Message from the new EAACI President

Articles from EAACI 2007 in Göteborg

EAACI-UEMS Examination

and more...
After another big success, this time in Göteborg – many thanks to Jan Lötvall and his team – the EAACI is already preparing for the next steps! We look back at the Congress in Göteborg in this issue and you will read exciting reports of scientific highlights, but the EAACI flag has now been handed over to Ignacio Ansotegui, who is in full preparation of next year’s event in Barcelona (see www.eaaci.net).

At the Congress in Göteborg, the new President of the EAACI, Roy Gerth Van Wijk, took over from Anthony Frew; please read his views on the near future of our society in the “Message from the EAACI President”.

Finally, EAACI together with the UEMS (Union Européenne des Médecins Spécialistes) succeeded in developing the first pan-European allergist examination. The test comprises 30% immunology questions and 70% questions coming from clinical allergology, and thus should filter out the true allergist! However, no reason to panic facing another test: take it as a challenge and learn from the questions! Once you have passed, you can count yourself among the people with the highest standard of knowledge in allergology and clinical immunology. Read more in the interview with Werner Pichler, who was so instrumental in getting this project on track.

Well, for today, you are strongly invited to read this issue of the EAACI Newsletter. Even without having passed the allergy exam, I am sure you will learn from it.
A new President and Board of Officers

The XXVI Congress in Göteborg was extremely successful and was attended by 5,000 people. I would like to extend my congratulations to organisers Jan Lötvall and Cezmi Akdis on their achievement. Many new opinions were heard and suggestions were made at the congress, and some will result in immediate changes and improvements to the structuring of our meetings.

EAACI members were asked, for the first time, to propose ideas for the symposia, speakers, and topics. The Scientific Programme Committee (SPC) was put in charge of the challenge of sorting through all the suggestions from members, and varying sections and interest groups, and succeeded in finalising an excellent programme. We value the input of our members and we will continue to request suggestions and advice. Secondly, the Göteborg Congress introduced postgraduate courses as an important and integral part of the meetings, and this initiative will be continued.

The success of the congress illustrated EAACI’s stability and strength. Although different venues and locations may result in some variation in the number of attendees, the success of consecutive meetings underlines the attractiveness of EAACI meetings in general. The new elements of this congress mark the innovations we aim to introduce over the next two years.

For me, personally, it is an honour and a challenge to be entrusted with the position of EAACI President and to give new direction to our academy. In co-operation with the newly chosen Board of Officers (BoO), I have proposed a programme for the next two years that is detailed in 39 sections. All interested in the proposed path to the year 2009 are invited to take a look at the EAACI website.

One of our first tasks is to implement the new BoO structure that was initiated in 2006 by the General Assembly. The scope of the BoO is extended by three new positions: the Vice-Presidents for Congresses; Education & Specialty; and Communication & Membership.

Cezmi Akdis, Vice-President of Congresses, will focus on the organisation of our meetings. Akdis will address issues such as how to attract more participants, how to optimise the overall organisation of the annual meetings, how to identify new sources of income and savings, and how to measure participant satisfaction. He will also co-ordinate the interest groups. A new SPC co-ordinator will take the lead in building the scientific programme.

Luis Delgado is the new Vice-President of Education & Specialty and co-ordinator of the Summer and other Allergy Schools. He is responsible for communicating with applicants and organisers, and bringing structure to schools, meetings, and workshops outside the annual meeting. His portfolio includes liaison with the Specialty Committee and the CME chair, and the implementation of the European Exam.

Finally, Nikos Papadopoulos, Vice-President of Communication & Membership, has the task of professionalising our communication strategies further, using not only available avenues of communication such as our newsletter, website, and journals but also developing new tools including professional campaigns, membership analysis, and membership recruitment strategies. We aim to enhance and optimise our communication with other sectors of society, as well as expanding membership and increasing active membership participation and interaction with national societies.

This expansion of the BoO gives Jan Lötvall, our Secretary General, the opportunity of focussing on the general EAACI structure, in particular on the Executive Office and updates to our Constitution and By-Laws.

It will be my task to weld all these initiatives into a coherent global plan. One important constituent of this challenge is my goal of strengthening work in the area of Clinical Allergy. We all aim to use the ExCom structure to better serve EAACI.

I look forward to using the term of my mandate to working for EAACI and its membership.

Roy Gerth van Wijk

EAACI President
eaaci.net is increasingly becoming an indispensable resource for researchers, physicians, and scholars. Numbers have actually doubled this year with hits now exceeding 1.5 million monthly and visits of over 60000 a month, which means more than 2000 daily.

Visit www.eaaci.net and make use of the various E-learning center features, such as Case Reports from centers all around Europe, Expert Opinions, written by leading scientists in the field of Allergy and Immunology, Position Papers, some of which are presented exclusively on the EAACI website, Web Casts from both official EAACI Allergy schools and the annual EAACI congress.

You may also get informed about the Academy’s latest news, including activities such as congresses and Allergy Schools as well as outcomes of Task Forces generated within the EAACI.

Become an EAACI member and enjoy all the on-line benefits such as access to the journals “Allergy”, “Pediatric Allergy and Immunology” and the EAACI Newsletters.

Junior members of the EAACI have their own website corner, through which they are presented with information motivating communication, career advancement and active involvement within the Academy.

Now, there are many reasons to visit www.eaaci.net and we plan on making them more.

EAACI Website Team

www.eaaci.net

EAACI Executive Committee

2007–2009

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XXVI EAACI Congress
Göteborg, Sweden
9–13 June, 2007

Number of delegates: 4455 from 95 countries
Exhibitors: 587
Abstracts: 1650
Posters: 1470 (270 poster discussions)
Asthma is a serious global health problem. This chronic airway disorder affects people of all ages in all countries. When uncontrolled, it severely limits everyday activities and can, in some instances, even be fatal. The prevalence of asthma is on the increase in most countries, especially where children are concerned. The disorder places a significant burden on family life, not only in terms of health-care costs but also in terms of lost productivity and reduced participation.

Many accurately performed studies have shown evidence that correct treatment can provide a marked improvement in the disease. Patient compliance is an absolute necessity in achieving the optimal response to medication. Education is also a very important issue, as well as the investigation into and the reduction of all risk factors. Atopic asthma can be induced by animal hair, dust mites, feathers, pollen, and mould. However, with intrinsic asthma, bronchial hyper-reactivity is caused by the inhalation of chemicals such as sulfur dioxide, ozone, and cigarette smoke as well as viral infections, cold air, exercise, and stress. Analgesics, including aspirin, can also trigger an asthma attack.

The Revised Global Initiative for Asthma (GINA) guidelines were published online in November 2006. They outline the new principles in the treatment of bronchial asthma that have been proposed in recent years. The main aims of asthma treatment comprise: complete control, the continuation of physical activity by patients, the maintenance of spirometry values on the highest levels, the effective control of exacerbations, and a decrease in patient mortality. Therapy should always be safe for patients.

Levels of control should be evaluated regularly to make medication effective. The revised GINA guidelines suggest three control levels. (See Graph 1)

Treatment is given in periodically repeated phases: The control of level estimation, treatment to achieve better control or sustain the current state, and the monitoring of asthma control. Controlled asthma should exhibit the complete absence of manifestations and a normal spirometry level before therapy is reduced. When asthma is partially controlled, basic therapy can be stepped up to reach the control level or preserved at its current level. Increased medication is necessary in instances of uncontrolled asthma. (See Graph 2)
an initiative from Bochum, Germany for an international study to monitor time trends and determinants of the prevalence of asthma and allergies in children. ISAAC is a unique project and has attracted world-wide interest and participation on an unprecedented large scale.

A list of ISAAC publications and abstracts is available online at (http://isaac.auckland.ac.nz).

Antigen-presenting cells (APCs) in the bronchial mucosa capture inhaled allergens and present them to CD4+ T-cells, which then differentiate into T-cells of the Th2 phenotype. These cells secrete IL-4, IL-5, IL-9, IL-10, and IL-13, and promote a switch in B-lymphocyte immunoglobulin secretion, inducing the production of IgE. Eosinophilic and basophilic granulocytes are also activated by IL-13, leading to the release of chemokines and proteolytic enzymes. The IgE molecules circulate in the blood, and then bind to high-affinity receptors (FcRI) on basophils, mast cells and to low-affinity receptors (FcRI, CD23) on eosinophils and macrophages. The allergen can next rapidly interact with the IgE molecules that are already bound to the cell surface. Histamine, proteases, leukotriene, prostaglandins, and platelet-activating factor (PAF) are released.

**Bronchoconstriction in asthma occurs in two phases:** the “early response” case involves histamine, prostaglandinD2 (PGD2), cysteinylleukotrienes (LTC4, LTD4, LTE4), and PAF. The cysteinyl-leukotrienes induce protease release: tryptase cleaves D3a and bradykinin from protein precursor molecules, leading to bronchial muscle cell contraction and increased vascular permeability. Chymase promotes mucus secretion. The induction of bronchoconstriction with mucosal edema and mucus secretion results in coughing, wheezing, and breathlessness. In “late reaction” cases, LTB4 and PAF attract eosinophils, which in turn attract major basic protein (MBP) and eosinophil cationic protein (ECP), with a toxic effect on epithelial cells resulting in epithelial destruction. The accumulation of mucus takes place in the bronchial lumen due to the increased number of goblet cells and hypertrophy of the submucosal mucous glands. The hypertrophy of smooth muscle in the basement membrane increases and the...
so-called remodelling process develops.

Genes and environment in asthma Atopic diseases are the result of complex interactions between largely unknown genetic and environmental mechanisms. The identification of environmental factors offers the real possibility of preventing disease, and unravelling the genetics of allergic illnesses will likely change their classification and treatment. Early life seems particularly important, when the initiation of allergic disease may result from genetic and environmental modification of the immune interaction between mother and child.

Perhaps the greatest potential for environment and genes to interact is in exacerbations LPS and CD14, TNF, IL-8, IL-1b; Bacterial infections and TLR2, TLR6, TLR10; Viral infections and TNF, IL-8, IL-1b; Air pollution, tobacco smoke and TNF, IL-8, IL-1b. Other associations for viral infections and asthma include -251A polymorphism of IL8 associated with asthma.

Virus-induced asthma exacerbations The great majority of acute asthma exacerbations is associated with respiratory viral infections. Of the viruses implicated, approximately 60% are human rhinoviruses (RVs). The mechanisms of RV-induced asthma exacerbations are poorly understood. Adults with asthma have an increased susceptibility to naturally occurring RV infections. Initially, primary bronchial epithelial cells from subjects with asthma were shown to replicate RV in vitro to several logs, whereas those of normal control subjects were resistant to infection. This resistance was a result of the rapid induction of apoptosis and of interferon (IFN)-beta in the normal cells, whereas these responses were deficient in asthmatic cells. The studies were recently extended to a novel family of three related proteins, the IFN-lambdas 1–3, production of which was also deficient in vitro and related to asthma exacerbation severity in vivo. These studies identify novel mechanisms for the increased susceptibility of subjects with asthma to RV infection. Further studies are now required to investigate whether the administration of IFN-beta or IFN-lambda may be beneficial in treating asthma exacerbations, to determine whether similar deficiencies are observed in children and in subjects with nonatopic asthma, and to investigate the mechanisms of deficient IFN production in asthma to help identify better therapeutic strategies for asthma exacerbations.

Little is known regarding genetic polymorphisms related to asthma exacerbations, similar to the lack of data on gene-environment interactions, deficient rhinovirus induced IFN- and – production in asthma, as related to rhinovirus replication, the exacerbation of its severity and virus-induced airway inflammation. The mechanisms of rhinovirus induction of interferons are also poorly understood. It is considered likely that polymorphisms in IFN-inducing genes interact with the environment in altering the risk of exacerbations. New approaches to treatment may result from the study of these mechanisms.

Molecular mechanisms of asthma The treatment of
asthma and allergy is experiencing a paradigm shift. In the 1950s, asthma was regarded as a muscle spasm disease and was treated with spasm-alleviating drugs such as adrenaline. In later years, it was considered an inflammatory disease in the central airways, and was widely treated — and still is — with inhaled cortisone, mainly depositing in the central airways. But the results of 21st-century research show that the entire airway system is linked. The molecular mechanisms of asthma are complicated and not fully investigated. T helper cells release specific cytokines that mediate inflammation. Th1-type cells produce interferon-gamma (IFN-γ), and tumour necrosis factor alpha (TNF-α), whereas Th2-type cells produce IL-4, IL-5, IL-6, IL-9, and IL-13. In addition, both Th1 and Th2 produce some common cytokines (i.e., IL-1, IL-3, IL-8, TNF-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF). The Th2 and common cytokines are the signaling molecules that have been most strongly linked to asthmatic responses.

Immunoglobulins, cytokines, and chemokines appear to play important roles in the inflammatory foundation of asthma. For example, IL-5 promotes the development and survival of eosinophils, the cells that help drive the chronic asthmatic response. IL-8 is a potent chemo-attractant for neutrophils, eosinophils, and peribronchial CD4+ cells. Moreover, ovalbumin-induced increases in mucus and airway eosinophils, and peribronchial CD4+ cells are also reduced. Increased inflammation and remodelling in these mice are accompanied by lower levels of the chemokines eotaxin-1 and thymus- and activation-regulated chemokine, as well as TGF-b1. In all, these data suggest that epithelial cell-specific NF-kB participates indirectly in airway remodelling by regulating inflammatory responses that contribute to mucus production, fibrosis, and airway wall thickening in experimental asthma. Overall inflammation and eosinophilia were inhibited, as was AHR, indicating a broad anti-inflammatory effect.

Conclusion The question “Why does asthma occur?” remains unanswered. Despite the successes of contemporary science, many questions remain regarding the disorder’s molecular level, pathogenesis, epidemiology, and treatment and prevention issues. Leading scientists continue to apply themselves and their studies to the investigation of this probe – to achieve the aim of improving the quality of life for all patients.

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References

Prof. L. Bjerner

September 2007 - Issue 13
Augmented Bronchial Constriction and Impaired Bronchial Relaxation in Asthma

Augmented constriction – bronchial hyperresponsiveness

The airways of asthmatic patients respond to a lower dose of bronchoconstrictors and the effect is more pronounced than with that of healthy subjects. This phenomenon is called bronchial hyperresponsiveness (BHR), and has been considered one of the most characteristic features of asthma for many years. The presence of BHR in asthmatic patients can be clinically demonstrated as a significant bronchoconstrictive response to nonspecific stimuli such as histamine, methacholine, adenosine, cold air, and exercise. The evaluation of BHR in asthmatic patients has practical implications, as an accurate correlation has been demonstrated between BHR and the frequency of asthma exacerbations. Moreover, asthmatic patients with greater BHR are at increased risk of developing irreversible airflow limitation.

Some correlations between the degree of airway inflammation and sensitivity to bronchoconstricting stimuli have been demonstrated in asthmatic patients. However, the correlations are more accurate with some bronchoconstrictors and less so with others. Direct stimuli are the substances which act directly on smooth muscle receptors, such as histamine on histamine receptor H1 and methacholine on muscarinic receptors. Those that induce bronchoconstriction through the activation of mast cells are considered indirect stimuli, such as adenosine and exercise. Airway response to indirect stimuli is more closely associated with the intensity of airway inflammation than the response to direct stimuli.

As a result, the rapid and variable changes in airway inflammation that occur during infections or with allergen exposure seem to have a stronger effect on BHR to indirect stimuli. Bronchoconstriction induced by histamine and methacholine reflects persistent BHR associated with the remodelling of the bronchial wall. The augmented bronchoconstriction induced by direct stimuli appears to be dependent on the increased contractility of smooth airway muscles. In fact, asthmatic patients have thicker airway walls than do healthy subjects. One major cause of that thickening is increased smooth muscle mass due to hypertrophy and hyperplasia. Anti-inflammatory medication, such as inhaled corticosteroids, predominantly affects that variable, dependent on inflammation BHR, while its effect on persistent BHR seems to be mild.

Impaired relaxation – response to deep inspiration

The increased propensity for constriction is not the only characteristic of asthmatic airways. An increasing body of evidence indicates that impaired relaxation is also an important feature of airways in asthmatic patients. This should not be confused with an improper response to a bronchodilator. Physiologically, several factors modulate airway resistance. These include nervous and endocrine factors which influence the circadian changes of lung function in both healthy subjects and asthmatic patients. With healthy subjects, drawing in deep breaths, or deep inspiration, results in bronchodilation and protection from bronchoconstriction. When healthy persons are restricted from breathing deeply, significant bronchoconstriction in response to methacholine administered at low concentrations can be demonstrated. This bronchoconstriction is totally absent when those persons are allowed to breathe deeply. For asthmatic patients, both beneficial effects of deep breathing are impaired. Moreover, deep inspiration in some asthmatic patients may even augment airway obstruction. Impaired bronchodilation after deep inspiration, seen even with patients with intermittent and mild persistent asthma, indicates the impairment of airway smooth muscle relaxation in those patients.

Remodeling progresses

Accordingly, not only an increased propensity for constriction but also defective muscle relaxation appears to characterise airway smooth muscle in asthmatic patients. The causes and mechanisms of the impairment of deep breath bronchodilatory and broncho-protective effects are still under investigation, but inflammatory mechanisms seem to play a role. Asthmatic patients with the reduced bronchodilatory effect of deep inspiration inflation of the airway smooth muscles by mast cells exhibit increased quantities of CD4+ lymphocytes in the lamina propria. Interestingly, no association has been demonstrated between the reduction of airway resistance induced by deep inspiration and the baseline lung function or age of asthmatic patients. Those findings indicate that the phenomenon is not simply related to the remodelling process but seems to be actively modulated by inflammatory processes in the airways.

However, the association between impaired deep inspiration-induced bronchodilation and the number of mast cells within the airway smooth muscle bundles indicates that the phenomenon is rather unique for asthmatic airway inflammation; as with eosinophilic bronchitis, no infiltration of smooth muscle zone by mast cells is seen. Finally, it seems that the inability of deep inspiration to overcome bronchoconstriction leads to decreased basal airway diameter and can contribute to BHR.

In conclusion, it would appear that augmented contraction and impaired relaxation represent two sides of the same coin. Asthmatic patients exhibit airways that are “stiffer” than in healthy subjects, and therefore respond to different bronchoconstrictive stimuli and are less prone to bronchodilation. The clinical significance of BHR is well established and correlates with asthma severity, while the clinical importance of impaired deep breath bronchodilation, which is also a characteristic feature of asthmatic airways, remains to be established. Potential therapeutic intervention should be sought to modulate impaired deep breathing bronchodilation.

Krzysztof Kowal
Early Diagnosis and Risk Prediction in Anaphylaxis
– Latest Research Highlights

Universal agreement on the definition of anaphylaxis does not exist, attested Professor Dean Metcalfe from the U.S. in his opening speech to the Practical Symposium at the EAACI Congress 2007. Anaphylaxis is an acute and potentially lethal multisystem allergic reaction presenting one or more of the following symptoms: laryngeal oedema, flashing, pruritus, urticaria, angio-oedema, bronchospasm, cardiac arrhythmias, hypotension, abdominal pain, and diarrhoea. The diagnosis of this life-threatening disorder is based on the acute onset of illness involving the skin, mucosal tissue or both and at least one of the following can be observed: compromised respiration, reduced blood pressure, or associated symptoms of end-organ dysfunction.

Anaphylaxis fatalities are airway and tissue oedema, pulmonary hyperinflation, tissue eosinophilia, elevated serum tryptase, and myocardial infarction. The treatment of anaphylaxis includes the removal of the participating agent, placing the patient in the correct position (supine), maintaining open airways, and giving medication such as epinephrine, corticosteroids, H1 and H2 antihistamines, vasopressors, or glucagon.

Professor Metcalfe also analysed the mechanisms of anaphylaxis and the mediators involved. The most convincing mechanisms in humans are IgE and mast cells and basophils, although mast cell mediators are not always elevated. Complementary activation may also have a role via mast cells and basophils or have a direct effect on target systems. Nevertheless, animal models demonstrate the possibility of other new mechanisms, despite the differences in the immune systems for mice and humans.

Professor Lawrence Schwartz, from the U.S., presented details about laboratory findings during anaphylaxis, such as mediators released from activated mast cells. Mediators produced in the first 15 minutes include histamine, heparine, chondroitin S04, tryptase, chymase, carboxypeptidase, and cathepsin G. Mediators produced in the following 30 minutes include LTC4 and PGD2, while in the following hours and days, cytokines and chemokines (IL-4, IL-13, TNF-α, IL-5, 6, 8, 13, MCP1, and MIP1α) are released. Professor Schwartz gave evidence of the increased production of tryptase and histamine in plasma during insect sting-induced systemic anaphylaxis, illustrating that histamine is a more sensitive factor but impractical for routine use. Concerning tryptase, immunoassays exist for both mature and total tryptase but the interpretation of their production should be of great concern, since total tryptase levels generally reflect the increased burden of mast cells in patients with all forms of systemic mastocytosis, while mature tryptase is elevated during most cases of systemic anaphylaxis, particularly with parenteral exposure to the inciting agent. Other important mediators include chymase, a serine protease stored mainly in the secretory granules of human mast cells. Chymase, in parallel with tryptase, appears to be elevated in the serum of eight cases of fatal anaphylaxis, and this might be an additional tool in the postmortem diagnosis of anaphylaxis. Professor Schwartz also showed the presence of the protease carboxypeptidase A3 stored in the secretory granules of MC(TC) types of human mast cells, which have been tested on mice and seem to evoke a delayed appearance.

Professor Ulrich Müller from Switzerland covered the risk assessment of anaphylaxis. The severity of previous reactions, the allergen responsible, the patient’s age, co-existing morbidity, and concurrent medication are the most important anaphylaxis risk factors. A positive clinical history, skin tests, venom-specific IgE in venom allergy, and sting challenge are believed to be the main tools in the diagnostic process. The skin challenge is supposed to be the golden standard, although it often shows double positivity due to true double sensitisation or crossreactivity. To distinguish between double sensitisation and crossreactivity, the RAST-inhibition test, sIgE against CCDs, and inhibition tests against CCDs should be conducted.

Focussing on food allergy, Professor Müller outlined the predictive value of food-specific IgE, which is frequently positive in asymptomatic patients, while high sIgE indicates an increased risk of further anaphylaxis. In addition to a patient’s clinical history and IgE, the food challenge is of great value. It requires a low level of sensitisation, clinical tolerance after previous anaphylaxis, and should only be performed at hospitals in controlled conditions. Cellular tests, as the release of leukotrienes (CAST), and the basophil activation test (BAT) are also performed for in vitro diagnosis of IgE-mediated reactions. CAST has almost the same sensitivity and specificity as skin tests, while the BAT test has higher sensitivity and specificity for venoms. It has been tested for foods, pollen latex, and drugs and its predictive values during venom immunotherapy are in some doubt. The professor concluded that more data for these tests are needed in relation to provocative tests.

Studies of the mechanisms have revealed some of the gaps in understanding the pathways of the cells involved in the initiation of the anaphylactic response. It is crucial that this life-threatening disease receives correct diagnosis and proper treatment. Clinical history, skin prick testing, specific IgE, cellular tests, and provocative tests all provide a powerful combination of diagnostic tools for the investigation of anaphylactic reactions.

Maria Xatzipsalti
EAACI JMA Paediatric Section Representative

EAACI 2007 in Göteborg
The term “allergen” is most often used in the vocabulary of everyday life to indicate the entire substance that can initiate an allergic reaction, such as certain pollens, moulds, house dust mites, animal dander, cow milk, and other inhalants or food items known to trigger immediate or late hypersensitivity reactions. The term is also used to denote environmental components that elicit delayed hypersensitivity reactions. Allergens also indicate the particular molecules which specifically take part in the immune reactions of an allergy.

Since most allergens belong to a limited set of protein families, this disproves the assumption that every protein can become an allergen. The classification of allergenic proteins (including the comparison of allergenic and non-allergenic members of a protein family) will lead to new insights into factors that contribute to allergenicity.

Allergens have no characteristic structural feature other than their need to reach (and stimulate) immune cells and mast cells. Within these constraints, any protein is potentially allergenic, particularly if it avoids the activation of Th2-suppressive mechanisms (CD8 cells, Th1 cells).

Hypothetically, three types of sensitising allergens can be noted:
1. Monomeric proteins: classical atopic allergens (unconventional antigens)
2. Oligomeric proteins and other conventional antigens
3. Secondary sensitisers (not to be confused with non-sensitising crossreactive allergens)

IgE breeds IgE
Pre-existing IgE antibodies to other components in the allergen source material are the most potent adjuvant for IgE. Although the search for “initiator allergens” is potentially interesting; no definite conclusions can be drawn as yet.

More than 25% of the population suffers from Type I allergy, a genetically determined hypersensitivity disease. The symptoms of Type I allergy (e.g. allergic rhino-conjunctivitis, asthma, atopic dermatitis) are due to the formation of IgE antibodies against per se harmless environmental antigens (i.e., allergens). Both allergy diagnosis and immunotherapy are still performed with natural allergen extracts comprising mixtures of allergenic and non-allergenic components that are difficult to define.
Allergen epitopes stimulate T-cells. The tools for local passive therapy are IgE-binding haptenes from major allergens and allergen-specific antibody fragments. Cross-linking effector cell (i.e., mast cell and basophil) bound IgE antibodies with specificity for at least two different IgE epitopes are required to trigger the release of inflammatory mediators. As a result, the precise knowledge of IgE-binding sites is crucial in the analysis of the allergic effector response. This can be achieved by mapping immunodominant IgE epitopes, as was recently demonstrated for the major timothy grass pollen allergen, Phi p 1.

This indicates that IgE and IgG responses in allergic patients may also evolve in a nonsequential way, and that IgE and IgG antibodies may possess different affinities or high specificity for certain epitopes.

As a result, it appears that the allergen-specific IgE and IgG response in allergic patients is poorly synchronised for epitope recognition and perhaps affinity. These differences in epitope recognition of IgE and IgG antibodies could recently be demonstrated for monoclonal human IgG antibodies specific to the major birch pollen allergen Bet v 1. However, the demonstration that certain Bet v 1-specific IgG antibodies can block IgE binding to Bet v 1, and inhibit the Bet v 1-induced histamine release in several donors, clearly indicated that blocking IgG antibodies effectively reduces anaphylactic effects.

The definition of crossreactivity is based on immunologic recognition. Two allergens are crossreactive if there is a single antibody (or T-cell receptor) that reacts with both. This basic definition can be extended and expanded by defining an affinity threshold and by including clinical relevancy. It is important to appreciate that it may be possible to show convincingly that allergens are cross-reactive, but that it is impossible to prove that allergens are not crossreactive.

The crossreactivity of IgE antibodies is of interest for various reasons, three of which are discussed. Firstly, from the clinical view, it is important to know the patterns of crossreactivity, because they often (but not always) reflect the pattern of clinical sensitivities. Clustering crossreactive allergens may simplify diagnostic procedures and therapeutic regimens. Secondly, IgE crossreactivity is of interest for its immunologic basis, particularly in relation to the regulation of allergic sensitisation. It is relevant to compare not only the structural relation between the two allergens in question, but also the relation to the human equivalent (if any) and how the latter influences the immune repertoire. Thirdly, the prediction of IgE crossreactivity is of interest in relation to allergic reactivity to novel foods. Crossreactivity is a property defined by individual antibodies to individual allergens (R. C. Aalberse, J. H. Akkerdaas, R. van Ree).

The modification of protein antigenicity in foods by thermal processing is complex, especially as there are so many variables within the composition, processing conditions, circumstances of exposure to the consumer, and the particular responsiveness and genetic make-up of the individual. But AGE modifications are formed through an important chemical pathway, leading to distinct, if complex, patterns of protein derivatives. These are likely to be key sources of thermally induced neo-antigens. A more detailed understanding of such general routes of covalent protein modification can make foods safer (P. J. Davis, C. M. Smales).

Heat treatments alter the structure of proteins, i.e., the allergenic constituents of a food. As a consequence, the treatments alter the allergenic potential and therefore the allergenicity of the whole food. Although no clear or general relationship between the structure of a protein and its allergenicity has been established, this view assumes, albeit not explicitly, that allergenicity is an intrinsic property of a protein due or strictly related to particular structural features. This view, however, does not take into account the qualitative and quantitative variability of the allergen repertoire of a whole food, the multiplicity of epitopes on a given allergen or the genetic/geographic variability of the immune response in atopic human beings (J.-M. Wal).

Michael Rudenko
Official Representative of EAACI ENT Section
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EAACI Newsletter (EN): Dr Pichler, you are organising an EAACI task force to set up an EAACI-UEMS examination. Could you tell us something about the purpose of this examination?

Prof. Werner J. Pichler (WP): Allergology is a new area in medicine, and taught and trained from different perspectives in Europe. Papers have considered the optimal training in allergology and clinical immunology, but it seems to be difficult to put this into practice. This new examination will clarify the essentials required of a well-trained allergologist. It will also help to harmonise the practice of allergology in Europe and also increase standards in our discipline.

EN: How will the examination achieve this?

WP: The examination is based on a so-called blueprint that covers all the relevant topics of allergology and clinical immunology to be examined, and is already online on the EAACI website (http://www.eaaci.net/site/content.php). It comprises 30% immunology, covering the subjects of clinical immunology and basic immunology, and 70% allergology. In addition, we provide a list of relevant literature to help people identify the areas to be examined and prepare for the examination.

EN: Will this new examination be a substitute for those at the national level?

WP: Absolutely not. We do not want to compete with national-level examinations. The EAACI and UEMS believe that national organisations play a strong role. However, smaller associations do not have the facilities to take on the enormous work required to prepare a good written examination each year. The EAACI-UEMS examination may become part of the national system. For example, in Switzerland, there is a written and an oral examination for allergologists, who are admitted during or after their last year of training in allergology and clinical immunology. If EAACI and UEMS can offer an examination with a high standard, some associations could rely on it and supplement it with their own local, oral examinations. This would allow the consideration of local issues and a practical approach to working with patients. Combining the EAACI-UEMS exam and local examinations would definitely guarantee a high standard and include the consideration of local issues.

EN: Who is going to take this examination?

WP: This exam has generated a lot of enthusiasm, especially from young people. When I was a student, I took the so-called ECFMG examination, which was one of the requirements at that time to practice as a doctor in the U.S. It was very satisfying to have passed it: I knew I had acquired good overall medical knowledge, and it was useful when applying for medical positions. I believe the EAACI-UEMS examination will fulfill the same role in our discipline. People will be able to test their knowledge; they will see whether their learning covers the required topics; and all will be able to meet the same standard, irrespective of national origin, once they have passed the same exam. However, this document certifying their knowledge does not give them a licence to practice aller-
EN: Can anybody apply to sit the examination?

WP: The limits to applications are still under discussion. Theoretically, this exam in allergology and clinical immunology should be open to everybody, and we should welcome the inclusion of more people who can increase their knowledge about our discipline. However, serious concerns remain, as applications to take exams in other medical disciplines are restricted to trained specialists only. In addition, we want to hold this examination for doctors with practical experience in our area, which is as important as theoretical knowledge. Most of the people involved in preparing the exam would prefer it to be taken by students in the last year of their training programmes in allergology and clinical immunology.

Some countries define allergologists in different ways, as some consider allergology to be a subspecialty, while others accord it full specialty status. This new exam will not change these discrepancies, but it will emphasise that allergologists should possess certain knowledge independent from a specialty background. Dermatologists practising as allergologists should have a profound knowledge of asthma, while pneumologists practising as allergologists should be familiar with atopic dermatitis, etc. These diseases often occur together. We will try to emphasise the unity of this concept in the examination.

EN: Don’t you risk excluding some EAACI members by restricting applications to the exam to those who had the advantage of studying an established curriculum?

WP: That is a good point, and indeed, I emphasise that we do not want to exclude any allergologists because of differences in national perspectives. We are aware that the national training curricula for allergology are not optimal or even existent in some European countries. However, despite the lack of an official curriculum in any specific country, those persons who feel that they are eligible to take the exam are welcome to apply, and a committee will make a decision on the matter. The support of a national society will always be helpful.

EN: Will the standard of the examination be high?

WP: Naturally, the exam will identify the people in each country with the highest standard of knowledge in allergology and clinical immunology. It will contain more in-depth questions than, for example, examinations at medical school or the examination for internal medicine, dermatology, or pneumology, which also contain some questions about allergology. All questions will be multiple choice and will be analysed by a committee, which should surely rule out anything too exotic.

We have tried to define the topics and to cover those areas encountered in daily practice by a broadly active allergologist. I personally believe that any experienced allergologists, who reads literature on the discipline regularly and aims to keep up to date on new data, should be able to pass the exam. And I also believe that anybody passing the EAACI-UEMS exam should be proud of their accomplishment, although it will be possible to repeat the exam if required.

EN: What is the fee for the exam and when is the deadline for registration?

WP: Applications for the EAACI-UEMS exam will be accepted from February 1st 2008 until March 31st 2008. Each application costs €250 for EAACI members, and €400 for non-members. The payments will help to cover the immense costs in preparing and correcting the exam — one good multiple choice question costs a lot by the time it is completed. We all have to thank the EAACI for investing in this examination and it is obviously an important undertaking for the EAACI and the UEMS.

EN: Thank you very much for agreeing to do this interview.

WP: My pleasure, and don’t forget to register for the examination! The more people that participate, the better. Your participation will strengthen this EAACI-UEMS undertaking, and we will write up a nice certificate for you!
Allergic diseases including asthma are characterized by high serum and tissue levels of allergen-specific IgE, activation of mast cells, accumulation of eosinophils in the effector organs and presence of allergen-specific T helper cells secreting IL-4, IL-5 and IL-13 (Th2 cells). Allergen exposure results in further increase in the number of cells infiltrating bronchial wall and increased secretion of Th2 type cytokines. For many years it has been thought that interaction of IgE with a specific allergen is the most important step in the pathogenesis of allergic bronchial asthma. Increasing body of evidence however indicates that in the absence of IgE asthma phenotype can develop. It is well recognized that in nonatopic (“intrinsic”) asthmatic patients serum IgE concentration is within normal limits but histological analysis of bronchial tissue samples resemble those seen in atopic asthmatics. Moreover, activated T cell (CD4+) and eosinophil infiltration of the bronchial wall are observed in both allergic and nonallergic asthmatics. The crucial role of CD4+ cells for development of asthma has been demonstrated in several animal and human studies. Adoptive transfer of CD4+ cells from animals with allergen induced bronchial hyperresponsiveness to animals which had not been sensitized is associated with appearance of asthmatic phenotype in allergen challenged recipient animals. In humans application of medications which inhibit T cell function such as cyclosporin A or anti-CD4 monoclonal antibodies results in attenuation of asthma related outcomes. Further evidence for a crucial role of activated CD4+ cells in asthma comes from patients who develop asthmatic symptoms upon exposure to isocyanates. In those patients the appearance of bronchoconstriction is associated with activation of CD4+ cells in the absence of increased IgE production and IL-4 secretion. Similarly, some antigens such as Candida albicans induce T cell proliferation and activation in intrinsic asthmatics. Again that is not associated with increased production of antigen specific IgE.

Unfortunately in vivo studies concerning T cell function in allergic asthmatics were either limited to nonspecific modulation of their function (eg using anti CD4 antibodies) or were flawed by IgE dependent activation of effector cells whenever whole allergen extracts were used. The IgE dependent activation of other effector cells such as mast cells or basophils is clinically manifested in asthmatic patients as an early asthmatic reaction (EAR) but under certain circumstances may be manifested as severe anaphylactic reaction. Immunoglobulins, including IgE, recognize three-dimensional structure of an antigen, therefore conformational changes or chemical modification of a native allergen may lead to disrupted interaction between a given antigen and the corresponding antibody. On the other hand CD4+ T cells recognize short peptides which are presented by antigen presenting cells in the context of major histocompatibility complex class II (MHC-II). Allergens like many other antigens are ingested by antigen presenting cells, which keep mucosal surfaces under surveillance, and subsequently are digested by proteolytic endosomal enzymes giving rise to short peptides which bind to MHC-II molecules. The fragment of MHC-II molecule which is responsible for binding of antigen derived peptides are highly polymorphic and therefore in individual patients different peptides derived from the same antigen may be responsible for induction of the adaptive immune response. Ingestion and processing of antigens is associated with maturation of antigen presenting cells and migration of these cells to the regional lymphoid organs where they encounter T cells. Whenever allergen fragments attached to MHC-II molecule on antigen presenting cell is recognized by a T cell receptor (TCR) and appropriate co-stimulatory signals are present activation and clonal expansion of T cell takes place.

Recently a new approach utilizing T-cell specific allergen derived peptides has made it possible to study the role of allergen specific T cells in...
**T Cells in Asthma**

asthma in humans. Application of new molecular biology techniques allows to synthesize short peptides which contain sequences of an allergen which are recognized by MHC-II molecules and TCR of patients sensitized to a given allergen. The peptides have to be short, usually containing 16-17 aminoacids, to avoid IgE dependent activation of effector cells including mast cells and basophils. Intradermal or intrabronchial challenges of cat sensitive asthmatic patients with short peptides derived from Fel d 1, a major cat allergen, result in the development of an isolated late asthmatic reaction (LAR) without early bronchoconstriction. The appearance of a LAR after administration of those peptides is associated with activation of T cells, influx of inflammatory cells into the bronchial wall and increased airway hyperresponsiveness. This observation supports the major role of T cells in chronic allergic inflammation.

Since application of short allergen derived peptides allows targeting T cells without IgE dependent activation of effector cells, it may become a good candidate for specific modulation of T cell function in allergic patients. In fact several studies in animals and in humans demonstrated that mixtures of allergen derived peptides covering the relevant epitopes are safe and efficient when used as immunotherapy in allergic asthma and allergic rhinitis. Cat allergen peptide immunotherapy results in significant symptomatic improvement and reduces whole allergen induced early and late cutaneous responses. Moreover, in cat sensitive asthmatic patients these peptide immunotherapy attenuates late asthmatic reaction in response to both peptide and whole allergen challenges. Those beneficial clinical effects are associated with decreased secretion of Th2 type cytokines and increased production of IL-10 by peripheral blood mononuclear cells. Moreover, Fel d 1 derived T cell peptide therapy was associated with significant increase in the number of CD4+/CD25+ regulatory cells in the site of allergen induced late phase cutaneous reaction in cat allergic patients. Of interest, in animals, tolerance can be induced by application of allergen derived peptides intradermally or by inhalation. On the contrary, in humans, only intradermal injections of allergen derived peptides resulted in tolerance to the whole allergen challenge. Those differences in the immune tolerance induction may reflect changes between human and mice in terms of immune reaction to antigens. However, the inability of tolerance induction by application of allergen derived peptides to the effector organs (eg intrabronchial application in asthmatic patients) may reflect changes in the microenvironment present in those organs in symptomatic allergic patients. Similar observations were made while using intrabronchially whole allergen extracts for immunotherapy of asthmatic patients.

Clearly, application of allergen derived T cell specific peptides for immunotherapy of allergic diseases is not associated with IgE dependent activation of effector cells and therefore enables to conveniently schedule the dosing regimen. Further studies are warranted to establish the most effective dosage. Moreover, possible adjuvants and/or other immunomodulatory molecules which may enhance efficacy of this therapeutic approach should be considered. Understanding the mechanisms responsible for developing and perpetuating allergic inflammation may help in creation novel, safer and more effective therapeutic strategies.

Krzysztof Kowal
The “Third Child” of the PRACTALL Initiative:

A Consensus Report on Diagnosis and Treatment of Paediatric Asthma

“The asthmatic child is not a little adult suffering from asthma,” said Professor Ulrich Wahn, PRACTALL Chairman and Head of the Department of Paediatric Pneumology and Immunology at Charité-Humboldt University, Berlin. “There are remarkable differences in natural history, pathophysiology, and treatment as well as substantial differences in the diagnosis and therapeutic management of pediatric asthma practiced by pediatricians in different countries,” the professor outlined.

These observations are the result of the nomination of 38 experts in 18 countries in 2005 by the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Allergology and Clinical Immunology (AAAAI) to agree on guidelines for clinical practice in Europe and North America. The result is a consensus report: The “third child of the PRACTALL Initiative.” PRACTALL is the abbreviated term for “Practicing Allergology” and is an initiative by the EAACI and AAAAI to focus on practical issues in allergology.

These new guidelines offer clinicians practical recommendations for diagnosis, management, and monitoring dependent on the asthma phenotype and the age of children. Professor Wahn established guidelines for the diagnosis and treatment of atopic dermatitis and anaphylaxis.

Asthma Diagnosis in Children

The diagnosis of paediatric asthma comprises several components. Age-specific questions regarding previous medical history are considered crucial, since symptoms vary by age. Andrew Liu, Associate Professor at the Department of Pediatrics, National Jewish Medical and Research Center, University of Colorado School of Medicine, pointed out that noisy breathing, vomiting, coughing, retractions, and difficulty feeding are key symptoms in children younger than two years of age, whereas shortness of breath and impairment are often reported in older children. Impairment can affect physical activity and school performance and attendance, but is also characterised by fatigue and the avoidance of physical activity.

The new guidelines recommend asking all children questions regarding wheezing, coughing, trigger factors, frequency, severity of symptoms and pattern (recurrent/persistent, seasonality, etc.), as well as questions about co-morbid conditions (e.g. gastroesophageal reflux disease (GERD), and rhino-conjunctivitis) and differential diagnosis. Standardised, validated questionnaires should be used whenever possible, such as the Childhood Asthma Control Test (C-ACT) and the Asthma Quiz for Kids.

The guidelines also recommend chest examinations, chest x-rays, and lung function tests, including spirometry, variations in peak flow, bronchodilator response, and exercise challenge tests.

Special emphasis has been placed on IgE-mediated allergy testing, which is recommended for children of all age groups. “IgE-mediated allergies are a major risk factor for asthma persistence,” Professor Liu said. However, both skin prick testing and in vitro testing have advantages and disadvantages. Skin prick testing provides results in about 30 minutes and does not have an age limit, but must be conducted by trained and proficient personnel. Analysis is not possible for patients taking antihistamines, and adverse reactions are observed rarely. In contrast, in vitro allergy testing can also be performed in children pre-treated with antihistamines, but a major disadvantage is the delay in diagnosis due to the required lab work.

After asthma is diagnosed, the new guidelines advise regular routine follow-ups. The aim of these visits is to assure that the diagnosis of asthma is correct and to achieve and maintain control of symptoms. Routine follow-ups should include the assessment of impairment and exacerbation risk. In addition, it is recommended to perform spirometry and, if possible, to measure exhaled nitric oxide (NO) in order to have objective criteria for disease activity.

Asthma Management Plan

The PRACTALL Management Plan comprises recommendations regarding appropriate pharmacotherapy, allergen and irritant avoidance, specific immunotherapy, and asthma education, explained Professor Erkka Valovirta of the Turku Allergy Centre in Finland.
To achieve and maintain control, the guidelines introduce a new treatment algorithm for asthmatic children below and above two years of age. Although evidence for pharmacological treatment in children below two years is limited, intermittent treatment with short-acting β2-agonists is the first choice. Leukotriene receptor antagonists (LTRA) are recommended in control therapy for viral wheezing, and nebulized corticosteroids for persistent asthma.

For children older than two years of age, first-line treatment should be performed with inhaled corticosteroids (ICS), which has been proven to be efficient especially for children with high IgE levels, or LTRA. If the child’s asthma is not sufficiently controlled, physicians can increase the ICS dose, or add an ICS to LTRA therapy. Treatment can be stepped up further to achieve control by adding long-acting β2-agonists, and, if necessary, theophylline and systemic corticoids. The guidelines recommend that treatment should subsequently be reduced to the lowest dose at which good control can be maintained.

In addition to pharmacological treatment, the new consensus report emphasises the need to avoid any potential triggers of an asthma attack. Although exercise will trigger an asthma attack in many asthmatic children, the guidelines strongly recommend exercise and sporting activity. If an allergen cannot be fully avoided, allergen-specific immunotherapy by either subcutaneous injections or sublingual application should be considered by physicians.

In addition, the guidelines highlight the need of a self-management education programme that targets parents and caregivers. “Since improvement has been reported even in children younger than five years,” said Professor Valovirta, “very young children should be trained.” Professor Wahn noted: “A good asthma education programme should increase knowledge about the disorder, allay any fears about medication, and increase communication between children, caregivers, and health-care providers. Parents need to be aware of the benefits as well as the potential risks of all therapies so that they can make informed choices for their children.”

The detailed Consensus Report on Diagnosis and Treatment of Paediatric Asthma will be co-published in future issues of Allergy and The Journal of Allergy and Clinical Immunology by the end of 2007.

Christina Nassenstein

Report on PAPRICA Symposia in Groningen and Utrecht
4–5th April 2007

PAPRICA, the organisation Pediatric Allergy for PRimary Care physicians, was initiated to provide continuous education for primary care physicians involved in the care of allergic children.

In April 2007, two half-day symposia took place in the central Dutch city of Utrecht and in Groningen in the north of the Netherlands. They were organised in close co-operation with the Dutch Pediatric Allergy Society, as well as the local continuous education programmes of general practitioners. The topics: Food allergy, Respiratory allergy, and Prevention were covered respectively by Dutch experts Ewoud Dubois, Hans de Groot, and Maarten Hoekstra and visiting speakers Antonella Muraro, Graham Roberts, and Philippe Eigenmann. As usual, the programme allowed time for lively discussion with the delegates at the end of each session, and this often continued during coffee breaks.

Approximately 200 participants in total attended the symposia hosted by the continuous education programme of primary care physicians. Many participants expressed significant interest in the selected topics and said the presentations were of a high standard in terms of quality and were also highly educational.

We are convinced that these sessions in The Netherlands have provided our Dutch colleagues from primary care with state-of-the-art allergy knowledge as well as clinical insight through case discussions, which will result in constantly improving care for their allergic patients.

Philippe Eigenmann, Geneva, and Maarten Hoekstra, Utrecht
Does rhinitis lead to asthma?

Rhinitis and asthma, united airways disease

Rhinitis and asthma are often treated by different medical disciplines. However the “united airways disease” hypothesis show the benefits of considering diseases of the upper airways and lower airways together to significantly improve patients’ global condition and disease management.

Whether or not the link between rhinitis and asthma is causal, it is important for primary care physicians to recognise rhinitis in asthma patients and similarly that rhinitis patients are evaluated for asthma.

Never consider rhinitis as trivial!

2 brochures for Patients and Primary care Physicians - jointly realized with EFA - are already available in English at www.ga2len.net

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