Life-threatening Allergies

Food Allergy

Cells of the Allergic Immune Response

Göteborg 2007
ALLERGY – A LIFE-THREATENING DISEASE.

Allergy is not only a disabling disease for millions of patients; it can also be life-threatening and, in the worst-case scenarios, mortal. Therefore, EAACI continues to focus on anaphylaxis caused by food allergy, bee/wasp stings, drugs, occupational allergens, asthma and therapeutic interventions such as specific immunotherapy.

In this issue, anaphylaxis in childhood is one of the subjects. Between one and twenty out of one hundred thousand persons a year are struck by anaphylactic reactions, mostly adults, but the number of affected children is increasing. It is important that the youngest patients and their families are supplied with emergency kits and taught how to recognise and avoid the allergens. It is also important that health care institutions and schools are fully aware of the anaphylaxis problem and able to provide legislative measures and first aid based on guidelines. In most European countries, such measures and guidelines do not exist. To improve the situation, EAACI has formed a task force on anaphylaxis in children, which will make key information available to our members and to the public. As allergologists it is our mission to point out risks and create awareness among our colleagues, the public and healthcare managers.

Drug allergy is another dangerous clinical problem which can result in severe skin and systemic reactions with high mortality rates. A new understanding of drug hypersensitivity is evolving within the area of pathophysiology, which we address in this issue of the Newsletter. The treatment of aspirin intolerance and drug desensitisation for antibiotics in selected patients is also discussed, as well as the recently emerged problem of hypersensitivity reactions against antiretroviral agents in AIDS patients. We hope you will find interesting points and be inspired to further reading in the various scientific journals distributed by the EAACI.

Following the tradition from previous issues, you will find the message from the EAACI President, Prof. Tony Frew, and reports from different activities such as the Summer Schools and the PAPRICA programme. The preparations for the next EAACI Congress in Göteborg, Sweden, are in full progress and I am delighted to report a new record: the highest number of scientific abstracts ever has been received. We expect high attendance as well as an excellent scientific and social programme – be prepared for EAACI 2007!

Claus Bachert
Editor
Looking back at another successful EAACI year and preparing for New Activities in 2007

2006 was generally a very good year for EAACI. We had an excellent congress in Vienna and a better than expected final settlement from the Munich 2005 meeting. This means that when we met in Gothenburg in November, the Executive Committee was able to approve almost all the requests that were made for activity in 2007. This includes support for the winter allergy school in Davos, support for the molecular allergology meeting in Rome in April, a further series of PAPRICA meetings (see special article in this issue) and about 5 further allergy schools to be held later this year. In addition, we put extra money into the exchange research fellowship programme and we have invested in the task force that is developing the new European exam in allergology.

Perhaps our most important achievement last year was our successful lobbying of the EU parliament which led to the inclusion of allergic diseases within the highest possible priority of the health programme for the EU research framework programme 7 (FP7). Many people contributed to this effort. We held meetings with parliamentarians in Brussels and with national government representatives throughout Europe, and individual members of the ExCom and the GA\2\LEN partners also argued the case for allergy to be included. Although the EU parliament voted initially to include allergies, the commission wanted to remove this from the wording. We were very pleased that our lobbying efforts were finally rewarded when allergic and respiratory diseases were included in the enabling legislation for the health programme. Now it is up to the research community to put forward ideas about projects that should be funded and to submit appropriate proposals.

The state of the specialty in Europe continues to cause some concern. It is not clear how this will work out in the long-term but EAACI has decided to take the initiative and is developing a European exam in allergology. We recognise that this will not have any statutory power to start with but we hope that people training in allergy will find it an interesting exercise to measure their skills against the standard test and gain something that they can add to their CV. All professional exams started out this way and gradually acquired the authority and standing that they have today. We will obviously keep an eye on how European regulations develop but our general view was that sitting still and waiting for developments was not an option.

Although it only seems a short while since I took office as president in Munich, my term of office will come to an end in June and with it, there will be a new set of officers and members in the executive committee. June will also see the implementation of the constitutional reforms that were made last year with the creation of the 3 new vice presidents and their specific portfolios. I count myself fortunate to have a talented team working with me and we are lucky to have keen and enthusiastic volunteers for the new positions. The nominees for the various officer positions will be listed in the next issue of the newsletter and officially confirmed in their positions at our General Assembly in Gothenburg. EAACI members will be sorry to hear that our past-past president, Paul van Cauwenberge, was taken ill while lecturing in India, and is now recovering from a small stroke that has affected his vision. Our thoughts and prayers go out to Paul and his family, with best wishes for a speedy recovery. We want to see our “travelling man” fit and well as soon as possible! For now, Cezmi Akdis, Jan Lötvall and the local organisers are putting the finishing touches to the Gothenburg programme. All the indications are that we will have a large number of abstracts for the meeting and a very good attendance in Sweden in June. It truly is the best time of year to visit that part of the world and I hope that you will join us there.

Tony Frew
Anaphylaxis in Childhood

The Main Symposium on Anaphylaxis in Childhood, with a report from the EAACI Task Force that took place at the last EAACI Congress in Vienna, was chaired by Philippe Eigenmann from Switzerland and Estelle Simons from Canada. Speakers Jonathan Hourikane (the U.K.), Graham Roberts (the U.K.), Anne Moneret-Vautrin (France), and Antonella Muraro (Italy) provided excellent lectures, sharing their expertise with the audience on a topic which is actually extremely important in daily practice and which requires some clarification and recommendations.

More research needed

Anaphylaxis is a severe life-threatening systemic allergic reaction that compromises two or more target organs. It is an under-diagnosed and under-treated entity with enormous socio-economic implications.

There are not many studies on the epidemiology of anaphylaxis in Europe, although its increasing incidence is commonly accepted. Nevertheless, some studies that aim to evaluate its epidemiology and risk factors report 1–20/100000 persons/year being affected, with anaphylaxis being more frequent in adults than in children. The majority of cases is related to food allergy, with the culprit varying according to country and food habits (for example, peanuts in the U.K.), the minority to exercise. Great concern emerges in regards to food allergies once a considerable number of anaphylactic reactions occur in the home, and also in regards to hidden allergens, and food manipulation.

In order of incidence, latex, especially for high-risk children with spina bifida or urological malformations often exposed to surgery, and drugs are the next main causes of reactions, with the latter group particularly due to neuromuscular blocking agents.

Recognition is important

It is extremely important to recognise an anaphylactic reaction, to recognise the risk factors for fatal reactions such as asthma history, pre-existent latent cardiomyopathy, previous respiratory/cardiovascular reactions, previous reaction to trace amounts of allergen, allergy to peanuts or tree nuts (especially cashew nuts), particular susceptibility in the teenage years, and finally to treat the reaction properly and immediately. The administration of IV epinephrine and putting those affected in an upright position are also associated with lethal results. Regarding the risk factors for a worse prognosis, it should be stressed that 33% of food allergic patients have asthma and that 8% of asthmatic children have food allergies. Moreover, the majority of fatal anaphylactic reactions to food allergy occurs in asthmatics, so it is becoming crucial that the clinician be aware of the presence of asthma and food allergies when treating children.

Treatment

Regarding anaphylaxis treatment, there are some studies that report that only one in five patients is treated with the gold standard therapy, epinephrine, which must be administered intramuscularly, which is very often not done. The treatment must be prompt, since an early use of epinephrine is associated with an improved outcome. Nevertheless, there is no consensus on who should self-administer epinephrine.
Patients with a history of anaphylaxis need an individual management plan with a personal photo, identification and contact details, instructions with lay terms on how to recognise the reactions, instructions on management, and on what to avoid. This must be accessible and kept with the emergency medication kit. Together with technique training, it should commence in the emergency room and be reviewed by an allergist regularly. It is also extremely important to include reassurance and support, including education, regarding allergen strict eviction and eventual hidden allergens, once there is a considerable rate of recurrence. Family and child caregivers should also be informed about anaphylaxis, its recognition, and its prompt treatment. Family and school staff must be notified and trained, provided with an emergency kit, and a management plan emphasising the need for periodic checks on epinephrine availability and expiration. Eventually, some patients will need a second injectable epinephrine if there is no improvement in the clinical condition, and so clinicians should prescribe at least two epinephrine auto-injector kits for each patient. In instances of asthma exacerbation, patients should have inhaled bronchodilators and corticosteroids. Regarding assistance from caregivers, some countries legally forbid teachers to give drugs and it is forbidden to have one drug in the classroom available for any child if needed (for example, epinephrine). There has been some involvement by the EAACI to try to evolve a European strategy that could allow this procedure in the instance of a student with a history of anaphylaxis. Some problems are related to self-injectable epinephrine such as palpitations, tremors, and digital ischemia in the case of technical errors in administration. In addition, it is a source of social anxiety and stigma, and it is a cumbersome procedure since the patient must remember to take the medication with them and to replace it after expiration.

The Task Force continues its work
The EAACI maintains a Task Force of Anaphylaxis in Children, which aims to provide European guidelines for preventing and managing anaphylaxis in children. The task force sent a short questionnaire about each country’s management of anaphylaxis to members of the EAACI all over Europe. By analysing the responses and reviewing the literature, the conclusions suggested that anaphylaxis guidelines do not exist in two thirds of EU countries, that all countries but one have self-injectable epinephrine, that 50% reimburse patients for more than two doses per year, and that most treatments are levels III–IV and are related to grade recommendations C–D.

The management of anaphylaxis must be co-ordinated through a multifaceted, integrated approach. Medical doctors should be trained to recognise and treat anaphylaxis, and there should always be a link between family doctors (trained to be aware of this condition) and allergists in a referral centre, in order to maintain a network geared to emergency response.

There is a lack of prospective studies of children regarding anaphylaxis which could contribute enormously to the understanding of this condition. The Task Force of Anaphylaxis in Children will make information available about its activities and issue a statement about this condition in this newsletter in the near future.

Miguel Borrego
Drug allergy is the most enigmatic and dangerous clinical problem in allergology. The Main Symposium on severe drug hypersensitivity, held on 11th June, 2006, generated, as always, great interest with all the participants, as demonstrated by an auditorium packed to capacity and heated discussions during the symposium.

Two concepts
Professor Werner Pichler, a leading expert in the field of drug allergy, opened the symposium with a comprehensive lecture entitled Immunological Principles of Drug Hypersensitivity: Many Questions, Some Answers. He addressed the most difficult questions about the pathophysiology of drug allergy, comparing the two main concepts of drug recognition: the hapten/prohapten concept and the P-I concept. The hapten concept, which has prevailed for many years, describes the covalent binding of a small drug compound to a carrier molecule to further interact and stimulate the immune system. The prohapten model, the metabolism leads to reactive intermediates, with one example being sulfamethoxazole. However, the hapten/prohapten hypothesis leaves many questions unanswered, such as the antigenicity of drugs with unknown reactive metabolites and skin positivity with drugs metabolised in liver.

The P-I concept (Pharmacological interaction with Immune receptors) was a major breakthrough in our understanding of the pathogenic role of T-cells in drug allergy. According to this concept, drugs directly stimulate drug-specific T-cell clones through the activation of T-cell receptors. The particular features of this drug-immune interaction are labile binding, the involvement of antigen-presenting cells, and the possibility of immediate reactions before processing. Thus, drug antigenicity results from either chemical drug properties for hapten-peptide interaction or the structural features for direct drug-receptor interaction with T-cells. While the hapten concept can explain any type of allergic reactions to drugs, the P-I concept is mainly relevant for maculopapular rashes. These data served as the basis for a new subclassification of Type IV reactions according to the involvement of different effector cells such as monocytes, T-cells, eosinophils, and neutrophils.

As a result, the P-I concept, discovered by Pichler, offered new insights into several clinical features of drug allergy such as clinical heterogeneity, the development of allergy without prior exposure, and the simultaneous involvement of several mechanisms. Some similarities of the P-I concept with superantigen activation of T-cells shed light on extraordinarily strong and sometimes lethal immune stimulation in severe drug allergies such as DRESS, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and AGEP.

Severe skin reactions
Dr. Maja Mockenhaupt focussed her outstanding talk on the life-threatening, drug-induced skin reactions SJS and TEN, characterised by blister formation, mucosal involvement, fever, and malaise. According to consensus, the definition of severe skin reactions is based on the type and distribution of lesions and the extent of skin detachment. SJS is characterised by generalised atypical targets and spots with less than 10% of blisters and erosions, whereas TEN with macule is the most severe type of skin reaction, with more than 30% of skin detachment related to the body surface area. Mockenhaupt stressed the importance of differential diagnosis with staphylococcal scalded skin syndrome and generalised bullous fixed drug eruptions.
Although severe drug skin reactions are rare, they are associated with high mortality rates. Mockenhaupt presented unique epidemiological data on SJS and TEN from the German Registry of Severe Skin Reactions and the international Euro-SCAR study on severe cutaneous adverse reactions. Research in drug metabolism and genetic markers is a rapidly evolving area for clarifying the pathogenic pathways in severe adverse skin reactions. Mockenhaupt specified a list of drugs associated with a high risk of SJS and TEN. She also warned that a delay of four to 28 days between commencing drug use and the onset of a reaction is considered as the most suggestive timing for SJS and TEN. For clinical practice, she advised that the timing of administration is the most important clue for identifying the culprit drug in instances of exposure to several medications.

**Drug-induced hypersensitivity syndrome – cause, recognition and treatment**

Dr. Genevieve Choquet-Kastylevsly from France lectured on the clinical features, the aetiology, and the pathophysiology of potentially life-threatening drug reactions associated with eosinophilia and systemic symptoms (DRESS), appearing in medical literature under different names including drug-induced hypersensitivity syndrome, anticonvulsant hypersensitivity syndrome, XXX-syndrome, dapsone-, sulfone-, allopurinol- syndrome, etc. DRESS develops in two to eight weeks after the onset of therapy and is characterised by skin rashes, fever, lymph node enlargement, systemic involvement, and marked eosinophilia. The most common causes of DRESS are anti-epileptic drugs, allopurinol, antimicrobial, salazopyrine, dapsone, etc. The pathophysiology of DRESS remains elusive, but seems to result from a combination of genetic predisposition, metabolism peculiarities, drug antigenicity, and specific immune drug recognition, leading to T-cell activation and IL-5 synthesis. Choquet-Kastylevsly guided us through a diagnostic approach to this syndrome, including the major and minor diagnostic clinical criteria, the temporal relationship of drug usage, and the onset of symptoms. Treatment strategies focus on the prompt recognition and the withdrawal of the suspected drug, and supportive care measures. Remarkably, symptoms may persist for weeks and months after drug cessation. Particular attention should be paid to avoiding re-exposure, and therapists should be alert for cross-reactivity and symptoms in first-degree relatives.

**Risk factors in AIDS patients**

Dr. Pierre Wolkenstein from France approached the serious issue of the prospective evaluation of risk factors of cutaneous drug reactions in patients with AIDS. It is widely known that AIDS patients are at high risk for severe drug-induced cutaneous reactions, particularly to antimicrobial sulfonamides and other drugs, including antiretroviral drugs. On the other hand, in the SCAR study, HIV/AIDS was shown to be an important non-drug risk factor for TEN. Therefore, identifying reliable risk factors for adverse cutaneous reactions in AIDS patients is an urgent clinical problem. In retrospective studies on AIDS patients with adverse cutaneous reactions, the risk factors were female gender, a history of cutaneous adverse reactions, CD4 cell count between 25-200.mm3, and metabolic risk factors, whereas protective factors included having black skin and using corticosteroids. Some specific metabolism risk factors are associated with AIDS, including GST M1 null genotype, glutathione deficiency, and slow accelerator phenotype. In conclusion, Wolkenstein summarised by saying that immunosuppression, slow metabolism rate, HLA associations, and apoptosis may contribute to drug-induced skin eruptions in AIDS patients.

_Elena Borzova_
Drug Desensitisation – a Possibility?

Professors Pascal Demoly and Marek Kowalski chaired the symposium, which addressed the exciting area of drug desensitisation. Drug allergy has become a daily problem in clinical practice, but many aspects of the problem remain unresolved, although avoiding the culprit drug is the best treatment option for drug allergy. However, when there is no therapeutic alternative to a specific drug, clinical management poses a serious challenge. Professor Hans Merk from Germany, the first speaker, said that drug desensitisation may play a crucial role in these cases and can be accomplished by administering the offending drug in gradually increasing doses to induce tolerance in patients with a prior history of hypersensitivity to this drug. However, Professor Merk said that the precise mechanism of drug desensitisation has still to be elucidated at the cellular level.

Treatment of aspirin intolerance

Drug desensitisation can also be used in non-allergic hypersensitivity, for example, in aspirin intolerance. Professor Kowalski from Poland focussed on the role of aspirin desensitisation in the management of aspirin-sensitive asthma and rhinosinusitis. He gave an overview of the current concept of mechanisms underlying aspirin intolerance. In addition, the professor outlined the classification of NSAIDs according to their potency to inhibit cyclooxygenase-1, thus laying the groundwork for a high risk of cross-reactivity with other potent inhibitors of COX-1 and, on the other hand, for the safety of recently developed highly selective inhibitors of COX-2 (COXIBs) in aspirin-sensitive patients. Kowalski traced the history of aspirin desensitisation from Widal’s first report in 1922 to the present, and gave the results of clinical trials and analysed the existing protocols of aspirin desensitisation. Long-term treatment with aspirin desensitisation was reported to result in significantly improved symptoms and decreased doses.
of required medication in 87% of patients with asthma and rhinosinusitis. Thus, aspirin desensitisation is recommended for aspirin-sensitive patients who require NSAIDs treatment for concomitant rheumatic or cardiovascular diseases, and also for patients with asthma/ rhinosinusitis, which is poorly controlled with conventional pharmacological therapy, and for patients with nasal polyps requiring repeated polypectomies and sinus surgery.

**Hypersensitivity to antibiotics**

*Professor Andreas Bircher* from Switzerland focussed on the important role of drug desensitisation in hypersensitivity to antibiotics when no alternatives are available. In drug desensitisation to antibiotics, the desensitised state should be rapidly induced in order to avoid the development of resistance to the antibiotic. Drug desensitisation to antibiotics can be carried out in patients with immediate types of allergic drug reaction (for example, lactams, vancomycin, ciprofloxacin, tuberculostatics, etc.). Moreover, successful drug desensitisation has also been reported in delayed type reactions (maculo-papular rashes, fixed exanthes) to antibiotics such as clindomycin, ticarcillin, tetracycline, etc. Bircher emphasised that the selection of route, timing, and dosing in drug desensitisation depends on drug pharmacokinetics and the type of adverse drug reaction. He warned that after drug desensitisation patients should be under long-term supervision because of the risk of delayed drug reactions.

**Desensitisation to antiretrovirals**

The higher prevalence of drug hypersensitivity in HIV-positive patients compared to immunocompetent individuals poses a substantial challenge in the clinical management of this devastating disease. Until recently, allergic drug reactions to co-trimoxazole have been the major concern in the treatment of opportunistic infections (Pneumocystic carinii pneumonia) in patients with HIV, while hypersensitivity to new antiretroviral drugs currently receives the greatest attention. Indeed, the introduction of highly active antiretroviral therapy (HAART) has been a tremendous advance in the treatment of AIDS, and has resulted in patients surviving longer. However, hypersensitivity reactions have been described involving all classes of antiretroviral agents with AIDS patients. Given the absence of alternative drugs, desensitisation to antiretrovirals has been tried with some HIV-positive patients. Professor Demoly informed the audience about his unique clinical experience with desensitisation protocols for antiretroviral drugs of different classes. In conclusion, he stressed that the need was urgent to standardise protocols for drug desensitisation in patients with AIDS.

**Significant debate**

These experts discussed the most difficult practical issues in the field of drug desensitisation, and inspired significant debate in the audience. In general, the symposium was of great interest to clinicians and engendered a spirit of enthusiasm about this fascinating but yet unexplored treatment method.

Elena Borzova
Food Allergy: From Epidemiology to Treatment

The EAACI Congress in Vienna presented a Main Symposium on Food Allergy: From Epidemiology to Treatment, chaired by Bodo Niggemann from Germany and Hermo Breiteneder from Austria. As speaker, Niggemann was joined by Morten Osterballe (Denmark), Barbara Bohle (Austria), and Arne Host (Denmark), and all gave excellent lectures.

Food allergy or not?
Food allergy is a common condition with a cumulative incidence in prospective birth cohorts of 6–8%, and it currently exhibits a rising prevalence worldwide. There is a discrepancy between self-reported and food hypersensitivity at the age of three years, revealing that the general population often misclassifies unrelated reactions to food as allergies. There is an urgent need to unify the criteria and inform the public about food allergy reactions and their potentially lethal prognosis.

Primary or secondary food hypersensitivity
Food hypersensitivity can be primary or secondary. In the first group, the clinical symptoms are usually urticaria and asthma exacerbation. The culprit allergens are different in children and in adults, and in fact, the most common food allergens in children are eggs and milk, in contrast to adults, for whom the culprits are peanuts and fresh fruit.

Food allergy is dependent on age, with the following pattern of foods exhibited in relation to years of age: milk, eggs (>1 year); fish (1–2 years); fruit, legumes, vegetables (>2 years); pollen-related cross-reactivities (>3 years). The pattern of food allergy is variable among and within countries since it depends on food habits and traditions.

In the secondary group of food hypersensitivity, the main clinical manifestations are oral allergy syndrome, with hazelnuts being the most frequent allergen involved. Allergic reactions to hazelnuts, apples, and kiwi fruit may occur in pollen (birch, grass, and mugwort) sensitised adults. Oral allergy symptoms occur due to antigen-presenting cells (APCs) that present to T-cell linear peptides. The end result is that the T-cells are always stimulated by allergens/peptides despite their desnaturation/degradation. T-cell epitopes are linear and IgE epitopes are conformational, with the former being destroyed by higher temperatures and digestion.

Accurate diagnosis
It is vital to establish an accurate diagnosis of food allergy, since avoiding allergens and hidden allergens can be very disruptive to personal, family, and social patterns and can even cause negative economic impact. The medical history must be examined to find reproducible or unequivocal reactions to a food allergen, and eventually the existence of a risk factor for food allergy, for example, prenatal exposure to cow milk.

Testing allergy
The most common food allergens are eggs, milk, soy, whey, peanuts, tree nuts, and fish. The vast majority of children, at least two-thirds, is allergic to one food only. In vivo and in vitro tests are used to test for food allergy, with in vivo tests including skin prick tests (SPTs) and epicutaneous/patch tests. SPTs are commonly used and have a highly negative predictive value, as they are very sensitive, although some authors report that SPTs may have a predictive value for positive food challenges in children under the age of two years old. Patch tests are more frequently used to evaluate delayed reactions to foods, as the tests consider more specific and have a higher predictive positive value when used in isolation. In a study performed by Niggemann et al, patch tests combined with SPTs had the best sensitivity and specificity. Nevertheless, it should be emphasised that patch tests are not standardised and should only be performed by specialised and trained personnel at reference centres.

Specific IgE (sIgE) is used to prove the existence of sensitisation, to calculate decision points, to assess the risk of anaphylaxis, and to monitor the development of tolerance. Despite recent publications about decision points for sIgE, the cut-off values vary between European and U.S. studies and should be defined for each specific population.
Food Allergy

These studies may have different cut-off points due to methodological differences such as the target population, the clinical relevance (history and double-blind food challenge tests), the criteria for positive challenge tests, the pattern of clinical relevance, the definition of late phase reaction (two or 24 hours), the age pattern, the time point of diagnostics, the duration of the condition, and the assay used for sIgE measurement. Some studies document that there is no correlation between levels of sIgE and the severity of the reaction or its threshold.

Other tests have an unproven value for food allergy diagnosis such as sIgE, citotoxic food tests, bioresonance, kinesiology, iridology, and electrodermal tests. The double-blind food challenge test is unequivocally the gold standard for food allergy diagnosis. If placebo and verum are positive, then the test should be repeated. If verum is positive, then an elimination diet must be implemented.

Milk allergy tests should commence with an open challenge, which can be negative excluding milk allergy that will be reintroduced to the diet, or positive leading to an elimination diet, or even a late phase reaction implicating the need for a double-blind food challenge test. The challenge tests should be performed in a hospital setting if there is any risk of anaphylactic reaction, if clinical reactions cannot be accurately estimated (such as when the patient is sensitised but food introduction has recently commenced), in instances of severe atopic dermatitis (when it is difficult to assess the outcome of the challenge), or in the case of subjective symptoms.

**Diagnosis, treatment and diet**

In order to establish a correct, therapeutic plan for a patient with food allergy, the diagnosis should be confirmed with a food challenge, which is also important in establishing a threshold for reaction. The correct diagnosis will ensure a correct diet, with the proper assistance of a dietician who should provide a balanced diet and education on this for the parents. Parents should always be aware of food labelling, hidden foods, and sources of contamination. Doctors should reassure the child and the parents, monitor growth, and delay the introduction of solids.

In regards to allergy to cow milk proteins (CMPA), it must be emphasised that partially hydrolysed baby formula cannot be used for treatment, and that soy formula is not recommended, especially for infants. The only accepted treatment is with casein or whey hydrolysates. Amino-acid mixtures are prescribed when children have multiple food allergies and are intolerant of extensively hydrolysed formula. Children with CMPA that is IgE-mediated often develop allergies to other foods, such as eggs and soy. Soy should not be used in instances of non-IgE-mediated gastro-intestinal symptoms such as allergic eosinophilic esophagitis, allergic eosinophilic gastritis, allergic eosinophilic gastro-enterocolitis, enterocolitis syndrome, dietary protein colitis, and dietary protein enteropathy.

In addition to an adequate diet, patients with food allergy can be treated with sublingual immunotherapy or with oral tolerance induction. The first option has been shown to be efficient for hazelnut allergy and the second has been tried with milk, and with hen eggs, although it is unfortunately not used often because the tolerance is transitory and the patient must eat the food daily to maintain that tolerance.

Probiotics may alleviate intestinal inflammation for patients with food allergies, raising the level of faecal IgA and diminishing TNF-α and α1 antitripsin. Some recent immunomodulatory therapies, such as anti-IgE monoclonal antibodies, specific allergen proteins immunotherapy, peptide immunotherapy, plasmid DNA immunotherapy, and cytokine modulate immunotherapy, may constitute future avenues of exploration, but the treatment of choice for anaphylactic reaction to a food allergen remains intramuscular epinephrine.

The prognosis of food allergy is often good. Most children with CMPA that is IgE-mediated develop tolerance in the first three years of their lives.

To define the achievement of food tolerance it is important to perform a food challenge test. If this is positive, the diet elimination should be maintained and a test should be done once or twice a year for younger children and every year or two for older children, depending on the type of food allergy and the age of the patient.

Generally speaking, food allergy develops in the first two years of life and recovery is variable. A good prognosis has been documented with cow milk, hen eggs, and soy, but a worse prognosis with peanuts, tree nuts, fish, and seafood, although some patients allergic to peanuts have been reported to have recovered from this condition.

It is very important to clarify the importance of food allergy, the diagnostic march, and appropriate treatment for clinicians to avoid misdiagnosis of food allergy and its potentially serious consequences.

**Miguel Borrego**
Atopic diseases are characterised by a TH2 biased immune response to environmental allergens. Th2 cells are the key mediators in allergic reactions, initiating and propagating inflammation through the release of a number of cytokines such as IL-4 and IL-5. However, little is known regarding the mechanisms that control the initial Th2 polarisation.

Dendritic cells (DCs), because of their potent antigen presentation function, are critical in the initiation and the type of emerging immune response. Georg Stingl (Vienna, Austria) gave an overview of the DC subtypes able to modulate the allergic immune response. DCs are highly specialised professional antigen presenting cells found in skin and mucosa, representing a major portion within the infiltrate of atopic dermatitis (AD) lesions. In vitro experiments showed the presence of the high affinity receptor for IgE (FcεRI) on DC subtypes. It appears that FcεRI-bearing DCs play an important role in the pathogenesis of atopic dermatitis, not only in the initial phase of AD, but also in the amplification or maintenance phase of the allergic inflammatory reaction in the skin and blood of AD patients.

Stingl showed very promising results from treatment of atopic dermatitis with a humanised monoclonal IgG antibody against free, circulating IgE, resulting in the reduction of anti-IgE/Anti-FcεRI-reactivity of basophils, mast cells, and DCs. Further investigation of the effects of omalizumab treatment on the long-term course of atopic dermatitis is needed.

A distinct subtype of DCs are Langerhans cells (LCs) that reside in their immature state in the epidermis and mucosal epithelia. Their role in immunity is not fully understood. They acquire antigen in the skin and migrate to the draining lymph nodes, where they are thought to initiate immune responses. Studies in contact hypersensitivity (CHS) showed that, unexpectedly, in the absence of LCs, reactions are amplified rather than abrogated. LCs act only during the priming and not the effector phase, and they are dispensable for triggering the hapten-specific T-cell responses through skin immunisation. It appears that they serve to regulate the response, a previously unappreciated function.

Plasmacytoid dendritic cells (pDCs) are absent in normal human skin, but they represent a major DC subtype in allergic contact dermatitis (ACD) skin. Their close proximity to NK cells and the subsequent pDC-induced IFN-γ production in these cells may indicate that pDCs contribute to the T1 bias of the ACD immune response.

Donata Vercelli (Arizona, the United States) presented some brand-new data on IgE regulation in vivo. Immunoglobulin E (IgE) isotype antibodies are associated with atopic disease. IgE is produced as a result of class switch recombination.

In 2001, the Alex study (Riedler et al, Lancet 2001) generated interesting results on the effect of early farm exposure on asthma and allergic diseases. Long-term and early-life exposure to stables and farm milk induces a strong protective effect against the development of asthma, hay fever, and atopic sensitisation. It appears that farm exposure protects from switching to IgG1, IgG4, and IgE, and that living in a farming environment affects the expression of Th2-dependent isotypes. Exposure failed to affect IgG2 and IgG3 responses, which are likely to be controlled by separate mechanisms. The protective effects of farm exposure were confined to Th2-dependent IgG1, IgG4, and IgE expression.
A number of recent studies indicates that regulatory T-cells play an important role in controlling Th2-biased immune responses. Cezmi Akdis (Davos, Switzerland) explained the importance of different T-cell subtypes, and the regulation of the balance between these T-cells. Th1 cell types are important in a delayed type of hypersensitivity, involving macrophage activation but B-cell inhibition with the production of IFN-γ, TNF-α and TNF-β. Th2 cells are involved in chronic eosinophilic inflammation with high IgE production via IL-4, 5, 6, 13 and 25. T-cell equilibrium between Th1 (predominant in auto-immunity) and Th2 (predominant in allergic diseases) is controlled by T-regulatory cells via the production of TGF-beta and IL-10. TGF-beta and IL-10 have been shown to induce T-cell suppression in normal immunity to mucosal allergens and during allergen specific immunotherapy (SIT). Allergen-SIT induces the antigen-specific suppressive capacity of T-regs from allergic patients.

Massimo Triggiani (Naples, Italy) explained the dual role of basophils and mast cells (FceRI cells) in allergic inflammation. In their most classic role, they drive inflammation through the release of pro-inflammatory and immunoregulatory cytokines, responsible for acute allergic reaction. Another less classic role played by basophils and mast cells is their involvement in angiogenesis. Angiogenesis is crucial for numerous inflammatory and immune disorders, including asthma, and is a prerequisite for remodelling.

Basophils and mast cells might regulate angiogenesis through the synthesis and immunologic release of various forms of VEGF and PIGF. Significant differences in the expression of angiogenic factors and their receptors between basophils and mast cells further emphasise their distinct role in allergic inflammation.

Nicholas Van Bruaene

Asthma – a key disease for any EAACI congress

EAACI is acknowledging asthma as a very important disease for any allergist. Regardless of whether asthma is associated with atopy or not, the pathological features have many similarities. The EAACI Congress in Göteborg is giving extra focus on asthma at the opening plenary symposium on Sunday morning 10th June, with a title “Asthma – from clinical impact to basic mechanism. Two of the world super-experts in the area have confirmed their participation, Paul O’Byrne, Hamilton Canada, and Peter Barnes, London, UK. Don’t miss this important session.
The clinical educational sessions organised in co-operation with the ENT, Dermatology, and Immunology sections of the academy comprise a new initiative in annual EAACI JMA activities. The dermatology session, which took place on 10th June, 2006, covered issues related to the management of contact eczema in a largely interactive discussion with attending participants. The workshop was chaired by Elena Borzova, the JMA Dermatology Section representative, and started with a talk by Professor Dr Bettina Wedi from Hannover Medical University in Germany.

Considerable debate has, to date, been associated with the definition of, as well as the appropriate nomenclature for, the different types of dermatitis. In any case, allergic contact dermatitis is the most frequently cited type of dermatitis with irritant and occupational contact dermatitis to follow. Professor Wedi provided insight into the aetiology, clinical components, and histology of these entities and attempted to present a systematic methodology based on the history, location, and pattern of disease for the investigational approach of the physician in everyday practice. Although allergen sensitisation has been widely considered specific in nature, very recent data underline that patients with a strong reaction to a specific allergen have an increased likelihood of developing further positive reactions to unrelated contact allergens. The professor also dealt with the issue of predictive testing for new allergens in animal models (guinea pigs) and depicted the value of local lymph node assay as the best predictor for human sensitisation. The measure of the latter is the concentration of any chemical required to produce a threefold stimulation of proliferation in the lymph nodes draining the site of application, compared to vehicle-treated controls. Special mention was made of occupational contact dermatitis, and professionals such as hairdressers, printers, machine tool operators, and setters were said to be at increased risk of this form of dermatitis. Early referral for diagnostic patch testing is recommended as there is evidence that the duration of dermatitis is a poor prognostic factor.

The session continued with a presentation by Peter Schmid-Grendelmeier, University Hospital of Zurich, who spoke on the practical approaches and pitfalls associated with contact dermatitis. He discussed the factors to consider when diagnosing allergic contact dermatitis, the patch testing technique, and instructions for the patient under testing. Moreover, the causes of false negative and false positive results and adverse reactions were analysed, and open patch testing and the repeated open application test were described.

In all, this new initiative from the Junior Section of the academy proved to cover an underestimated need for the clinical education of allergy trainees. Indeed, the session was highly attended (a total 140 participants) and the interactive nature of the discussion offered an ideal environment for the education of all on the practical issues they encounter in their daily practice. Similar workshops are being designed for the next annual congress of EAACI and are expected to be as welcome as the first.

Chrysanthi Skevaki, JMA Webmaster
The session took place on 11th June, 2006, with presentations by Professor Rudolf Valenta, chair of the local organising committee, and Dr Gert Jan Braunstahl from the Erasmus University of Rotterdam. Traditionally, the scope of this session has been to educate Junior members of the academy on the basic skills and techniques regarding research data collection and analysis as well as manuscript composition and publishing. However, experienced clinicians and researchers found the session equally didactic as it offered them the opportunity to improve their skills.

Professor Valenta gave a talk on “How to be successful in publishing” from the editor’s point of view. An author’s success is assessed both in the short and long term, based on the number of papers s/he publishes, the impact factor of the academic journal, but also on the originality of the paper and the citations it retrieves. The personal success of a scientist/researcher reflects the development of his/her career, the acquisition of degrees and positions, as well as the national and international recognition s/he achieves. On the other hand, editors aim to maintain a high impact factor for their journal by achieving a low number of published articles to citations ratio. Citations in turn depend on the type of article, its originality and quality, the reputation of the authors, the accessibility of papers, the relation of the research conducted with the mainstream fashion, the publication of papers with numerous quotes from the same journal, as well as advertisement.

The decision to publish a paper is made usually by at least four independent persons, thus minimising the risk of not recognising pieces of original, novel, and important research. The professor described practical guidelines regarding the preparation of a manuscript and finally prompted young researchers to treat science and manuscripts as a piece of art.

The next speaker, Dr Braunstahl, mentioned the benefits arising from publishing such as the advancement of knowledge through the dissemination of clinical and basic scientific data, the advancement of authors’ institution by enhancing their prestige and research grants, as well as personal benefits e.g., promotions, reputation, and the development of research ability. The speaker also gave a historical account of the evolution of the format of scientific papers up to the established “introduction-methods-results-discussion” form, which emerged in the 1980s.

The title of an article is very important as it serves as the initial attraction for the reader and therefore ought to be specific and reasonable in length. The abstract is a concise summary of the manuscript, which should be well structured, limited in word count, and not contain detailed descriptions or any information not covered in the paper. The introduction section serves to provide background information, to stress the importance of the problem, and to state the research question/hypothesis of any given study. The methods section is designed to allow readers to assess the validity and the appropriateness of the results and to provide information for future replication of the study.

This section should describe the subjects, materials/equipment, study design, and the methods used for data analysis. The results section ought to provide data to confirm or reject the original hypothesis, and should include tables/graphs when necessary. Finally, the authors may present any generalisations arising from the results, depict agreement/dissagreement with previous work, summarise their key findings, and also comment on the strengths and limitations of the index study in the discussion section.

In all, the JMA Educational Session was well attended, as it presented two experienced speakers in this field who gave the audience constructive advice.

Chrysanthi Skevaki,
JMA Webmaster
New structure of the EAACI membership fee from 2007

We are delighted to inform that the EAACI Executive Committee has agreed on a plan to reduce membership fees for members from less advantaged parts of Europe.

The new membership fee will be linked to the average per capita income of each European country according to the current World Bank Report.

Any EAACI member from a country within Europe with a GNP of less than US$10,000 will receive a 50% reduction on the EAACI membership fee, including full membership benefits.

The new structure will automatically apply for existing members. The invoices covering the membership fee for 2007 will be reduced by 50% for members from the countries which are subject to the reduction.

For new members applying for membership 2007 online the valid fee will automatically appear upon registration of the applicant’s country.

The PAPRICA programme, now in its third year, is an initiative by the EAACI Section on Pediatrics, co-financed by EAACI and GA\LEN. From its original name “Pediatric Allergy for PRimary Care”, it has evolved to become “Prime Allergy for PRimary Care”, in order to address primary care physicians treating allergies in adult patients as well.

In September 2006 we held two one-day symposia in Skopje (Macedonia), and in Tirana (Albania). These were organized in close cooperation with the national Macedonian and Albanian allergy societies, and were open to pediatricians, internists and general practitioners. Six topics: “Allergy from childhood to adults”, “Food allergy”, “Atopic dermatitis”, “Asthma”, “Upper airway allergy” and “Immunotherapy” were covered by visiting speakers (Thomas Werfel, Christian Virchow, Philippe Gevaert, Tony Frew and Philippe Eigenmann). As usual, the programme was organized to allow plenty of time for discussion with the delegates at the end of each topic. These lively discussions
were often continued during the coffee breaks.

About one hundred and forty participants attended the Symposia. These included doctors working in primary care, pediatrics, dermatology, pneumology, ENT, as well as allergy. Although the national allergy societies of Macedonia and Albania have a long tradition of continuous education for specialists, both countries welcomed these first international Symposia jointly organized with EAACI and GA²LEN.

In addition to the Symposia, a press conference was held in both countries leading to coverage by national TV networks, as well as by daily newspapers. It is hoped that this will help to further promote allergy care in Macedonia and Albania.

Strong friendly contacts were established thanks to the efficient local organizers. Both these meetings and future PAPRICA symposia will help to promote the care of patients with allergic conditions and the standing of our specialty in Europe.

Philippe Eigenmann, Geneva, Dejan Dokic, Skopje, and Alfred Priftanji, Tirana, co-organizers of the Symposia
More than 20 countries in Europe and elsewhere were represented by 126 participants in this 20-hour scientific programme themed Exacerbations of respiratory allergy, a topic approached from both the clinical and mechanistic perspectives. The course, evaluated at 18 European CME credits and co-organised by the Hellenic Society of Allergology and Clinical Immunology (HSACI), focussed mostly on the needs of allergy and asthma clinical trainees to build competence and knowledge in dealing with asthma and allergic rhinitis. The school allocated 57 travel grants to the participants.

On Friday 23rd June, the Organising Secretariat welcomed all the participants in a brief opening ceremony, which was followed by a Greek-themed night out with drinks at the beach bar, so that each participant had an early opportunity to get to know the others in a relaxed atmosphere. Despite unexpectedly heavy showers, everyone enjoyed the evening and ended it with a spontaneous demonstration of Greek dancing in the rain.

The scientific core course started on Saturday 24th June in a full auditorium. The four sessions comprised asthma exacerbations, exacerbations in the upper airways, virus-induced asthma exacerbations, and allergen-induced asthma exacerbations. Each session was followed by active discussion, creating some remarkable feedback, although this extended the sessions slightly longer than scheduled.

The participants then met on the beach for a beach volleyball tournament in which everyone was keen to take part. The evening closed with a barbeque night at a traditional Greek tavern, one with a big wine cellar and a magnificent view of Pefkohori village.

The programme on Sunday 25th June commenced with an early boat trip to the central peninsula in Chalkidiki. As it was quite hot, the participants made the most of their opportunity to swim in the crystal-clear water, with the bravest ones jumping directly from the boat and others venturing out on to the nearby small, rocky islands. The highlight of the trip was unquestionably a group of dolphins that suddenly made an appearance behind the boat and seemed to be following us, a scene that made everyone immediately start taking numerous pictures.

Back at the venue, the evening opened with Oral Presentations on Basic Science & Epidemiology and Clinical Science, in which participants presented their work and tackled a demanding audience in animated debate. The evening continued with a Poster Session in a relaxed atmosphere and high-standard presentations from selected participants. After the course, a group continued to socialise by exploring Chalkidiki by night, whereas others relaxed at the hotel's beach bar under the moonlight.

On Monday 26th June, participants had the chance to familiarise themselves with the topics “Special considerations and other triggers of asthma exacerbations”, “Exploration of the practical aspects in assessing asthma activity”, and “Treatment of respiratory allergy exacerbations, offering high-level science”.

After these sessions, everybody played a final game in the beach volleyball tournament, with the winners of the final match celebrating their victory with a bottle of Champagne.

In the evening, the entire group was taken to a traditional fish tavern with a magnificent view of the sea in the village of Potaia. Although it started out quietly, the night turned into a traditional Greek extravaganza with plenty of wine and dancing to the music of the “mpouzouki”, and the participants created a wonderful evening for both themselves and the local people.

During a short break in the dancing, the President of the LOC, Nikos Papadopoulos, thanked everyone for attending the course and announced the names of the participants who had been awarded symbolic prizes for the high standard of their contributions. These were:

**Best Poster Presentation:**
Mohammad Fereidouni, Iran
Biday Katayoon, Iran

**Best Oral Presentation:**
Maria Xatzipsalti, Greece
Andrei Malinovski, Sweden

**Excellence Award:**
George Konstantinou, Greece

The night ended with a late-night swim beside the beach at the hotel.

On Tuesday 27th June the final day of the school, the scientific programme closed with the most contrasting current views on the prevention of asthma exacerbations, presented and debated in one, industry-independent session that everyone fully enjoyed, despite the exigencies of the previous evening.

When the time came for everybody to depart, there was much regret that such an experience had to come to an end, and the participants thanked the organisers for their hospitality and a unique Greek summer school experience.

Once again, we would like to express our thanks to our core organisers, EAACI and GA²LEN, for their financial and scientific support, as without this the school could not have taken place. Most importantly, though, we would like to thank everyone who attended the school for their enthusiastic participation in terms of science and social interaction.

Nikos Papadopoulos
Chair of the Local Organising Committee
EAACI 2007 in Göteborg – already a success!

When this Newsletter is reaching you, the very final touches on the planning of the 2007 EAACI congress in Göteborg is underway. Again, the congress is expected to bring between 5500 to 6000 delegates, and there will be more than 1600 abstracts presented. This proves again that the EAACI congress is becoming established as one of the absolute top events in allergy in the world. We see a constant growth of the attendance at the congress, and the communication of new science is very strong.

All fields of allergy are represented, and the programme is generally planned with different tracks, highlighting the fields of interest for any delegate. We have developed the tracks for any allergy associated specialist, such as paediatrician, dermatologist, immunologist or ENT-doctor. The track for general practitioners and allied health workers is strengthened, with a clear track within the main programme instead of being organised on a separate day. The asthma track is strengthened compared to several previous congresses, as we view asthma as a main disease for the allergy specialist. As in any EAACI congress, we put a special focus on our juniors, with special abstract sessions, opportunities for travel grants, and plenty of poster prizes.

We guarantee that you will find the social events of EAACI 2007 very enjoyable. The main event is being organised on Saturday, with an opening key-note speaker, junior poster session and a very special show, and of course a great buffet dinner. The Tuesday evening event is a boat excursion along the Göteborg coastline, including a delicious seafood buffet.

Don’t miss EAACI 2007! For detailed information, go to www.congrex.com/eaaci2007

Jan Lötvall
EAACI 2007 Congress President
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