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1. Bitter taste and bronchospasm

Theme: Asthma

Key words: Bitter taste, taste enhancer, bronchodilation

The bitter taste receptors located on the tongue are meant, from a practical point of view, to avoid ingesting toxic substances. The original discovery, by a Baltimore University (USA) team of scientists, of the same receptors on the airway smooth muscle (ASM) (Deepak. A. Deshpande et al. Nature Medicine 2011/16/11 November 1299-1304) suggests that their purpose is to avoid inhaling irritating products (such as air pollutants), leading when provoked to ASM contraction and bronchospasm. In other words, and to put it more simply, bitter taste and bronchospasm: two sides of a coin.

The other paradoxical and unexpected discovery of this study is that taste enhancers, such as artificial sweeteners (saccharine) or bitter sapid compounds like denatonium and chloroquine which act through a complex molecular mechanism associated to the opening of calcium channels, lead when activated to a bronchodilation threefold greater than that provoked by β 2-agonists (albuterol).

Besides, in confirmation of that notion is the authors' observation that inhaling those bitter taste enhancers (chloroquine as well as denatonium) decreased airway obstruction in a mouse model of ovalbumine-triggered asthma.

Given the existence of a thousand-odd natural or synthetic bitter tastants, we realize that their bronchodilating activity, stronger than β 2-agonists, constitutes a particularly promising and original research path.

2. Occupational asthma: the best and safest diagnosis criteria

Theme: Asthma, occupational allergies

Key words: Occupational asthma, bronchial hyperresponsiveness, sputum eosinophils, sputum neutrophils, skin prick tests, specific IgEs

Montreal's Hopital du Sacre-Coeur (Quebec, Canada) managed by Jean-Luc Malo is the World Investigation Centre for Occupational Asthmas (OA). Hence the interest raised by the author's synthetic and retrospective study concerning his experience over the past 10 years (J. L. Malo et al Clinical & Experimental Allergy 2010 early on-line 20 November) and concerning 665 investigations from which 519 patients are discussed in this highly documented report.

The authors first recall that the basic diagnosis factor is the reproduction of bronchospasm, on work sites or in the lab, by inhaling the suspected causal substance, whether it be low molecular weight compounds, such as isocyanates for instance, or high molecular weight compounds, such as flours, cereals or a variety of allergens (animal hair, for instance). But this process is often risky for it is likely to trigger asthma exacerbation, even when using, as the Canadian authors did, safe new apparatus. That is why an attempt is being

made to base the diagnosis on non-specific bronchial hyperresponsiveness (BHR) to methacholine associated with evidence of airway inflammation: sputum eosinophils and neutrophils, the sputum being either spontaneous or provoked before the challenge with the causal agent) as well as, in the case of allergens, skin prick-tests and serum specific IgEs.

Among the 519 subjects studied 2/3 were male, with an average age of 41.6 +/- 11.1 years. In 25% of them, 129, OA was confirmed; in 187 (36%) OA was not confirmed; in all others neither OA nor asthma could be identified. N.B. for 34 wheat flour-allergic subjects prick-tests and specific IgEs were assessed. Lastly, half the subjects were under corticoids. All these results were submitted to detailed statistical studies: bivariate analysis, logistic regression analysis, in order to identify the best predictive criteria. Results showed that BHR alone (PC20: the metacholine concentration which lowers FEV1 by over 20%) is more often normal with OA than with non-OA: its positive predictive value (PP) is consequently low (35%). Coupling information on the level of eosinophils in sputum (1-3%), the PP rises to 69%.

With flour-allergic subjects, the triple association of PC20, eosinophils, and positive immunological tests, point to a very high probability of OA diagnosis. Therefore, wishing to avoid the risks of a direct provocation to the suspected occupational agent, the authors give us the best diagnosis criteria based on the OA-suspected subject's triple status, i.e. functional tests, bronchial inflammation and immunological status.

3. *Alternaria* asthma

Theme: Asthma

Key words: Asthma, *Alternaria*, bronchial provocation test, skin prick-tests, specific IgEs

Asthma related to *Alternaria* sensitization (AA) has never enjoyed a great credibility among allergists, due partly to aerobiological and climatic differences between regions, partly to the rarity of the isolated sensitisation to this mould, and finally to the more or less reliable standardisation of extracts used for diagnosis. Hence, an article written by specialists from Madrid (C. Fernandez et al: *Clinical & Experimental Allergy* 2010 early on-line 20 November) brings a welcome scientific connotation.

The authors recall that the prevalence of this sensitisation varies from 3% in Portugal to 20% in Spain. They based their study and confirmed the diagnosis on the positive results of a bronchial specific challenge (BSC) carried out on 74 patients sent for asthma checks whose seasonal worsening of symptoms had evoked the possibility of a sensitisation to *Alternaria*. The BSC is described in detail and was conducted with the utmost precautions, monitoring the progressive FEV1 decrease in order to prevent any worsening of asthma. The retrospective study concerns 43 women and 31 men of 14-41 years of age, subject to moderate asthma; 64 (86.5%) presented an allergy concomitant to that of *Alternaria* (57 to grass pollen, 29 to another mould, mainly *Aspergillus*, 25 to cats and dogs, 14 to dust mites). For *A. alternata* the results for 74 subjects were as follows: skin prick-tests (SPT) were positive in 47 subjects; 26 negative SPT had a positive intradermal reaction (ID°); the specific IgEs were positive (9.6+/-17 kU/L) in 55 (in 21 cases the allergen recombining rAlt a 1 was used); the

BSC was positive in 45 subjects (61%) with a dual reaction, immediate and delayed, in almost half the cases.

All these results were submitted to a close statistical analysis: Receiver Operating Curve (ROC) and logistic regression analysis (LR), with two main findings:

1) SPTs almost certainly predict a BSC positive result (area under the ROC curve of 0.957); a negative SPT shows only a 4% probability of a positive BSC (LR), while ID^o is only moderately efficient; however, a weal over 5.5mm in diameter had 90% probability of a positive BSC.

2) Specific IgEs (CAP?16 kU) predict a positive BSC with 99% accuracy.

In conclusion, Alternaria-positive SPTs are sufficient to confirm diagnosis and BSC positivity. They make it possible to inform and treat of allergic subjects according to weather conditions. The authors even think that they can justify a possible immunotherapy with this mould.

4. Attendance of day care centres and prevalence of childhood eczema

Theme: Atopia, skin allergies

Key words: Day care centre, attendance of day care centre, eczema

A group of German paediatricians and epidemiologists has just made a series of surprising observations: 10 years after reunification they observe, in a cohort of 3097 children followed from 1997 up to the age of 6, a distinctly higher prevalence of eczema in children living in East Germany compared to those living in West Germany (Cramer C. et al Allergy 2011 66 1 68-75).

They then attempted to explain the reasons for such a difference via a yearly questionnaire among the populations of the West (Munich and surroundings) and the East (Leipzig), searching for and quantifying a number of co-variables (over sixteen) likely to act as risk factors.

All the data underwent detailed statistical analysis.

First results confirmed a higher incidence and prevalence in children from the East than in children from the West, whether it be parent-reported or doctor-confirmed eczema, which cannot be accounted for by demographic or genetic factors (e.g. atopic family) nor by socio-economic factors or local traffic emissions or parental smoking, nor by breast feeding for the first 4 months, nor even by presence of allergens (cats or dogs) at home.

The only highly significant factor found is day care attendance during the first 2 years of life. Day care attendance was in fact more frequent in the East than in the West (here, in Leipzig more than in Munich).

The authors are all the more surprised since day cares centres are normally considered as a source of recurrent respiratory infections due to the promiscuity they create between attendants. And according to the “hygienic hypothesis”, this should have play a protective role against allergy. But it is the reverse which is observed here.

The authors evoke hypothetical emotional stress or more generally the role of psycho-neuro-immunologic factors that are sometimes found to be at the root of eczema.

5. Indoor Air Quality (IAQ) and childhood asthma: variations between urban and rural areas

Theme: Asthma

Key words: Indoor air quality, indoor pollutants, allergic risk, urban dwelling, rural dwelling, Nitrogen Dioxide (NO₂), aldehydes, BETEX (benzene, ethylbenzene, toluene, xylenes)

The harmful impact on respiratory health of indoor pollutants (IP) of urban dwellings (UD) are well known. On the other hand, epidemiologists evoke (cf. December 2010 BUA) the protective role of the rural dwelling (RD) against allergy and asthma. The French Clermont-Ferrand team of lung specialists (Prof. Caillaud) has attempted to compare the IAQ of both types of dwelling: urban and rural, in a clearly-delineated region: Auvergne, and to study the respective IP impact on childhood asthma (Hulin et al : Indoor Air 2010 December Vol 20 N°6 502-514).

Two groups of children aged 10-14 were the subject of this 'case-control' study: an urban group of 32 asthmatics and 31 controls belonging to the ISAAC cohort (French study of 6 major cities) and, in collaboration with the Auvergne Mutualite Sociale Agricole, a rural group of 24 asthmatics and 27 controls picked out of a school population in regular contact with farm animals (FERMA study).

The protocol prepared with the epidemiologists included, beside the dwelling characteristics (age of the buildings, thermal insulation, ventilation type), the quantification of the usual IPs in both types of dwellings by a 7-day continual assessment of NO₂, PM_{2.5} particles, aldehydes (formaldehyde, acetaldehyde) and BETEX (benzene, ethylbenzene, toluene, xylenes), during summer and winter in the towns, summer only in the countryside. As to the demographic parameters (age, sex, family history of asthma or allergy, environmental smoking habits) these were established through medical examination, standard parental questionnaire and phone interviews. A thorough statistical analysis using several models made it possible to compare all the data between UD and RD and the respective health effects.

It appears that indoor pollution is twice as high in UD as in RD. Besides, in all the subjects tested, exposure to acetaldehyde and to toluene is significantly associated with a higher risk of asthma. Among children living in UD, that association is significant for toluene in winter and for BETEX with current asthmatics. With children living in RD, a significant relationship exists between formaldehyde and asthma levels.

Hence, daily exposure to even low concentrations of indoor pollutants can be implicated in childhood asthma.

But what this study also reveals is that specific health effects of IP could occur in rural environments.

6. Stress and asthma

Stress is often invoked by patients as a trigger factor for asthma outbreaks or even its cause, provoking scepticism from doctors who see there an obstacle to the continuation of deeper etiological research.

The recent article by American physicians (T.Ritz et al AJRCCM 2011 183 26-30) brings in a new point of view on this possible interrelation.

A group of 20 adult patients with asthma aged 20-30 (compared to 19 healthy control subjects, of the same age, gender, race, social and professional status) was submitted to a 'psycho-social' test involving a 5-minute talk (after 5 minutes of preparation) in front of a panel of 3 experts with the view to selecting the best possible applicant for an important position in an international company. This was followed by a mental arithmetic problem. For the next 45 minutes they were measured every 15 minutes for exhaled FeNO levels (as an airway inflammatory marker), respiratory function by plethysmography, and salivary cortisol levels (as a marker of the activation of the hypothalamic-pituitary-adrenal axis).

Results were as follows:

- Exhaled FeNO levels were statistically higher for asthmatics than for controls independently of changes in ventilation. However, endogenous cortisol levels were statistically lower (and independently of steroid therapy stopped before the test). An inverse relationship between exhaled FeNO and cortisol was revealed, since the post-test increase in cortisol levels measured in all subjects was associated for asthmatics with smaller increases in FeNO. As a whole, acute stress therefore increases airway inflammatory markers, although in a manner attenuated by stronger stress-related activity of the hypothalamic-pituitary-adrenal-axis.

Indeed, such a short test is not representative of the often prolonged stresses of daily life and the small number of patients means that these observations cannot be generalised. However, we have here a quasi-experimental demonstration of the possible role of stress in the development of asthma.

7. Commemorating 100 years of Allergen Specific immunotherapy: its mechanisms

The anniversary of NOON first publication (1911) is giving rise to numerous articles by the American Allergy Academies among which an impressive 774-pages, 99-chapter and 479-references document, a real allergist's handbook (JACI 2011 Suppl.1. 127 1 81-588). We shall only analyse here immunological mechanisms which underlie this subcutaneous allergen SI and can be summed up in 4 steps:

1) Immunologic response is characterised by decreases in specific sensitivity of end organs: skin, conjunctiva, nasal mucosa and bronchi, to allergen challenges, as much for early as for late response; a decrease in tissue cell infiltration: eosinophils, mastocytes, basophils;

a decrease in nonspecific bronchial reactivity to histamine and acetylcholine, all associated with blood and cellular changes.

2) Shortly after the first injections there is an increase in CD4+CD25+ regulatory T lymphocytes secreting IL-10 and TGF- β associated with immunologic tolerance. With continued immunotherapy there is some waning of this TH2 response to TH1 cytokine response.

3) Specific IgE levels initially increase and then gradually decrease. Levels of specific IgGs increase: IgG4 (formerly known as a blocking antibody), IgG1, and IgA. However, none of these changes in antibody levels have been shown to consistently correlate strongly with clinical improvement.

4) Increases in IgG levels are not predictive of the degree or duration of efficacy of immunotherapy, but the functional alterations in these immunoglobulins, such as high affinity for allergen, might play a non-negligible role in clinical efficacy.

On the whole, the authors prefer the term Immunotherapy to desensitisation which they consider as a faster technique to obtain a more or less sustainable tolerance and which applies to some substances such as drugs and chemical products.

Still along this line of immunological mechanisms, the paper by E. M. Shakir et al. (Annals of Allergy, Asthma & Immunol 105 2010 340-347) deserves to be mentioned, which presents a historical perspective.

8. Oral (sublingual) immunotherapy and cow's milk allergy

If sublingual (or oral) immunotherapy initiated by Italian authors has been widely adopted in Europe, particularly for treating grass pollen: Oralair[®] (Grazax[®]), or dust mite or animal dander allergic rhinitis, this is not the case in the USA where this technique, to which a short chapter is devoted in the above-mentioned report, is limited to a few trials in the case of peanut, milk, eggs or kiwi allergy. So far, results have been modest, risks of side effects non-negligible, and treatment looking like a desensitisation or a kind of adaptation more than immunotherapy, the obtained tolerance often proving only temporary.

That is why the Sicilian trial (G. B. Pajno et al Annals of Allergy Asthma & Immunol 2010 105 376-381) seems an interesting therapeutic approach. The protocol consists in orally administering, for 18 weeks and in hospital, progressively increasing weekly doses of milk, from 1-2 drops to 200ml.

Thirty children, with cow's milk allergy established by double-blind food challenge and high specific IgE levels, were submitted to this treatment while 30 others acting as controls were treated with soy milk.

At the end of the trial, 10 subjects presented full tolerance confirmed by (again) double-blind challenges and an increase in IgGs for 4 patients, which, for the authors, is the marker of a true immunotherapy. It should be noted that there were 2 severe reactions leading to interruption of treatment, whereas the control group did not present any side effects. True, this was not a real ambulatory treatment at home, but under an easy-to-understand, hospital control.

Besides, as observed in some previous trials, tolerance may disappear when the food is reintroduced. Nevertheless, this interesting trial offers hope in the future for the complete recovery from these cases of food allergy, more and more frequent and severe in Europe.

9. Omalizumab (O) as an add-on treatment for asthma

While Europe recommends the use of O to be limited to the severest forms of the disease, given the risks inherent to any monoclonal antibody, two recent papers have underlined efficacy and safety of O (Xolair®) but as add-on therapy to the basic treatment of asthma in adults and children.

1) The first is a meta-analysis of 8 random / placebo trials, conducted between 2004 and 2009 in the USA and Europe by 8 teams for a total 3 429 patients, 1843 treated with O and 1546 by placebo (G.J Rodrigo et al Chest 2011 139 28-35). The aim was at first to reduce the use of corticosteroids (C), to prevent exacerbations and then, to improve symptoms and respiratory function, keeping an eye on side effects. In all the trials, the treatment recommended by the pharmaceutical laboratories included two phases: a 16-week adjustment phase with a subcutaneous injection of O every 2 or 4 weeks (0.016g/kg) followed by a reduction phase of steroids use.

The overall results are as follows: at the end of the reduction phase, the O-treated subjects were more likely to be able to withdraw from C than the controls. Moreover, at the end of each stage, they showed fewer exacerbations. The thorough analysis revealed that this effect was independent of subject's age and treatment duration. The frequency of side effects was practically identical in both groups (3.8% as opposed to 5.3%) but injection site reactions were more frequent in group O (19.9%, i.e. 1 out of 5, vs 13.2%). No sign of increased risk of hypersensitivity reactions, cardiovascular effects or malignant neoplasms was observed.

2) The more recent personal trial conducted by New York authors (J. Karpel et al Annals of Allergy. Asthma & Immunol 2010 105 465-470) on 1 071 patients in 2 groups, all aged 12-75 and suffering from moderate or severe asthma, with the same protocol, and for 52 weeks, leads to the same conclusions of efficacy and safety as the above-mentioned studies.

All the studies, albeit perfectly clear but sponsored by pharmaceutical firms, merely confirm the benefits of O in the treatment of asthma, but do not, in our opinion, allow practitioners recommend O, a biological and fairly costly medication, as an add-on to the treatment of moderate asthma in adults and above all children.

10. Sick Building Syndrome and allergy

A recent epidemiological work by Japanese authors puts back in the spotlight the famous 'Sick Building Syndrome' (SBS) which made such a media buzz in the 1990s, explained as 'Syndrome of unhealthy buildings' (not to be confused with unsanitary flats). This syndrome appears in modern, air-conditioned, office buildings and is characterised by symptoms of discomfort and itching (skin, eyes, nose) with no objective signs but felt by numerous occupants. In a survey initiated by the Ministry of Housing and following the report

we had prepared for the Commission of the European Communities, we visited some large buildings with an average of 1800 clerks. We observed with occupational physicians that, beside physical, chemical, and psychological factors, ergonomic ones played an important role, and that 30% of the complaining subjects had an atopic history, SBS being a diagnosis of exclusion.

The Japanese authors (Y. Saijo et al: Indoor Air: December 2010 on-line) conducted a survey through questionnaires with 1 479 residents in 425 new housings, 80% of them in wood, in 6 Japan regions and during the autumn (to eliminate possible **pollen allergy**). The subjects, aged 19-60, answered yes or no to questions on their symptoms. Physical, chemical (13 aldehydes and 29 VOC, Volatile Organic Compounds) and biological (dust, mould) factors were targeted in the indoor environment.

After a step by step statistical study, by multiple logistic regression, it appeared that: 46% of the patients had a history of allergy.

The careful research of a correlation between each of the biological or chemical elements discovered and the symptoms (Odd-ratio, OR) produced the following results: Derp1, Aspergillus, and Rhodotorula have a significant correlation with SBS.

The house dust mite DerP1 with nose symptoms, a spergillus for eye symptoms with a significantly high OR, and Rhodotorula for all the symptoms.

As for Cladosporium which is the most frequent of the collected fungi, or Eurotium, they have a very low OR with clinical signs and might have a protecting role.

This interesting survey stresses the importance of biological SBS factors, although they only represent part of the etio-pathogenic factors of the disorder.

11. Cross allergy: cough suppressants – neuromuscular blocking agents

Theme: drug allergy, anaphylaxis during anaesthesia

Key words: Muscle relaxant, Pholcodine, Suxamethonium

Everything started with the observation by Norwegian doctors of the abnormal frequency of anaphylactic reactions during anaesthesia (1 case in 20 vs only 1 in 5200 in Sweden or other European countries), quickly linked to the use of muscle relaxing agents of the suxamethonium (SUX) type. After thorough investigations, it appeared that Norwegian patients were over-using a cough suppressant: Tuxi which contains Pholcodine (PHO), a powerful sensitiser which, like SUX, carries the quaternary Ammonium epitope.

Pr. Johansson's Stockholm team highlighted the presence of PHO- and SUX-specific IgEs in 5 to 10% of treated subjects. This cough suppressant was then withdrawn from the Norwegian market in March 2007. The Norwegian authors (E. Florvaag et al., Allergy 2011 17 January early view) wished to know the situation 3 years later concerning anaesthetic reactions as well as the patients' immunologic condition.

First of all, the occurrence of anaesthetic accidents thought to be SUX-induced has considerably and significantly decreased according to the figures.

In a group of 300 subjects monitored yearly from 2006 to 2010 and having been diagnosed for PHO- and SUX-specific IgEs and also some morphine (MOR) derivatives,

antibody prevalence of PHO and SUX had significantly decreased after one year (respectively from 11 to 5% and from 3.7 to 0.7%).

At the 3rd year SUX had fallen to 0.3%, PHO to 2.7% and MOR to 1.3%.

The authors consequently emphasize the benefits of having withdrawn cough suppressants from the Norwegian pharmacopeia and the relevancy of the sensitizing role of Pholcodine. At a time when in France a considerable number of cough suppressants contain this product, when a great number of medicines are under increased surveillance and taking into account the fact that practically no cough depressants are now used in Respiratory diseases, this raises the question of maintaining such substances in the pharmaceutical nomenclature.

12. Bronchial mucosa mast cells and severe asthma (SA)

Theme: asthma, bronchial histology

Key words: asthma, tryptase mast cell, tryptase-chymase mast cell

A group of American doctors has tried to establish a correlation between the phenotype of the bronchial mucosa mast cells (MCs), their number, their location and their activation, and the severity of asthma, by studying a cohort of asthmatics spread over 7 specialised centres throughout the US (S.Balzar et al : AJRCCM 2011 183 299-309). We already know that MCs are differentiated according to their enzymatic equipment identified by immuno-histo-chemistry into : tryptase mast cells (MCTot), most frequently found in the lungs, and tryptase-chymase mast cells (MCTC), normally accounting for less than 20%. The study was carried out on 157 asthmatics (A), aged 18-65, mostly female (an average of 2/3), and divided into 4 groups by the authors : 57 with Severe Asthma (SA), needing high doses of corticosteroids, taken per os in half the cases, with frequent exacerbations and some hospitalisations during the past year ; 22 said to suffer from Type 1 Mild Asthma (MA), i.e. with a normal respiratory function and without inhaled corticosteroids (IC) ; 31 with Type 2 Mild Asthma (MA²) with ICs ; and 13 with Moderate Asthma (Mod A) with FEV1 ? 80% of normal and treated by ICs +/- β 2 and/or anti-leukotrienes. Finally, the addition of 34 healthy paired controls to the study allowed a statistical approach (multiple logistic regression). All these subjects were submitted to biopsies and epithelial brushings leading to the identification of MCs, and bronchoalveolar lavages (BAL), making it possible to dose tryptase and prostaglandin D2 (PGD2), two markers of mast cell activation.

Results were as follows:

1) In the submucosa: the number of MCT is higher in Type 1 MA, it is significantly lower in SA but with a predominance of MCTC.

2) In the epithelium: MCT are still the majority in Type 1 MA, but they persist in SA, always in the MCTC phenotype.

3) While the tryptase dosage cannot differentiate between MCs, that of PGD2 is highest in SA.

Thus, the predominance of the Chymase-positive phenotype in bronchial mucosa and high rates of PGD₂ are the most significant predictive factors for Severe Asthma. The authors suggest that it may be interesting to aim at PGD₂ metabolic pathways to fight against the severity of asthma.

13. Obesity and asthma in children

Theme: asthma, metabolic abnormalities

Key words: asthma, obesity, diabetes, triglycerides

Both diseases have individually reached worrying heights throughout the world and the question has been raised of a link between them. The work of L. Cotrell, of the Virginia Paediatrics Department (USA), justly draws attention to the frequency of metabolic troubles in obesity which could thus explain this link, regardless of course of mechanical consequences of excess weight on the respiratory function (AJRCCM,2011-183 441-448).

A cross-sectional analysis of a representative sample of a rural community including 17 994 school-age children (4-12) was carried out through a questionnaire with demographic informations : family history, parental smoking, reported asthma diagnosis, body mass index (BMI), evidence of acanthosis nigricans (AN) a brown to black skin rash around the neck and armpits as a marker for developing insulin resistance, and fasting serum lipid profile including total cholesterol, triglycerides, HDL and LDL lipoprotein cholesterol. While a little less than half the subjects were male, it is here that obesity was the highest; most asthma diagnoses were also to be found in this group ; finally a family history of diabetes was found in half the cohort.

At the end of the statistical study it appeared that, regardless of BMI, the asthmatic children had a higher rate of triglycerides than the non-asthmatics; they also show a higher frequency of AN, whatever the age and the possible exposure to parental smoking. Besides, the prevalence of asthma with obese or morbidly obese children is higher than in children with normal or slightly increased BMI.

This study thus shows a significant association between asthma and abnormal lipid and glucose metabolism, without making it possible to prove which is the *primum movens* nor to establish the chronological sequence from metabolic troubles to inflammation observed in asthma and obesity. It is nevertheless possible to imagine that dyslipidemia and insulin resistance, precursors of diabetes, can be associated with the development of asthma and constitute, by interaction with immune mechanisms, the missing link with obesity. Such data also stress the benefits of a dietary and metabolic monitoring in the management of childhood chronic asthma.

14. Childhood acute urticaria

Theme: skin allergy, paediatric allergy

Key words: urticaria, temperature, humidity, season

A retrospective study on childhood acute urticaria (AU) was undertaken by a Greek-English team with a view to comparing the possible role of environmental factors on the occurrence of the disease, between the English Norwich (N) and the Greek Heraklion (H) Hospitals (GN. Konstantinou et al *Ped. Allergy & Immunol* 2011 22 36-42), with the hypothesis of cyclical trend.

Conducted between 2005 and 2007, it concerned 729 children under 14 (324 in N and 405 in H), respectively on cohorts of 28 931 and 27 653 subjects. Climate and demographic data, as well as associated clinical factors, were recorded and compared, all then submitted to a Poisson regression curve for the meteorological data and Edwards tests for seasonality. In N, the incidence of AU was more frequent from October to April, but not significantly so. In H, the incidence was significantly higher from December to May.

Temperature was inversely associated to incidence of the disease, whereas humidity was variable in both geographical sites.

As to the associated factors, which cannot be considered as etiological, they reveal that seasonal respiratory infections were statistically the most commonly triggers and (that is largely unexpected) food allergy was the least.

On the whole, the only plausible element derived from the study is the seasonal factor which could explain the association between AU and respiratory infection. However, there were no notable epidemiological differences between the observations made in northern and southern Europe.

Such somewhat disappointing conclusions can also be found concerning chronic childhood urticaria (CU), reviewed in a paper (Church MK *mem revue* 2011 22 Issue 1 Fevrier 1-8) insisting on the need for intensive research on AU, as on CU, both affections which are not rare in the paediatric field and always difficult to treat.

15. Prenatal fatty acid exposure and risks of early childhood allergy

Theme: atopia

Key words: fatty acids, diet, pregnancy, allergy risk

A Dutch team (ML. Nottenboom et al : *Clin &Exp. Allergy* 2011 early view), emitting the hypothesis of a pro-inflammatory effect of maternal diet fatty acids (polyunsaturated ω 6 FA in such as Linoleic Acid, LA, which can be found in vegetable oils and margarine and is a precursor of Arachidonic Acid, AA) on the risks of atopy in children, has monitored in a prospective study a cohort called KOALA from birth and periodically up to age 6-7.

Other studies, including researchers of the same group, have suggested on the contrary that polyunsaturated ω 3 FA such as the α Linoleic acid ALA (found in green

vegetables) and the Long Chain FA ω 3 (LCP) (found in oily fish) or even the ω 3 LCP of breast milk (C. Thijs et al Allergy 2011 66 58-67), had a protective role against allergy.

To check those assumptions, the authors took blood samples from 1374 pregnant women between 34th and 36th week and dosed the polyunsaturated long-chain fatty acids in ω 3 and ω 6, in order to establish a fatty acid status for each subject. At the same time, by questionnaires or visits by trained assistants, the whole range of atopic manifestations among the children was recorded: wheeze, asthma, rhino-conjunctivitis, atopic dermatitis, and a total serum IgE.

The comparison between all these data, meticulously recorded and submitted to a precise statistical analysis (multiple logistic regression), gave the rather unexpected following results:

- No association was found between the maternal fatty acid status (whether it be the sum of FA in ω 6 or ω 3) and atopic disorders or IgE levels.
- However, associations were found between high ω 6/ ω 3 ratios and lower eczema risk in children, above all during the first 7 months of life and particularly when AA rates were high.

It can be concluded that the development of atopic disorders is not a function of maternal diet alone (although the foetus's lipid metabolism is entirely dependant on the mother) and that other factors, no doubt including genetics, play just as important a role.

16. Decreased response to inhaled corticosteroids (ICS) in obese asthmatic children

Theme: Asthma

Key words: asthma, obesity, BMI, emergency hospitalisation

We have already analysed the possible interrelations between asthma (A) and obesity (O) in children. E. Forno's paper (JACI 2011 127 3 741-749) brings in a new contribution to this "exchange of bad conduct" between the two diseases.

This US group of Paediatricians and Physicians (Boston and St Louis) isolated, within a cohort of moderately asthmatic children enrolled between 1993 and 1995, 1041 subjects (aged 5-12, 65% boys, 2/3 whites) split for a post hoc analysis into 2 large groups: 322 (31%) obese (O, 146) or overweight (W, 176) in consideration of their BMI (Body Mass Index), and a placebo-treated control group. Hypothesizing an inflammatory activity of Obesity, the aim of the research was 1) to assess the efficiency of an ICS (Inhaled Cortico- Steroid), Budesonide[®], 200 μ g twice a day, by comparing respiratory function before and after treatment, and 2) to monitor (carried out over 4 years) outcome of A and risks of exacerbation and/or hospitalisation.

The functional tests included mainly FEV1 and the FEV1/FVC (Forced Vital Capacity) ratio; blood samples were also taken for IgEs, eosinophils and Vitamin D levels (a decrease in Vitamin D is possibly a severity marker). Monitoring comprised 2 phases of 2 years each. After a statistical analysis it appeared that:

- During Phase 1, there was no significant difference between the 2 groups in lung function improvement after Budesonide, which causes a more or less marked bronchodilation;

- However, while this improvement carried on through Phase 2 for the non-O group, it was absent in the O group, for which each BMI increase caused a significant decrease in ICS efficiency.

- And finally, whereas the risks of emergency hospitalisation for the non-O asthmatic subjects dropped 44% over the survey period, there was no decrease at all for the Os. This is something to be remembered in the treatment of A in overweight children, both diseases needing to be treated at the same time. To this paper on A/O relations should also be added a recent Australian work (C. Farah et al : Chest 2011 18 03 early on-line) which shows, after a thorough functional and statistical study of 49 asthmatic children treated by ICS, that BMI is an important and indisputable determinant of A treatment, but regardless of inflammatory or mechanical factors. The chapter is not closed.

17. Anti-acid medication as a risk factor for food allergy

Theme: Food allergy

Key words: anti-acid medication, Proton Pump Antagonist (PPA), AntiH2

Two Austrian physicians (Isabella Palli-Schol et Erika Jensen-Jarolim Allergy 201166 469-477) have published a very well-documented and convincing paper, drawing our attention to the risks of food allergy in taking anti-acid gastric medication, research based on personal clinical and experimental observations.

Everything started from the observation of a patient who became allergic to Beluga caviar (!!), whereas he had been taking Proton Pump Antagonists (PPAs) like Omeprazole[®] for a few years and could remember the starting point of his sensitisation. An identical allergic reaction, with IgEs and positive skin tests, was reproduced in mice, using PPAs but also Ranitidine[®] type anti-H2s and other allergens different from caviar such as hazelnut, fish or ovalbumin.

The authors' argument is developed in 3 points: the molecular characteristics of food allergens, the role of gastric digestion, and the mode of action of the anti-acids. As for allergens, it is recalled that eight groups of ingested foods represent 90% of the sensitizing proteins: crustaceans, eggs, fish, milk, peanuts, nuts, soy, wheat. The gastric function is decisive in discovering their allergenic potential. On a physiological level, indeed, it is gastric acidity which induces digestion through activation of gastric pepsin and release of pancreatic proteases through Secretin.

This means that drugs which neutralize gastric acidity leave intact allergenic foods, hence the risks of sensitisation which sets in insidiously. The same is true of atrophic gastritis, often caused in old patients by long NSAID treatment, or of achlorhydria in the context of alcoholism or gastro-intestinal surgery.

As to gastric anti-acid medications, they consist, apart from Bismuth which has no longer been authorised in France for several years, of PPA and anti-H₂s which blocks acid production.

True, they are necessary to treat ulcers or heartburns, particularly in the elderly, or for gastro-oesophageal reflux in pregnant women or as co-medication in the treatment of rheumatism or intestinal inflammation. Therefore, long term use should be avoided as much as possible.

In any case, two practical conclusions can be drawn from this research:

- It is essential in anamnesis of an allergic patient to include a question on possible PPA or anti-H₂ treatment.

- These drugs must not be authorized as self medication (“over the counter”) as is the case in some European countries but must be medically and appropriately prescribed.

18. Drug hypersensitivity reactions: current data

Theme: Drug allergy

Key words: drug hypersensitivity, immediate allergic reaction, non-immediate allergic reaction, patches, intradermal tests, habituation

An update paper on this vast theme, subject of the Rome 4th April 2010 Congress, has recently been published (A. Romano et al 2011 JACI 127 3 Suppl.1 67-73 et 74-81 W. J. Pichler et al).

The distinction between Immediate Reactions (IR) and Non-Immediate Reactions (NIR) should first be re-underlined.

The former, most often IgE-dependent, occur within one hour in the form of urticaria, angioedema, rhinitis, or bronchospasm, sometimes even anaphylaxis. The responsible agents are mostly antibiotics (β -lactams) and neuro-muscular blocking agents, among others. The latter, non-immediate reactions, mostly through cell mediation (T lymphocytes), consist in maculo-papular eruptions but also urticaria. Some are severe : bullous exanthema, sometimes with eosinophilia and malaise, or pustulous exanthema, even toxic epidermal necrolysis (Lyell or Stevens-Johnson syndrome) caused by Non-Steroidal Anti-Inflammatory Drugs (NSAID), but mostly, for the past few years, agents of anti-cancer chemotherapy (platinum salts or monoclonal antibodies) and biological medications in general. With IRs, allergic tests : prick, ID or patch-tests or serum IgEs (possible only for some drugs), help to avoid drug reintroduction : a “gold standard” diagnosis, but neither a 100% reliable nor a harmless one. New biological tests using basophils or lymphocytes are currently being assessed, but none provides total certainty.

The same is also true of the NIRs, for which the Nancy dermatological team (Barbaud), as well as Haddad (Creteil), stress the benefits, to start with harmless patch-tests in severe skin forms, but also the necessity, in some cases, to use higher sensitivity IDs. Finally, desensitisation, when medication is indispensable (or there is no other alternative) is mentioned with interesting results obtained, particularly by Castells (Boston) with a 6-hour

protocol for drugs such as Rituximab, Infliximab, Trastuzumab and with no cases of fatal side-effect.

As for immune mechanisms, where dendritic cells and T lymphocytes, particularly T regulators play an important role, they already make it possible, thanks to progress in pharmacology and genetics, to foresee, for certain medications, a personalised therapy. An interesting bibliography is given at the end of these papers, providing details on the attempts and results obtained by the major speakers at this International Congress.

19. A non-invasive method of diagnosing asthma

Theme: Asthma

Key words: airway inflammation, NMR (Nuclear Magnetic Resonance), NMR spectrometry

Looking for an objective, non-invasive measurement of airway inflammation in asthma, particularly among children, a group of Canadian authors (E. J. Saude et al JACI 2011 127 757-764) has attempted to study its metabolic profile in urine by Nuclear Magnetic Resonance (NMR). Urine appears indeed as a biological fluid whose chemical composition can be easily studied, particularly its protein and cell content. NMR spectroscopy led to identification and quantification of 70 metabolites and to application of this method to children aged 4-16, divided into 3 groups: 33 stable asthmatics under ambulatory treatment and examined in consultation, 20 asthmatics hospitalised for exacerbation, and 20 controls.

In a first stage, the authors did not observe any significant difference between those 3 groups.

They then eliminated the least important metabolites and drew up a list of 23 chemical substances which validated a model applicable for discrimination between asthmatics and healthy controls. In so doing, they could correctly diagnose 31 asthmatics out of 33, with a 5% error margin, 94% sensitivity and 95% specificity; only one of the controls, i.e. 1 out of 20, was erroneously classified as asthmatic.

Similarly, by comparing urine metabolites of stable and exacerbated asthmatics, they could draw up a statistically valid model of 28 metabolites, which lead to the correct discrimination of 31 asthmatics out of 33, i.e. a reliability of 94%.

Many tables illustrating this paper list these metabolites. Among them, we could quote those of the citric acid cycle (succinate, fumarate, threonine, etc.) which seem the most useful in the model differentiation, and the best known such as adenosine, creatine, histamine and methyl histamine, with high levels in severe asthma, and decreased by anti-allergic drugs.

The authors admit the limits of this important work, spread over 2 years of observation and monitoring. They nevertheless found it interesting for improving the differential diagnosis among infants and children between asthma and a simple cough of viral origin. As a practical conclusion, the sophistication of these techniques is such that they are not within the reach of all laboratories, even if possible improvement through robotised versions allows those researchers to predict a drop in the cost of examinations. They however hope to

be able to refine a diagnostic method which is the only one known so far based on NMR urine analysis and think that the metabolic approach of the asthmatics' airway dysfunction will lead to new research tracks and to the discovery of anti-asthma drugs.

20. Risks of using Inhaled Corticosteroids (ICS) for asthmatic women during pregnancy

Theme: Asthma

Key words: asthma, inhaled corticosteroid, cortisol, estriol, osteocalcin

At a time when the French Academy of Medicine devotes a theme session to the perinatal determinants of health on children's and adults' pathology, the Australian authors' paper (N. A. Hoidyl et al AJRCCM 2011 183716-722) will be helpful in reviewing the possible risks of ICS among pregnant asthmatic women. It must be said that asthma affects 14% of pregnant women in Australia (vs 8% in the USA). ICS are accused of being responsible, not only for deleterious effects in the mother (eclampsia) but above all in the foetus: prematurity, congenital malformations, low birth weight, hormonal balance disorder.

The study concerned 156 asthmatics and 51 controls. Concentrations of cortisol, estriol (a marker of the foetus's adrenal activity), osteocalcin and corticotrophin were measured in the mothers. Besides, the cumulative dosages of ICs used were recorded each trimester of the pregnancy and ultrasound was performed at weeks 18 and 30, and the foetus's weight and sex were noted.

Results were as follows: the mother's hormonal concentrations, among which estriol, were not affected by the presence of asthma. That is to say that the foetus's adrenal function was not modified and therefore that ICS do not influence foetus growth and development. However, in the mother, everything depends on the sex of the foetus: whatever the dose, ICS had no effect on cortisol, estriol or osteocalcin if the foetus was male; but they increased corticotrophin rates during the 1st trimester of pregnancy.

On the contrary, if the foetus was female, then ICS did inhibit 1st trimester maternal cortisol and 2nd and 3rd trimester osteocalcin, and in a dose-dependent manner. The Australian members of Women's Lib have not yet expressed their worries about such discrimination, already present in utero!!

As for ICS, they are, once more, found innocuous, since it appears that the appropriate control of asthma is beneficial, both for the mother and the foetus.

21. Microflora and allergy

Theme: Asthma

Key words: Atopy, exacerbation, asthma, virus, ribosomal RNA, microbial diversity, bronchial hyperresponsiveness, eurotium, aspergillus, penicillium, gram (-) germs, hygienic theory, macrolides

Like Aesop's language, Microflora may be for Allergy, the best and the worst of things

1.1. "The worst of things"

It is well known that infection is strongly associated with asthma exacerbations. A timely reminder is published in an European review with recommendations (N.G.Papadopoulos *et al* :*Allergy* 2011 66 458-468). The main responsible agents are respiratory viruses (*Rhinovirus*, *Syncitial virus*, *type-C-virus*, *as well as metapneumovirus in children*, *influenza virus in adults*) and bacteria such *Chlamydophila* and *Mycoplasma*, more often involved with asthma persistence.

But the mode of action of this microbiota, relatively unknown, is the subject of a very interesting scientific study. In some cases, improvement of respiratory symptoms, after macrolide therapy, has incited a group of American researchers (*Yvonne J. Huang et al JACI* 2011 127 2 372-381) to detect, through modern, culture-independent, techniques, one or more characteristic microbial profiles in asthmatics' distal airways, and compare them with clinical features of asthma. In a pilot multicenter study among 65 asthmatic adults, more or less under control thanks to claritromycine treatment (vs 10 healthy control subjects) bronchial epithelial brushings were collected and 16S ribosomal RNA (present in all bacterial cell walls) was sequenced, amplified by PCR and parallel clone library-sequencing analysed. They first observed the great diversity of the microbial population, statistically higher among asthmatic patients than controls. Moreover, comparing patients' microbiota composition to corresponding clinical criteria, they observed a significant correlation between bacterial diversity and bronchial hyperresponsiveness (BHR). It is difficult to assign this association to a particular group of germs, (about 100 families were analysed and identified, including *Comamonadaceae*, *Sphingomonadaceae*, *Oxalobacteraceae* and other taxons). But it could very well account for the severity and treatment difficulties of certain forms of asthma.

1.2. "The best of things"

The commensal bacterial flora may be beneficial for allergic and asthmatic patients. Two very interesting studies prove it.

One is an elegant experiment, by N.Harris's Swiss team (*T.Herbst et al. AJRCCM ahead of print* 2011 25 Mars) which makes use of a model of allergic airway inflammation in transgenic germ-free mice, then sensitized by ovalbumin, and shows that the induced Th2-type humoral and cellular allergic response is strongly reduced with re-colonization by commensal bacterial flora, such as that detected on human intestinal, pharynx, or bronchial mucosa. It also ensures the recruitment and maturation of immune cells in the lung.

The second excellent study is published by the German-European group, led for many years by Erika Von Mutius and devoted to the beneficial role of farm life in preventing and protecting children against asthma. It appears that exposure to the various microorganisms of agricultural environment accounts for this effect (*M.J Ege et al NEJM 2011 364 701-9*).

Two groups of children, living on farms and going to school, were the targets of this bacteriological and epidemiological survey:

In the 1st group (over 6000 subjects) samples of mattress dust were screened for bacteria (16S ribosomal DNA) using modern genetic identification techniques; in the 2nd group (over 9000 children), samples of settled dust from children's rooms taken by electrostatic collectors were evaluated by means of traditional germs and fungus culture.

In both groups the prevalence of asthma and atopy was significantly lower in farm children than in controls and the former are exposed to a larger number of germs. In the 1st group the microbial diversity was inversely and significantly related to the prevalence of asthma (but not atopy). In the 2nd group bacterial detection revealed also a large variety of bacteria, including *Listeria Monocytogenes*, *Corynebacterium* but mostly two predominant species: Eurotium, a sexual form of *Aspergillus*, and *Penicillium*: their protective role against asthma is consistently suggested, whereas on the other hand, Gram(-) germs could protect against atopy.

Thus, the beneficial role of the environmental bacterial population is a striking confirmation of the hygienic theory of allergy.

22. Blood biomarkers for asthma and chronic bronchitis

Theme: Asthma

Key words: Asthma, chronic bronchitis (COPD), biomarkers, ceruloplasmin, haptoglobin, hemopexin, macroglobulin

A group of researchers from 9 Australian universities suggests, as a diagnosis method, identification, in the blood of adult subjects, of novel specific protein biomarkers of these respiratory diseases, through two-dimensional electrophoresis followed by mass spectrometry (N. M. Verrills et al AJRCCM 2011 18 March ahead of print). In a first analysis, they detected 70 proteins of which 58 were validated, 20 considered as possible candidates and grouped in 3 categories : iron metabolism (ceruloplasmin (C), haptoglobin (H), hemopexin (Hx)), coagulation cascade (prothrombin (P), α -2 macroglobuline (α -2M), fibrinogen...) and Complement.

3 groups of adult patients were tested: 21 asthmatics (A), 5 suffering from chronic obstructive pulmonary disease (COPD) and 17 controls (T), plus , later on 16 older subjects (7 A and 9 COPD).

After a first stage of major biomarker validation, proving that a panel containing several of them is necessary for an accurate diagnosis, and after a statistical comparison in subjects and controls of those markers' respective sensitivity and specificity, the authors

arrive at the following conclusion: 4 biomarkers are able to discriminate between the 3 groups tested: C, H, Hx and $\alpha 2M$.

Thus, H+Hx clearly discriminate between A and T, while C+Hx distinguish between COPD and T. In differentiating between A and COPD, which is often a problem for the clinician, the H+C+ $\alpha 2M$ combination provides the highest sensitivity and H+Hx+ $\alpha 2M$ the best specificity. Finally, the use of inhaled corticosteroids does not modify these observations.

This meticulous research demonstrates that while blood is easy to obtain for diagnostic purposes in an adult (as urine is in a child, cf. our April BUAs), these tests are not within the scope of all laboratories and are only useful in a small number of cases where clinical examination is unclear; moreover, they are not decisive and are certainly costly. However, they open new perspectives on physiopathology and biochemical mechanisms which support these diseases.

23. Resolution to well-cooked egg allergy: the tolerance mechanism

Theme: Food allergy

Key words: Egg, uncooked egg, well-cooked egg, tolerance, ovalbumin, ovomucoid, protein degradation, intestinal digestion

Two recent articles, one clinical and the other experimental, evoke this problem. The British team of Cambridge Paediatricians (A.Clark et al Clin. Exp.Allergy 2011 13 April ahead of print) undertook a longitudinal study between 2004 and 2010 on 95 children suffering from egg allergy (EA) with a median onset at 12 months. The disease was typically marked by cutaneous and gastrointestinal symptoms, with anaphylaxis in 7 cases, (needing to resort to adrenalin 5 times) and respiratory reactions in 11 cases.

The authors, aware of the lack of national or international recommendations on the issue, , performed repeat challenges at least once a year, with a total of 181 “open” trials, of which 77 with well-cooked egg and 104 uncooked.

Out of the 28 positive cases among the 77 (37%), 65% had cutaneous reactions, 68% intestinal and 39% rhinitis with no other respiratory reactions. Adrenalin was never required. Tolerance was gained twice as rapidly to well-cooked than uncooked egg (an average of 5 vs 10 years) and continued to 13 years. Nearly one-third had resolved allergy to well-cooked egg at 3 years, and two-thirds at 6 years. The authors consequently suggest the initiation of home reintroduction of well-cooked egg into the child’s diet from age 2 or 3, particularly if EA was moderate and without asthmatic reaction.

As to the tolerance mechanism, it is evoked in the interesting experimental work by the New York Mount Sinai Hospital paediatrician group (G.Martos et al JACI 2011.127 . 4 990-997) who have studied ovalbumin and egg white ovomucoid allergenicity. Thus, in the sensitised mouse, ingestion of cooked egg white causes no allergic reaction, whereas peritoneal administration induces anaphylaxis. Heating breaks down those proteins which, digested and absorbed in the intestinal tract, become unable to triggering basophil activation. So, degradation of cooked egg white proteins, strengthened by gastro-intestinal digestion, is

one of the explanatory mechanisms of egg tolerance in the majority of children allergic to that food.

24. The come-back of “intrinsic” asthma

Theme: Asthma

Key words: Intrinsic asthma, dust mites, total IgE, specific IgE

The term “intrinsic asthma” had been banished from recent medical literature, partly because its definition was based on negative criteria (presumed absence of allergy) and partly because it incited the over-worked clinician to shorten his/her questioning and examination of the patient, by-passing thorough etiological research and adopting the easy solution of corticoid prescription.

But a team of pneumologists and researchers from several Belgian universities has recently reopened the file by stressing the fact that in these allergy-free A (Asthma), IgEs were locally detected but that antigen-response specificity was elusive (J. Mouthuy et al. AJRCCM. April 2011 ahead of print).

They therefore submitted a group of 29 non-atopic A (negative skin and IgE tests), compared to 24 allergic As and 25 controls, to a classical series of biologic and functional respiratory investigations (looking for bronchial hyperresponsiveness), Identification of dust mite – specific IgE in sputum (Der p and recombinant Der p1 and p2) was also performed to define their clinical meaning and functional relevance (through both whole-lung challenge and basophil activation test).

Results were as follows:

The intrinsic asthmatics’ sputum (IA) contained, like that of the allergic asthmatics (AA), high and significant levels of total IgEs and dust mite - specific IgEs (Der p), as compared to controls (C). Those IgEs recognise in vitro major allergens Der p1 and Der p2 and are able to trigger activation of blood basophils from atopic donors.

However, dust mite (Der p) nasal provocative challenges performed in 12 IA vs 6 AA and 6 C, did not translate into any functional or cellular response from IAs, contrary to the bronchospastic and inflammatory reaction caused in AAs.

As a whole, for these authors, IAs do locally produce IgEs, including dust mite – specific IgEs which can be detected in sputum and are able to activate effector cells in vitro - albeit without clinical response in vivo.

It is certainly a valuable study but is based on too few cases. The authors put forward the weak postulate of a second signal (viral?) that promotes in atopic patients, IgE-mediated asthmatic responses through FcεR1 which would not be found in IA. However, the definition of this entity still remains questionable.

25. Allergy to psocids: parasites of ecological buildings

Theme: Asthma

Key word: psocids, booklice, ecological materials

Psocids are small insects known and described as indoor allergens in India and more recently observed in Western countries, particularly in houses built with ecological materials for insulation and heating. The Reims (France) Pulmonary Allergy team led by F.Lavaud describes a rare case of allergic asthma (J.M Perotin et al: Allergy early view 22 April 2011) occurring in a 33 year-old woman presenting rhinitis and conjunctivitis for 2 months, recently associated with wheezing cough and – after pulmonary function testing – reversible airway obstruction. She lived in a flat recently insulated with some ecological material (hemp). Antihistamine and inhaled corticosteroid dramatically decreased the symptoms.

The allergy investigation showed skin prick tests and IgEs negative to common airborne allergens, but the patient mentioned little insects in her room, identified as psocids (*Liposcelis*) by an entomologist. Extracts prepared from these parasites provoked positive skin tests and specific IgEs (negative in control patients, just as they were to tropomyosin from *Dermatophagoides farinae* and cockroaches which could be co-sensitisation responsible with psocids).

These insects are usually found in tree bark or leaves, as well as damp houses, cellars or food hangars (they are called “booklice”). They can also be observed in emerging countries as straw, hemp and hessian parasites, but also as occupational allergens in entomologic or stuffed animal collections.

Few reported observations can be found. This is the first documented case of non-occupational allergic asthma due to this insect behaving like an indoor allergen, whose proliferation is boosted by the use of ecological materials: here, hemp, whose eviction induced a favourable outcome without relapse in 6 years.

Thus, beside dust mites, cockroaches, bees, wasps and other insects, with psocids the Allergist enlarges his expertise and competence in entomology.

26. Allergens, television and children airway inflammation

Theme: Asthma

Key words: exhaled NO (FENO), house dust mites, sedentary behaviour, daily hours of TV /video games, physical activity

We know that the fraction of exhaled nitric oxide (FENO) is a marker for airway inflammation and is clinically used to monitor asthma evolution. The Harvard (Boston, USA) medical group has attempted to define the contribution of allergen exposure in children to FENO levels (J.E Sordillo et al JACI May 2011 vol 127 5 1165-1172e5).

The study objective was:

- 1) To evaluate the increase in FENO levels in asthmatic and/or allergic children.
- 2) To evaluate the increase in FENO levels in sensitised and non-sensitised children after allergen exposure.
- 3) To evaluate the children's sedentary behaviour, through the number of daily hours of television viewing or video game playing, on FENO levels independent of allergen exposure.

On a cohort of 505 children monitored till age 12, with a parental history of asthma or allergy, the following parameters were measured: bed dust allergen levels (dust mites, cats, and cockroaches), corresponding specific IgEs, respiratory status (rhinitis, asthma or wheeze) with functional assessment, bronchodilation tests, and FENO levels. Finally, a questionnaire noted the number of hours per day spent on television viewing or video game playing (for weekdays and weekends).

The results were as follows:

- FENO levels increased in subjects with current asthma (32.2 ppb), wheeze (27.0 ppb) or rhinitis (23.2 ppb), compared with subjects without these respective symptoms (16.4-16.6 ppb, $P < .005$).
- Sensitisation to indoor allergens (cat, dog, dust mite) predicted higher FENO levels and explained 1/3 of the variability in their levels.
- FENO levels were highest in children both sensitised and exposed to house dust mites. Finally greater than 10 hours of weekday television viewing or video game playing was associated with a significant FENO level increase, regardless of allergen exposure, body mass index (BMI) and allergen sensitisation.

In conclusion, allergen exposure and excessive TV viewing can cause child airway inflammation as measured by FENO levels. This emphasizes once more the role of environmental conditions on the immune response, and particularly here the sedentary behaviour which reduces physical activity, increases calorie intake and food consumption.

27. Anaphylaxis during anaesthesia in France

Theme: drug allergy, allergy due to anaesthesia

Key words: neuromuscular blocking agents (NMBAs), latex, antibiotics, man, woman, child, pholcodine

The French Group devoted to anaphylactoid reactions during anaesthesia (P. Mertes, JACI ahead of print 2011 19 avril) is once more drawing our attention to the subject. This group which consists of 31 French regional centres (including Jacques Gayraud's) has colligated all over France 7 million anaesthesias which, combined with the Drug Safety Monitoring data bank, has led to a assessment of anaphylactic reactions between 1998 and 2004 on the part of 2516 patients, including 266 children and teenagers.

These reactions were classified into 4 severity grades, most of them of grade III, i.e. with cardio-vascular manifestations, rhythm disorders, bronchospasm, whereas grade I, the most frequently non-IgE dependant, was marked only by skin reactions.

The diagnosis of immediate reaction to IgE, as confirmed by histamine and trypsin dosages, was established in nearly 72.18% cases (1816 cases, i.e. 72.18%).

The most frequent cause was neuromuscular blocking agents (NMBAs): 1067 cases, i.e. 58%, of which 356 for Suxamethonium or succinylcholine (Celocurine®), and 313 for Rocuronium. Second came latex (361 cases, 19.65%), then antibiotics (236 cases, 12.85%). The median annual incidence rate per million procedures was higher for females 154.9 (5th-95th percentile, 117.2-193.1) than for males: 55.4 (5th-95th percentile, 42.0-68.0). It even reached 250 (189.8-312.9) for women in the case of allergic reactions to NMBAs. With children, the IgE-dependent anaphylaxis diagnosis was obtained in 122 cases, i.e. 45.9%, less frequent with age 2-12 subjects than those aged 16-18. Most common causes were : latex (explained by the few cases of spina bifida but mostly by former use of medical material), NMBAs and antibiotics; in contrast with adults, no female predominance was observed. On the whole, the incidence of more or less severe allergic reactions, estimated on a national basis, was higher than expected ; the similar incidence of reactions according to sex before the teenage years leads the authors to suggest a role for sex hormones in the increase in adult anaphylaxis accidents observed in women.

Finally, let us recall the role of Pholcodine should be remembered in sensitisation to NMBAs, hence the French health authority's recent recommendation to only provide on prescription the 20 or so cough mixtures which contain this drug.

28. Vitamin D deficiency in the USA and risks of allergy

Theme: atopia

Key words: vitamin D, specific IgEs, peanut, ragweed, oak

A number of preliminary studies have shown a possible link between low vitamin D levels and atopic diseases and emphasized the immunomodulator and anti-inflammatory role of this vitamin.

But S. Sharief et al. from Chicago (JACI 2011 127 5 1195-1202) wanted to go further and evaluate the relationship between vitamin D and allergen-specific IgE serum levels. For this purpose, they used a national survey on nutrition and health problems in a US nationally representative sample of 3136 children and adolescents and 3454 adults, monitored between 2005 and 2006.

They measured serum vitamin D levels (25 Hydroxyvitamin D, 25(OH)D) in cases of deficiency (<15 ng/ml) and insufficiency (15-29 ng/ml) and compared them to levels of specific IgE to 17 different allergens after adjustment for potential confounders, i.e. age, sex, ethnicity, obesity, socio-economic status, frequency of milk intake, daily hours spent watching television, playing video games or using a computer, serum cotinine levels, and vitamin D supplement use (by prescription).

Results were as follows:

In deficient children and teenagers, sensitisation to 11 of the 17 tested allergens was more common than in controls.

Compared to normal vitamin D levels (≈ 30 ng/ml), and after multivariate adjustment, deficiency was significantly associated to an allergy, mainly peanut, ragweed and oak. Eight other allergens were associated to vitamin D deficiency with less significant P values (less than 0.5 but greater than 0.1).

In adults, by contrast, there was no association between 25(OH)D levels and allergic sensitisation.

In conclusion, vitamin D deficiency is indeed associated in the US child and adolescent to allergenic sensitisation. Since vitamin D deficiency and prevalence of allergic manifestations are increasing in the USA, this US-representative study points to a link between these two phenomena.

29. Vocal cord dysfunction (VCD), a diagnosis and therapy trap

Theme: asthma

Key words: vocal cord dysfunction (VCD), digitalised dynamic tomography

A paradoxical adduction of the vocal cords, above all during inspiration, VCD causes an obstruction of upper airway which can simulate asthma (and is thus often the source of useless treatments) or combine with asthma, which complicates both diagnosis and therapy. L. M. Gimenez and H. Zafra (*Annals of All. Asthma, Immunol* 2011 Apr 106 267-274) present an excellent overview of the subject, on the basis of the publications of the past 8 years. M. J. Morris and K. L. Christopher (*Chest* 2010 Nov.138 1213-1223) had also recently drawn attention to this often forgotten vocal cord functional abnormality and recalled the clinical, functional and endoscopic criteria of the trouble.

The Australian pneumologist group from Melbourne University Hospital, in a 110-page article with 90 pages of tables, graphs and figures (K. Low et al *AJRCCM* 2011 ahead of print 31 Mars) stress that VCD is one of the reasons why certain asthmas are difficult to treat, that it is uneasy to evaluate by simple endoscopy, admittedly the 'gold standard' for diagnosis but ill-tolerated by asthmatics, and they propose an original technique based on dynamic 320-slice computerised tomography (CT).

46 chronically asthmatic patients, under usual treatment, aged 18 to 65, with a majority of women (36 vs 9 men), were involved in their study.

Previously, and with the same technique, they had developed in 15 healthy volunteers an analysis algorithm, twice validated in 7 subjects, allowing them to quantify the vocal cord function and the ratio of VC diameter to the tracheal diameter, over the breathing cycle. The results were as follows:

Vocal cord movement was abnormal with excessive narrowing in 23 of 46 subjects (50%) and severe in 9 others (19%) (over 50% abnormality both for inspiration and expiration times).

Moreover, images also revealed general laryngeal dysfunction characterised by an abnormal larynx movement, rather than isolated vocal cord disorder.

Thus, thanks to the non-invasive quantification by dynamic computerised tomography it is possible to observe that significant numbers of patients with difficult-to-treat asthma had excessive narrowing of the vocal cords and upper-airway dysfunction.

30. The allergist faced with HIV/AIDS

Theme: Immunodeficiency

Key words: HIV, AIDS, allergic rhinitis, adverse drug reaction, skin manifestations, asthma, chronic bronchitis

The use of highly active antiretroviral treatments (tritherapy: i.e nucleoside reverse transcriptase inhibitor: NRTI + non-NRTI + Protease inhibitor) has completely modified HIV infection prognosis. Whereas the life expectancy of AIDS syndrome used to be less than 10 years, HIV-infected patients live over 25. This means that affection has practically become a chronic illness, with more complications or co-morbidities like allergic manifestations. This is the theme of a recent review based on 62 references (Medline) and published in the *Annals of Allergy, Asthma & Immunology* (S.C Stokes and M.S Tankersley 2011 107 July 1-9). Already before the era of tritherapy, some symptoms were noted in the course of AIDS, suggestive of allergy such as higher serum IgE levels (in inverse correlation to CD4+ cell count) or rhinitis, rhino-sinusitis, symptoms becoming rarer as HIV developed into AIDS. Adverse reactions to drugs such as Bactrim[®] (Trimethoprim-Sulfamethoxazole) and Abacavir (an NRT) were also observed.

With antiretroviral therapy, the situation has completely changed.

True, the most serious complications needing to be monitored during the first months of treatment, remain the opportunistic diseases, lipodystrophy, renal, neurologic or psychic (nightmares) and cardiovascular complications, but allergic skin manifestations are appearing, as well as respiratory syndromes akin to bronchial hyper-reactivity and asthma, accompanied among smokers, by risks of chronic bronchitis, all symptoms possibly linked to immune reconstitution, which the allergists and pneumologists must take into consideration.

The use of vaccines against influenza, measles or chicken pox can now be even envisaged in asymptomatic HIV infected children under treatment.

Finally, let us not forget the ongoing research for new better tolerated antiretroviral drugs such as rilpivirine (JM Molina et al *Lancet* July 2011 378 9787 238- 246) which is proving as efficient as efavirenz, non-NRTI, one of the 'pillars' of tritherapy.

31. Specific IgEs and molecular allergens

Theme: molecular allergy / specific IgEs

Key words: CRD (Component-resolved diagnostics), Micro-array ISAC, Advia Centaur

Hitherto specific IgE detection techniques were based on total allergenic extracts, i.e. on the allergen source. Recombinant DNA technology makes now possible to reproduce purified allergens in large quantities and at a reasonable cost, and to identify the individual molecules to which patients are sensitised. These molecular diagnosis methods (component-resolved diagnostics, CRD) are clearly explained in three articles of the June 2011 15-20 CIAB, respectively by H. Chabane, V. Doyen and J. Vitte, as well as in the *Annals of Allergy, Asthma & Immunology* 107 July 2011:35-41 (M.T Lizaso et al). This could lead to more accurate diagnoses, better immunotherapy indications, and also offers an explanation of cross-reactions between airborne and food allergens (e.g. birch / apple) and to definitely rule out non-IgE related Allergy.

The most current technique, and currently the only one available in France (although not yet covered by Social Security) is the micro-array technique, which simultaneously tests a range of allergens on a glass surface and in the form of micro spots. This is known as a biochip which, thanks to the ISAC concept (Phadia[®] : Immuno-Solid-phase Allergen Chip), maps a large number of natural and recombinant molecular allergens on a 1cm² chip. Other techniques (Avia-Centaur) detecting individual allergens, are being developed and improved, and compared with usual IgE dosages.

Thus, out of the 103 allergens identified on the ISAC biochip, 36 were not available in individual detection; and in comparison, with the traditional ImmunoCAP, the ISAC technique may be less reliable for dust mite allergy. By using the Advia-Centaur technique for pollen allergy, the diagnosis was modified in 30% of the cases, through either the detection of new sensitisations (to Olea for instance), or the ruling out of those irrelevant to clinical data and skin tests. Moreover, some allergenic sources were absent: nuts, vegetables, some milks, plantain for ISAC, cypress for Advia-Centaur.

Finally, according to R.C.Aalberse & R.Cramer (Allergy 66 2011 1131-1132t ahead of print 02/08 2011), the range of IgE epitopes is so vast that it would be illusory to pick just one of them as a realistic target for diagnosing or treating an allergy.

All this means that these new techniques, albeit representing a breakthrough in the biological diagnosis of allergy, must be reserved for multiple or IgE-related allergies, or when molecular profiles are not available for unit identification, or even for non-elucidated anaphylactic shocks. In any case, the results must be interpreted in the light of clinical, biochemical, immunological data, and must take into account the relevance of the diagnosis. This is another case for calling to collaboration between biologists and clinicians.

32. Urinary leukotriene E4 in asthmatic children exposed to passive smoking (PS)

Theme: children's asthma

Key words: leukotriene LTE4, uLTE4 (urinary leukotriene), asthma exacerbation

A group of US paediatricians from Denver (N.Rabinovitch et al JACI 2011 128 2 August 323-327) thinking that asthmatic children exposed to PS were running the risk of severe exacerbations, have been looking for useful and convenient biomarkers for testing sensitivity to this environmental factor. LTE4 urinary dosage was used for this purpose. 44 children suffering from moderate to severe asthma and being treated with inhaled corticosteroids (ICS) were monitored for 5 months with repeated urinary LTE4 measurement, PS was revealed by preliminary questionnaires and repeated measurement of urinary cotinine, and asthma exacerbations were counted by emergency hospital consultations (EC) or intensive care hospitalisations (IC).

The results were as follows:

- 9 out of the 20 PS-exposed children (45%) did suffer exacerbation of their asthma requiring EC or IC, compared to 3 of the 24 not exposed to PS (12.5%), i.e. a relative risk of 3.6 (95% IC 1.1-11.5 P=.02).

- uLTE4 was a significant predictive factor of exacerbation risk in PS-exposed children (area under the curve 0.85 P=.003). Other factors such as the frequency of nocturnal symptoms, the pre- and post-bronchodilation pulmonary function, or expired NO, were unrelated to exacerbations.

- As to uLTE4 levels of 106 pg/mg and above, they revealed 67% sensitivity (6/9) but 100% specificity (11/11).

In conclusion, asthmatic children exposed to PS run a higher risk of exacerbations and the urinary LTE4 levels constitute, despite the use of ICS, the most reliable predictive factor.

33. Anaphylaxis to argan oil

Theme: particular allergen

Key words: argan oil, argan bush, oleosins

Argan oil is extracted from nuts contained in the fruits of the argan tree (*Argania spinosa* of the Sapotaceas group), which grows in arid or semi-arid zones of south-western Morocco; oil is extracted by heating, roasting and pressing the nuts according to ancestral processes and is traditionally used locally for its cosmetic but also medicinal and nutritional properties.

The observation reported has already been published and summarised in *Allergy Net* (2010 65, 662-63 Astier et al), but it was developed more recently by Y.El Alaoui (Journées Pneumo-allergologiques d'Agadir, organised in collaboration with Cefcap in June 2010). The case is that of a 34-year-old man, without allergy history, who suffered from rhinitis and

conjunctivitis when smelling argan oil; the ingestion of the oil also induced hypersalivation and epigastralgia.

The prick tests to argan paste (residue after oil extraction) were positive and after a few minutes provoked generalised erythema and urticaria as well as pharyngo-laryngeal discomfort. Proteins extracted from the oil were analysed by SDS-PAGE and IgEs by immunoblotting and immuno-competition in contact with the patient's serum. Oil electrophoresis revealed a protein profile close to that of the argan fruit stones, and serum IgEs recognised a 10KDa band which disappeared after inhibition with extract of the nuts. These proteins probably belong to the oleosin family, known to be powerful allergens like those described for peanut or sesame.

This first case should attract our attention, as argan oil is used more and more frequently, locally where the price is rising but also in the West and the Far East, without forgetting the many tourists who visit Morocco. Its unsaturated fatty acid profile has made it attractive from a nutritional point of view.

The argan tree is 8-10m high and lives for an average of 250 years. It is generally estimated that 100 kg of fruit and 8-10 hours of work are necessary to obtain 1 to 1.2 litres of oil. Three types of producer can be distinguished: individuals (i.e. village women using traditional methods), cooperatives (of which there are over 40, using more or less mechanised extraction), and private industries (set up in Casablanca and which only buy nuts or kernels). Attention should also be drawn to the need to further refine the oil, a step likely to inhibit its allergenicity.

34. Two new monoclonal antibodies in asthma treatment: anti-IL13 Lebrikizumab (L) and anti-eosinophil Reslizumab (R)

Theme: anti asthma treatment

Key words: anti IL13 Lebrikizumab, anti eosinophil Reslizumab, asthma, uncontrolled asthma, cytokine IL13, periostin, FEV1

Two simultaneous articles, one from the USA (J. Corren et al NEJM 2011 August 3), the other from Quebec and USA (M. Castro AJRCCM 2011 August 18), have been focusing on asthma which are poorly controlled by Inhaled Corticosteroids (ICS).

Type-Th2 IL13 cytokine plays a part in the allergic asthma mechanism, but, while ICS theoretically inhibit its production, large quantities of it are found in sputum from uncontrolled asthma, which could account for resistance to corticoids. Besides, IL13 induces the secretion by bronchial epithelial cells of a protein of the extra-cellular matrix: periostin (P), which causes the production of mucus and acts upon fibroblasts, thus capable of intervening in bronchial remodeling. L is an anti-IL13 IgG4 humanised monoclonal antibody, and the authors of the article made use of serum P as a marker of its activity, easier to dose than IL13.

219 randomised patients, presenting high levels of IgE (>100 UI/ml) and eosinophils ($>0.14 \times 10^9$) which revealed a Th2 status, were treated by a monthly injection of 250mg of L (or Placebo) for 6 months.

- After 3 months, FEV1 was 5 points higher than that of the placebo group ($P=.02$) and 8.2 points higher for the high P-rate group. But, the number of exacerbations at the 6th month was no different from the placebo group.

- From a biological point of view, the decrease in IgE level and Th2 chemokines (CCL13 and CCL17) proves the efficiency of L. Side effects were musculoskeletal, generally benign. The anti-IL5 monoclonal antibody R was applied to eosinophilic asthma: 53 patients and as many placebo patients received infusions of 3mg/kg over 15 weeks. In addition to significant reductions in the number of exacerbations ($P=0.083$), a modest FEV1 increase was observed, particularly among subjects also suffering from nasal polyposis. Adverse effects were mostly naso-pharyngo-laryngeal and the treatment was well tolerated on the whole.

Thus, a breakdown of asthmatic disease into several phenotypes is on its way, with therapy aiming at different targets: IgEs with Omalizumab (Xolair®), IL13 with L, eosinophils with R. But these treatments are heavy, costly and not without long-term risks. They should be reserved for particularly difficult cases.

35. Sublingual immunotherapy (SLIT) to grass pollen (GP) : recent data

Theme: specific immunotherapy

Key words: sublingual immunotherapy – grass pollen – Oralair – pollen calendar – symptom score

SLIT efficiency in treating GP allergic rhino-conjunctivitis is well known and recent data mainly concerns its administration modes and length of efficacy. This was the purpose of the survey conducted by the Euro-Canadian group led by A.Didier (Toulouse) in a multicenter randomised study whose carefully elaborated protocol made use of Oralair tablets (5-grass 300-IR Stallergens)® for 2- or 4-month periods before co-seasonal treatment (A.Didier et al : JACI 2011 128 3 September 559-566).

633 adults, aged 18 to 50, were then taken in charge from 2007 to 2009, firstly by watching the region-specific pollen calendar (23 countries took part in the survey), secondly by adjusting the individual symptom score according to the intensity of observed signs and the more or less urgent need for rescue medication, i.e. inhaled or per os antihistaminic drugs or corticosteroids.

Three consecutive seasons were monitored with three groups: 1 Placebo (P, 216 subjects) and 2 patient groups respectively treated for 2 months (147) and 4 months (149) before the beginning of the co-seasonal treatment, a treatment undertaken when the atmospheric pollen concentration was over 30 grains/m³ for three consecutive days.

The first goal was to statistically calculate a mean score adjusted for the study's various parameters, at the end of the 3rd season, by comparing it to group P's. The second was to compare the overall and individual symptomatology (including the rescue medication

score) and the treated patients' quality of life to those of group P. and, finally, to appreciate the general tolerance of the drug.

Results showed a significant reduction in the mean adjusted symptom score, respectively by 36% and 34.5% in the 2- and 4-month pre-seasonally treated groups ($P < .0001$), for the mono- as well as the poly-sensitised subjects, whereas the questionnaire on quality of life showed marked improvement in both active groups. Finally, most adverse effects (essentially local) decreased in number and intensity over the 3 seasons, thus making it possible to compute 97% treatment compliance. Moreover, this favourable evolution was sustained without treatment for the 2 following seasons.

In conclusion, this long-term, very carefully conducted 5-year survey offers two interesting lessons:

- 1) It is not necessary to start the treatment long before the pollen season (2 months are generally sufficient), on the condition that it is followed by the co-seasonal treatment
- 2) It is not necessary to continue the treatment longer than the usual 3 years, since SLIT remains efficient for at least 2 more years

Overall, this is an accurate and convincing argument in favour of an economical treatment which will surely be appreciated by doctors and patients.

36. Chronic urticaria (CU) treated by single-dose Omalizumab (O): a randomised study

Theme: urticaria / treatment

Key words: chronic urticaria – auto anti-IgE antibodies, auto anti-FcR antibodies– urticaria activity score

It is a fact that the treatment of CU is particularly difficult and several isolated observations in recent publications have mentioned a variety of drug trials.

This is the case of beneficial effect recently observed with O, which, according to the authors, can be explained by the presence in some patients of IgG auto-antibodies, anti-IgE or anti-Fc ϵ , its high affinity receptor, which cause degranulation of mast cells and skin basophils and release of histamine. We have here the first randomised, multicenter, US-German, phase II study, with a substantial number of patients (90), which brings in convincing results on the efficacy of single-dose Omalizumab (Xolair[®]) in CUs resistant to usual antihistaminic treatment (S. Saini et al: JACI 2011 128 3 567-73).

The US patients were aged 12-75 and the Germans 18-75, all suffering from idiopathic CU, i.e. with daily or almost daily occurrence, in the form of pruriginous papules and erythema, sometimes of angio-oedema, an eruption lasting for more than 6 weeks without a known cause and needing the permanent use of antihistamines (AH) which can usually be recommended in quadruple dose in case of insufficient efficacy.

These subjects, AH-resistant and presenting an urticaria activity score (UAS) of 7-12 days (pruritus, papules) and severity-graded from 0 to 6, were divided into 4 groups: a Placebo group (21 patients), and the 3 others respectively treated by a single O injection of 75mg (23 patients), 300mg (25), or 600mg (20).

The first objective was to evaluate the UAS improvement after 4 weeks. Only the 300mg and 600mg groups showed significant improvement vs the Placebo group, by 13 points

for the first (-19 vs -6.9 i.e. $P?.001$) and 7 points for the second (-14.6 vs -6.9 i.e. $P?.047$). This improvement was confirmed during the 12 following weeks both for pruritus and eruptions. Only among the O-75mg group was no meaningful difference observed to that of the placebo.

However, what is remarkable is that the onset of improvement occurred as early as week 2 (when 1 to 2 months are generally needed to appreciate O efficacy on asthma). As to tolerance, this did not differ from the placebo group: no notable side effects were observed. Admittedly the study must continue on a larger number of patients, and in all cases, this was a symptomatic treatment whose mechanism has not yet been elucidated. Besides it cannot be specified whether further injections will be necessary in the longer term.

However, and in conclusion, a 300mg (or 600mg) single-injection of O is capable of efficiently and rapidly treating chronic urticaria resistant to antihistamines; which represents a valuable option in a disease such as CU the evolution of which often causes despair.

37. Obesity (O) surgery in asthmatics (A)

Theme: asthma

Key words: obesity – asthmatic – inflammation marker – bariatric surgery – serum IgEs – adipokine – lymphocytic markers

Asthma is difficult to treat in an obese patient. By assuming a pathogenic interaction between the asthmatic airway inflammation and obesity, the US authors of Burlington-Vermont (A.Dixon et al: JACI 2011 2128 508-15) wished to check whether :

- 1) inflammation markers were higher with O than with non-O;
- 2) corrective O surgery (also known as “bariatric surgery” BS) did improve treatment of A and decrease these markers.

With this view, they enrolled 41 OAs and 35 control and eventually followed 23 OAs and 21 non- OAs. over 3, 6, 9 and 12 months. All subjects underwent BS.

Beside the BMI (Body Mass Index in Kg/m²), the study focused on respiratory functions (particularly airway hyperresponsiveness (AHR) to methacholine) and markers (among which lymphocytes in the bronchoalveolar lavage fluid) as well as levels of serum IgEs and adipokine.

At the end of the surveillance period, and whatever the BS type, (laparoscopy with derivation: by-pass or stomach ringing or strapping) the patients observed a significant improvement in their A score and quality of life ($P?.0001$ for both groups).

AHR was also improved ($P?.03$), particularly in older, non-atopic subjects, with normal IgE levels suffering from late onset asthma, but without relation to airway inflammation

Paradoxically, these subjects presented increased rates of lymphocytic markers and bronchoalveolar lymphocytes after BS.

On the other hand, the younger atopic obese subjects, with high IgE levels, suffering from early onset asthma, also experience an improvement, albeit with no changes in their AHR.

Thus, post-O-surgery dissociation seems to occur between asthmatic symptomatology, airway hyperresponsiveness and airway inflammation, whether the subject

is atopic or not. And this suggests that O lead to a distinct and unique A phenotype, possibly suitable for surgery.

38. Psoriasis (P) vs atopic eczema (AE): clinical coexistence and biological antagonism

Theme: eczema / skin allergy

Key words: psoriasis – atopic eczema – interferon γ - lymphocyte Th1 - lymphocyte Th17 – lymphocyte Th2 – lymphocyte Th22 - HLA alleles - Filaggrine – IL 4 interleukin – staphylococcus aureus

These two common diseases, of an epithelial or immune origin, involving hereditary factors and environment, often associated to other body disorders (joints for P, airway for AE), have a distinct physiopathology: the former (P) is characterised by involvement of Th1 lymphocytes with release of interferon γ and Th17 with their cytokines IL17A, 17F and IL22; the latter (AE) is dominated by the Th2 with higher levels of IgEs, total or specific to one or more allergens. Such an antagonism could account for the rarity of their clinical association in the same patient. Therefore, the file presented by the Munich (Germany) group of dermatologists and allergists (S. Eyerich et al NEJM 2011 365 231-238) only involves 3 patients, but these are particularly well studied, and complemented by 5 others suffering from P associated with Nickel-contact dermatitis (CD).

In addition to their history and clinical observations, including a severity score for P and the SCORAD index for AE, the study includes classical biological investigations, a series of allergic tests (Nickel and Dermatophagoides pteronyssinus patch-tests) and a skin biopsy for each type of lesion, divided in two parts : one is histological, the other is for studying cell lineages and their cytokine profile ; at the same time, a genomewide study of the leukocyte DNA was performed for HLA alleles and for Filaggrine gene mutations.

The results are shown in the numerous tables and graphs illustrating this article, from which a lesion-specific histological aspect appears: acanthosis, chequer plaques, neutrophilic micro-abscess and spongiosis for P, and mixed infiltrate with eosinophils, T cells and granulocytes for AE.

The cytological study confirms that P presents a number of Th1 and Th17, with secretion of interferon γ and IL17, and AE a large number of Th2 and Th22 with secretion of IL4 in vitro. IL22 (coming from Th17 and 22) is liberated in equal quantities in both lesions. As for the CD lesions resulting from Nickel allergy, they are dominated, like those of P, by Th1 and Th17, but few T cells of P react to Nickel.

Moreover, atopic lesions (and not those of P) frequently harbour microbiological colonies (Staphylococcus aureus), which proves that the immunity due to Th1 and Th17 is partially inhibited by the Th2, whereas the histochemical expression of Filaggrine is higher in P, also suggesting its inhibition by the Th2.

Therefore, the pathogenesis of these 2 diseases does not seem to be based on an intrinsic epithelial anomaly, but more likely on a migration of different T sub-populations, in response to a triggering factor, either known in AE or unknown in P, and leading to skin inflammation.

The treatment of these 2 affections confirm their antagonism: anti-TNF α molecules (Infliximab) are very efficient in P but exacerbate AE lesions. IL4, which opposes INF γ and IL17 effects on keratocytes, could be an interesting therapy for P but would be inefficient or even contra-indicated for AE.

In fact, non-specific treatments such as the antibody Ustekinumab which targets Th1 and Th17, just like Ciclosporine which inhibits the 2 sub-populations, were efficient on P and AE conjunctive lesions in the subjects studied.

39. Treating atopic dermatitis (AD) with narrow-band UVB phototherapy (NB-UVB)

Theme: eczema / skin allergy

Key words: atopic dermatitis - UVB phototherapy, narrow band (NB-UVB) – lymphocytes TH1 – lymphocytes Th2 – cytokine IL22 –Th2/T22 axis

Among the many treatments of AD, the NB-UVB has the advantage of being usable with young subjects and for relatively long periods of time, with no major side effects and relatively low cost.

The multicenter US-Italian-Israeli study of this issue aimed to establish the reversibility of lesions, bio-markers of therapeutic response, and to specify the immuno-modulator effects of the treatment (S.Tintle et al JACI 2011 128 3 583-593).

12 patients aged 24 to 54, 9 male and 3 female, were treated 3 times a week for 12 weeks with the same protocol. Skin biopsies before and after treatment were carried out and evaluated by using gene expression and immunohistochemistry studies.

Results are as follows:

- All patients benefited from a clinical improvement with a 50% reduction in their SCORAD score.

- The lesion reversibility, in close correlation with the clinical symptomatology, was accompanied by a genomic reversal of the epidermal hyperplasia and above all of the inflammatory markers: the authors observed a decrease in the expression of 372 genes and an increase for 192 others, in whose list T-cells (CD2), activated T-cells (CD69), Th2 (CCL13, CCL26, CCL18 and mostly IL10), TNF α and IL12 could be found.

- It is then a strong suppression of the Th2/T22 pathogenic axis and of associated cytokines that can be found in these lesions, with elimination of inflammatory leukocytes, including T-cells and dendritic cells.

- As to the reduction of epidermal proliferation (decrease in thickening and in keratocyte proliferation), it is correlated with a reduced expression of the IL22 cytokine, responsible for this hyperplasia.

- Finally, a normalised expression of epidermal barrier proteins completes the therapy. The authors believe that the reversibility of chronic AD lesions results both from a correction of epidermal alterations and a reversal of immune activation. This runs against the fixed genetic phenotype theory and underlines the usefulness of checking the impressive list of Th2/T22 axis bio-markers drawn up by the authors, in the treatment of chronic AD.

Such treatment is widely targeting the immune factor: in addition to local (corticosteroids and calcineurine inhibitors such as tacrolimus) or general treatments (such as cyclosporine, UVA with psoralens and, for the severest forms, high intensity UVB), narrow-band UVB has definitely confirmed its place.

40. Allergy or rhinovirus as the cause of childhood asthma

Theme: asthma

Key words: aeroallergen sensitization, rhinovirus, respiratory syncytial virus (RSV), serum IgEs, asthma

The chicken or the egg paradox

For many years now, allergists and pneumologists have been wondering which of aeroallergen sensitization (AS) or rhinovirus (virus-induced wheezing) was the initial cause of childhood asthma. As suggested by some animal models and clinical studies on severe RSV bronchiolitis, it is the virus which induces AS. But, if AS precedes and predisposes to viral wheeze, it is allergy prevention which must be the strategy in fighting asthma. In order to answer this question, D.J. Jackson et al (AJRCCM 29 Sept 2011 ahead of print) of Madison University (Wisconsin) selected within a cohort of USA children, 285 subjects at high-risk for asthma, given their family histories, and followed them from birth to age six.

The chronology of events during these 6 years was studied in great detail with: precise virus identification, obtained in 90% of the cases (HRV or Human Rhinovirus, RSV or Respiratory Syncytial Virus, Adenovirus, Influenza virus, Coronavirus...), and corresponding clinical manifestations in the form of asthma-like wheezing, clinically diagnosed and requiring appropriate treatment (anti-infection and bronchodilator). At the same time serum IgEs to common aeroallergens were assessed each year. These data were treated using a multi-states Markov statistical model in continuous time. Results are significant:

1) children who were sensitized to aeroallergens have a greater risk of developing viral wheezing than non-sensitized children and, if this absolute risk is greatest at 1 year of age, the relative risk is consistently increased at every age assessed;

2) AS leads to an increased risk of HRV- but not RSV- viral episodes;

3) By contrast a viral wheezing episode does not induce a greater risk of AS.

Thus, for the authors, these results are indisputable: AS precedes HRV viral wheezing and the converse is not true. So, the prevention of allergy can indeed limit the development of viral wheezing, and consequently of childhood asthma.

41. Cross sensitization of food and environmental allergens

Theme: food allergy

Key words: tropomyosin, shell food allergy, dust mites, D.Farinae, cockroach, Blatella Germanica

It is known that food allergens such as shrimp, dust mite or cockroach, own a common protein: tropomyosin, which could account for the cross sensitization (CS) in subjects exposed to one or the other allergen, and who present high rates of specific IgEs, without clinical manifestations.

Based on data from USA national cohorts, which indicated that food allergy was particularly frequent – with an increased prevalence of high IgE shrimp allergy – in a population of inner-city black children, Julie Wang et al (JACI 128 4 834_837) wanted to check the possible correlation between IgE-mediated sensitization to shrimp and allergen exposure to dust mite and cockroach.

For this purpose, they studied the serum of 500 subjects in a cohort of 1528 children aged 4-9 and living in New-York, St Louis and Baltimore inner-cities, while their homes were checked for concentrations of Dermatophagoides Farinae and Blattela Germanica.

They first observed a strong correlation between shrimp, cockroach and dust mite specific IgE levels. Furthermore, high exposure to cockroach in the home, particularly in the bedroom and television room, was significantly correlated with higher shrimp and cockroach IgE levels. In contrast, high exposure to dust mite in the home was highly correlated with IgE levels to D. Farinae but not with shrimp IgE levels. Besides, exposure and presence of cockroach IgEs are predictive of high shrimp IgE levels.

Thus, in children with evidence of joint IgE-mediated sensitization to cockroach and shrimp, having high exposure to cockroach in their inner-cities' home can contribute to higher shrimp IgE levels, which might not correlate with clinical allergic reactivity.

This notion should be taken into consideration for the interpretation of a shrimp sensitization in such subjects, and before any attempt of provocative tests usually recommended for confirmation of the corresponding food allergy.

42. Practical aspects of human genome study in asthma

Theme: genetics, asthma

Key words: asthma, Single Nucleotide Polymorphism, inhaled corticosteroids, genome, gene GLCC11, allele rs37972, allele rs37973

The explosion in genetic research, the speed and accuracy of new generation techniques, call for acquaintance with interpretation of results and their present and future relevance for allergic diseases. A recent review does this with reference to respiratory diseases (J.Todd et al AJRCCM 2011 184 873-880). Up to February 2011 a total of 22 studies had been published, 13 of which on the genetic basis of asthma. The validity of results depends on an accurate classification of the disease, a great rigor in the genetic study, a platform large enough to cover the whole genome, quality controls, a study of the many genotypic nucleotides (SNP: single nucleotide polymorphism), a bio-informatic and statistical

analysis and a confirmation in other patient groups (replication populations). The difficulty with asthma comes from the heterogeneity of clinical phenotypes, and the probable role of associated environmental factors in the development of the disease. Hence, the limited practical relevance of this research at present.

In contrast, by addressing a well-targeted category of asthmatics, i.e. subjects where inhaled corticosteroid therapy is ineffective (1 in 3 on average), the genome study (Genome-Wide Association) has led to identifying a genetic variant associated to the pharmacological treatment response (K.G.Tantisira et al NEJM 2011 365 1173-83).

The authors followed 1041 asthmatic children aged 5-12, enrolled in a large cohort (Childhood Asthma Management Program: CAMP) clinically and functionally monitored and random-treated either by Budesonide (®), Nedocromil® or Placebo, for an average of 4.6 years. 422 subjects were selected and genotyped (DNA) as well as their parents; out of this group 118 trios (child + both parents) were isolated. From these examples, the researchers identified, based on family statistics, 13 possible SNP candidates among the 534290 tested ones. These SNPs were replicated in 4 different patient groups, which made it possible to isolate within gene GLCC11 (gluco-corticoid transcript) an allelic variant, rs37972, associated with a lower FEV1 in response to inhaled corticoids (ICs).

To confirm this observation, the authors made use of cell lineages isolated in vitro and managed to isolate re37973 which is in total correlation (linkage disequilibrium) with rs37972, both associated with decrements in gene GLCC11 expression, i.e. the absence of response to ICs.

This substantial pharmacological effect, prefiguring personalised treatment (according to J. M. Drazen in an Editorial on this research), is not however outstanding : if, in the IC-treated CAMP patients with rs37973 the FEV1 decrease is statistically 3 times lower than in those who do not own this allele, the values are low and only concern a small number of asthmatic patients.

43. The protective effect of farm milk consumption on childhood asthma and atopy

Theme: prevention, atopy

Key words: asthma, farm milk, raw milk, boiled milk, whey

This is the new factor identified by the German and Swiss epidemiologists of the E. von Mutius group, among those which have been suspected to account for the protective effect of the rural life against asthma and atopy. The authors again used their data base (GABRIEL), sent a questionnaire to the parents of 8334 school children and obtained serum samples from 7606 of these children for the detection of specific IgEs. Moreover, on 800 samples of milk from the parents' farm, they conducted bacteria counts and measured fat content and whey protein levels; this data was confronted to asthma, atopy and pollinosis, and statistically analysed by multiple regression (G. Loss et al JACI 2011 128 766-773).

It appears that raw milk consumption is inversely associated with asthma, atopy and hay fever, independent of other farm exposures. Boiled farm milk did not show this protective effect, nor bacterial counts or total fat content of milk.

In contrast, the whey proteins account for the protective effect against asthma, but not against atopy. It is the case for the bovine serum-albumin, α -lactalbumin, and β -lactoglobulin, all proteins pertaining to the residual liquid from milk skimming and contributing to the production of cheese and buttermilk.

On the whole, the protective effect of raw milk consumption on asthma could be attributed to the whey protein fraction of milk.

But, in *cauda venenum*, the authors admit that, even if this research is interesting from an epidemiological point of view, the consumption of raw milk for protection on asthma or atopy cannot be recommended in practice because it could contain a number of pathogenic elements!

44. Treatment of perennial rhinitis by nasal insufflation of CO₂

Theme: ORL, allergy

Key words: allergic rhinitis, nasal CO₂ insufflation

The authors, who in 2008 had already pointed out the effect of CO₂ administered by nasal insufflations, without inhalation (Casale et al JACI 2008 121 105-109), have extended their research by a multicenter random study with a view to confirming the efficacy and safety of this treatment, a symptomatic but non-pharmacological treatment which can be useful in certain persistent forms of rhinitis affecting quality of life of patients (Casale et al: Allergy, Asthma, Immunol 2011 107 364-370).

The technique consists in administering CO₂ out of a standard gas high-capacity cylinders, fitted with a regulator and valves to control the flow rate (5 to 10 ml/s in the random trial), connected to a tube ending with an adaptable and disposable nasal piece. The insufflation is performed under medical supervision, for duration of a few seconds in each nostril (10 to 30 depending on the group) while the patient is asked not to inhale the gas but invited to breath by mouth if necessary. At the same time, symptom scores are assessed from 1 to 6 according to the severity of nasal symptoms (congestion, rhinorrhea, sneezes, itching) and non-nasal symptoms (eye and ear itches, pharyngeal lacrimation, red eyes).

Thus, 6 groups (including the Placebo ones) are formed, totalling 348 subjects suffering from rhinitis for over 2 years and presenting signs of allergy to common aeroallergens (except pollens).

It is group B (70 subjects), treated for 10 seconds at 10 ml/s in each nostril, which showed the most statistically significant results, with regression of all symptoms (nasal and non-nasal) in less than 30 minutes and for several hours (4 to 6); in the previous trial conducted by the authors the improvement could last up to 24 hours.

The other groups (5ml/s for 30 seconds, or 5 and 30 or 10 and 30) are more efficacious than the 2 Placebo groups, but not significantly enough. As to adverse effects, these were limited to some headaches and temporary nasal discomfort.

As a conclusion, we have evidence here of the treatment of symptoms, almost immediate but short in duration, which could be useful in young or elderly subjects, intolerant to drug treatments. But the effects of insufflation of CO₂ several times a day, as well as the still unknown action mechanism of this treatment, call for further researches.

45. Atopy heredity: Paternal or maternal?

Theme: atopy, asthma

Key words: heredity, asthma, cytokines, atopy

A Danish university team involved in research on child asthma and hereditary transmission of atopy hypothesized different parental imprinting on the cytokines and chemokines in the upper airway mucosa lining fluid of neonates (NN), a set of chemical mediators considered as markers of natural and adaptive immunity.

This team developed an original, clever and non-invasive technique (N. V. Folsgaard et al AJRCCM November 2011 ahead of print) of sampling by absorption on a filter (of the blotting paper type) of the nasal mucosal lining fluid, applied for 2 minutes, thus avoiding the dilution coming from lavage, for mediator concentrations just above the detection threshold. This technique proved safe for neonates and later for children.

It was applied on 309, 1 to 31-day-old NNs of a Danish cohort, and 18 cytokines and chemokines were quantified. At the same time, atopy was diagnosed among 173 mothers and 142 fathers (47%). In all, 241 NNs had either an atopic father or mother, without showing different characteristics from non-atopic parents' NNs. These data were statistically treated (principal component analysis).

The results showed that atopic mother NNs presented a significant decrease in cytokine levels (IL10, IL12p, IL2, IL4, TNF α , Eotaxin 3, MCP-1, CP-4 and TARC) as compared to NNs with atopic fathers and non-atopic mothers.

Generally speaking, maternal (but not paternal) atopy shows a strong down-regulation in all these mediators, suggesting some delay in NN's immunity maturation and therefore a notable influence of the maternal milieu on his immunity programming, either in utero (depending on nutritional factors or pregnancy microbiome) or perinatal life by placental transfer of IgEs.

...And the answer is... the Mother!

46. Peanut allergy: can severe reactions be predicted?

Theme: food allergy, allergens

Key words: peanut, food challenge, specific IgE, eliciting dose, age, atopic dermatitis

Dutch paediatric allergists (Groningen et Amsterdam: T. van der Zee et al JACI2011 128 1031-6), noting that severe reactions can occur after accidental ingestion of peanuts, have attempted to look for risk factors in children. They based their research on the eliciting dose in double-blind, placebo-controlled food challenges (DBPCFC) as a marker for clinical responsiveness.

This was a retrospective study of a 2001-2009 data base of 126 peanut-positive DBPCFC in subjects aged 3-17, two-thirds male, a majority with family atopic history, and having suffered themselves from a severe reaction to peanuts 4-36 months before the test. Specific IgEs were high (18.6 kU/L on average, with a dispersion of 3.8 to 76.6 kU/L). Some

subjects were also suffering from atopic dermatitis (79 cases), asthma (79) or rhinitis (53). The symptoms observed after the challenges (the eliciting dose varying from 200 to 820mg, with an average of 310mg) were either: Objective (angioedema, urticaria, dermatitis, rhinoconjunctivitis, coughing, wheezing, vomiting, diarrhoea) or Subjective (itching, nausea, dyspnoea). A score was given on the basis of these data and then statistically analysed (Cox regression model).

Results reveal that the eliciting dose (ED) is statistically correlated with 3 main risk factors:

- 1) Subject's age: those over 10 years of age have the lowest ED and therefore the severest clinical response, a somewhat surprising result in view of the usual belief that peanut allergy is becoming milder as time goes by.
- 2) Specific IgE levels: over 5.6kU/L, which is understandable.
- 3) Absence of associated atopic dermatitis, which is unexpected.

As to other factors, incriminated in other research or in clinical experience, such as gender, association with asthma or rhinitis, or previous severe reactions, no significant correlation was shown.

The authors however, knowing that a risk of accidental ingestion is still possible recommend a strict eviction diet and a self-injectable epinephrin kit in case of accidental ingestion of peanuts.

47. The psychological impact of diagnostic food challenges to confirm resolution of peanut allergy

Theme: food allergy, allergens

Key words: resolution diagnosis, peanut, food challenge, skin test, specific IgEs, anxiety, quality of life

Publications on the psychological factors of allergy are often of limited interest in current practice. The originality of this work by a British team from Southampton- (R. C. Knibb et al Clin. Exper Allergy 2011 November ahead of print) is that it is based on precise scientific criteria (case-control study).

The authors point out that peanut allergy resolves itself in 20% of children and walnut and hazelnut allergy in 10%. Such resolution, clinically established by absence of reaction over several years and negative skin tests and specific IgEs, has to be confirmed by a per os food challenge; it was interesting to evaluate anxiety, stress and quality of life of children and their mothers, on the day of the test and during the following 3-6 months.

103 families took part in this research and completed the corresponding questionnaires, which were validated in Great Britain. 40 children, aged 6-16, underwent the challenge and answered the questions on their social, school and emotional life. 63 children, with persistent allergy in the opinion of the allergist, were used for comparison and answered the same questions (the mother rather than the father being interviewed).

Results: 17 tests (43%) were positive, indicating the persistence of the allergy; 50% of the children had a negative test. From a psychological point of view:

1) Mothers reported raised anxiety on the day of the challenge ($P=0.007$) whereas children were less anxious than usual.

2) Children ($P=0.01$) and mothers ($P=0.01$) had improved quality of life with regards to the role of peanut in their diets, but not concerning food allergy in general.

3) Children reported lower anxiety levels in the 3-6 months following the negative test ($P=0.02$) but mothers' anxiety remained unchanged.

4) Finally, the improvements in children's and maternal anxiety and quality of life were independent of the test results.

So, as could be expected, and unlike their children, mothers were more anxious on the challenge day, thus reflecting differences in risk perception. But what is curious is that children's and mothers' quality of life was improved even in the case of a positive food challenge. The authors believe this reveals a real appreciation of the challenge, considered as both a diagnostic and therapeutic tool by the parents and even is disappointing, as a clarification of information that influences management and imparts psychological benefits.

48. Nasal polyposis (NP) and anti-IL5 monoclonal antibodies (MA)

Theme: ORL allergy, immuno-physiopathology

Key words: nasal polyposis, anti-IL5 monoclonal antibodies, Mepolizumab, eosinophils, cytokines

The Belgian university hospital ENT team (Gand et Liege P.Gevaert et al JACI 2011 128 989-95) famous for its expertise in NP, assisted by a group of English specialists, has in a recent paper rehabilitated the anti-IL5 MA Mepolizumab (M) which, presumably due to inaccurate indication, had been considered as inefficient in the treatment of asthma.

It should be remembered that, contrary to Chinese patients, in white Europeans 85% to 90% of nasal polyps are infiltrated by eosinophils, for which IL5 is the key driver of cell differentiation and survival. The authors sought to investigate the efficacy and safety of two intravenous injections (28 days apart) of M in severe NPs with chronic rhino-sinusitis, after a period of 11 months.

30 patients refractory to corticosteroids, some having relapsed after surgery and nearly half suffering from concomitant asthma, were randomised and treated (20 active and 10 placebo) ; the first objective was a reduction in NP size, to be seen via endoscopy and scanner, while at the same time monitoring the symptoms which usually accompany NPs (rhinorrhea, loss of smell, nasal peak expiratory flow, obstruction) and the biological signature of activity (blood and tissue eosinophils, IL5, IL6, ECP and IgE dosage on nasal secretions), are on the whole, subjected to statistical analysis.

At week 8, 12 patients of 20 in the active-group had a significantly improved NP size (compared to 1 of 10 placebo), calculated at 60% as opposed to 10% in the placebo group. The first objective was then achieved and confirms the authors' first trial with a single M injection. As to the other symptoms, improvement was noted, except for rhinorrhea, but not statistically significant.

Finally, on a biological level, the treatment shows a significant reduction in blood eosinophilia, whereas the eosinophilia rebound observed with Reslizumab (another anti-IL5

mentioned in our September BUAs) was not observed, albeit frequently reported with these two anti-IL5 AMs. At the same time, blood and nose cytokines levels were also reduced. Indeed, these improvements persisted until the 36th week and with no notable side effects, but the authors remain reserved on the long-term use of M.

49. Rhinovirus and risks of asthma exacerbation

Theme: infection and allergy, asthma

Key words: rhinovirus, asthma exacerbation, neutrophilic inflammation

We have already reported (cf. November BUAs) the frequent appearance, even if not decisive, of rhinovirus in atopic children, as shown in the work of the Madison university team (Wisconsin, USA). The same authors, whose expertise in this field is prominent, now study the question with adults to assess its role in asthma exacerbations (L. C. Denlinger et al AJRCCM 2011 184 1007-14).

In other words, can an asthmatic's routine seasonal cold be followed, in all cases, by greater viral multiplication and an infection of lower airways with neutrophilic inflammation?

For this survey, during 9 consecutive winter seasons, they enrolled 52 asthmatics and 10 control, all volunteers, who were monitored daily at the first sign of a cold for the next 10 weeks, and with whom they went to specify, over and above the symptoms, the use of drugs, and the peak expiratory flow, performing periodical nasal lavage and sputum sampling for viral (including molecular) identification, and respiratory functional exploration, all this until all symptoms have disappeared.

25 participants developed an asthma exacerbation, preceded 5 days earlier by detection of human rhinovirus HRV. But among all the viral infections (3/4 being due to the rhinovirus), it is subgroup A's rhinovirus which was statistically 4.4 times more likely to cause exacerbation.

However, it should be noted that neutrophils, and even virus, were present in sputum, in the non-atopic control lower airways and in the asthmatic group, which shows that these viruses can behave no longer like pathogens but as 'guests' of these airways. Nevertheless, asthma exacerbations were marked, and significantly so, by greater neutrophil counts.

On the whole, among adult asthmatic patients likely to catch a routine seasonal cold due to a rhinovirus, those who, over ...upper airway infection, experience asthma exacerbation, have a high neutrophil count and a greater viral proliferation in sputum than in nasal samples. But the authors cannot specify by which mechanism ...allergic inflammation influences the antiviral response, or on the contrary sensitizes lower airways to viral injury.

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