to the relevant test procedure: epicutaneous testing with the standard series supplemented with relevant allergens selected from the exposure history. The same patch test materials and patch test concentrations are used in children and adults. The test reactions should be evaluated in relation to the clinical pattern and known exposures.
Through the last decade most publications document the prevalence of contact allergy in children and adolescents mostly based on retrospective investigations comprising selected eczema patients. Few are based on prospective studies in unselected populations of children.
The contact allergens affecting children are the same as in adults. The most frequently occurring allergens are nickel, cobalt, rubber chemicals - from shoe eczema - preservatives and perfumes present in skin care products, topical drugs and other consumer products in contact with the skin

032

DIRECT AND INDIRECT COSTS FOR ALLERGIC DISEASES IN SWEDEN

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The Swedish Institute for Health Economics has estimated the costs for allergic diseases in Sweden 1983–1993 at the request of the National Institute of Public Health. Other Swedish cost-of-illnes studies have recently been made regarding asthma. The direct costs include outpatient care, hospital care and drugs whereas indirect costs refer to sick listing, premature retirement and mortality and other related costs. The number of drug prescriptions has increased by 33 percent but the costs for these drugs have increased by 77 percent. The number of outpatient visits for allergy has increased by 20 percent whereas costs for outpatient care have more than doubled over a ten year period. The need for hospital care for asthma has diminished over 30 percent from 1980 to 1991 and the costs for hospital care by 35 percent in fixed price values during this period. The economic burden of the allergic diseases to the society is substantial but the estimates seem to be extremely difficult and uncertain. However, changes in medical therapy and intervention policy seem to have a great inpact on the costs and the outcome both for the individual and for the society.

033

A SYSTEMATIC PERSPECTIVE ON ASTHMA PATIENT CARE

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A total system perspective on asthma patient care reveals that significant improvement potential may exist. Focusing on the patient with the disease as the relevant unit of management suggests that better outcomes could be achieved, measured by clinical results, cost and patient satisfaction.

In many countries expenditures for medical care services continue to rise. During the recent recession years in many countries, health care budgets have come under heavy pressure, but traditional cost-containment measures focused largely on separate cost components have not been very successful. A more fundamental change in how patient care is set up is required. For allergic diseases, e.g., asthma, this is highly relevant.

Studies that take a total system perspective on a disease, i.e., that include both direct and indirect costs, patient outcomes, and patient satisfaction throughout the entire disease period, often provide many new perspectives and valuable insights into how one can affect the patient care outcome. There are very few studies where the total system effects in the community of asthmatic patients have been studied.

When optimal use of resources is badly needed in health care, setting strict priorities becomes necessary. A systematic analysis of the use of resources in the health care system, insurance-based or private, including costs of pharmacological treatment and magnitude of sick leaves etc., is a required platform for discussion of possible changes of the distribution of and coordination between preventive, secondary, and tertiary activities within the health care system. A small pilot study of this kind described the chain of care in a limited number of asthmatic children, i.e., mapped the disease in a small sample of patients. The results will be presented at the congress.

To study the patient care and cost drivers for asthma, several parameters have to be present or developed, such as information from patients records, record knowledge of the disease, assessment of severity and segmentation of patients, mapping of care chains (episodes of care), and direct and indirect costs. This type of study also gives information about the more exact and true costs for patients with different severity of asthma. It allows for studying the quality and effectiveness of care and comparison of treatment costs, indirect costs, and direct costs of different levels of care.

Several broadly applicable findings emerged from the pilot study. An extension of computerized patient records combined with information about transactions will make it possible to evaluate the efficiency and quality of available health care strategies. It will also allow for comparison of the cost-effectiveness of different forms of therapy.

From the pilot study it could be concluded that in these four cases our current health care system does not allow for an effective follow-up of medical problems and economical results. Despite the small sample, the study highlighted the likelihood of achieving significant cost savings, improving quality, and enhancing patient satisfaction by taking a total system approach to patients with asthma.

Improving health care is an objective that people around the world are struggling with, from politicians to government officials at all levels to hospital administrators, private as well as public, to individual physicians and nurses. With the simultaneous demand to reduce costs, it is a struggle that is both hard and often unsuccessful in the medium or long term.

In times when many cost-saving programs in health care are producing unpleasant side effects in terms of lower quality and lower patient satisfaction, it is enlightening to see the improvement potential shown with a system perspective on asthma care.

034

COST-EFFECTIVE ASTHMA TREATMENT IN FINLAND

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Cost-effective (CE) analysis for different treatment strategies has become more important because of limited social resources for health care. Critical evaluation of treatment strategies as a whole is important and makes possible to select those programmes which are effective also economically.

In CE analysis the costs of treatment are related to some types of clinical effectiveness measures. To find out which is the least costly way to achieve a certain goal, the goal has to be specified (1). Is the goal of treatment to improve outcomes, prevent progression of asthma, reduce exacerbations or reduce duration of asthma? Most frequently used measures are need of health services, lungfunctions, quality or life years gained or symptomless days. It should be noticed that the situation of mild asthmatics is different from that of moderate or severe cases. Amount of emergency visits, hospital admissions, improvement in lungfunctions, sickness days etc tell more about the effectiveness of therapy of moderate or severe asthmatics than that of mild ones. On the other hand the functions of mild asthmatics are often so good from the beginning that it is difficult to show any significant improvement in the intervention sudies The costs of asthma include both medical and nonmedical resources as well as indirect economic losses and the psychosocial impact.

Some figures of asthma in Finland

In 1991 prevalence of asthma was about three times greater than ten years earlier. In 1995 according to a Social Insurance Institution's interview study 3.8% of men and 4.7% of women stated asthma to be their longterm disease.

Total costs of asthma were in the beginning of 1994 about 25 milliard, of which about 37 million FIM for sickness leaves. In the end of 1994 asthma was the third most common chronic disease after hypertonia and coronary heart disease.

In 1994 approximately 4.7% of population, that is about 240 000 patients, received reimbursment for prescriptions of anti-asthma drugs in Finland.

In Finland asthma mortality has long remained around 100/year, but after 1992 it decreased to a 60–70 level although the prevalence has increased (2).

Effective early treatment

It is supposed that it is CE if asthma is diagnosed after the very first symptoms, and effective treatment is then started. Actually we don't know the proportion of patients who will develop more severe asthma if untreated or undertreated (3). Selroos has pointed out that the longer astmasymptoms lasted before effective treatment was started the worse were the lungfunctions after 3 years follow-up (4).

International studies have shown that care of asthmatics by specialist reduced the use of medical healthcare (5, 6). There are no such studies from Finland. In our country lungspecialists have until now had main responsability for studies and treatment of asthma patients in lungclinics. It is very important

to do longterm follow-up studies of the CEness of different treatment graduation.
From the economical standpoint inhaled anti-inflammatory medication appears to improve resource use effiency (7).
The Boston group calculated the costs of asthma in Finland according to different categories of asthma. Costs of severe asthma patients are about 50 000 FIM/patient and for mild asthmatics they are 4000 FIM per year. The social, nonmedical cost are least 40% of total costs.
If we compare to earlier amount of pensions and sickness leaves in Finland and the situation now, one can suppose that the treatment with anti-inflammatory medication has been CE. Already now the amount of sickness leaves has decreased by 30 000 from 1990 to 1994 and that is in spite of increased prevalenve (2).

Patient education and self-management
Neither effective drugs nor early started treatment will help if the patient is not willing to use medication. Asthma patient education and self management programme are shown to be CE in many studies after 6-12 months follow-up (2, 8, 9). In the sudy of Trauner et al. the follow-up time was three years and the result was the same (10). Generally the use of emergency services and the need for hospital treatments have decreased. Educational interventions appear to be effective in improving patient self-management and alherence to medication. Muhlhauser suggests that a teaching programme and regular asthma treatment are associated with reduction in morbidity in moderate to severe asthma patients (11). Asthma is a chronic condition and therefore long-term effectiveness of intervention is important.

Self-management education for new asthmatics
In my study the CEness of intensive education for self-management for few asthma patients was calculated. There were 76 new asthmatics in the intervention group available for analysis after 3 years, mean age 39.4 year, 23 men. They were randomly selected from 160 new asthma patients. All costs for intervention were calculated, also the use of extra health services, sickness days and extra medications. The figures after 3 years follow-up will be presented at the congress. For the analysis of compliance the number of used drugs will be calculated as divided daily doses (DDD)/ patient for the presentation. The number of extra courses of drugs, corticosteroid and antibiotics were 15 in the intervention group and 45 in the control group. On the other hand the number of sickness days are 30 in the intervention group and 71 days in the control group.
After one year the education was not CE when calculated with the quality of life index. Costs for one improved qol index were 708 FIM in the intervention group and 613 FIM in the control group. But when lungfunctions are used as a measure, intensive education seems to be CE. The cost per improved forced expiratory volyme in one second (FEV1) are 310 FIM in the intervention group and 805 FIM in the control group. Between the groups the differences in the changes of lungfunctions after one year's treatment were significant in FEV1 ($p< 0.01$) and nealy significant in Forced vital capacity (FVC), Forced expiratory volyme per cent (FEV%) and Peak expiratory flow (PEF) $p< 0.05$ tested by t-test. When the CEness is calculated with quality of life index there was not any difference between the groups although all the extra costs for intervention were included in the calculation for the first treatment year. The follow-up will be interesting, to see can the advantage gained during the education be reserved over a numer of years. CE treatment is a whole starting from early diagnosis, effective treatment, patient education, self-management, and good patient compliance. Treatment can be effective if all these parts function correctly.

References
1. Jönsson B. A health economist's view. Eur Resp Rev 1995;5:30:271-4.
2. Ministry of Social Affairs and Health. Report of a Working Group: Asthma Programme in Finland 1994-2004. Clin Exp Allergy 1996;26 (suppl 1).
3. Bousquet J. A physician's view of health economics in asthma. Eur Resp Rev 1995;5:30:275-8.
4. Selroos O, Pietinalho A, Löfroos AB, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. Chest 1995;108:1228-34.
5. Zieger R, Heller S, Mellon M et al. Facilitated referral to asthma specialist reduced in asthma emergency room visits. J Allergy Clin Immunol 1991;87:1160-5.
6. Myon O, Richman J, Harris H. Results of programm to reduce admission for adult asthma. Ann Intern Med 199o;112:864-71.
7. Rutten-van Molken MPMH, van Doorslaer EKA, Jansen MCC, Kertjens HAM, Rutten FFH. Cost and effects of inhaled costicosteroid and bronchodilators in asthma and chronic obstructive pulmonary disease. Journal of reapiratory and critical care medicine. 1995;151:975-82.
8. Söndergaard B, Davidsen F, Kirkeby B, Rasmussen M, Hey H. The economics of an intensive education programme fos asthmatic patients, a prospective controlled trial Pharmacoeconomics. 1992;1(3):207-12.
9. Bolton MB, Tilley BC, Kuder J, Reeves T, Schultz LR. The cost and effectiveness of an education programme for adults who have asthma. J Gen Intern Med 1991 (6):401-7.
10. Trautner C, Richter B, Berger M. Cost-effectiveness of structured treatment and teaching programme on asthma. Eur Respir J 1993;6:1485-91.
11. Muhlhauser I, Richter B, Kraut D, Weske H, Worth H et al. Evaluation of a structured treatment and teaching programme on asthma. J Intern Med 1991;230:157.

035

COST-BENEFIT OF PATIENT EDUCATION

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Good health can't be measured in terms of money, but bad health can indeed. The purpose of the study was to determine if patient education of asthmatics besides improving the condition of the patient, also results in economic savings, and if so, to what extent. Chronic illnesses, i.e. asthma, generate heavy expenses of various types for both patients and society. It is of high priority to find possibilities to reduce these costs. The results from six different studies from Sweden (4), USA (1) and Finland (1) will be presented. They represent different models of patient education, most of them connected with out-patient care. The number of emergency visits, days of hospital care, days off work, number of physician visits and medication (antibiotics) costs have been compared before and after the patient education started. The costs have then been calculated for these various consequences. The results shows that substantial economic savings are possible with relatively small and cheep inputs. The conclusion is that a well organized patient education for asthmatics results in both improved health and economic savings for both patients and society.

036

AEROSOL OF MAGNESIUM SULPHATE IN TREATMENT OF ASTHMATIC PATIENTS

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The purpose of this study was to assess the antiasthmatic activity of a magnesium sulphate aerosol (solution osmolarity 260 mmol/l, pH 6.6) using a randomised design. Forty-three patients (20 men, 23 women, aged 19-55) with mild and moderate atopic bronchial asthma were divided in two groups. The first group was treated with a inhalation of magnesium sulphate (a single dose contained 2.5 mmol Mg^{+2}) for two weeks. The second group received placebo (isotonic saline aerosol) for the same time. The single dose of magnesium sulphate aerosol had no greater bronchodilator activity than placebo but, significantly decreased bronchial hyper-reactivity to acetylcholine (ACH) and graded physical exercise (GPE). After long-term treatment bronchial conductivity did not significantly differ from its initial mean in both groups of asthmatics. However, the aerosol of magnesium sulphate, unlike placebo, reduced bronchial hyper-reactivity to ACH and GPE. We concluded that magnesium sulphate aerosol can reduce nonspecific bronchial hyper-reactivity and mast cell secretion in atopic asthmatics.

037

ONSET OF ACTION AND DOSE RESPONSE WITH INHALED BUDESONIDE

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Two hundred and sixty-seven patients with mild-moderate asthma (mean age 50 years; mean morning PEF 294 L/min) and not using anti-inflammatory medication participated in a double-blind, randomized, placebo-controlled parallel group study consisting of a 2-week run-in and a 6-week treatment period. They received Pulmicort Turbuhaler 100 µg, 200 µg, 400 µg or placebo Turbuhaler twice daily. Already after treatment for 1 week morning PEF had increased significantly in all Pulmicort groups; 23, 22 and 27 L/min ($p=0.037$, 0.020 and 0.004 compared with the 5 L/min increase in the placebo group). During week 6 the mean increases were 15, 45, 53 and 71 L/min in the placebo group and the 100 µg, 200 µg and 400 µg b.i.d. Pulmicort groups, respectively. All Pulmicort doses were significantly superior to placebo ($p=0.042$, 0.004 and 0.000, respectively). A statistically significant dose response was found; Jonckheere test, $p<0.0001$). Dose response relationships were also found for e.g. evening PEF, time to response, symptom scores, daily activity scores and sleep scores.
Conclusion: A rapid onset of action and a clinically relevant dose response were documented for Pulmicort Turbuhaler.

038

EVIDENCE THAT TREATMENT WITH HIGH-DOSE INHALED CORTICOSTEROIDS IS MORE EFFECTIVE THAN LOW-DOSE WHEN STARTING ANTI-INFLAMMATORY MEDICATION IN ASTHMA

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We have previously shown that the increase in PEF (and FEV_1) when starting treatment with an inhaled corticosteroid for the first time is negatively correlated with the duration of asthma symptoms (Chest 1995;108:1228-34). In that study 88 patients started medication with Pulmicort Turbuhaler 400 µg b.i.d., corresponding clinically to appr. 1600 µg/day Pulmicort pMDI. The increases in FEV_1 have now been compared with those of patients starting treatment with 400 µg/day pMDI (Pulmicort or Becotide). Results of mean FEV_1 in % of predicted values:

	400 µg/day pMDI		800 µg/day Turbuhaler	
Duration	<2 years	>2 years	<2 years	>2 years
No of pat	18	35	57	31
FEV_1 % pred				
Baseline	67	60	71	62
1 month	70 (b)	63	84 (a)	65
3 months	74 (b)	62 (b)	83 (a)	71 (a)
1 year	79 (a)	64 (b)	85 (a)	73 (a)

a=sign comp with baseline, b=sign comp with high dose.
Conclusion: high dose compared with low dose resulted in faster incease in FEV_1 (all patients) and in greater increase in FEV_1 in patients with a duration of asthma >2 years.

039

TILADE™ (T) INFLUENCE ON IMMUNE STATUS IN PATIENTS WITH BRONCHIL ASTHMA

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Clinicoimmunologic examination of 30 patients aged between 20 - 50 with moderate to severe bronchial asthma (BA) was undertaken. All the patients received T. by 2 inhalations 4 times a day for 18 days. Before treatment in patients with BA a decrease of relative and absolute CD_3+, CD_4+ and CD_8+ - limphocites, phagocytosis suppressions, heterogenous alterations of serum immunoglobulines and high circulating immune complexes (CIC) levels were reported. The content of CD_{22} - limphocytes did not changed truly. After T. treatment CD_8+ - limphocytes increase dueto suppressible link, CD_4+/CD_8+ ratio normalization decline of CIC content and phagocytic activation with expressed clinical improvement of patients condition were observed. BAL investigation has shown both neutrophile and limphocyte increase and alveolar macrophage decrease. Thus, antiasthmatic membrane stabilised effect of T. is associated with it's corrective influense on immune status.

040

PROTECTIVE EFFECT OF INTAL / SODIUM CROMOGLYCATE / ON PAF - INDUCED REACTION IN PATIENTS WITH ATOPIC ASTHMA

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Efficiency of Intal for suppression of PAF - induced reactions were investigated in atopic asthma. The influence of daily Intal inhalations during 4 weeks on platelet aggregation, the amount of cAMP in them before and after therapy, changes in platelet functions after 15 minutes incubation with Intal in vitro were investigated. In patients with high level of platelet aggregation activity the improvement of clinical symptoms and correction of platelet hyperactivity were observed simultaneously during the course of Intal therapy. Maximum amplitude of ADP-aggregation / Born determined / in patients with atopy was 68,8± 3,6% before treatment / in healthy persons - 47,3±4,5% /. After Intal treatment the maximum amplitude of ADP-aggregation in asthmatics did not differ from healthy people / 46,2 ± 3,8% /. Basic levels of cAMP in atopic asthmatics platelets were 13,11± 1,71 before and 13,41± 1,94 after treatment respectively and did not differ from normal. The research is based on the conception that Intal has ability to interfere directly in regulation of functional activity of platelets. Due to this point of application Intal becomes especially effective in patients with increased functional activity of platelets.

041

DECREASE OF EXHALED NITRIC OXIDE LEVELS BY INHALED CORTICOSTEROIDS IN ASTHMA

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The purpose of the study was to evaluate the change of exhaled NO (NO_{EXH}) during treatment with inhaled corticosteroids. The study group consists of nine patients with asthmatic symptoms (cough/wheezing) and significant diurnal variation of PEF and/or reversible bronchial obstruction. NO_{EXH} was measured by chemiluminescence method before and after 6 - 8 weeks therapy (budesonide, fluticasone). The results were expressed as peak values of NO during a standardized exhalation. 5 patients had peak levels > 60 ppb (mean 96, SEM ± 13, range 66 - 126) and 4 patients < 40 ppb (25, ± 6, 15-35). The difference was very significant (p = 0.0015). Peak NO_{EXH} decreased in the former group 62 ppb (SEM ± 14) and in the latter group 7 ppb (SEM ± 4). The means of peak NO_{EXH} after treatment were 34 (±7) and 18 (±2).The difference was not significant. The two patients with lowest basal levels and smallest change during treatment were the oldest subjects of the study (57 and 71 years). These results support the view that NO_{EXH} is a promising new lung function test in evaluation of effects of inhaled corticosteroids especially in younger asthmatics.

042

LOW DOSE OF SALBUTAMOL INHALED VIA TURBUHALER® PREVENTS EXERCISE-INDUCED ASTHMA IN CHILDREN

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We have investigated protection against exercise-induced asthma (EIA) in children using single doses of salbutamol administered via Turbuhaler® versus placebo.
Twenty-four children with EIA, mean age 9.6 years (range 4-14), FEV_1 85% (range 62-114) of predicted normal, were included in a randomized, double-blind, placebo-controlled, cross-over study at three centres. Single doses of salbutamol via Turbuhaler (50 and 100 µg) or placebo were given 20 minutes before exercise challenge. Inhalation technique was standardized and each inhalation was supervised. Standardized exercise challenge was performed using a bicycle ergometer. Spirometry was performed before and after the challenge.
Fall in EIA (%) based on FEV_1 just before challenge and the lowest FEV_1 value after completed challenge was 2.1, 3.1 and 11.5 % for salbutamol 50 µg, 100 µg and placebo, respectively. Active treatments had significantly lower fall than placebo (p=0.01 and p=0.02 respectively) and did not differ significantly.

043

SYSTEMIC EFFECTS OF A SHORT COURSE OF BETAMETHASONE COMPARED TO HIGH DOSE INHALED BUDESONIDE

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Forty children aged 1-3 years completed a study of the effects of a short course of inhaled budesonide (BUD) for asthma caused by upper respiratory tract infection. The study was double-blind and placebo-controlled. The effects on symtoms were significantly better in the active group which has been reported elsewhere*.
In 20 of the children systemic effects were evaluated by measurement of morning cortisol in serum, cortisol in night urine and the bone markers osteocalcin, ICTP and PIIINP in serum before and on the last day (day 7-10) of treatment (1600 µg/day for the first 3 days and 800 µg/day for up to 7 more days). In 9 of the children the same measurements were also done before and after a 3 day course of betamethasone (BM) (6, 4 and 2 mg on the resp. days) for asthma exacerbation and 14 days after this treatment. There were no signs of systemic effects after 7-10 days of BUD. Nor was there any difference between the 10 children who received active or the 10 with placebo treatment. After 3 days of BM, serum cortisol decreased from median 263 to 26 nmol/L, urine cortisol from 19.9 to 7.2 nmol/L and osteocalcin from 31.4 to 5.5 µg/L, ICTP from 19.4 to 8.5 and PIIINP from 12.3 to 5.9 µg/L. Ten days later the levels were back to normal.
Conclusion: Short courses of oral betamethasone have pronounced systemic effects while 10 days of high doses of BUD in these young children have little systemic effects. When possible inhaled BUD is preferable to oral steroids in children with periodic asthma.

*Ref. Svedmyr J et al. Europ Resp J 1994;7:24A

044

AIRWAY RESISTANCE IN NON-BPD AND BUDESONIDE TREATED BPD INFANTS BORN VERY PRETERM

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Specific effective airway resistance (sReff) and thoracic gas volume (TGV) were measured with total bodypletysmography (Baby Body, Jaeger®, Germany) at corrected age of 3-4 months in 17 infants born very preterm . Six infants had bronchopulmonary dysplasia (BPD) defined as oxygen dependency at 36 weeks postconseptional age, and were treated with continuous inhaled budesonide (A). Eleven non-BPD infants with similar birth weight (BW) and gestational age (GA) were included (B): mean BW 1055 g / GA 28.3 weeks (A) and 1145 g / 28.4 weeks (B). The median duration of ventilator/ oxygen treatment were significantly longer in BPD than in non-BPD group: 30/144 vs 1/18 days. At baseline, sReff and TGV means were similar and within normal range given by Jaeger in both groups: 0.38 kPa/l/s and 39 ml/kg (A) and 0.4 kPa/l/s and 32.1 ml/kg (B). After salbutamol no significant changes in Reff and TGV were noted. Generally, BPD is characterized by airway obstruction. Our finding of normal lung function values in moderate or severe BPD and non-BPD infants may reflect effectiveness of steroid inhalation therapy.

045

MOUDLS, MICROBIOLOGICAL GROWTH AND WATER DAMAGE

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Dampness or moisture that causes permanent or regular moistening of materials leads to the growth of molds and bacteria. These environmental strains may grow on any moist material. In buildings, this microbial growth leads to exposure to various emissions via the indoor air. The emissions include spores and other particles; volatile, irrative metabolites and mycotoxins. All these types of indoor air pollutants include numerous components in low concentrations. However, the epidemiological association between damp and moldy housing and repiratory health effects has been shown in many studies. The causative relationship between the components of exposure and the health effects still remain obscure.

With careful microbiological characterization of the building, certain characteristics of the exposure can be defined. The airbone concentrations are slightly higher in buildings with a mould problem than in normal buildings. Even more important seems to be the qualitative aspect of the microbiological exposure. A list of microorganisms indicating a mould problem has been produced at an expert workshop. Their mere presence indicates that there is moist material available. The list can be used in exposure assessment both in environmental sampling and in screening specific IgG levels of patients. Due to the complex nature of the exposure, observations of dampness and moisture have been used as a proxy of the indoor mold problem and subsequent exposure to microbial emission. We have used this method for both research purpose and practical applications, as a first screening tool for moisture and mold problems.

In the borealic climate of Scandinavia where the heating season is long, up to eight months the relative humidity of indoor air low for most of the year and the buildings well insulated, moisture and dampness problems can be avoided with careful building and maintenance practices. This is not always the case, and moisture problems occur in the constructions due to leakages, condensation or insufficient ventilation. Moisture problems of buildings and subsequent mold growth have been observed in both private houses and public buildings. Increased awareness of the possible health risks of building-associated mold have raised a lot of public concern in Finland, and it has been necessary to assess the magnitude of the problem and its importance to the public health and national economy. As the first phase, the prevalence and types of moisture problems in private houses were studied.

A random sample of 450 houses was taken from the building registers on five cities. The sample included houses that were erected in the 1950ies, 1960ies, 1970ies and 1980ies. These houses were carefully walked through and inspected for signs of water leaks or condensation by a building engineer, specifically trained for this purpose. The signs of moisture recorded were: most spots on walls or other surfaces, visible mold, signs of water leaks, change of color of wooden floors, detached surface materials, e.g., plastic floor coverings, ceramics tiles or paint. A check-list was used to standardize the procedure, and surface moisture recorders were used to verify the visual observations of moisture. The tenants were interviewed for the their moisture observations and the history of the house using a questionnaire.

In 80% of the houses studied, signs of present or prevoius moisture problem could be observed. However, in only half of the cases, the tenants were aware of those problems. Part of the defects were caused by flaws in design or construction, and part were due to natural aging of materials. Some defects had been repaired, but the signs were still visible. The inspectors also assessed whether there was need for repair or opening the structures for more thorough inspection: 55% of the houses went into this category which means that there are 500 000 houses in need for moisture repair. These results show that in most cases, some kind of a moisture problem will occur during the life-span of the house, and that attention should be paid upon both building practices and maintenance of the house.

Certain types of moisture damage were characteristic to certain constructions or period of building practice. In the houses built in the 1950ies, moisture problems in the roofs and in the basement rooms were common. The roof leakages had only caused minor damages and the open attics had allowed their proper repair. In most of the cases of the basement damage, the original basement was built for potato and vegetble storage purposes, and the necessary high relative humidity was obtained from the soil in the uninsulated space. Later, as the need for this type of storage had decreased, these spaces had been panelled and decorated to serve as TV rooms or other living rooms, but without adding a proper moisture insulation and drainage outside.

In the houses from the 1960ies, moisture damage was equally often observed in roofs, basements, walls and plumbing systems. Most types of damage could be explained by material aging. The flat roofs common in the 1970ies dominated the moisture problems in the houses from this period. Flat roof became popular for energy-saving reasons. However, these results show that it is not a favorable construction in the Northern climate.

Even in the newest houses, built in the 1980ies, had frequent moisture problems. Typical to these houses were moist walls in the bathrooms, due to insufficient moisture barriet under the ceramic tile finishing. The results of this study showed that moisture problems are common in our housing stock. Moisture is harmful for the building itself, and subsequent mold growth may lead to health consequences. This emphasizes the importance of prevention and control of moisture problems. The results of this study are used in developing strategies for building maintenance and control of moisture problems in the future.
A health survey made parallel with this study will be reported separately.

046

BARRIER FUNCTIONS AND HYPERRESPONSIVENESS IN AIRWAY INFLAMMATION

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Allergic rhinitis and common cold are airway diseases characterized by mucosal processes of inflammation. Nasal challenge and lavage techniques have successfully been employed to study these processes. The nasal pool-device is one challenge and lavage technique that compared with others may have certain advantages: Hence, the technique allows concomitant challenge and lavage of a large and defined mucosal surface area for a selected period of time. Furthermore, the employability of the nasal pool-device makes it suitable for challenge and lavage in children. Important characteristics, including microvascular and cellular indices, of the nasal mucosa in health and disease may be well examined using the nasal pool-device and other challenge and lavage techniques. The microvascular and epithelial exudation of bulk plasma (mucosa exudation) is of key interest in airway inflammation. Proinflammatory factors e.g., histamine, leukotrienes, bradykinins, and select cytokines including TNFα, produce extravasation of bulk plasma by action on the endothelial cells of post-capillary venules. Promptly, the extravasated plasma then moves up between the epithelial cells and creates transient separation of the tight junctions between these cells so that ubiquitous paracellular pathways for the clearance of plasma into the airway lumen are redily created. The luminal entry of plasma, although involving movement of large proteins such as α_2-macroglobulin, is non-injurious as it leaves the structure of the epithelium intact. Furthermore, the integrity of the mucosa as an absorption barrier is uncompromised. Indeed, in sustained airway inflammation mucosal exudation may even be associated with a reduced absorption permeability. The physiological, non-injurious mechanisms involved in extravasation and luminal entry of bulk plasma in animal and human airways are the basis for the proposal that mucosal exudation should be considered a major first line defence mechanism of the airway mucosa.
Mucosal exudation of bulk plasma is induced by challenges that activate disease-like inflammtion, e.g. allergens, isocyanates, and common cold viruses. Accordingly, incresed concentrations of plasma proteins in airway mucosal surface liquids have been demonstrated in allergic rhinitis and common cold, as well as in nasal polyposis, asthma, and chronic bronchitis. The bulk plasma exudate has a widespread and intriguing distribution in these disease: The lamina propria, the basement membrane, the airway epithelium and the mucosal suface are thus furnished by potent plasma-derived peptides and proteins. Therefore, the mucosal macromolecular milieu in airway inflammation would be dramatically different from that of the normal mucosa. In addition to its function as a mucosal defence mechanism, the plasma exudate may be a pathogenetic factor in these airway disease: Physical properties of the plasma exudate may e.g., interfere with the normal hydration of the airway and impair mucociliary transport. Furthermore, the plasma peptide and protein systems may sustain airway inflammation. Moreover, in allergic rhinitis and common cold, an exudative hyperresponsiveness may develop: Histamine thus produces greater plasma exudation responses in on-going allergic and infectious rhinitis than in control situations. This increased proclivity of the airway subepithelial microcirculation to repond with plasma exudation may be a key feature of inflammatory airway disease. The exudative hyperresponsiveness may not be explained by an increased absorption permability of the airway mucosa, as this may be reduced in allergic rhinitis and unaffected in common cold. The microcirculation is but one of the mucosal end-organs that may develop a hyperresponsivseness in airway inflammation.
The lumina entry plasma may reflect the intensity and time course of airway inflammatory processes. Accordingly, the efficacy of anti-inflammatory treatment in rhinitis and asthma may be expressed as decreased amounts of plasma proteins on the mucosal surface. In human airways, in contrast to animal airways, this effect appears to be mediated almost exclusively by effects on the inflammatory process rather than by pharmacological actions directly on the microcirculation.
In summary, mucosal exudation of plasma is a key further of airway inflammation in rhinitis and asthma. The process indicates the inflammatory nature of these diseases and it provides an opportunity for quantitative meansurement of the inflammatory involvement. Mucosal exudation is primarily a defence mechanism, but in rhinitis and asthma the plasma exudate with its potent peptides and proteins has a multipotential role in the perpetuation of airway inflammation.

047

INFLAMMATORY CELLS AND CELL PRODUCTS

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A variety of both residential and infiltrating cells may partake in complex cellular processes in allergic airway inflammation. In allergic rhinitis these cellular processes include infiltration and activation of e g eosinophils and mast cells, as well as cells involved in immunological processes (e g Langerhans cells, and T-lymphocytes). Cellular products can be measured in nasal lavage fluids after experimental allergen challenge and at seasonal pollen exposure to elucidate the activation of different cell types in allergic rhinitis. Increased levels of both ECP and tryptase can be demonstrated in post-challenge nasal lavage fluids after acute allergen challenge (increased ECP-levels can de demonstrated also during seasonal allergic rhinitis) indicating eosinophil and mast cell activation, respectively, in allergic airway inflammation. There is also the possibility that structural cells including epithelial cells, fibroblasts and endothelial cells may be important effector cells in chronic rhinitis.

Mucosal exudation of plasma is a specific inflammatory-induced tissue (microvascular) response reflecting inflammation in different types of airway diseases. This process is derter-mined by the specific ability of the subepithelial microvessels (endothelial cells of the post-capillary venules) to respond with increased permeability on inflammatory stimulation resulting in extravasation of plasma in the lamina proparia and the subsequent paracellular epithelial passage of bulk plasma into the airway lumen. Increased lavage fluid levels of plasma proteins, as albumin, fibrinogen ans α_2-macroglobulin, can be demonstrated in both allergic and virus-induced rhinitis. While exudative inflammation thus characterise both of these types of rhinitis, the cytokine profiles in the lavage fluids indicates different cellular mechanisms. Thus, we have demonstrated increased levels of GM-CSF, but not interferon-γ, in allergic rhinitis and interferon-γ, but not GM-CSF, in coronavirus-induced common cold.

The bulk nature and the widespread mucosal distribution (lamina propria, epithelium, and airway surface) of the plasma exudate indicates that plasma with all its potent protein systems may dramatically determine the biologically active molecular milieu of the mucosa. For example, plasma-derived products (e g fibrinogen and fibronectin) may decide cellular function and traffic, α_2-macroglobulin distributes and targets several cytokines, and an endless number of plasma-derived peptides are produced (clotting, complement, and kinin systems). The plasma exudation process may thus influence cellular activities and the distribution and flux of cellular products within the mucosa and onto the airway surface. In agreement, we have demonstrated that the mucosal output of IL-6 in seasonal allergic rhinitis is dramatically increased by a simple challenge with an exudative concentration of histami-ne, suggesting that the mucosal exudation process alone can increase the concentration of this cytokine in airway mucosal surface liquids. Increased concentrations of cellular products in mucosal surface liquids may thus be due to increased cellular production and release, increased transport to the mucosa surface by the plasma exudation process, or a combination of these processes. Treatments that reduce the cellular inflamma-tory processes (e g glucocorticoids) reduce the concentrations of plasma proteins in airway mucosal suface liquids. We have further demonstrated that budesonide reduces the number of eosinophils in the nasal mucosa together with the mucosal output of albumin and fibrinogen in seasonal allergic rhinitis, and that loratadine reduces markedly allergen challenge-induced mucosal output of α_2-macroglobulin and moderately tryptase in exerimental acute allergic rhinitis. However, the anti-exudative effects of antihistamines, in contrast to that of glococorticoids, may not be well maintained in nasal allergic disease conditions.

In summary, the nasal mucosa is a suitable part of the airways where well-controlled challenge and lavage techniques can be used for studies of airway inflammation. Cellular products and indices of plasma exudation can be analysed in the lavage fluids to determine cellular activation and tissue involvment, respectively, in different diseases. The plasma exudation process may also influence cellular activities and the flux of cellular products into airway surface liquids. These possibilities emphasise the importance of in vivo observations in studies of airway inflammation.

048

PULMONARY FUNCTION TESTING IN INFANCY - MORE POSSIBILITIES

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Lung function is an important tool of monitoring airways imflammation and disease. Young children's lack of cooperati-on necessitates simple methods, natural sleep and sedation. Sedation limits the use in infants and children with dyspnoea, and in healthy children due to ethical reasons. The different methods have depended on sedation or natural sleep until recently, when lung function measurements in awake infants and children without active cooperation have become possible. Lung volumes are measured by body plethysmography, helium dilution spirometry or nitrogen washout, and airways resistance by body plethysmography. The main limitation is the necessity of sedation.

Partial expiratory flow volume curves are obtained in infants by rapid compression of the chest by an inflatable jacket (squeeze jacket tecnique). Flow is measured through face mask and pneumotachograph. The jacket pressure is increased until flow limitation is reached. Maximum flow at the probable FRC (VmaxFRC) is measured. Although several limitations, the method has shown useful in epidemiological work. The need of sedation limits its usefulness.

Tidal flow-volume (TFV) curves have recently gained much interest as no cooperation other than quiet breathing is re-quired, and may be measured in awake infants and young children. The ratio between time to peak expiratory flow and

total expiratory time (*t*PEF/*t*E) is the usual parameter. TFV loops may also be obtained by inductance plethysmography (Respitrace®) without face mask. TFV curves measured by a pneumotachograph and by inducance plethysmography, showed similar results with similar intraindividual variation. TFV curves exhibit typical patterns in infants with obstructive airways disease with effect in inhaled bronchodilators. A predictive effect of TFV curves upon later wheezy illness in fants was reported. Reference values from 803 newborn infants were published from Oslo, and recently a correlation (r=0.70) between the change to inhaled salbutamol in *t*PEF/*t*E and eosinophil cationic protein in early infant wheezers was reported.

Resistance and compliance of the total respiratory system (Rrs and Crs) may measured by obtaining a passive expiratory flow–volume curve after relaxation of the respiratory muscles by passive occlusion of the respiratory tract at end–inspiration (eliciting the Hering–Breuer reflex). By extrapolating the flow–volume curve to volume at zero flow, Crs eas calculated by dividing this volume by occlusion pressure. Rrs could then be calculated by dividing the time constant by the Crs. The passive single occlusion technique has been used to measure Rrs and Crs in awake newborn infants. Recently, recference values from measurements in 664 awake newborn infants were presented from Oslo. Crs may also be measured by the multiple occlusion technique by determining the slope of a pressure–volume line produced by the multiple occlusion.

Resistance of the respiratory system may be measured by the forced oscillation technique, by superimposing pressure loudspeaker oscillations to the airways. The resulting airflow oscillations allow measurement of the impedance (pressure–flow relationship) of the respiratory system. The method has been used in pre–school children. However, further evaluation is required before this method can be used in a clinical setting. Methods suited for measurements in awake infants and children are urgently needed to monitor the airways inflammatory processes. TFV curves represent a promising method in this respect.

049

EARLY INTERVENTION IN CHILDHOOD ASTHMA

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For many years improvement in **1) symptoms and 2) lung functions** have been the most extensively studied outcome parameter for asthma drugs. However, during recent years it has been realized that other ourcome parameters including reduction in **3) frequency and severity of acute exacerbations**, reduction in **4) mortality, 5) cost–effectiveness** control of **6) airway hyperresponsiveness**, normalization of the **7) chronic inflammatory changes in the airways, 8) prevention of airway remodelling and irreversible airway obstruction** and **9) normal growth (children) or decline (adults) in lung function**, may be of similar or even greater importance than improvement in peak expiratory flow rate and symptoms. Furthermore, the question of whether early intervention with inhaled corticosteroids can **10) change the natural course** or even **11) cure** the asthma disease or the **12) risk of systemic effects** are important parameters to consider when the reponse to inhaled corticosteroids in studied.

Inhaled corticosteroids have been shown to have a marked and significant effect upon parameters 1–9 and perhaps also an effect upon outcome parameter 10 without any clinically important systemic side effects. All other asthma drugs mainly have a reproducible effect upon parameters 1 and 2.

Normally quite marked and rapid clinical improvements and changes in lung functions are seen already at very low daily doses of inhaled steroids (around 100 μg) even in children with moderate and severe asthma. These improvements in lung function and symptoms precede and reach a pleteau before the reduction in reponsiveness. The additional improvement in symptoms with increasing doses is rather small, and often in takes an additional four–fold increase in dose to produce an additional significant effect on symptoms or peak flow measurements.

Low doses of inhaled steroids also have a significant effect on airway hyper responsiveness or lower airways functions. However, the dose response curve of these parameters in less steep so that it is possible to demonstrate a significant log linear dose response relationship over a much wider dose range on these parameters in children with moderate and severe asthma. A daily dose of 400 μg budesonide producing about 80% of the maximum achievable protection against exercise induced ashma. This indicates that the vast majority of school children can achieve optimal symptom control on quite low daily doses of inhaled steroids equivalent to 100–200 μg budesonide, whereas somewhat higher doses and longer treatment is required to control hyperreactivity as assessed by protection against exercise induced asthma.

An optimally controlled asthma child lives a normal life without any restrictions in physical activity and without any asthma symptoms or exacerbations. Lung functions are normal and increase over time as in healthy non astmatic children. Furthermore, the child experiences no side effects from the treatment. This level of control probably requires that the bronchial reactivity is within the normal range and that the inflammatory changes in the airways are minimal.

Several studies have shown that asthma severity and the impact that the asthma disease has upon the daily life of the child are often markedly underestimated because it is difficult to correctly assess symptoms and the extent to which the child has adapted its lifestyle to avoid symptoms. As a consequence many children are undertreated, optimal asthma control is not achieved and inhaled corticosteroids are either not prescribed or prescribed after the asthmatic condition has developed for many years. Recent findings suggest that if treatment with inhaled corticosteroids is not initiated until the asthmatic condition has developed for several years it is more difficult to achieve continuous, optimal long term control than if this treatment is introduced early after the debut of asthma symptoms. In one study an inverse relationship between the duration of asthma at the start of budesonide treatment and the annual increase in FEV_1 during budesonide therapy was seen. After 3 years of budesonide treatment children who started this therapy later than 5 years after the onset of asthma had significantly lower FEV_1 (96%) than the children who received budesonide within the first 2 years after the onset of asthma (101%). Furthermore, the children who started budesonide early required lower doses of budesonide to be well controlled than the children, who started budesonide after more than 5 years delay. This and other findings suggest that **early intervention with inhaled corticosteroids facilitates (is a precondition for?) long term optimal asthma control. This suggests that early use of inhaled corticosteroids may have a modifying effect upon the natural course of the disease. In addition it reduces the risk of undertreatment and ensures normal growth of lung functions.**

When the steroid treatment is discontinued there is a dete-

rioration if the asthma control and bronchial hyperreactivity to pretreatment level within months in the majority of children. In some children the effect is maintained much longer and a few will not relapse even when followed for a year. So, for the majority it seems that treatment with inhaled steroids only suppresses the underlying mechanisms of asthma and causes remission but does not "cure" the disease. However, steroid discontinuation has mainly been evaluated after less than two years continuous treatment, and not in a group of children in whom the treatment has been initiated shortly after the start of the disease. It seems as if better results are achieved in the studies on patients with mild and moderate asthma, who are treated early and for a long period with inhaled steroids. Therefore, more studies are required in such patients before final conclusions about the possibility of long term suppressive effects can be made.
In children with mild and moderate asthma low daily doses around 100–200 μg/day produce a clinical effect, which in most trials is better than the effect of any other treatment to which it has been compared. No clinincally important side effects have been associated with the treatment is this dose range. The marked efficacy and lack of clinically important systemic side effects of low doses in inhaled steroids support using this treatment as first line therapy in all children with asthma assessed to require continuous prophylactic treatment. Since the occurrence of measurable systemic effects increases with dose, the lowest dose which controls the symptoms should always be used. Furthermore, inhaler–steroid combinations with a high clinical effect/systemic effect ratio should be preferred. When these precautions are taken early intervention with haled corticosteroids can be used as an effective, safe treatment of childhood asthma.

050

SYSTEMIC EFFECTS OF INHALED GLUCOCORTICOIDS

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Inhaled glucocorticoids (iGCs) are highly effective in the treatment of asthma, confirmed by numerous efficacy studies. Also, the safety of these agents has been studied extensively. When sensitive methods are used, the systemic effect of iGCs could be detected, even during low-dose therapy. All detectable systemic effects are, however, not necessarily of clinical relevance.

Short-term studies. **The treatment of asthma with budesonide in a dose of 0.8 mg/day may produce a reversible, mild insulin resistance without effects on fasting blood glucose. According to the serum indexes, daily doses of 0.4 - 0.8 mg budesonide may reduce both collagen synthesis and, also, degradation. Short-term growth assessed by knemometry showed a growth suppression for prednisolone (2.5 -5.0 mg/daily), for beclomethasone (0.4 mg/daily) and for budesonide (0,8mg/daily). By measuring nocturnal cortisol secretion, GC effects can be detected even during low-doses of iGCs. However, no significant changes have been observed in the clinically important cortisol secretion reserve with budesonide 0.4-0.8 mg/daily.**

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051

IDENTIFICATION AND CLASSIFICATION OF NEW CONTACT ALLERGENS

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Today 3,700 contact allergens have been described and new ones are identified every year. Usually, a formulated product has caused contact eczema in an exposed individual and when he or she is patch tested with the product as well as its ingredients the new allergen is identified. It is crucial to use analytically defined chemicals, to avoid testing in a patient with current eczema, to use serial dilution tests to define a threshold of sensitivity and to prove by testing non-exposed subjects that the test preparation is non irritant.

Animal models are used to define the detected allergen's potential to induce contact allergy, dose-response relationships and the pattern of cross reactivity with chemically related substances.

By applying the principles of evaluation for carcinogens - the model used by the International Agency for Research on Cancer - to allergens, it may be possible to exclude substances only causing contact dermatitis sporadically from the significant contact allergens. Information that can be used in the evaluation is human evidence and evidence from animal experiments (sufficient, limited or inadequate) or other supporting evidence, including QSAR. Based on the evaluation, the allergens are finally classified into the groups 1, 2A, 2B, 3 and 4 as for carcinogens.

052

CORTICOSTEROIDS AS ALLERGENS

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Corticosteroids - systemic or topical - are an essential medication for allergic diseases. Interestingly, they are themselves also capable of causing allergic reactions. Systemic corticosteroids may cause a variety of allergic symptoms from flare to anaphylaxis-like reactions. The latter have been considered to be usually caused by pseudoallergic mechanisms and they are also rare. The most common allergy to corticosteroids is contact allergy and it has not been shown to be associated with anaphylactoid reactions. In several studies corticosteroids have been shown to be common contact allergens. Corticosteroid that has caused most patch test reactions is tixocortol pivalate. Tixocortol pivalate reactions reveal contact allergy to hydrocortisone, the most commonly used corticosteroid, by allergic cross-reactivity. Tixocortol pivalate itself is not used as dermatologic preparation and sensitization through contact to it is therefore not likely. Other corticosteroids that often cause patch reactions are budesonide and hydrocortisone butyrate.

053

COMPOSITAE - DERMATOLOGICALLY IMPORTANT PLANTS

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Contact allergies to *Compositae* plants may cause a severe and frequently chronic dermatitis. Typically it starts in the summer with acute eczema either on light and air exposed areas or on areas of plant contact; it disappears spontaneously during the fall. Repeated exposure over a number of years may cause severe intractable dermatitis affecting the patient throughout the year. The major allergens responsible are sesquiterpene lactones. Since 1990 we included the sesquiterpene lactone mix (SLmix) in the standard series. Patients suspected of having *Compositae* dermatitis were further tested with the Compositae extract mix (Hausen) and we found 101 of 2433 (4%) consecutively tested patients *Compositae* sensitive, mostly women. Both the SLmix and *Compositae* plant extracts are necessary for routine screening when plant dermatitis is suspected. Many patients have multiple allergies and the relevance of the patch test reactions is often obvious. Fever-few, chamomile and tansy are important markers of a *Compositae* allergy in Denmark.

054

PLASTICS AS OCCUPATIONAL ALLERGENS

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A great number of plastics (synthetic resins) can sensitize, and can cause both skin and respiratory allergies. Both immediate (type I) and delayed (type IV) allergy may develop.The most common sensitizing monomer resins are the epoxies, acrylics, polyurethanes, phenol-formaldehydes, polyesters, amino resins, and polyester resins. A curing agent or hardener is added to complete the polymerization reaction, and many of e.g. epoxy resin hardeners are sensitizers: aliphatic polyamines (triethylene tetramine), cycloaliphatic polyamines (isophorone diamine), aromatic amines (diaminodiphenyl methane), acid anhydrides (methylhexahydrophthalic anhydride), isocyanates, etc. Sensitizing additives include inhibitors (e.g. hydroquinone), initiators (benzoyl peroxide), plasticizers (phthalates), flame retardants (bromine containing compounds), heat stabilizers (epoxidized oils), antioxidants (4-tert.-butylcatechol), ultraviolet light absorbers (benzophenones), and colourants (organic pigments). -Synthetic resins and plastics are the third most common cause (after rubber chemicals and metals) of occupational allergic dermatoses in Finland. The ranking list in the last years has been (1) epoxy resins, (2) acrylics, and (3) phenolformaldehyde resins. Extensive skin testings are needed to diagnose skin allergies caused by plastics. Furthermore, provocation tests are needed to confirm respiratory allergy.

055

T CELLS IN ALLERGIC DISEASES

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Allergic diseases are the result of abnormal responses of our immune system to environmental substances/allergens. Allergic reactions can be subdivided into two main varieties; the delayed hypersensitivity reaction like contact allergy to nickel and the immediate IgE-mediated form as in atopic asthma and hay fever. T lymphocytes are important effector cells in both forms.

The first contact between an antigen/allergen and the antigen-presenting cells (APCs) is crucial in dictating the outcome of the immune response. Inhibition of the LFA-1/ICAM-1-mediated interactions between APCs and T cells during sensitization to an allergen will induce long-term allergen-specific unresponsiveness (Scheynius et al. J Immunol 156:1804, 1996). The route for introducing an allergen is also important since APCs from different tissues have the capacity to favor either cellular or humoral immune responses by influencing T cell cytokine production (Everson et al. J Lekoc Biol 59:494, 1996).

CD4+ T lymphocytes can be classified into functionally distinct subsets on the basis of their cytokine production (Mosmann et al. Annu Rev Immunol 7:145, 1989). Th1 cells secrete interleukin (IL)-2 and interferon (IFN)-γ and are essential in the host defence against intracellular pathogens. Th2 cells produce IL-4 and IL-5 and are important in antibody-mediated immune reactions and in the defence against parasites. IL-4 stimulates B cells to IgE production, while IL-5 stimulates eosinophils. When CD4+ T cells produce both types of cytokines, they are denoted Th0 cells. Th1 cells dominate in contact allergy whereas Th2 cells are more prominent in IgE-mediated allergic reactions. However, the analysis on biopsy specimens and of allergen-reactive T cell clones isolated from peripheral blood or target organs have indicated that there is not only a mixture of different Th-type cells but also that Th1 cells are able to produce some IL-4 (Haanen et al. J Exp Med 174:583, 1991) and Th2 cells can secrete low levels of IL-2 and IFN-γ (Yssel et al. J Immunol 148:738, 1992).

There has been a search for a more convenient marker to differentiate between Th1 and Th2 cells than the laborious methods based on analysis of their cytokine production. CD30 has been claimed to be a surface marker for Th2 cells (Del Prete et al. FASEB J 9:81, 1995) allowing flow cytometry analysis of cells for recognition of Th2-mediated immune reactions in different diseases. CD30 is a 120-kDa molecule originally defined as a tumor-specific antigen in Hodgkin and Reed-Sternberg cells in Hodgkin's disease. We have found that not only Th2 cells but also Th1 and Th0 cells have a high CD30 expression after activation (Bengtsson et al. Leukoc Biol 58:683, 1995). Our observation has recently been confirmed by another group (Hamann et al. J Immunol 156:1387, 1996). Thus, CD30 expression cannot be used to discriminate between human Th1- and Th2-like cells.

056

ANTAGONIZING THE DIFFERENTIATION AND FUNCTIONS OF Th2 CELLS

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Recently, considerable progress has been made in the understanding of the mechanisms underlying the pathogenesis of atopic disease. Allergen-specific T-cell responses in atopic patients are dominated by the T helper (Th) 2 subset, which produces, among other cytokines, high levels of IL-4, IL-5 and IL-13, and low levels of IFN-γ. IL-4 and IL-13 induce IgE synthesis by human B cells whereas, IFN-γ, which is predominantly produced by Th1 cells and $CD8^+$ T cells has inhibitory effects. IL-4, but not IL-13, also induces naive $CD4^+$ T cells to differentiate into Th2 cells. Furthermore, IL-3 and IL-5 produced by activated allergen-specific Th2 cells account for growth, differentiation and survival of eosinophils, which are implicated in lung damage associated with asthma. In addition, combinations of IL-13, IL-4 and IL-10 produced by Th2 cells synergize with c-kit ligand in promoting the expansion of mast cells, which together with basophils, are the main effector cells in the immediate allergic response. This information indicates that allergy is a Th2 cell disease and that Th2 cytokines account for the hallmarks of the allergic inflammatory response. Therefore, inhibition of the biological activities of allergen-specific Th2 cells, or intervention of differentiation of these cells could provide an efficient way to intervene in allergic disease.

It will be discussed that an IL-4 mutant protein (IL-4.Y124D), which binds with high affinity to the IL-4 R α chain, without receptor activation, acts as a strong IL-4 receptor (R) and IL-13R antagonist, inhibiting both IL-4 and IL-13 induced IgE synthesis *in vitro*, which is consistent with the notion that the IL-4R and IL-13R share the IL-4R α chain, which is involved in signal transduction. Administration of IL-4.Y124D also inhibits ongoing human IgE synthesis in a SCID-hu mouse model. In addition, IL-4.Y124D efficiently prevents IL-4-driven Th2 cell differentiation *in vitro*.

It will also be shown that IL-4-driven differentiation of *Der p*I-specific Th2 cells obtained from skin biopsies following *Der p*I challenge can be redirected into a Th0 phenotype by stimulating the T cells in the presence of IL-12 or through co-stimulation via SLAM, which is a novel receptor involved in T-cell activation. The clinical implications of these findings will be discussed.

057

TH1/TH2 SPECIFIC TRANSCRIPTIONAL ACTIVATING EVENTS

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Subpopulations of effector $CD4^+$ helper T cells that produce distinct sets of cytokines are important in various infectious, allergic and autoimmune diseases. Th1 cells secrete IL-2 and IFN-γ, and Th2 cells produce IL-4, IL-5 and IL-10. These polarized subsets of differentiated helper T cells arise from a common a naive $CD4^+$ T cell precursor that produces small amounts of IL-2 and no detectable IFN-γ or IL-4. In order to gain insights into the molecular basis of subset-specific cytokine gene expression, we have analyzed cytokine gene transcription and transcription factor activation in Th1 and Th2 murine helper T cell clones and in bulk populations of TCR-transgenic T cells as they undergo subset differentiation *in vitro*. Our findings suggest that differences in NFκB and Stat6 (IL-4Stat) activation are related to differences in T cell subset phenotype and differentiation.

In studies with long-term cloned T cell lines, Th1 cells were defined as those which produce IL-2 and IFN-γ but no IL-4 mRNA by RT-PCR. Th2 cells were conversely defined as those producing IL-4, but no IL-2 or IFN-γ mRNA. We have found that NFκB activation is differentially regulated in these two types of clones. TCR stimulation of Th1 clones induces a consistent increase in nuclear p65(RelA) which binds to an IL-2 promoter NF-κB site probe in gel shift assays. The nuclear p65(RelA):p50 ratio, as determined by gel shift assay, is significantly greater than 1.0 in activated Th1 clones. In contrast, TCR signaling does not induce a significant increase in nuclear p65(RelA) in Th2 cells, and the p65(RelA):p50 ratio is consistently less than 1.0. Western blot analyses indicate that there are equivalent amounts of cytoplasmic p65(RelA) in Th1 and Th2 cells, but TCR signaling is not efficiently coupled to nuclear translocation of p65 in Th2 cells. Additional studies suggest differences between TCR and cytokine effects on IκB and differences in IκB expression between Th1 and Th2 clones.

Our studies addresing cytokine gene expression in naive T cells as they undergo subset differentiation indicate independent regulation of each cytokine over time. Expression of IFN-γ mRNA in IL-12 plus antigen stimulated naive T cells occurs early, within 6 hours. In contrast, expression of IL-4 mRNA in IL-4 plus antigen stimulated naive T cells does not occur until 48 hours. IL-2 mRNA is equivalently expressed in both IL-4 and IL-12 treated populations during the primary stimulation. No consistent differences are found in NFAT, AP1, NFκB, or NFIL-2A activation between Th1 and Th2 differentiating populations. We have identified a sequence in the murine IL-4 promoter which shares features of Stat6 (IL-4NAF) binding sites previously described in other promoters. Gel shift assays using a probe with this sequence indicate that it does bind purified Stat6 but not Stat4 or Stat5, and it also binds Stat6 found in the nuclei of IL-4 stimulated T cells. We have also demonstrated that this site can mediate IL-4 induced transcription of a linked reporter gene. Gel shift and Western blot studies indicate that Stat6 is induced early in the IL-4 treated naive T cells, and activation (i.e. nuclear presence) is maintained for over 48 hours. We have also demonstrated autocrine Stat6 activation in these Th2-differentiating populations. Stat6 can be activated in Th1 populations by IL-4 treatment, consistent with our finding that IL-4 promotes a switch from Th1 to Th2 phenotypes. Thus prolonged Stat6 activation is the only transcription-regulation event which we have identified which distinguishes Th1 and Th2 differentiation of naive T cells. Studies are underway to further define the functional effects of Stat6 binding to the IL-4 promoter and the possible interaction of Stat6 with other transcription factors.

058

LEUKOCYTE ADHESION IN INFLAMMATION

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A basic requirement for normal functioning of the immune system is continuous recirculation of lymphocytes between blood and lymphatic tissues. It allows a close contact between lymphocytes and their cognate antigens and other cell types needed to create effective immune reponse. In lymphoid organs, lymphocytes leave the blood by adhering to specialized vessels called high endothelial venules (HEV) because of the morphological appearance of their endothelial cells. Binding of migrating lymphocytes to endothelial cells is mediated by sequential interaction between lymphocyte surface molecules and their endotheial cell counter-receptors. There are at least four steps in this cascade: 1) recognition detected as rolling of the lymphocyte on the endothelial cell, 2) activation, 3) tight adhesion, and 4) transmigration. In physiological conditions two functionally distinct systems mediate lymphocyte traffic to peripheral lymph nodes and mucosa-associated lymphatic tissues.

In inflammatory situations lymphocytes together with other leukocytes migrate to sites of inflammation. Inflamed skin and synovium are tissues to which lymphocyte homing has been studied most. The recent results show that the mechanisms controlling lymphocyte entrance to inflamed skin and synovium are different from each other and also distinct from those mediating the extravasation to peripheral lymph nodes or mucosa-associated lymphoid tissues.

An important molecular pair mediating lymphocyte traffic to inflamed skin is cutaneous lymphocyte antigen-1 (CLA-1) that binds to its endothelial cell ligand E-selectin, Moreover, peripheral lymph node addressin (PNAd) is induced and vascular adhesion protein-1 (VAP-1) is upregulated in inflamed skin endothelium, and they both seem to be important in mediating lymphocyte interaction with vascular endothelium in inflamed skin. In animal models, lymphocyte homing into inflamed skin has been shown to involve also lymphocyte function associated antigen-1 (LFA-1), very late activation antigen-4 (VLA-4) and CD44. Participation of these molecules belonging to different molecular families in lymphocyte homing into inflamed skin suggest that at least three distinct, but most likely overlapping, adhesion mechanisms (CLA-1 - E-selectin; L-selectin - PNAd; unknown lymphocyte receptor - VAP-1) are involved in relatively early phases of the multi-step cascade resulting in lymphocyte extravasation into the cutaneous sites. Moreover, integrins (LFA-1, VLA-1) may be functioning during the firm adhesion phase. The exact location of CD44 in the cascade is most speculative. Based on the published results from other systems, both the rolling phase and activation step are possible.

Lung harbours significant numbers of intravenously injected lymphocytes that form a massive marginating pool while failing to migrate in large numbers into the interstitial and bronchoalveolar spaces. Very little is known about the molecular interactions functioning in margination or homing into the lung. In any case, the phenotype of pulmonary T cells is strikingly different from the phenotype of the T cells selectively migrating into the skin, and the data gathered so far indicate that leukocyte trafficking into the lung has some unique characteritics. It is possible that the lung-seeking leukocytes are not capable of rolling in the capillary bed of the lung and therefore, the molecules of the multi-step cascade work simultaneously rather than sequentially there.

Anti-inflammatory therapies aimed at to block the functions of homing-associated antigens have in many experimental settings given promising results. Indentification of the optimal target molecules also in the skin and the respiratory tract is feasible for future efforts to develop new anti-adhesive drugs to control inflammations in these locations.

059

OCCUPATIONAL RHINITIS. DIAGNOSTICS

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Most cases of occupational rhinitis (OR) are caused by organic substances, but some chemicals can also cause OR. The most important causes of OR are animal dander, flours, wood dust, textile dust, food, spices, storage mites, enzymes, latex, and various chemicals. A patient suffering from rhinitis symptoms may have OR, if: 1) the rhinitis symptoms are connected to work, 2) the patient has been exposed to allergens or irritating factors at work, 3) other than an occupational cause of rhinitis has been excluded, and 4) a provocation test (PT) confirms the causality between the disease and the exposure.

Diagnosis of OR: The diagnosis of OR must be better confirmed than in allergic rhinitis of other etiology, as a diagnosis of occupational disease often means many changes to an employee. The diagnosis methods depend on the symptoms (immediate or delayed type) and the allergens. A careful exposure history has to be taken and differential diagnosis has to be done. Skin prick and RAST tests are important. Spirometry and histamine provocation are often needed if bronchial hyperreactivity is suspected.

A **provocation test** (PT) is required to confirm the diagnosis. Different provocations are used in the diagnosis of occupational rhinitis: nasal, chamber and work PTs. The nasal and chamber PTs are used to diagnose immediate or late reactions. Depending on the exposure time, the work PT can be used to register either immediate, late or chronic responses.

Nasal PT: A nasal PT is used when the allergen to be tested is of organic origin. Different ways to perform the nasal PT have been

reported. In our Institute we place the provocation material bilaterally onto the fronto-topical surface of the inferior turbinate. A patient undergoes nasal PTs with different test materials on consecutive days. Each test series is started with placebo. The test is done single-blinded, so that the patient does not know which provocation material is tested until all tests have been done. The choice of test material is based on the patient history, and skin prick and RAST tests.

Chamber and work PT: In the case of suspected OR, a chamber PT is used when different chemicals are tested. The PT can also be done at the patient's workplace. In these two PTs not only the nasal status but also the response of the pharynx, larynx and lungs can be registered.

Response recording: The changes in rhinorrhea and blockage of both nasal cavities are registered. Status and symptom scores (e.g. visual analogue scale) are used. Some patients tend to overestimate their symptoms. This means that some objective measurements should be included in the response recording. The change in nasal airway resistance, using rhinomanometry, can be measured. The change in the nasal geometry can be registered with acoustic rhinometry. Nasal peak expiratory flow is also sometimes used as well as nasal cytology, mucous membrane biopsies, or tryptase and other mediator measurements.

Conclusions: 1) most of the diagnosed cases of OR are immediate type allergic rhinitis, 2) the status change is most important in the registration of the response to the PT, but also an objective measurement should be included in the response recording, 3) nasal symptoms and status changes caused by various industrial exposures are underestimated.

060

SERIAL MEASUREMENTS OF LUNG FUNCTION AT WORK AND AT HOME IN THE DIAGNOSIS OF OCCUPATIONAL ASTHMA

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Occupational asthma can usually be strongly suspected from the history of deterioration of symptoms in relationship to exposure at work and improvement while away from exposure. It is important to confirm the diagnosis before serious decisions about relocating a worker or altering the workplace are made. Serial measurements of lung function in relationship to work exposure are the most appropriate first step in the diagnosis, provided the reactions at work are not catastrophic (in which case carefully controlled bronchial provocation testing is safer).
If occupational asthma exists, there should be measurable changes in lung function related to exposure to the offending agent. The problem is in distinguishing these changes due to exposure from those due to diurnal variation and the major confounding factors of infection, treatment and the day-to-day non-specific precipitants of asthma. To overcome these many confounding factors, records need to be made at times when the treatment does not change and when respiratory infections are absent. The best results are obtained from approximately 2 hourly readings of lung function from waking to sleeping with initial records lasting 4 weeks. Reducing the number of daily readings increases the reliance on individual readings which might be affected by exercise,late waking etc.,reduces the measured diurnal variation, and reduces the diagnostic sensitivity of the record. Workers with severe occupational asthma may however, show obvious work-related changes even with very small numbers of readings per day. Differences between work days and rest days are accentuated by plotting the lung function as a daily maximum, mean and minimum which can be assessed either visually or by using a computer-aided scoring system. We have developed such a system (OASYS)which plots the record in an interpretable manner and provides a score based on either a discriminant or neural net analysis, achieving a sensitivity of about 85% and a specificity of around 95%. The quality of the records is the single most important determinant of a good test. Records can be prefabricated and the quality of measurement is less than is ideally achieved in a laboratory.In the future,logging meters with quality control of data input in real time are likely to improve the quality of the data.In our experience, good quality readings are obtained in about 50% of workers after postal instruction and in a further 30% of workers after a clinic visit,leaving 20% of workers who never provide adequate readings.

061

OCCUPATIONAL CONTACT URTICARIA

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Aims: To review the current understanding of occupational contact urticaria (OCU), and give statistical data on OCU.
Methods: The diagnosis of OCU should include an appropriate history, combined with specific skin tests, IgE determinations (e.g., RASTs), provocation tests, RAST inhibition tests, immunoblotings etc.
Results: Altogether 815 cases of OCU were reported to the Finnish Register of Occupational Diseases during 1990-1994, compared with 1944 cases of occupational allergic contact dermatitis. Accordingly, the total number of occupational allergic contact dermatoses was 2759, 29.5 % being contact urticaria and 70.5 % being allergic contact dermatitis. Occupational contact urticaria was much more common in women (70 %) than in men (30 %). The six most common causes of contact urticaria were (1) cow dander (44.4 %), (2) natural rubber latex (23.7 %), (3) flour, grains and feed (11.3 %), (4) handling of foodstuffs (3.1 %), (5) industrial enzymes (1.7 %) and (6) decorative plants (1.6 %). The occupations with the highest numbers of occupational contact urticaria were (1) farmers, (2) domestic animal attendants, (3) bakers, (4) nurses, (5) chefs and (6) dental assistants. The ranking list of the most common occupations with occupational contact urticaria per 100 000 employed workers was as follows: (1) bakers (140.5 cases per 100,000 employed persons), (2) preparers of processed food, (3) dental assistants, (4) veterinary surgeons, (5) domestic animal attendants, (6) farmers and silviculturalists. Low-molecular weight chemicals caused very few cases of occupational contact urticaria, the most common being 2-ethylhexyl acrylate (5 cases).

062

PRACTICAL ASPECTS OF SIT

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The results of the Preventive Allergy Treatment Study (the P.A.T. study)(1) showing preventive aspects in the development of asthma children suffering from allergic rhinitis give a new challenge in the treatment ff patients with allergic rhinitis. Whether specific allergen injection immunotherapy is effective and safe in the treatment of allergic diseases is no more questionnable, S.I.T. has become to a new phase. This new phase regarding the preventive aspects of S.I.T. is a great challenge for all doctors treating children with IgE-mediated allergic disorders.
S.I.T. is effective in selected patients; effeciency must always be blanced against possible side-effects (2). New consepts of the mechanisms (3, 4). of allergen specific immunotherapy has given clear evidence how S.I.T. influences in IgE allergic inflammation (5).

EAACI recommendations for it
In 1988 a subcommittee under the auspices of EAACI (European Academy of Allergology and Clinical Immunology) worked out recommendations for Europe concerning indications, allergen extracts, monitoring efficacy and safety, and practicals for IT. These guidelines are updated regurlarly (2). There is a Committee for Immunotherapy in Cildren in ESPACI (European Society for Pediatric Allergology and Clinical Immunology) chaired by E. Valovirta, Finland, in order to produce guidelines especially for S.I.T. among allergic children in co-operation with EAACI.

Indications for it
Immunotherapy is an effective treatment of allergic diseases under optimal conditions (2). Allergen sensitization must play a predominant role in arising symptoms. IT has shown to be effective in IgE mediated rhinitis and asthma (6). In venom allergy IT is highly effective (7).

Allergen extract for it
The availabbility of a high-quality allergen extracts and the administration of a proper dose are basic factors for a good clinical results of IT with as few side-effects as possible. Efficacy has been demonstrated with extracts from pollen. mites animals (doag and cat), alternaria and caldosporium.

Practical guidelines for it
EAACI IT-subcommittee (2) has collected data on practical guidelines based on large international experience and controlled clinical studies. There are still several questions without answers: dosing regimen, optimal dose, years of treatment (3 or more), booster injections, prediction of outcome, the mechanism of IT, cost benefit, selection and identification of patients suitable for IT.

Conclusion
Current thinking of the use of IT in the treatment of allergic disease should focus on the long-term advantages of instituting IT in the early course of allergic disease in combination with the best possible pharmacological treatment. The P.A.T. sudy is the first prospective study using high-quality allergen extracts to evaluate the ling-term efficacy of IT in relation to reduce development of asthma in children suffering from allergic rhinitis. The preliminary results of the P.A.T. study arise a new challenge in the treatment of allergic patients. Medical personel and doctors treating these patients need in the future more and more education in the field of IT to be able to offer to their patients optimal treatment with long-term effect reducing symptoms and influencing the natural course of the allergic disease.

References
1. Jacobsen L et al. Immunotherapy as preventive allergy treatment (P.A.T.) J Allergy Clin Immunol 1996;97:1, part 3:232.
2. Malling HJ, Weeke B. (Editors). Immunotherapy. EAACI position paper. Allergy 1993;48 (suppl 14):7-30.
3. Walkers SW et al. Grass pollen immunotherapy (IT) 4 year follow-up study: the late cutaneous response but not the early response parallel clinical improvement. J Allergy Clin Immunol 1995;95;1, part 2:708.
4. Durham SR et al. Changes in allergic inflammation associated with succesful immunotherapy. Int Arch Allergy Immunol 1995;107:282-4.
5. Rak S et al. The effect of immunotherapy on bronchial hyperresponsiveness and eosinophil cationic protein in pollen-allergic patients. J Allergy Clin Immunol 1988;82:470-80.
6. Abramson MJ et al. Is allergen immunotherapy effective in asthma? A meta-analysis of randomizen controlled trials. Am J Crit Care Med 1995;151:969-74.
7. Muller U, Mosbeh H. (Editors). Immunotherapy with hymenoptera venoms EAACI position paper. Allergy 1993;48(suppl 14):36-46.

063

THE FUTURE OF IMMUNOTHERAPY

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Allergen-specific immunotherapy is an effective treatment of allergic diseases, under the conditions of a carefull selection of patients and the use of quality allergen extracts. The advantages of immunotherapy to interfere with the pathophysiological mechanisms of the allergic inflammation, with potential for a long-term effect or even cure, compared to a phamacological treatment reducing symptoms only while being administered but without long-term preventive capacity should be investigated. The beneficial additive effect of combining immunotherapy and drugs are related to a higher likelihood of increasing efficacy, reducing side effects, and improving patient compliance by combining a treatment having an immediate effect with one having a more slowly onset of action.

Treatment of allergic diseases
The treatment of allergic asthma and rhinitis has benefited from the improved understanding of the mechanisms of the allergic inflammation. Unaswered quentions are, however, the long-term capacity to prevent destruction and to avoid long-term side effects. Another problem is related to patient compliance. Several studies have documented that less than half of the prescribed drugs are actually being used. The treatment strategy of allergic diseases imply interference in the inflammatory cascade and the advantageous of combining intervention at different levels should be considered. Allergen-avoidance is always the firstline attempt and althought not

completely effective, may reduce the need for further intervention. Drug treatment often is the next logical step to reduce disease severity, but in patients with a constant need for preventive (local steroid) pharmacotherapy, the advantages of instituting immunotherapy early in the cause of the disease, i.e. before the development of chronic irreversible structural changes take place, should be seriously considered.

The future of allergen-specific immunotherapy

Subcutaneous injections of allergen represent the prototype of allergen-specific intervention. The improve clinical effecacy much research has focused on optimizing the quality in terms of potency and consistency of commercial allergen extracts. Increased potency ilvolve a higher likelihood of improving the clinical efficacy but on the other hand also increase the risk of inducing anaphylactic reactions. The reduce the risk of side effects and to retain the clinical efficacy, physically or chemically modified extracts have been developed. Clinical studies indicate an efficacy of modified ectracts. Problems are related to difficulties in standardization due to the reduced IgE-binding capacity, and to the need for injection of higher doses in order to obtain efficacy - and thereby increasing the risk of inducing systemic side effects. Based on the knowledge of the regulatory effect of T-cells, fractionation of the allergen molecules (epitopes) into peptides which will not be recognized by mast cell and basophil bound IgE but with the capacity to switch off allergen-specific T-cells provide prospectives for future treatment. Clinical studies using cat-allergen specific T-cell peptides are currently being performed. The clinical efficacy has not been clearly documented , and in spite of the lack of IgE-binding capacity and thereby the induction of anaphylactic reactions, T-cell peptides induce delayed systemic side effects, probably related to the release of cytocines and other mediators. The intended hope of an effective and safe treatment seems not to be achieved.

Based of the recent development of recombinant allergens, the availability of large quantities of major allergens gives the opportunity to manipulate amino acid sequences. Substitution of a single amino acid reduce the IgE binding capacity with a factor 100 (probably due to remodelling of the 3-D conformational structure of the allergen). The recuded IgE-binding capacity might imply a reduced risk of inducing side effects without influencing the sequential based T-cell recognition of activating sites in the allergen. Future aspects of immunologic intervention could be based on a principle used in vaccination. From gene libraries, DNA coding for a major allergen could be incorporated into the genetic material of harmless viruses and after injection into humans induce a permanent production of allergenic proteins activating T-cells.

Another attempt to avoid injections and to reduce the risk of side effects in based on ingestion of allergens either as swallowing the allergen extra (oral immunotherapy) or retaining the extract in the mouth (sublingual immunotherapy). Clinical efficacy has been documented for a few allergens with oral immunotherapy and less convincing with sublingual immunotherapy. Topical adminstration of allergens using either intra-nasal or bronchial inhalation also have shown clinical efficacy and few side effects. Unsolved quentions are realted to comparative studies of alternative immunotherapy versus injection treatment. A slightly less effective treatment or more slowly onset of action might be compensated by a reduction in side effects.

Conclusion

The avantages of allergen-specific intervention in the allergic inflammation (allergen-avoidance and immunotherapy) should be carefully considered in designing the future treatment strategy of allergic diseases. Applying a specific treatment interfering with the activation of the pathophysiological mechanisms involved in allergic diseases in contrast to treating symptoms may have obvious advantages. Furthermore, the exlusive use of drug treatment may have a fundamental impact on the diagnosis of allergen sensitization in the future. Basically, allergy diagnosis is a must for prescribing specific treatment. The demand to know the allergens to which a patient is sensitive is not essential for drug treatment (effective for both allergy and non-allergic symptoms). The drawback of not knowing the allergy state might reduce to possibilities of avoiding allergens responsible for inducing symptoms and exacerbations.

The advantages of combining allergen avoidance, immunotherapy and drug treatment require further investigations of individual and combinations of treatment focusing on patient compliance, long-term preventive aspects, and cost/effectiveness/side-effects. As long as the long-term preventive capacity and safety of topical steroids is almost completely unknown, a strategy relying almost exclusively on inhaled corticosteroids might turn out to be erroneous.

New insights into allergic inflammation provide a platform for further investigations of the advantages and drawbacks of different intervention strategies and for the development of new effective and safe treatment principles. The future role of conventional immunotherapy using native allergen extracts may be substituted by a more refined and precisely targeting allergen-specific immunological intervention based on efficacy/side effects validation. While waiting for this development allergists must continue to use the conventional allrgen-specific intervention strategy.

064

RECOMBINANT ALLERGENS: FROM THE GENE SEQUENCE TO THE CLINICAL APPLICATIONS

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A phage surface display system (pJuFo) for selective isolation of genes of interest by specific gene-product/ligand interaction has been developed. A panel of phage displaying allergens was isolated applying selective enrichment with human serum IgE to an *A. fumigatus* cDNA library displayed on the surface of filamentous phage. After sequence determinations, 10 different cDNAs were subcloned into an *E. coli* high level expression vector, produced and affinity purified. The pure proteins were analysed for their diagnostic value in serologic studies and for the *in vivo* relevance in skin tests. Patients suffering from different *A. fumigatus* complications, allergics without sensitisation to *A. fumigatus* and healthy controls were enrolled. Skin test results and serologic determinations with the recombinant allergens showed a quantitative correlation. Two of these allergens have been evaluated for their performance in the Pharmacia CAP-System. The close correlation between ELISA determinations and ImmunoCAP values (r=0.997) demonstrates that recombinant allergens can be used to develop perfectly standardised diagnostic reagents having the to potential to substantially improve the diagnosis of allergic diseases both, *in vivo* and *in vitro*.

065

IS THERE A NASO-BRONCHIAL REFLEX IN HUMANS?

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In animals there are several evidences for a naso-bronchial reflex, thus stimulation, e.g. chilling or irritation, in the nose may cause bronchoobstruction. In man a naso-bronchial reflex has not been proved and the bronchoobstruction seen in patients with asthma after inhalation with cold air has been supposed to be due to the amount of heat and water loss from the airway mucosa. However, this might not be the complete explanation and therefore it was worth studying the relationship between the upper and lower airways. Eight healthy subjects and 10 asthmatics with a history of cold sensitive asthma took part in this study. They were provoked in the nose with air of different temperature without possibility for the air to reach the lower airways. The effect was measured with spirometry (FEV_1) and body pletysmography (specific conductance).
In healthy subjects, no effects were seen after provocation with ambient air, cold air or warm air. In the asthmatics, however, provocation with cold air induced bronchoobstruction and provocation with warm air had an opposit effect.
There is a relationship between the upper and the lower airways, an effect which could be explained by a naso-bronchial reflex.

066

SPECIFICITY OF Bet v 1-SPECIFIC T CELLS SUGGESTS THE INVOLVEMENT OF MULTIPLE Bet v 1 ISOFORMS IN THE SENSITIZATION TO BIRCH

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Tree pollen and grass allergens have been shown to consist of many isoallergenic forms that display single or multiple amino acid substitutions. To gain more insight into the relevance of the occurrence of isoallergens for allergic sensitization, we investigated the T cell epitope-specificity and the interspecies crossreactivity patterns of T cells reactive with Bet v 1, the major allergen of white birch (*Betula verrucosa*). To this aim, we generated Bet v 1-specific T cell lines and clones from the peripheral blood of three allergic patients. The clones were generally $CD4^+$, and displayed a Th0-like cytokine production.
Using overlapping synthetic peptides, we were able to identify multiple T cell epitopes in Bet v 1. However, 7/21 native Bet v 1-reactive T cell clones did not react with recombinant Bet v 1 or with synthetic peptides, indicating that they may react with other other Bet v 1 isoallergens. Therefore we decided to study the crossreactivity patterns of the clones with group 1 pollen allergens of other members of the *Fagales* order. The results showed the presence of several distinct crossreactivity patterns. These results strongly suggest that multiple isoforms of Bet v 1 are involved in the sensitization to birch pollen, giving rise to distinct isoform specificities and crossreactivity patterns.

067

CROSS-REACTIVITY BETWEEN CHITIN BINDING DOMAINS OF WHEAT GERM AGGLUTININ (WGA) AND PROHEVEIN, A MAJOR LATEX ALLERGEN

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The 43 amino acid N-terminal chitin binding domain of prohevein, known as mature hevein, shows high homology to chitin-binding domains of WGA and also to several other chitin-binding proteins. We wanted to examine whether WGA is capable of binding anti-hevein IgE antibodies in sera from NRL-allergic patients and whether WGA is able to elicit hypersensitivity reactions in these patients.

In immunoblotting, 48% of NRL allergic patients (n=25) showing IgE antibodies to prohevein but none of the controls (n=22; including 12 atopic individuals) showed IgE to WGA. In ELISA, 35% of unselected NRL-allergic patients (n=54) and none of the controls (n=64; including 12 atopic individuals) had IgE antibodies to WGA. However, 58% of the patients showing IgE to hevein (n=26) had IgE antibodies to WGA. Hevein inhibited in a dose-dependent manner IgE binding to solid-phase WGA and *vice versa* in ELISA inhibition. Three NRL allergic patients, showing IgE to both hevein and WGA, but none of the 5 non-allergic controls studied showed positive reactions in skin prick testing with WGA. Remarkable similarity between three-dimensional structures of the chitin- binding domain of WGA and hevein was observed.

These results suggest that chitin binding domains of WGA and prohevein, a major latex allergen, contain cross-reacting IgE binding epitopes. This finding may open new avenues for studying cross-allergies by using information based on sequence comparison of the allergens.

068

MODULATION OF LYMPHOCYTE FUNCTIONS BY CASEIN DEGRADED BY INTESTINAL BACTERIA

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The purpose of the study was to determine the immunomodulatory characteristics of food antigens degraded by intestinal bacteria. Purified bovine casein was hydrolysed *in vitro* by proteases isolated from a human intestinal bacterial strain Lactobacillus GG (ATCC 53103). Cytokine production by peripheral blood monocytes and purified T-cells, and lymphocyte proliferation, were separately evaluated in patients with atopic dermatitis (AD) and healthy controls in mitogen-induced cultures with casein or degraded casein. Undegraded casein increased the production of IL-2, IL-4 and IFN-γ in cultures of AD patients. Degraded casein significantly reduced the production of IL-2, IL-4 but not IFN-γ in cultures of AD patients and healthy controls. Table presents the effect of degraded casein on the cytokine production by T-cells of healthy controls as median of cytokine concentration (interquartile range) in pg/ml.* $p<0.05$, Wilcoxon signed rank test for comparison of cultures containing mitogen,with or without casein or degraded casein.

Culture type	IL-2	IL-4	IFN-γ
control	185 (0-364)	28 (12-46)	3780 (2688-14375)
casein	136 (0-416)	17 (12-40)	6640 (2395-15125)
degraded casein	0 (0-64)	12 (7-26)*	3320 (2045-11280)

Intestinal bacteria can degrade allergens and generate tolerogens from them. Degraded bovine casein downregulates T cell responses in particular IL-4 production in both atopics and nonatopics. Food allergens degraded by intestinal bacteria may thereby dampen IgE hypersensitivity to food allergens. Gut processed tolerogens may provide an immunotherapeutic model for food allergy.

069

CALCIUM INTAKE AND CALCIUM AND PHOSPHORUS METABOLISM IN CHILDREN WITH COW'S MILK ALLERGY

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The aim of this transversal study was to evaluate the consequences of this elimination diet by the analysis of calcium intake and calcium and phophorus status of these children. 26 children, aged 8-36 months (mean 20), with CMA and having undergone an elimination diet for at least 6 months were included in the study (group I). Control subjects (group II) were 9 healthy children on a free diet. The dietary survey evaluated the daily calcium intake which was compared to the 1989-recommended dietary allowances by age and gender (%RDA). In group I, the calcium intake was lower than recommended (74±26 %RDA) and than in control subjects (135±25 % RDA, p=0.0001). Abnormal biological parameters were found in 3 children of group I (12%): isolated increase of alkaline phosphatase in 2 , ricketts in 1. In conclusion, children with CMA exhibited a reduced calcium intake and, in 12%, biological abnormalities, including one case of ricketts. The nutritional follow-up of these children is warranted and should include regular measurements as alkaline phosphatase.

070

THE DOUBLE-BLIND PLACEBO-CONTROLLED FOOD CHALLENGE IS AN OPTION IN CLINICAL PRACTICE

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Background. The optimal diagnostic procedure of cow milk allergy has not been determined, but double-blind placebo controlled food challenge (DBPCFC) is considered the gold standard.
Aim. To assess parental perception of the clinical procedure to diagnosis of cow milk allergy.
Subjects and Methods. Parents of 265 patients, mean (95 % CI) age 21 (20-23) mo, subjected to DBPCFC (n=110) or open cow milk challenge (n=155) were interviewed with a questionnaire 13 (12-14) mo later. Specific questions were asked on the time consumed, credibility of the diagnosis, and the overall response by the parents was rated as with thanks, all negative, both positive and negative or no comment. Family history was positive for atopy in 51 %, total IgE was 32 (24 - 43) kU/L, cow milk RAST positive in 36 %, and skin prick test in 31 %.
Results. The two groups were equal in response rate (68 %) as well as cow milk specific RAST and skin pick test. The DBPCFC resulted in fewer diagnoses of cow milk allergy, i.e. was less often positive ($\chi 2$=4.0, p=0.04). Interestingly, regardless of challenge result, the DBPCFC was more credible to the parents ($\chi 2$=7.12, p=0.007).
Conclusion. The DBPCFC is not considered by the parents as overly laborious and the diagnosis does become more credible. The DBPCFC should be considered an option when positive challenge results in elimination of an essential food such as cow milk.

071

REVERSIBLE BRONCHIAL OBSTRUCTION IN INFANTS WITH PROLONGED COUGH

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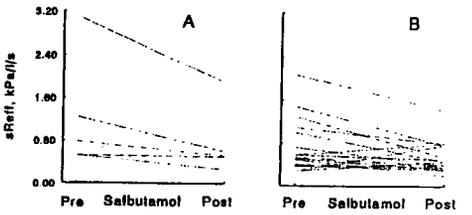
Specific effective airway resistance (sReff) and thoracic gas volume (TGV) were measured with total bodypletysmography (Baby Box, Jaeger^R, Germany) in 23 consecutive infants, aged 0.3 to 23 months with a history of wheezing (n=6; A) or prolonged cough only (n=17;**B**). The duration of cough ranged from 1 to 17 months. After the measurements at baseline, the infants inhaled salbutamol (0.15mg/kg) through a jet nebulizer. At baseline, sReff medians were 0.75 (A) and 0.72 kPa/l/s (B); values >200% above reference were observed in 3/6 in A and in 7/17 infants in B. After salbutamol, sReff medians were significantly reduced (p<0.05): 0.49 (A) and 0.46 kPa/l/s (B). The decrease was >40% in 2/6 infants in A and in 5/17 in B. No changes were observed in TGV.



Our finding of reversible bronchial obstruction in infants with a history of prolonged cough is in keeping with the view that functionally important asthma is underdiagnosed in infancy.

072

THE MORTALITY CAUSED BY BRONCHIAL ASTHMA IN CHILDREN

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The clinical and pathological analysis of deaths of asthmatics in St. Petersburg for 21-year period was done. 29 children died, the mortality rate before 1984 was 0 - 0,2 per 100,000 of children population / the mean for 10 years - 0 ,075 /, for the period 1985 - 1995 - 0 - 0,55 / the mean - 0,2 /. In all the cases the diagnosis of asthma was confirmed by autopsy and clinico-anatomical parallels were determined. 65% of deaths occurred on the top of severe asthmatic status. There were no deaths outside medical institutions before 1986, after 1986 they comprised 45% including deaths "with inhaler in hands". Possible medical and social causes of severe asthma course and fatal outcomes in observed group of children are analysed and discussed in details.

073

MARKERS OF INFLAMMATION

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During recent year the development of several assays, for the unique measurement of the activity in vivo of various inflammatory cells, have been developed. These included assays for the reflection of eosinophil activity such as ECP (eosinophil cationic protein), EXP (eosinophil protein-x) and EPO (eosinophil peroxidase). For the assay of neutrophil activity one can use elastase, HNL (human neutrophil lipocalin) or MPO (myeloperoxidase) and for the assay of mast cell activity, tryptase. Assays for monocytes/macrophages include cytokines such as TNFα, IL-6 but also lysozyme, although these proteins may also be produced by other cells. The soluble receptors for IL-2 and E-selection may be used as quite specific markers of T-lymphocyte and endothelial cell activity, respectively. In addition to these cell markers the assay of several cytokines such as IL-8, GM-CSF, G-CSF, IFN-γ is possible and of potential interest in allergy and asthma. Measurement of inflammation markers could be made in blood i.e. plasma or serum or in any other body fluid.

The rationale for the use of inflammation markers is several-fold. One is the objective assessment of the inflammatory activity of the disease, since this is notoriously difficult in many of our patients and since current methods often are very insensitive or not at all affected by the inflammatory process.

Another is the diagnostic use of inflammation markers, since the knowledge of the involvement of various inflammatory components may enable us to make more fine tuned diagnosis of our patients and possibly identify subgroups within certain diagnostic entities, which may have a bearing on treatment strategies. Still another is the pathophysiological insight provided by the knowledge of the quantitative and qualitative aspects of the components involved.

The current knowledge of the use of inflammation markers for the above purposes is still fairly limited and restricted to a few markers and certain areas. The currently most studied marker in allergy and asthma is ECP in serum and increased levels are related to the disease severity in asthma and to allergen exposure. It is also valuable to use ECP measurements in the monitoring of anti-inflammatory treatment in both children and adults. Indeed the complicance of the patients in this respect may be followed with serum-measurements of ECP. Another interesting possibility is the use of ECP in the prediction of asthma exacerbations. Especially in small children the measurements in inflammatory markers in blood may be difficult. Therefore demonstration of EPX in urine as a possible alternative deserves some attention. The experience of using of EPO is still very limited, but available data indicate that EPO discriminates better between allergic and non-allergic asthma than do ECP.

Neutrophil markers such as MPO have shown somewhat elevated levels in serum in asthmatics, which could mean that the circulating neutrophils are primed in these patients. The otherwise most useful property of these markers is the discrimination between acute infections of viral and bacterial causes. This was especially clear for HNL, which showed a sensitivity and specificity in this respect of about 95%. The marker of mast cells, tryptase, has so far mostly been used to diagnos anaphylactic episodes, but with a better sensitivity of the assay it should be a useful marker in asthma. Serum levels of soluble IL-2 receptor has been shown to be elevated in asthma, but its clinical value still has to be proven.

The use inflammation markers is still at its infancy, but the rapidly expanding knowledge of the interpretation of the results in clinical terms will undoubtedly lay the grounds for the sound clinical use of these markers and include them in everyday management of patients with asthma and allergy.

074

THEOPHYLLINE AND SELECTIVE PHOSPHODIESTERASE INHIBITORS AS ANTI-INFLAMMATORY DRUGS IN THE TREATMENT OF ASTHMA

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The non selective phosphodiesterase inhibitor, theophylline has long been recognized as a drug of use in the treatment of airway diseases such as asthma. Traditionally this drug has been suggested to act as a bronchodilator. Recent evidence however has suggested that theophylline can have effects as an anti-inflammatory agent. Theophylline has been reported to inhibit the release of inflammatory mediators from a variety of inflammatory and immunocompetent cells including alveolar macrophages, neutrophils, eosinophils, mast cells and T-lymphocytes[1]. Additionally, theophylline has been shown in experimental animals to reduce eosinophil infiltration into the airways induced by allergen and the levels of eosinophil derived peroxide in BAL fluid (2). These effects have also now been demonstrated with selective PDE IV inhibitors suggesting that this action of theophylline may be related to inhibition of phosphodiesterase (3). Recent clinical evidence has also shown that theophylline can inhibit both eosinophil and lymphocyte trafficking into the airways of asthmatics following allergen exposure (4). Furthermore, recent data have shown that theophylline withdrawel leads to a worsening of asthma, even in patients taking glucocorticosteroids (5). These results suggest that theophylline should be considered as more than a bronchodilator substance and demonstrates that

theophylline possesses significant anti-inflammatory activities. Considerable evidence now exists that selective phosphodiesterase IV isozyme inhibitors can inhibit antigen induced bronchial hyperresponsiveness in experimental models of asthma (6) and recent clinical evidence with the selective phosphodiesterase IV isozyme inhibitors CDP840 in allergic asthmatics suggests that this drug has a significant effect on the allergen-induced late response(7). If these results are reflected in larger scale clinical studies in asthmatics then it suggests that novel PDE IV inhibitors may be useful anti asthma drugs. These recent findings suggest that it is time to reappraise the role of theophylline in the treatment of asthma and to look forward to the arrival of selective PDE IV isoenzyme inhibitors..

(1) Sullivan,P. et al. In "Drugs and the Lung", Eds. Page,C.P., Metzger,W.J. Raven Press, New York. p.p. 69-99 (1994).
(2)Banner,K. et al. Pulm.Pharmacol. 8: 37-42 (1995).
(3)Banner,K. et al. 114: 83-88 (1995).
(4) Sullivan,P.J.et al. Lancet. 343: 1006-1008 (1994).
(5)Kidney,J.C.et al. Am.J.Crit.Care.Med., 151: 1907-1914 (1994).
(6)Gozzard,N. et al. Br.J.Pharmcol. In press.
(7)Harbinson,P.L et al. Am.J.Hops.Crit.Care.Med. In press.

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IMMUNOLOGICAL EFFECTS OF THE CHERNOBYL DISASTER

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This study was conducted to obtain quantitative data on the degree of the lung delayed immunological local disorders in Chernobyl liquidators. We studied 35 patients with chronic obstructive bronchitis (20 liquidators and 15 non-liquidators, aged 30-46) by bronchoalveolar lavage (BAL). The cytological, cytochemical, immunochemical, cytobacterioscopic, and biochemical techniques were carried out. In the recent studies we had demonstrated the presence of the several so-called "Chernobyl" chemical elements in the alveolar macrophages cytoplasm, cytological signs of the neutrophil alveolitis in liquidator's group. Now the evaluated criteria were: 1) the presence of distal bronchial microflora; 2) ferritin level in BAL fluid and blood serum; 3) lymphocytes sub populations in BAL fluid and blood. Compared with non-liquidators in liquidators contained increased presence of distal bronchial microflora (Gram positive and Gram negative); decreased CD^{2+} functional activity, and significant increase of BAL and blood ferritin.

076

CHILDHOOD ALLERGIES IN EAST AND WEST GERMANY – ARE THERE EXPLANATIONS FOR THE DIFFERENCES IN PREVELANCE?

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The unification of Germany provided a unique opportunity to study the impact of different environmental and social conditions on the development of allergies in two ethnically similar populations. Whereas motorization was the characteristic of many West German cities, heavily polluting industrialization with scanty motorization and private coal burning for heating purposes was typical of East German cities. From a social point of view, very significant differences existed between both parts of the country in many aspects of daily life that may affect allergic sensitization. Children in East Germany lived in smaller, more crowded homes, in larger families, and were more exposed to many other children in day care setting (and thus to viral infections) much earlier than their counterparts in the West side of the country. Living conditions of children in East Germany were almost invariably lower of children raised in the West.

The objective of our study was to compare the prevalence if asthma and allergic disorders among children living in East and West Germany. We assessed the prevalence of asthma and allergic disorders in 9–11 year old children in Leipzig and Halle in East Germany, as well as Munich, West Germany. All fourth grade pupils (n=7,445) at all primary school in Munich were included in a first study in 1989/90. Immediately after the fall of the wall, all pupils (n=1,429) attending classes of the fourth grade at a random sample of 28 schools in Leipzig were studied in 1990/91. In addition, all schoolchildren (n=3,105) attending classes of the fourth grade of a random sample of 39 schools in Leipzig and of 23 schools in Halle were studied in East Germany in 1991/92.

Children in Leipzig, Halle and Munich were similar with regard to sex and age distribution as well as height and body weight (1, 2). The lifetime and period prevalence of doctor diagnosed asthma was higher in Munich than in Leipzig/Halle. A significant excess in the prevalence of doctor diagnosed recurrent bronchitis was found in Leipzig/Halle as compared to Munich. Conversely, the prevalance of doctor diagnosed hay fever and of typical symptoms of rhinitis such as running, stuffy or itching nose were significantly lower in Leipzig and Halle than in Munich. Parents were also asked to indicate whether symptoms occurred during specific months. In Munich rhinitis symptoms showed a strong peak during the summer months, when pollen counts are high whereas in Leipzig the reported frequency of these symptoms increased only slightly during the summer and also increased during the winter months. Baseline measures of pulmonary function did not differ significantly between Leipzig, Halle and Munich. BHR difined as a significant drop in FEV1 alter cold air challenge was higher in Munich than in Leipzig and Halle. Atopic sensitization to mites, pollen and cats as assessed by skin prick tests were all significantly more frequent in children in West Germany, whereas children in both parts of the country reacted with similar frequency to dog dander. These differences were independent of the wheal size chosen as cut-off level for positivity.

In each study area, the prevalence of atopic sensitization decreased significantly with increasing numbers of siblings (3). This relation remained significant when controlling for potential confounding factors such as a family history of asthma or atopy, gender, parents' education, passive smoke exposure, the presence of pets at home, the age of the subject, the month of testing and the study area.

High rates of road traffic impaired pulmonary function and increased respiratory symptoms in children (4) in Munich. However, the prevalence of allergic rhinitis, asthma, bronchial hyperresponsiveness and atopic sensitization was not associated with increasing car traffic. The decrease seen in peak flow rates was comparable with the effect of passive smoke exposure in the same population.

The reason for the difference in the prevalence of atopic diseases between the two parts of the country are unknown. Our findings suggest that outdoor air pollution by SO2, particulate matter and vehicle exhausts is not a strong determinant for the development of atopic diseases. Rather domestic factors characteristic of East European living conditions may interfere with the process of IgE production. Housing conditions and thus exposure to mites and other indoor allergens may differ substantially between East ja West Germany. Measurements of house dust mite allergen (Der pl and Der fl) in dust of East and West German homes, however, point towards a higher mite exposure in Eastern dwellings (2). Thus, it is unlikely that differences in exposure may explain the difference in the prevalence of atopic sensitization between West and East Germany.

A characteristic of East German living conditions has been the easy access to early day care setting, since most women were working in the formed GDR. Day care setting were attended at their first birthday by the large majority of East German children, whereas only a small minority of children in this age group had access to day care in Munich. Moreover, in our data, children from East Germany had significantly more siblings than those from West Germany. This suggests that in part exposure to infectious diseases early in life may play a role in the difference of the prevalence of atopic diseases between West and East Germany.

References:

1. von Mutius E, Fritzsch C, Weiland SK, Roell G, Magnussen H. Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. Br Med J 1992;305:1395-9.
2. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. Am J Respir Crit Care Med 1994;149:358-64.
3. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Reitmeir P, Thiemann HH. Skin test reactivity and number of siblings. Br Med J 1994;308:692-5.
4. Wjst M, Reitmeir P, Dold S, Wulff A, Nicolai T, von Loeffelholz-Colberg E, von Mutius E. Road traffic and adverse effects on respiratory health in children. Br Med J 1993;307:596-600.

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THE ROLE OF ENVIRONMENTAL FACTORS FOR THE DEVELOPMENT OF ALLERGIC DISEASE AS REVEALED BY STUDIES AROUND THE BALTIC SEA

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The downfall of the Soviet empire in Europe has opened the formerly socialist countries of Central and Eastern Europe to epidemiological studies. The prevalence of allergic diseases among children and young adults is low in these countries with a life style which is similar in many respects to that prevailing in Western Europe 30-40 years ago. It is not known whether "western life style" is associated with an introduction of new unknown adjuvants enhancing sensitisation, or whether these is a lack of factors that are necessary for the induction of tolerance.

The likelihood of developing allergic disease in an individual is not constant over time, even if the general propensity is genetically determined. Thus there seems to be a period in early life during which an infant is particularly susceptible to sensitisation. Variations in individual susceptibility to sensitisation over time may also partly be explained by the presence and absence of repiratory tract infection. The role of infections in the respiratory tract as risk factors for the development of childhood allergic disease and asthma is complex, however. It is well established that infections may trigger and aggravate asthma in already sensitised individuals and that infections increase bronchial hyperreactivity. Recent studies suggest, however, that respiratory infections could modify primary immune responses to allergens and reduce the likelihood of sensitisation.

The environment has undergone major changes. The discussion on the possible impact of the various enivironmental changes on the incedence of asthma and other allergies has mostly been limited to the possible effects of a deteriorating air quality, poorly ventilated houses and a increased exposure to certain allergens, notably house dust mites. "Endovironment" is much more than emissions from traffic and exposure to mites, however. Urbanisation has lead to major changes in habits, the food that we eat are in many respects different than only a few decades ago, the intestinal microbial flora has undergone changes, new building materials and methods for construction have been introduced, the homes are larger dwellings, there are many new chemical compounds at home and the life style has changed with more time spent indoors and extensive travelling and exposure to new environments. The concept of "life style" should therefore be expanded considerably.

An understanding of the role of environmental factors has recently become complicated by some recent observations. Air pollution is a major problem in many formerly socialistic countries in central and eastern Europe, yet the prevalence of atopy among children is much lower than in western Europe. For example, the prevalence of positive skin prick tests is much lower in Eastern Germany, Estonia and Poland than it is in Western Germany and Sweden. Mirroring the observed differences in skin prick test positivity in an urban and rural area of Sweden, the prevalence of at least one positive skin prick test was significantly higher in Tallinn, an industrialised coastal city than in Tartu, which is an inland university town. Thus although air pollution does seem to play a role in the development of atopy, other factors connected with western life style are much more important. The nature of these factors is unknown.

The hypothesis that early childhood is a period of particular susceptibility to environmental influences and the onset of the

"atopic march" is supported by studies showing that the large differences between Eastern and Western Germany in the prevalence of sensitisation to inhalant allergens are limited to the age groups born after 1961. Very recently similar data were obtained in a comparative study between two university towns in Estonia and Sweden.

In addition to the intriduction of many new chemicals in the environment, there have been many changes in life style in industrialised countries over the past decades, The type of foods eaten has changed dramatically with the introduction of new industrial products with numerous additives. Even fresh food items differ in many respects from those available only a few decades ago. As an example, by genetic manipulation and use of various chemical compounds the storage time of food has been much prolonged, often allowing a shelf life e.g. apples for months. Virtually nothing is known regarding the possible influence on childhood allergy of such changes in the diet.

Even if all the known environmental risk factors are taken together they cannot explain the large geographic differences in the prevalence of allergy. The conclusion from a broad compilation of what is known regarding tiggers of allergy is that we cannot identify which environmental factors that are the major reason for the large increase in the prevalence in recent years. The future search for significant environmental factors should be direct towards other areas that have not yet been explored. Future research should be truly interdisciplinary and "life style" should be given a broad interpretation.

Further reading:

1. Björkstén B. Risk factors in early childhood for the development of atopic diseases. Allergy 1994;49:400–7.
2. Holt P, O'Keeffe P, Holt B et al. T–cell "priming" against environmental allergens in human neonates: sequential deletion of food antigen reactivity during infancy with concomitant expansion of responses to ubiquitous inhalant allergens. Peadiatr Allergy Immunol 1995;6:85–90.
3. Strachan D. Is allergic disease programmed in early life? Editorial Clin Exp Allergy 1994;24:603–5.
4. Strchan D. Epidemiology of hay fever: towards a community diagnosis. Clin Exp Allergy 1995;25:296–303.
5. Wichmann H. Environment, life–style and allergy: the Germany answer. Allergo J 1995;4:315–6.

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THE FINNISH ISAAC STUDY

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The self–reported prevalence of asthmatic symptoms and associated early childhood factors was studied among 9163 schoolchildren aged 13–14 years in four regions of Finland, as part of the international ISAAC study.

The 66 schools included in the study were randomly selected from the Helsinki area, Turku and Pori county, Kuopio county and southern part of Lapland county. In addition to the ISAAC written and video questionnaires, children were asked about their smoking habits and their parents were sent a detailed questionnaire on risk factors for respiratory diseases. Response rates among children were over 94% in all four areas, but ranged between 64% (Helsinki) and 89% (Turku) among parents.

The self–reported prevalence of wheezing during the previous 12 months according to the written questionnaire was 13% in Kuopio, 17% in Helsinki, 14% in Turku and 15% in Lapland. The respective prevalence for any wheezing in the video questionnaire were 10%, 11%, 12%, and 10%, and of doctor diagnosed asthma 4%, 6%, 7%, and 6%.

Having more siblings was associated with lower prevalence of doctor diagnosed asthma. Also, children attending day–care during the first 3 years of life tended to have less asthma. Analyses were adjusted for age, sex, area, and atopy of the parents and siblings. Parent's socioeconomic status was not associated with asthma.

In conclusion, we found that the regional differences in the prevalence and severity of childhood asthma in Finland are small, but the prevalence may be lower in Eastern Finland. The high prevalence of asthma symptoms in Helsinki may be due to the fact that the survey in Helsinki was done during the pollen season. The observed prevalence of asthma was lower in Finland than in other western countries. The finding that the video questionnaire gave lower prevalence than the written questionnaire is in contrast to findings from other countries and suggests that using translations of the word 'wheezing' in Finnish questionnaires produces internationally incomparable results.

Our findings of decreased risk of asthma among children with several siblings conforms with earlier reports. Also children attending a day–care during the first 3 years of life tended to have less asthma. A possible explanation is a protective role of respiratory infections in early childhood on the risk of asthma.