Bibliographic updates in Allergology

2012

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Letter to the reader

To our readers

Dear Colleagues,

At the dawn of this new year, we would like both to receive your opinions and to inform you of our motivations and thoughts as to our goals relating to ongoing professional training in Allergy and Clinical Immunology.

As you know, what we have in mind, so as to keep in line with the spirit which has guided the CEFCAP (Comite Europeen de Formation Continue pour Allergologues Praticiens) founders, and particularly our dear friend and late colleague Franz Marrache, is to give priority, in our scientific paper abstracts, to those with the most practical conclusions and the highest quality of methodology. Indeed, in this time of globalisation, the number of publications is growing exponentially.

But at the same time, scientists in many emerging or developing countries are accessing to new technologies and providing us with very high-quality papers. Just to quote a few among the latest, documents from Morocco, China (Taiwan), Slovenia have joined the many Anglo-American and European publications which form our basic resources. And, of course, nearly all of them are in English, even those coming from France: it is the condition for worldwide identification.

Our aim is also to make them easier to understand for our French and French-speaking colleagues. Reading the abstracts alone, could lead to errors and misunderstandings; the full-text must be read to assess the quality of the research undertaken, its limits and weak points. That is why our BUAs (Bibliographic Updates in Allergy) which the EAACI publishes regularly each month, are not a simple transfer of the original abstracts but include all the comments and details added by us. Each month we glance at around thirty reviews, specialized in Allergy (Respiratory, Skin, ENT, etc.) and Clinical Immunology concerning Adults and Children and also covering Internal Medicine. Each month we pick out the 4 or 5 most striking and most original articles, across all various themes.

In 2012, we would like to reward your efforts by crediting your regular reading of these ABA/BUA with some CME points. For this, each ABA/BUA will be accompanied each month by a multiple-choice questionnaire in order to evaluate the knowledge acquired through reading.

If this experiment passes the test of method assessment by a sample of our readers, it will then be submitted to EBAACI (European Board of Accreditation in Allergy & Clinical Immunology) for validation. We will keep you informed of each step of this project.

To conclude, we would like to thank you retrospectively for your loyalty and in advance for your comments, and we also would like to thank all those who, in France and in Europe at

large, participate in our initiatives : the Syndicat des Allergologues (Allergist Union) and Dr Madeleine Epstein who has for many years been in charge of publishing our texts, the Library teams of the Academie Nationale de Medecine and the Paris-Descartes Inter-University Library who are so helpful in our research, as well as Dr Taborda ,then Bernard and Sue Prefol who translate our French ABAs into English BUAs, and Dr Chrysanthi Skevaki who has opened the doors of the EAACI web site to us. Thank you all, and our very best wishes for 2012.

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1. Preventive Inhaled Corticotherapy (IC) with pre-school children at high risk for asthma

Theme: paediatric allergy, asthma
Key words: preventive Inhaled Corticotherapy (IC) – Low-dose daily IC – High-dose intermittent IC – Frequency of exacerbations – Oral corticotherapy

A US paediatrician multicentre study led by the California Allergy Department (R.S Zeiger NEJM 2011 365 1990-2001) was conducted among pre-school children considered at high-risk for asthma, in relation to a predictive index based on the frequency of wheezing and/or hospitalisations in the past year. The official recommendation in these cases was the use of IC, at varied doses but daily and for a long period. The major drawback observed was retarded growth and parents' reluctance concerning continuous treatment. As a result, the authors undertook a new randomised study comparing the benefits of a daily low-dose regimen to an intermittent high-dose.

Thus, 278 children aged 12 months to 5 years, enrolled in 7 different US centres, following an ethically validated protocol, received for 1 year either a nightly dose of 0.5mg IC (Pulmicort® in an inhalation suspension) or a 1mg twice-daily dose, from the onset of respiratory symptoms and for periods of an average 7 days. (Note: the protocol also included the on-demand addition of a bronchodilator, Albuterol, similar to Salbutamol® for 48hrs). The primary objective was the decreased frequency of exacerbations requiring oral glucocorticoid therapy.

At the end of the study, there appears no statistically significant difference between the two regimens, both equally efficient in the prevention of exacerbations and other symptoms (side effects or others). However, there is a notable reduction in the exposure to glucocorticoids (104mg over 1 year) in the intermittent as compared to the daily regimen, which is not negligible for young children in full growth.

As a conclusion, the authors recommend the intermittent rather than the daily regimen, something that clinical common sense could predict, but which from now on is supported by a precise statistical study and a clear protocol.

2. Monitoring honeybee venom immunotherapy with the Basophil Activation Test (BAT)

Theme: allergy to insect venom
Key words: immunotherapy – honeybee venom – rush treatment – specific IgEs – IgG4

31 Slovenian children with a history of honeybee venom-induced anaphylaxis were submitted to a specific, rush- immunotherapy, in a single-blind prospective study, monitored through the new Basophil Activation Test (S.E.K Zitnik et al Pediatr.Allergy&Immunol 2011, early view). This test is based on the biology of basophil cells whose degranulation is quantified by the expression of the CD63 marker and gauged by flow

cytometry followed by fluorescent staining. Indeed, in non-active basophils, CD63 is strictly localised inside the granules, then, at the time of exocytosis and fusion with the cell membrane, transferred to the cell surface and measured through venom concentration.

BAT results are considered positive when CD63 gives a positive reaction in at least 15% of basophils, for 1µg/ml of venom. Moreover, there exists a correlation between CD63 positivity and histamine liberation. The test was applied before starting the treatment, 5 days later and after 6 months or even 2-4 years in some subjects.

Before treatment, the BAT helped identify the culprit insect in 74% of the cases, while specific IgE reactivity was only observed in 52% of the children. Five days later, i.e. at the end of the rush-treatment, there is no statistically notable BAT modification.

However, after 6 months of regular immunotherapy (100µg every 4 weeks) specific IgEs remain at comparable levels (22.8kU/l on average, with a maximum of 100kU/l) whereas IgG4 levels are significantly higher. As for the BAT, it revealed in 85% of the children a marked CD63 decrease in the presence of 0.1µg/ml allergen (limit of cellular sensitivity) four times lower than at the start of treatment. The same observation is made after 2-4 years, whereas specific IgEs levels are also now significantly reduced.

In addition, the authors observed that, during rush-treatment, BAT positivity was associated with the appearance of side effects.

In conclusion, the Slovenian authors recommend the BAT as a reliable monitoring method of hymenopterous insect immunotherapy. Senior French-speaking allergists will certainly rejoice in the rehabilitation and renovation of the basophil degranulation test, much favoured by our late colleague J. Benvesiste : it was known as the TDBH (Test de Degranulation des Basophiles Humains).

3. Type-1 diabetes (T1D) and atopy

Theme: atopy
Key words: Type 1 diabetes – Atopy – atopic dermatitis – Allergic rhino-conjunctivitis – Th1/Th2 balance

On a schematic point of view, T1D is controlled by the Th1-type immune response whereas atopy is considered as dependent on Th2-type immunity. Early studies had suggested an inverse association between T1D and allergic diseases. The Danish authors (S.F.Thomsen et al. Allergy 2011 66 645-647) therefore undertook a retrospective study of the association in a population of twins. They sent a questionnaire to 54,530 Danes, mono or dizygous, aged 3-71, having suffered from asthma, hay fever or atopic dermatitis, and who had been treated or hospitalised for T1D between 1931 and 2000.

After statistical crossing and adjusting for age, sex, and zygosity (96% confirmed), it appears that in the 3x 20-year groups there exists an inverse association between T1D and the 3 symptoms of atopy (asthma, rhinitis, dermatitis) but only statistically significant for atopic dermatitis (AD). This AD risk is indeed 4 times lower in type-1 diabetics when compared to non-diabetics. Finally, with the dizygous T1D subjects (except for 91 pairs of twins) there is always a statistically lower risk than with their non-diabetic twin.

As to the genetic factors responsible for susceptibility to T1D or AD, they are also negatively correlated. For the authors, these findings substantiate the T1D/AD antagonism and the Th1/Th2 dichotomy.

This article was contested by an Italian group (Tosca et al. Allergy 2011 1612-14) who, in a prospective study of 112 children, aged 11 on average and suffering from T1D, on the other hand observed a positive correlation between this affection and allergic rhino-conjunctivitis. Besides, within the framework of the ISAAC epidemiologic study – which compares the incidence of T1D in the preceding 12 months in a group of 12-14 children from 31 countries, and the prevalence of atopic diseases – the authors (P.Fsadni et al Clin Resp.J 2012 6 18-25) also observe a positive T1D/AD correlation but no correlation at all with rhino-conjunctivitis.

It is clear that these conflicting findings can be explained by differences in methods of research, and also by the probable role of environmental factors. Whatever the case, these reports do not particularly affect diabetes or allergy therapies but fuel the classical Th1/Th2 paradigm.

4. Adrenaline auto-injection by children and teenagers

Theme: anti-allergy treatment
Key words: auto-injectable adrenaline – anaphylaxis – food allergy

Although adrenaline is unanimously recommended for first-aid treatment of anaphylaxis, its use in autoinjectors continues to be a subject of discussion as to its indications and practical implementation.

That is why a group of English allergists (L.Noimark et al Clin.&Exp. Allergy 2011 early view 1-9) undertook a multicentre prospective study involving 14 paediatric hospitals spread throughout the United Kingdom.

In this study 969 patients, aged 4-18 (average age 8), for whom an adrenaline autoinjector had been prescribed for a previous anaphylactic episode or food allergy the year before answered a validated questionnaire.

503 of them had no new reaction and did not use adrenaline. 466 had another allergic reaction, 221 a serious but non-anaphylactic episode, and 245 an anaphylactic shock (A) defined in the protocol as: loss of conscience, dysphagia, feeling of imminent fainting, wheezing, dyspnea, hoarseness. Among them, 97 even suffered 2, 3 or 4 episodes in the year. Most of the time and by order of frequency, the responsible allergens were peanuts and nuts, egg, milk, shellfish. As for the most frequent symptoms of these allergic reactions, they were: urticaria, skin redness, oedema, and wheezing.

Statistically speaking, in a united or multi-varied model, apart from the symptoms mentioned, oedema, throat prickling and stomach ache are associated with A. while A. risk factors are: a previous episode by non-identified allergen, milk cow allergy, ethnicity (non-whites) and associated asthma.

Most allergic reactions were treated by oral anti-histamines (83.3% for A, 86.4% for others, P=0.3). Finally, out of the 245 As., only 41 did receive adrenaline (16.7%, 95% CI :11.7-

21.3), either by their parents or by a health professional and 2.4% by the patient himself. 13 patients who used their autoinjector needed another dose of adrenaline. The reason for not using autoinjectors were: 54.4% because it was not considered necessary and 19.1% probably not useful.

Thus, in the British community, adrenaline is only used by a minority of patients suffering from anaphylaxis. It is probable that a similar survey in Western Continental Europe would give the same results. This goes to show the need to explain more thoroughly the benefits of this process to families and young patients.

5. Particularities of severe asthma (SA)

Theme: asthma
Key words: severe asthma – corticosteroids – smoking habit – obesity – gastro-oesophageal reflux – bio markers – Vitamin D – Pet-scan – FeNO – Super Dismutase Oxide– Anti-cholinergic bronchodilators – Macrolides

A large research programme on SA carried out in the USA is providing a better understanding of its definition, aspects and treatment (Nizar et al: AJRCCM 2011 November 17 in press). To define SA the authors, propose two major criteria for treatment: use of high doses of oral or inhaled corticosteroids (IC), and 7 minor criteria based on: symptoms, frequency and severity of exacerbations, with or without hospitalisation possibly in Intensive Care Unit, troubles of respiratory function tests, extra medications, insensitivity to C. One major criterion and at least two minor criteria were considered as meeting the study conditions.

Lessons drawn from these researches confirm a large number of (sometimes classic) notions:

1) Risk factors: active and passive smoking, obesity, gastro-oesophageal reflux, ethnicity (black skin), post-puberty females.

2) Anatomical and functional aspects: incomplete bronchodilation and bronchial thickening, detected by tomography and MRI - a better technique for children than bronchial biopsy -, major alteration of small airways with alveolar inflation (trapping), and predominantly neutrophilic inflammation which can be detected by molecular imaging (Pet-Scan).

3) Severity biomarkers: high FeNO due to respiratory obstruction and hyperinflation, but also lesser activity of the Super-Oxide Dismutase (SOD) associated to a severe drop in FEV1, increased expression of pro-inflammatory cytokines in relation to the molecular asthma phenotype (for instance, with predominant Th2 or Th1), as well as lack of vitamin D in children (A.Gupta et al AJRCCM 201101034 1342-1349).

4) Therapeutically, it is often insufficiently regular treatment which is one of the causes of severity, together with either the brutal weaning from C or, on the contrary, the use of too high doses of β^2 agonists. Also worth noting (P.Barnes et al JACI 2012 1 129 48-59) is the benefit from long term anticholinergic bronchodilators of the Tiotropiun type, without

forgetting the macrolide-type antibiotics in cases of neutrophilic predominance, and anti-inflammatory and blocking medications for incriminated mechanisms or mediators (anti-IgEs, or anti-IL13, IL, IL9, PGD2) as well as the products likely to invert the corticosteroid-resistance such as “old” theophylline and nortryptiline. Thus, research is more and more oriented towards biomarkers of different subtypes of SA in order to respond by appropriate and more and more specific therapies.

6. Allergic reactions of medical personnel to allergen extracts

Theme: allergens
Key words: medical staff – allergen extracts – beta blocking agent – timothy grass – pollens – pets

A rare case of occupational anaphylaxis, is reported by two US authors in a 32-year-old female compounding technician while preparing an immunotherapy vial of timothy grass allergen extracts, who accidentally stuck herself on the hand with a needle (M.L Bandino et M.S.Tankersley JACI 2012 129 1 250-251). Within minutes, a local wheal-and -flare response appeared at the needle-stick site followed by rhino-conjunctivitis, diffuse urticaria, then a facial peri-orbital and tongue angio-oedema, requiring several adrenaline injections before stabilising. Admittedly, this woman was atopic, suffering from **allergic rhinitis**, which included sensitization to timothy grass, but usually treated by Loratadine®, and also from a regular hypertension by a β-blocking agent (Atenolol®), regarded as risk- factor of resistance to treatment.

Commenting on this observation, the Danish author S.Dreborg (JACI 2012 129 in press) reminds us that this type of risk can concern all medical staff. He quotes the case of a nurse, assigned to work on allergenic provocative tests in a Paediatrics hospital unit, with no allergy history, who started coughing the following winter, then as soon as she resumed work and undertook a 1st provocative test, had an asthma attack followed, despite having stopped working, by a rhino-conjunctivitis.

In 1970 in Sweden, 18 out of 20 paediatric allergy nurses showed signs of sensitization, despite installation of an air extraction system. A nurses’ Union sent a web- questionnaire to 570 participants on the subject of allergic risks at work and received 418 (71%) answers. Conducting skin tests (prick-tests, scarification or ID) was judged as responsible, but fingers were also pointed at immunotherapy and inhaled provocative tests. Allergens most frequently implicated were pollens and pets.

The authors set forth a series of recommendations on the training and careful handling of allergenic extracts, which they intend to submit to ad hoc Committees. A similar initiative in France and French-speaking countries, in the form of a Forum aimed at gathering similar observations would be welcome.

7. Cold Urticaria (CU): immuno-genetic and molecular data

Theme: skin allergy
Key words: cold urticaria – Ig deficiency – repeated infections – auto immunity – gene PLCG2 – phospholipase

CU is a diagnosis that allergists may be confronted by, atopy being not excluded from its pathogenesis. It is also due to mast cell degranulation by cold temperatures and can culminate in anaphylaxis.

In an article dedicated to an inherited CU associated with antibody deficiency and auto-immunity (M.J.Ombrello et al NEJM 2012 January 12 330-338) a group of US researchers undertook a large number of immunologic and genetic investigations with 27 subjects belonging to three families of European ancestry.

From a clinical point of view, every subject's CU began in childhood and continued throughout their life. But it is not the contact with cold that triggers CU (ice-cube tests were negative as well as cold water immersion) but essentially cold air or wind. 15 subjects out of 26 also showed allergic manifestations.

26 out of 27 suffered from immunologic disorders: in 75% of cases a deficiency in immunoglobulins, associated in 56% with susceptibility to sinus and lung infections. Signs of auto-immunity were also observed (auto-antibodies or associated auto-immune disease: granulomatous rash, vitiligo, inflammatory arthritis, thyroiditis, granulomatous lesion of larynx and soft palate).

Common lab tests showed reduced IgA and IgM serum levels, circulating natural killer cells and B lymphocytes, but higher IgE levels. In 13 of 21 treated subjects (62%) antinuclear antibodies were found.

From the genetic point of view, DNA sequencing, particularly through the Sanger enzymatic technique and identification of single nucleotide polymorphisms (SNP) showed some deletions in gene PLCG2 encoding phospholipase-active proteins, particularly PLCγ2, signaling molecule expressed in many cells such as mast cells, B lymphocytes and natural killer.

This genetic research highlights the importance of molecular mechanisms contributing to the defence of the organism and immune tolerance.

The possible treatment of CU clinical manifestations by phospholipase inhibitors is a current subject of research and a possible example of targeted molecular pharmacology. The administration of immunoglobulins IV may be useful in some cases but prescribing them in France is currently regulated.

8. Allergic consequences of climate changes

Theme: allergy and environment

Key words: global warming – CO2 – tree pollens – grass – Ambrosia – Alternaria

A series of publications on the health impact of climate changes and global warming in the years to come (L.Ziska et al: Proc.Natl.Acad.Sci.USA and JACI 2012 1 29 27-32) reveals that atmospheric gas accumulation, particularly CO2, influences photosynthesis and plant growth. This slogan sums up the consequences: “More sneezing in a warmer world”. Three types of plants are concerned: trees in spring, grass in summer and Ambrosias (ragweed) in autumn.

Tree flowering is now 2 to 4 weeks earlier, whether it be oaks or birches in the USA but also in Europe (Swiss and Denmark), and 1-3 weeks earlier for olive trees in Spain.

The same can be said of grass, whose pollen counts have increased as well as their allergenic protein contents, particularly for the US Artemisia and the European species Pellitory (Parietaria Officinalis). However, there is not always a direct relationship between atmospheric concentrations of CO2 and increased allergenic effect of these pollens.

However, for Ambrosia (ragweed) there is a clinical and experimental impact of CO2 and T° on pollen allergenicity, proved by the authors, They also remind us of importance of latitude, after having observed a 27-day lengthening in the pollen season over 15 years in some parts of northern USA, ending on a humoristic note when they recommend that Canadians should stock up on handkerchiefs for the years to come.

Finally, even molds are concerned by these climate changes. Such is the case of Alternaria whose sporulation has increased.

Thus, climate changes induce a higher exposition to allergens, in theory more so in the countryside than in towns. However, the role of gas (NO2 and Ozone) and particle pollutants (PM2,5) on respiratory mucous as well as pollen biology is, in large cities of the Western world, an exacerbation factor to **allergy symptoms**. Finally, let us recall that this anthropogenic accumulation of atmospheric gases also accounts for extreme climate events such as heavy rainfalls and thunderstorms; the latter were the cause of acute and spectacular episodes of **rhinitis** and asthma in Europe.

These notions should be kept in mind, if only for setting up the sequencing of preventive treatments (immunotherapy) of our allergic patients.

9. Risks of childhood allergy and asthma under phthalate exposure

Theme: asthma – allergens
Key words: asthma – phtalates – benzyl-butyl-phtalate

Phtalates (Pht) are indoor pollutants emitted by everyday consumer goods, such as food packaging, plastic components, medical equipment (tubes and perfusion bags), toys, and cosmetics. They are often considered as endocrine disruptors impacting reproductive functions, and carcinogenic. A group of Chinese authors from Taiwan, having assumed the allergenic effect of these Pht, the degree of exposure to which can be measured by their metabolites in blood and urine, conducted a case control study of 101 pre-school children (2-6 years of age) selected between 2007 and 2009 in a population of several thousand.

A considerable amount of data was collected from parental questionnaires, daily monitoring of clinical symptoms, specific and total IgE levels, concentration of various indoor pollutants in patients' homes, including 5 Phts in dust samples, and concomitant analysis of urine metabolites as well as creatinine concentration. The data were then subjected to statistical analysis.

Apart from the higher percentage of boys in the test group than in the control one, demographic, family, and environmental characteristics were almost identical in both groups, albeit with a higher percentage of atopic subjects in the 1st group.

Essentially, it appeared that high levels of benzyl-butyl-phtalate (BBzP) in home dust are significantly associated with cases of allergic manifestations (rhino-conjunctivitis, asthma or dermatitis) whereas its urine metabolite, mono-benzyl-phtalate (MBzP), was higher in asthmatics than in controls.

Overall, high levels of DBP (dibutyl-phtalate) and its metabolites MBP (mono-n-butyl-phtalate) and MEHP (mono-2-ethylhexyl-phtalate) may be regarded as risk factors for clinical manifestations concerning lung, skin or eyes.

Admittedly Phts, whose concentrations in urine were lower than in dust, are not the only culprits for poor quality indoor air (an important role is also played by exposure to fungus) but their contribution remains notable and for the first time quantitatively assessed, and particularly for BBzP.

10. Sputum eosinophilia and asthma (A)

Theme: asthma
Key words: sputum eosinophilia – asthma – blood eosinophilia – FENO

Having observed that a subgroup of asthmatics did not have airway eosinophilia, which it is regarded as asthma-typical, the NIH Californian authors (K.W.Mc Grath AJRCCM 2012 20 January in press) wanted to determine the size and characteristics of this group, through repeatedly analysing the cytology data from these patients' sputum.

995 asthmatics, aged 12-70, suffering from mild-to-moderate asthma and belonging to 9 different national cohorts, underwent repeated sputum induction, with the usual technique (2 to 4 times) followed by cytology examination in search of eosinophils (EO). The positivity threshold was fixed at 2% or more of the number of cells.

Three groups of subjects were discriminated: Asthmatics (A) with persistent EO, those with intermittent EO (at least once) and those who were consistently negative. Comparing cytological tests to blood eosinophilia or to FENO did not show any reliable sensitivity or specificity.

645 A. followed standard inhaled corticosteroids (ICS), 350 did not. The first statistical analyses reveal that 83% ICS have no sputum EO and 36% of the non-ICs. Which constitutes a large group of non-eosinophilic asthmatics. This absence of EO was observed even in A whose disease was well-controlled.

From a therapeutic point of view, eosinophilic A. reacted favourably to 2 weeks of anti-inflammatory treatment (IC + anti-leukotriene Zafirlukast) with an improvement in airflow obstruction. This was not the case for non-eosinophilic A in whom only albuterol (β2 agonist) induced bronchodilation.

On the whole, more than half the patients with mild-to-moderate asthma showed a persistent absence of sputum eosinophils.

Among the different clinical forms of A., this group definitely represents a particular phenotype which responds only poorly to anti-inflammatory therapy. Practically, this research should incite us to look more frequently for EO in our asthmatic patients' sputum.

NB: As part of a general bibliography, our readers are encouraged to look at the special issue of Nature (Outlook 24 Nov 2011 479 7374) which presents a 27 page exclusive paper on Allergies.

11. Breastfeeding (BF) and allergy prevention – 1°: Epidemiologic data

Theme: Atopy, atopy prevention
Key words: Breastfeeding – Asthma – Eczema – Infections

The role of breastfeeding in protection against allergic diseases is still arousing controversy: no less than 6 recent publications discuss it, mostly a confrontation between Europeans and Australians.

In 'A tale of two cities' (Brew et al: Ped.Allergy & Immunol 2012 23 75-82), the authors confront the randomised data from 2 cohorts, one from Sidney (419 subjects) and the other from Stockholm (463), i.e. 882 subjects in whom the definitions for breastfeeding (at least for 3 months), asthma and allergy**,** were harmonized, and who were enrolled if they had at least one atopic or asthmatic parent and had a gestational age of more than 36 weeks.

After statistical analysis, it appeared that BF reduces the risk of asthma at the age of 4/5 and 8 years in children with family history of asthma. This effect is more marked in the Swedish than in the Australian cohort. It is also the opinion of some New Zealand authors (KM Silvers et al J. of Pediatrics 2012 January in press).

However, a sceptical opinion can be found in a paper from Melbourne (Matheson et al: Clin & Exp. Allergy 2012 31 01 early view) which evokes an apparent protective effect of BF against asthma, but none against eczema or food allergy, nor any prevalence of sensitisation to airborne allergens. The authors believe that several confounders exist in the numerous epidemiologic studies and wonder whether BF is not merely active in the prevention of infection, rather than actually reducing the risk of asthma. In the Australian cohort itself, BF may even act as risk factor for sensitisation to cow's milk, eggs and peanuts at the age of 4/5 and, in both cohorts, at 8 years. Some authors had even suggested stopping it for under 1-year old children if some eczema or wheezing occurred, but the Melbourne authors found no evidence, in their joint study, that BF might have influenced any allergic manifestation.

On practical grounds, it is difficult for the clinician to adopt a dogmatic attitude in this matter, knowing however that in our Western countries it is recommended, depending on circumstances and environment, to breastfeed without exceeding 3 months.

12. Breastfeeding (BF) and allergy prevention – 2°: Mechanisms

Theme: Atopy, atopy prevention
Key words: Maturation of innate immune responses – Cytokines – Polyunsaturated fatty acids

Epidemiologic data being not always convincing, BF supporters, including the WHO which recommends 3 to 6 months depending on the country, have tried to better define possible mechanisms.

Thus, a recent Anglo-Swiss study (C.M Dogaru et al. AJRCCM 2012 3 early view) of 1458 children, concludes that breast feeding has a favourable effect on the child's future respiratory function by direct action on lung growth, particularly if the mother is asthmatic.

But a biology-focused Dutch group (M.G. Belderbos et al: Ped. Allergy & Immunol 2012 2365-74), considering that the 1st month after birth is the most sensitive to environmental factors which can modulate the infant's innate immune responses, undertook a prospective study of 291 healthy neonates (NN). They then statistically treated 6 exogenous factors (mode of delivery, BF, birth month, atopic siblings, passive smoking, pets), 7 types of total blood cells measured by flow cytometry (neutrophils, eosinophils, basophils, dentritic myeloid cells, monocytes, natural killers, T lymphocytes) and 9 types of cytokines induced by Toll-like receivers (TLRs 1 to 9) revealed by the ELISA technique.

On the whole, it can be said that BF was found to be the determining exogenous factor for neonatal immunity, with 5 associated parameters: the production of TLR7-induced IL10 cytokine which is 4 times lower than for a formula-fed NN, whereas the TLR3-induced cytokine IL12p70 is 2 to 3 times higher, a sign of fast immunity maturation. On the other hand, the reduction of this latter cytokine is associated to the caesarean mode of delivery and could express an asthma risk for the infant. So, it is the 1st month immunity maturation which appears to provide the protective effect of BF.

Let us also quote the Barcelona survey (Eva.Morales et al Clin.Exp.Allergy 2012 30 January) conducted by parental questionnaires, with 580 children submitted to predominant

BF during the first 4 to 6 months and whose long-chain polyunsaturated fatty acids (LC-PUFA) were dosed in colostrum. With high levels, a reduction in risk of wheezing and atopic eczema in 7- to 14-month old children is observed, as well as a lower risk of gastroenteritis in the first 6 months. This may account for the possible role played by nutritional factors in the preventive effect of BF, which some authors also attribute to the presence of TGFβ in mother's milk.

13. Nutrition and allergy: prebiotics and/or probiotics

Theme: allergy prevention
Key words: Intestinal micro flora – Infection – Antibiotics – Fatty acids – Prebiotics – Probiotics

The significant role of Intestinal Microflora (IMF) in the modulation of immunity is well known, with any change in its composition likely to trigger inflammation or allergy. Such is the case of antibiotics which, administered to children of less than 1 year, lead to allergic sensitisation. The high frequency of urban as opposed to rural allergies is also often explained by the presence in the former of a more limited microbe range. Food or ingredients are also likely to affect IMF. This is the case for long-chain polyunsaturated fatty acids, but also for polyphenols and substances like prebiotics and probiotics, supposed to preserve or restore the microbial balance.

Prebiotics are carbohydrates, non-digestible by man, which, like inulin (produced by plants) or galacto-oligosaccharides, have a positive impact on IMF, by allowing the proliferation of bifido-bacterial type germs, the same germs that can be found in the breastfed baby. The International Association of Pre- and Probiotics has recorded more than 700 therapeutic trials with no formal conclusion, because the specific Prebiotic of a given microbial population is not known, neither the proper dosage.

As for Probiotics, which are living micro-organisms, these are under intensive research, both experimental and clinical, particularly in the food industry. One thinks particularly of yoghurts or other fermentation products, and of Lactobacillus (C.Wylliard Nature 2011 479 S5-7). Many studies have been published of Lactobacillus casei administered to newborns in order to prevent eczema or asthma, or of Lactobacillus rhamnosus to infants or mothers before giving birth: more than 25 in 2008, randomised and often contradictory. In a recent Swiss paper (Wassenberg et al: Clin.Exp.Allergy 2011 4 565-573) the use of L.paracasei ST11 administered per os for one month in about 30 subjects, has shown some efficacy on the signs of pollen rhinitis. Other Japanese experiments were conducted successfully on mice with Clostridium (which has 46 different strains). But, on the whole and with the risk of playing the sorcerer's apprentice, care must be taken in modifying or regulating IMF in order to combat or prevent allergic manifestations.

14. Tuberculosis, BCG and allergy

Theme: allergy prevention
Key words: Tuberculosis – BCG (Bacille Calmette-Guerin) – Asthma – Eczema

An Anglo-Algerian epidemiologic retrospective randomised study, under the authority of the International Union against Tuberculosis and in the framework of the ISAAC study Phase 2 (C.Flohr et al Ped.Allergy & Immunol 2012 February early view), has attempted to discover whether previous tuberculosis (TB) or BCG vaccination in the first months of an infant could have a protective effect against the risk of allergy. 23,901 subjects, aged 8 to 12 and attending 20 different centres in developed and underdeveloped countries were the object of this study, conducted both by questionnaires and clinical examinations, concentrating on flexural eczema, and using skin prick tests. The odd ratios corresponding to a 95% confidence interval were calculated in the different centres according to the classical model. There were 245 TB cases and 66.3% of the children had received the BCG vaccine.

Findings showed that all allergic manifestations (asthma or wheezing, hay fever, signs of eczema) were significantly associated with TB the previous year. This was all the clearer for severe asthma and clinically established eczema. However, there is no association between TB and skin prick tests. As for BCG vaccination during the first year of life, it was in no way associated with subsequent allergic manifestation and does not seem to have a preventive effect against allergy.

All in all, this curious, positive association between TB and allergy does not, as the authors acknowledge, point to a causal relationship, but in view of the high number of subjects albeit in a cross-sectional study, it is possible to grant some value to this epidemiologic survey. It is above all interesting for those countries still struck by endemic tuberculosis.

15. Atopic dermatitis (AD): inflammatory disease of the epithelial barrier

Theme: physiopathology, eczema
Key words: atopic dermatitis, epithelial barrier, atopic pathway, filaggrin

The French Academie Nationale de Medecine has just allotted a session to this theme under the guidance of J.Bazex and M.Bagot, and two reports were presented: Alain Taieb (Bordeaux) on AD physiopathology and Y. de Prost (Paris-Necker) on immunosuppressive treatments.

We know that AD is very common in industrialised countries and affects approximately 15 to 30% of children and 2 to 10% of adults. The immunologic vision considers

it as the 1st stage of the atopic pathway followed by asthma, rhinitis and food allergy. And yet, the discovery of mutations in the Filaggrin gene (FLG), a major protein in the maturation of the stratum corneum, has refocused attention on skin and, as A.Taieb underlines, has produced a Copernician revolution in the understanding of the affection which appears to be a model of inflammatory disease of the epithelial barrier (ANM Bulletin 2012, in press).

Irvine and Mac Lean's experimental works have indeed shown that FLG-lacking mice have a thin, dry and porous skin, and that the gene mutations and lack of FLG in children are associated with a severe form of eczema. Moreover, although FLG has no expression in the lungs, it was observed with surprise that some of its mutations were strongly associated with asthma and others with peanut allergy. Simultaneously, the Holgate team from Southampton underlines the frailty of the bronchial epithelium in asthmatic patient whose mucous membrane is poor at self-repair after aggression. Such epithelial deficiency also affects nasal mucosa (hence the risk of rhinitis) and intestinal mucosa, (hence food allergy).

But dermatologists go even further, for skin appears no longer to be a simple mechanical barrier but an agent of immunity, as keratocytes secrete cytokines which play a part in the atopic path. The search is therefore on-going for molecules capable of stimulating the production of FLG, while avoiding or by-passing mutations: such is the case of gentamicin or growth factors like the Keratocyte Growth Factor, which is present in skin and intestinal mucosa and which reduces inflammation and epithelium leakiness of the airways in rats.

16. The role of immunosuppressive agents in AD treatment

Theme: eczema, treatment
Key words: eczema, atopic dermatitis, immunosuppressive agents, tacrolimus, pimecrolimus, cyclosporine, biotherapies

Y. de Prost, whose great experience must not be overlooked, believes that the severe AD, in the form of impetigo and intense pruritus alter the quality of life; they constitute 13 to 20% of cases in children and 15% in adults (an extreme form was observed in a 91-year old female patient). He gives a reminder of the treatment basics, i.e. dermocorticoids, limiting of infection and xerosis (emollients) and hygiene advice.

The most frequently used immunosuppressives (IS), when classic treatment fails and even for local medium or moderately intense affections, are Tacrolimus T (Protopic®) 0.1% and 0.03% ointment for children and Pimecrolimus P (Elidel), not yet on sale in France, equally effective and acting as calcineurin inhibitors.

T, particularly recommended in the zones where corticoids should be avoided, such as the face, eyelids, buttocks and deep folds in adolescents, is extremely effective and well-tolerated apart from some local irritation in the 3 days following its application; 6 weeks of treatment is advised. The only counter-indications are herpes and exposure to the sun. The risks of Carcinogenesis (Lymphomas), which were evoked when T was administered in case of organ grafts, are not confirmed for local short-term treatment.

P offers the same indications and results as T.

As for per os IS, these are mainly represented in France by cyclosporine (4 to 5 mg/day), clearly effective but requiring careful monitoring of kidney function and blood pressure, and gradual reduction in dosage before the end of treatment to avoid rebound occurrences.

Methotrexate has also been suggested when cyclosporine is ineffective.

Finally, biotherapies: Omalizumab or Retuximab have shown interesting therapeutic test results, but a larger number of patients is necessary to confirm their possible efficiency and justify their high costs.

17. Chronic Rhinosinusitis (CRS) in the elderly

Theme: ENT allergy, immunologic markers
Key words: rhino-sinusitis, elderly patients, nasal polyps

The physiopathology of CRS, little studied in elderly subjects, is the theme of the following article (S.H.Cho et al JACI 2012 129 3 858-860 e2). The US-Korean authors distinguish two types: 1°) CRS with nasal polyps (CRSwNP), polarised toward a Th1-type immunologic reaction, and 2°) CRS without NPs, with eosinophilia and tendency to Th2 skewing, and point to the increasing evidence that these are linked to impairment of the barrier function of the airway mucosal epithelium.

The aim of the study was to evaluate the age-related differences in the clinical characteristics and to assess the respective immunologic markers.

A 1st retrospective study of 252 patients led to identification of a lot of demographic and clinical characteristics, by subdividing the group into adults (230 aged 16-49) and the elderly (22 aged 60-77). In the latter, asthma and associated NPs tended to be more frequent, but with no statistical significance; only the sinus opacification score, assessed by tomography and CRS severity marker, was statistically higher.

In a 2nd stage, in different subject groups (58 with NPs, 51 without NPs, and 50 control, with the same age range), they went further and studied nasal lavages and immunologic markers. Among them, ECP (Eosinophil Cationic Protein) blood counts were higher, above all in adults with NPs than in elderly subjects, a sign that the eosinophilic inflammation was lower in the latter. However, the neutrophilic inflammation detected by HNE (Human Neutrophil Elastase) was not discriminated by age or by CRS type.

As for markers of the epidermal differentiation complex, S100 A7 (psoriasin) and S100 8/9 (calprotectin), levels of which are generally reduced in CRS, were significantly lower in elderly subjects, above all for calprotectin in CRSwNP.

On the whole, and despite the skew toward severity and more frequent association with NPs, CRS eosinophilic inflammation subsides with age, whereas simultaneously the epithelial barrier dysfunction, as revealed by the lower levels of corresponding markers and above all of S100 A8/9, plays an important role in the pathogenesis of lesions and therefore indicates a need to develop modified treatment strategies for elderly patients with CRS.

18. Crenotherapy and Chronic Rhinosinusitis in children

Theme: ORL allergy, nasal thermal aerosol
Key words: crenotherapy, rhino-sinusitis, child, inflammation markers

Thermalism for treating allergic or non-allergic rhinosinusitis, which had its golden age in France in the past century, has been more or less dropped over the past years. But a recent article by Italian authors published in English (A.Passariello et al :American Journal of Rhinology & **Allergy** January-February 2012 26 1 15e-19e), based on precise clinical, biological and statistical studies, now rehabilitates this treatment by the inhalation of sulphate-sodium chloride water from a thermal site in the island of Ischia.

65 children of an average 3.3 years of age received thermal aerosol inhalations for 15 days and 15 minutes per day. A complete preliminary ENT check up with sino-nasal severity score and sampling of nasal mucus by lavage, was performed with quantitative determination of inflammation markers such as TNFα, and immune-regulator anti-microbial peptides such as calprotectin and Hβ2 defensin. 60 other healthy children from a paediatrics ward were used as controls. All these parameters were compared in a thorough statistical study.

At the end of the treatment a marked improvement in symptoms (essentially nasal obstruction, and impairment of the sense of smell) and in the sino-nasal score was observed with significant values, whereas levels of calprotectin TNFα and Hβd-2 were also reduced in statistically significant proportions.

Crenotherapy is thus now taking on a new dimension, for it has already long been recognised as harmless, well accepted and perfectly tolerated, as well as an alternative to drug-based treatment. From now on it also appears as an inhibitor of cytokines and nasal inflammatory mediators.

Admittedly, one can be surprised, just as the authors were, to note a difference between the observations made in adults with CRSwNP for whom, as already said above, calprotectin and Hβd-2 levels are lower than controls. But in this study carried out with children, CRS is not associated with polyps or with eosinophilia, but rather with a mixed inflammatory cell population composed of lymphocytes, macrophages and neutrophils, which could account for a difference in the occurrence mechanism of lesions.

In any case and despite the absence in this study of an accurate allergist check-up (one single note pointing out the regression of allergic symptoms), the thermal treatment of chronic **rhinitis** in children, which was very fashionable a few decades ago, deserves to be taken once again into consideration.

19. Football and Exercise-Induced Bronchoconstriction/Asthma (EIB)

Theme: asthma
Key words: exercise-induced asthma, football, bronchial provocation, bronchial dilatation, doping

The diagnosis of asthma or Exercise-Induced Broncho-constriction (EIB), which is well-known in sportspeople, relies heavily on athletes' statements and is treated by bronchodilators or even corticosteroids, which are then authorised in high level sports competitions. Football, the most popular sport around the world, exposes its players to many factors of aggression: prolonged hyperpnoea causing loss of water, exposure to multiple and irritating aero-allergens during training or competition (10 to 13km run during each match, on grass or in cold weather).

Now, following a series of doping incidents with elite athletes in 2009, a change in the regulations of international competitions such as the Olympics Games for instance, allows the use of sympathomimetic or anti-asthma drugs, on condition that this is justified by a confirmed diagnosis after accurate pulmonary function testing.

A group of British authors from Newcastle, Liverpool and London (Ansley et al Allergy 2012 March 67 3 390-395) thus interviewed and examined 65 elite professional soccer players (English Premier League) thought to be suffering from EIB, in order to check the accuracy of the diagnosis.

They recorded by questionnaire the symptoms and the drugs used and conducted a bronchial provocation test with dry air (6 minutes of eucapnic voluntary hyperpnoea) in 42 players, and a mannitol challenge in 18 players. Five players with abnormal resting spirometry underwent a bronchodilator test. The results were surprising: in fact, of the 65 players assessed, 57 (88%) indicated regular use of asthma medication and 57 (88%) indicated EIB symptoms during a match. And yet only 33 (51%) had a positive bronchodilator or bronchial provocation test. Moreover, neither symptoms nor the use of inhaled corticosteroids were predictive of the outcome of pulmonary function tests.

Thus, a high proportion of English elite professional soccer players are wrongly medicated for asthma, some of them using as reliever therapy only, while they present neither bronchial obstruction nor hyper-responsiveness to possible environmental stimuli.

This is an important piece of information which should be brought to the attention of sports authorities and all Olympic sports teams. It once more underlines the fair play of the British medical and sporting community.

20. Pertussis and asthma

Theme: asthma, infection
Key words: asthma, pertussis, measles, anti-pertussis vaccination

The recent pertussis (P) outbreak in California, following that in Minnesota in 2004, despite vaccination, has induced C.R.Capilli of the Mayo Clinic (JACI 2012 129 4 957-963) to determine whether in a case-control population asthmatics (A) were more prone to contract P than non-asthmatics.

223 cases of P, identified in 2004 and 2005 by PCR (Polymerase Chain Reaction) on nasopharyngeal sampling on As, were studied but only 164 subjects were enrolled with 328 controls. 50% were male, 80% white, with a median age 14. 62 (38%) of them were suffering from A before contracting P as opposed to 85 (26%) of the 328 controls (OR 1.73 P=.013).

To sum up the statistical data of the study, it appears that within a population like the USA's with a high prevalence of A, the risk for an asthmatic person of catching P is 17%.

This means that asthmatics constitute a 'target' group for anti-P vaccination, with boosters and recall every 10 years at least, even in adults, and associated with anti-tetanus and anti-diphtheria vaccination, as is the case in France with the traditional DTCOQ.

Another point of view: P seems to be, like measles (M), a risk factor for child asthma, as shown by a study conducted in the Australian island of Tasmania by J.A.Burgess et al. (Chest March 2012 early view on-line) among 7-year old children. The authors recorded over a 37-year period from a school medical data base, cases of children's respiratory infections and their possible association with incidental, persistent or established asthma, all supported by a statistical logistic regression analysis. They were able to conclude that, while most children's infections protected them against the occurrence of adult A, as well as against chicken pox or rubella, P and M were, on the contrary, significantly associated with adolescent incidence of A for the latter and pre-adolescent incidence of the former. Another reason, according to the authors, for recommending vaccination against P and M to reduce the incidence of asthma.

21. Anti-influenza vaccination of egg- allergic patients

Theme: allergy, vaccination
Key words: anti-flu vaccine, egg, ovalbumin

The administration to an egg-allergic person of the anti-influenza vaccine (AIV) coming from an egg-grown virus and ovalbumin-laden virus is considered with some reluctance by doctors and families, above all when the child or the adult has a history of serious anaphylaxis (An) caused by this allergen. Yet AIV is unquestionably beneficial for public health, is generally harmless, and egg allergies are rare.

Two researchers from Philadelphia, USA (I.Feung et J.M.Spergel JACI 2012 129 4 1157-1159) undertook a retrospective review of 56 An-suffering children monitored between 2007 and 2009, who received 119 vaccinations using the Sanofi-Pasteur AIV (H1N1 excepted).

13 first underwent vaccine prick-tests (SPTs); children under 3 years of age received a 0.25-ml dose, those over that age 0.50ml in 2 or 3 doses.

Two children had a vaccine reaction: one of them, aged 2, had 2 reactions, he had had a positive SPT before the 1st vaccination but was not affected the following year, while the other, aged 18 months, suffering from asthma and for whom the SPT was not considered useful, had a reaction which was both moderate and reversible by simple anti-histamines.

On the whole, the authors concluded that AIV was harmless for the egg-allergic who have suffered a more or less recent An episode (on average 2 years before AIV). Besides, at the same time, 520 egg-allergy sufferers, without A, had only limited local reactions.

The authors refer to a few cases found in publications, from which it appears that AIV can be administered without serious problems to the egg-allergic, including subjects having had an An reaction.

The ovalbumin content (O) incriminated does not seem to play a negative role, as high O dosage vaccines did not provoke an increase in the risk of A. The AIV used in this study had a median ovalbumin concentration higher than those of other brands of vaccine.

As to the preliminary SPTs, these present no great interest, and neither does dose fractioning in 2 or 3 injections.

Allergists may therefore reassure their patients and families as to the harmlessness of AIV: post-vaccination monitoring of a few minutes or hours is nevertheless a necessity.

22. Archives, fungi (F) and occupational allergy

Theme: allergens, environment

Key words: fungi, archives, Penicillium Chrysogenum, Cladosporium sphaerospermum, Aspergillus versicolor

A French team of scientists from the Besancon University undertook an original survey on the possible contamination of the National Archives by fungi, trying to identify and quantify them through state-of-the-art techniques, to evaluate their concentration in the air and inside the documents, and finally to assess their effect on archivists' and research assistants' health, searching among other symptoms for allergic manifestations (S.Roussel et al Indoor Air 2012 22 2 early view). After an appeal on the National Archives website, the authors enrolled 10 volunteer centres for the survey.

2 techniques were used in the search for 50 or so F varieties: Air Impactor for the air, and Electrostatic Dust Collector for the archive zones.

2 methods were used and compared for F identification: culture-based analysis and quantitative PCR (Polymerase Chain Reaction). The criterion of 170 Colony Forming Units (CFU) per m3 was considered as potentially pathogen.

An inventory of symptoms suffered by subjects in contact with the archives was drawn up using a conventional self-report questionnaire distributed among the staff.

The results were as follows:

3 main F were isolated in terms of frequency and quantity: Penicillium Chrysogenum, Cladosporium sphaerospermum and Aspergillus versicolor, with converging results for the two techniques (the PCRq also helped to isolate Stachybotris chartarum considered as a potent toxin generator). On the whole, archive contamination was found to be moderate. Median concentrations ranged between 30 and 465 CFU/m3, with 93% between low and medium: only 3% of the archives showed high concentrations.

As regards the question of health, subjects working in contaminated zones did not report more frequent allergy symptoms than their fellows. However, they did report headaches, eye and throat irritation, coughing and rhinorrhea. Only eye irritation was statistically significant.

These reassuring results corroborate observations made in rare similar studies conducted abroad, and which may concern a large number of subjects (over 1 million worldwide).

23. Exposition of asthmatic children to home fungal species

Theme: asthma, environment
Key words: asthma, cladosporium, penicillium, aspergillus, basidiospores, epicoccum, pithomycea

Exposition to fungi (F) is known to play an important role in the development of asthma (A) and atopy, by increasing symptoms intensity and encouraging A exacerbation. A group of American paediatricians from Kansas City focused on fungal species in the homes of asthmatic children, trying to identify them in a large number of Middle West homes, according to geographical location, seasons, and the presence of at least one asthmatic child (J.Meng et al Clin. Exp**.**Allergy 2012 21 March accepted article).

Flats and houses enrolled in the study were part of a research project on home hygiene, which means that the more or less unsanitary ones were dropped and those with relatively comfortable conditions were given priority.

88 homes with one asthmatic child (aged 2-18) were then explored, particularly at the end of spring and in the autumn, when asthmatic and allergic subjects consult the doctor more frequently and were compared to 85 control homes (with no asthmatic child), and during the influenza season depending on the frequency of paediatrician consultations.

The technique consisted in sampling fungal spores from the child's bedroom and the living area, as well as in the outdoor environment, counting them per cubic metre of air, and cultivating them for CFU (Colony Forming Unit) identification and count.

Results reveal that 18 viable and potentially pathogenic species were isolated and 165 families out of 173 (97%) were host to at least one viable species.

Among them: Cladosporium in the first place, Penicillium, Aspergillus, Basidiospore, Epicoccum and Pitomyces were identified more often and in higher concentration in homes with an asthmatic child than in control homes, even after adjustment for outdoor fungal spore concentration. The cultures confirm these observations after adjusting for seasonal factors. It is surprising to observe that Alternaria spores were not found more frequently in asthmatic

homes than in controls. The responsibility of these fungi in the symptoms shown by the study asthmatics remains to be established through research already planned for the future (76% of them presented superior airway manifestations, 63% asthma-like symptoms, 43% skin signs). But we know that many of these F species are allergenic. This means that their detection followed by their elimination cannot but improve the treatment of asthma and benefit the asthmatic child.

24. From rhinitis to asthma: the role of workplace humidity

Theme: asthma, environment
Key words: rhinitis, asthma, moulds, flooding, fungus index

It is well known that exposure to fungi in a damp environment increases the risk of allergic rhino-sinusitis, but there is little information on the progression of rhinitis towards asthma in an occupational context in a water-damaged building. American authors (J.H.Park et al Indoor air avril 2012 early view) conducted 4 successive environmental and health surveys by questionnaires, in a 20-storey building in North East USA, built in 1985 and damaged by water flooding. Occupied in 1994, the building had been recognised as responsible for asthma cases and hypersensitivity pneumopathy among its occupants in the autumn of 2000, in relation with the inhalation of soil moulds. After several attempts to repair the damage in 2004, the authors monitored the evolution of 131 subjects between 2001 and 2007 initially suffering from rhinitis, compared to a control group of 361 other occupants.

Using logistic regression models, they analysed the risk of asthma development among these two groups, adjusting for demographic data, possible smoking habits, duration of occupation of the premises and exposure to fungi, endotoxin and ergosterol expelled by fungal cell membranes.

The findings suggest that the rhino-sinusitis group were at least twice more likely to contract asthma than the control group (OR=2.2, CI95%=1.3-3.6). This risk was even higher when the rhino-sinusitis group was exposed to the building's highest fungal concentration zones (OR=7.4, CI 2.8-19.9).

It is then possible to conclude with the authors that, in professional, water-damaged premises, the incidence of rhino-sinusitis among occupants may presage increased risk of asthma onset in the future.

An article in the same journal by a Japanese author (K.Abe Indoor Air 2012 22 3 June 173-185) is therefore all the more interesting. It presents a fungus detector encapsulating as sensitizer either xerophilic fungus spores (Eurotium herbariorum or Aspergillus penicillioides) for use in not very damp premises, or hydrophilic fungus spores (Alternaria Alternata) in the case of extreme damp. This would mean that a fungus index could be set up, which would be of use to architects and owners of water-damaged business or residential premises, and in very different climates.

25. Eosinophilic esophagitis (EoE): identification in children and adults

Theme: Food allergy
Key words: Eosinophilic esophagitis, gastroesophageal reflux disease, eosinophils, specific IgEs

An excellent review presented by a US-Swiss group (A.Straumann et al Allergy 2012 67 477-490) sums up the different phases of disease identification by the combined action of allergists and gastroenterologists.

In the 1990s, several cases of adult dysphagia with eosinophilic infiltration of the mucosa, different from gastroesophageal reflux disease (GRD), were published. Then, in allergic children were reported symptoms similar to GRD but refractory to medical treatment by the Proton Pump Inhibitors (PPI). From then on, an International Symposium define EoE as a primary clinico pathological disorder of the esophagus characterized by symptoms of the oesophageal tract with adult dysphagia for solids, and more frequently regurgitation and vomiting in children, together with mucosal inflammation on biopsy specimens containing at least 15 intra-epithelial eosinophils /high-power field (hpf) and in the absence of GRD confirmed by pH monitoring.

Symptoms are marked in adults by pain or retrosternal burning, the dysphagia being often due to the presence of a long-lasting food impaction and, in children, by irritability with abdominal pains, food refusal together with vomiting.

In most cases, the general condition is good and the diagnosis often late; as to blood eosinophilia, associated with a rise in specific IgE levels, it is generally moderate and is mostly due in children to a food allergy, whereas in adults an aeroallergen sensitization was observed.

The several occurrences of the affection within the same family led to suspect a genetic predisposition, which has not been established so far.

Finally, oesophageal biopsy by endoscopy confirms the diagnosis by revealing inflammation with eosinophil predominance, associated to IgE-carrying B and T lymphocytes and mast cells, and presence of a slight sub-epithelial fibrosis.

26. Eosinophilic esophagitis (EoE): pathology and immunopathogenesis

Theme: Food allergy
Key words: Eosinophilic esophagitis, eosinophils, remodeling, TH2 lymphocytes

Beside eosinophilia and the metabolites of its degranulation (MBP, ECP, EPO), the remodeling of the mucosa, with prior deposit of the extracellular matrix, is the hallmark of EoE and confirms its Th2-type immunologic mechanism, thus differentiating it from GRD

inflammation and defining it as an allergic entity like rhinitis or asthma. Moreover, it is remarkable to note that this esophageal infiltration is strictly limited, sparing at the same time stomach and duodenum. In order to study the mechanism of this remodeling, a Chicago multidisciplinary team (A.F.Kagalwalla et al JACI May 2012 in press) has examined, through histologic and immunologic markers, a series of esophageal biopsies in 60 children, exploring and quantifying the role of epithelial mesenchymal, transition. Out of 17 EoEs (+15 undetermined EoEs) compared to 7 GRDs and 21 normal controls, the authors observed that signs of subepithelial fibrosis (such as tissular presence of TGFβ1) were statistically correlated to tissue eosinophilia and its metabolites, a difference with GRD and control biopsies, all these elements being reversible after treatment, whether it be elimination diet or local glucocorticoids.

From an etiological point of view, considering that allergy is the initiating mechanism (over 50% of EoEs have a history of atopy: rhinitis, asthma, eczema), a classical allergic investigation is imperative (skin and immunologic tests). If, with children, some food allergy is found to be the origin, it is relatively easy to confirm it by prick and patch tests, elimination, or allergen reintroduction whenever possible and safe (peanut, soybean, egg white, cow milk).

In adults, where aeroallergen sensitization seems to be more frequent, the association with a food allergy is however not rare.

Two largely documented cases of eosinophilic esophagitis occurring 24 to 48hrs after a provocative test for milk proteins, were recently reported by Spanish authors (S.T.Cepeda et al JACI 2012 129 5 1416-1419).

27. Eosinophilic esophagitis (EoE): Treatment

Theme: Food allergy
Key words: Elimination diet, proton pump inhibitors (PPIs), glucocorticoids, esophagoscopy, skin tests

Three main options are open to the practitioner: drugs, diet, esophagoscopy (for the removal of a food bolus or a dilation in case of stenosis).

As for drugs, the particularities of PPIs must be underlined. In principle, they are useful for differentiating EoE from GRD. But, with a long term treatment, symptom improvement can be observed, without eosinophilic regression and persistence of a subepithelial fibrosis, but without complications, as in the recent work conducted in 38 EoE patients who were monitored and treated for 2-3 years (J.Levine et al Annals of Allergy, Asthma et Immunol May 2012 363-366).

Corticotherapy represents the 2nd alternative, albeit with risks of relapse when prematurely terminated : Fluticasone (inhaled then swallowed : an average 440µg twice daily for adults, over 50 weeks, depending on age and weight) or Budesonide (same dosage, including viscous form for young children) ; more recently, in case of failure of these steroids, Ciclesonide (Alvesco®) was proposed (S.Schroeder JACI 2012 129 5 1419-1421), a non-halogenated compound whose efficacy as a topical glucocorticoid is due to its conversion by

epithelial esterases into a much more active substance on the mucosal surface. As to biotherapies (mepolizumab among others), they have not so far proved efficient.

The 2nd big therapeutic option is diet: 3 diets were statistically compared (C.Henderson JACI May 2012 in press) :

1) Elemental diet, of the type used against Crohn illness, not very appetising and difficult to use with children;
2) A diet based on empirical elimination of the 6 main food allergens: milk, egg, soya, wheat, peanut and nuts, fish and sea-food;
3) A diet based on prick- and patch-tests. The remission, confirmed by biopsy, showed that all 3 diets were efficient, but the 1st one was statistically clearly superior to the 2 other ones, themselves equal in effectiveness.

Nevertheless, for the authors, skin tests are not reliable enough for establishing a valid personalised elimination diet.

28. Air quality at school and respiratory allergy

Theme: Respiratory allergy**,** allergy and environment
Key words: Indoor air quality, schools, fine particles, NO2, aldehydes, maximum breathing airflow, prick tests, rhino-conjunctivitis

A very large survey, designed for establishing a relationship between air quality at school and respiratory health of school-age children, was conducted in six French cities by a team of well-known Allergo-Pneumologists and Statisticians (I.Annesi-Maesano et al. Thorax 21/3 2012 on-line).

It concerned 6 590 children of an average 10.4 years of age, attending 401 classes in 108 primary schools of Bordeaux, Clermont-Ferrand, Creteil (Paris), Marseille, Reims and Strasbourg. It is true that these growing children spend, apart from the summertime, at least 80% of their time indoors, either at home or at school, and it was recently shown in the USA that indoor pollution could be 2 to 5 times higher than outdoor pollution.

The methodology consisted in measuring the concentration in classroom air of fine particles (? 2.5µm or PM2.5), NO2 and 3 aldehydes (formaldehyde (F), acetaldehyde, acrolein), for 5 days out of 7. In addition, 4 643 of these children underwent a medical examination with skin prick-tests for 10 major allergens, a peak flow meter to measure exercise-induced bronchospasm. A parental questionnaire was also completed. Results mainly reveal the poor air quality in French classrooms since 30% of pupils are exposed to pollutant concentrations which exceeded international standards for PM2.5 and for NO2. Clinically, rhinoconjunctivitis (RC) is the most frequently observed symptom, followed by exercise-induced bronchospasm (EIB) and asthma (A). One child in three reacts positively to aeroallergen prick-testing, 31 of them to trophallergens; After statistical adjustment and elimination of confounders, such as family history, sex, parental smoking habits, and taking into account inter- and intra-school variance, it appears that past year RC is correlated to high levels of F in classrooms.

The increased prevalence of A is linked to high levels of PM2.5, NO2, and acrolein in some classrooms, and particularly for allergic asthma as defined by positive skin prick-tests. Finally, a significant correlation was observed between EIB and high levels of PM2.5 and acrolein.

This excellent study is thus sending an important message for families, school health authorities and France public health in general.

29. Indoor air quality (IAQ) at school and student performance

Theme: Respiratory allergy**,** allergy and environment
Key words: Indoor air quality, school performance, CO2, d2-test

Another approach to the role played by classroom air quality among children is its influence on school performance, as assessed by student concentration and acquired knowledge.

This is the subject of an experimental survey conducted in Germany (D.Twardella et al Indoor Air 2012 on-line) where IAQ was assessed by CO2 concentration in 20 random-chosen classrooms of Bavarian primary schools. It must be stressed that these classrooms are, as often in Germany, mechanically ventilated.

The methodology consisted in measuring CO2 levels for 2 consecutive days of the week in each class for 3 weeks, together with temperature and humidity, and in sorting them into 3 categories depending on ventilation (without opening the windows) : usual, 'better' (? 1000 ppm) or 'worse' (2000 to 2500 ppm). To assess the students' concentration performance, and also their discrimination capability and response rapidity, the authors used the d2-test consisting in orally asking the subject to underline and highlight the letters d and p of a 14-line text within a time limit (normally 20 seconds per line). Using the number of letters picked out and the number of errors, one can calculate the student's performance. The students were half grades 3 and 4 and also half boys and girls, a level corresponding to CM1 and CM2 in France, i.e. children aged 7-9 or 9-11.

2 366 d2-tests were then recorded with 417 students. After hierarchical linear statistical regression, taking into account the variance of CO2 levels for the 20 classes and the various confounders, the authors could conclude as follows:

1) Low air quality in classrooms has no significant statistical effect on students' concentration, nor on the total number of letters processed.
2) However, the number of observed errors increased significantly (P=1.65, IC 95% 0.42-(2;87) in the 'worse' IAQ compared to the 'better'.
   On the whole, although this was a randomised study, relatively limited in number and time, and although its conclusions are a little contradictory to those of other comparable studies, German students (or their parents) will not be able to blame the school's poor IAQ for any low or bad marks obtained.

30. Vitamin D and allergo-immunology

Theme: Allergy physiopathology
Key words: Vitamin D, Severe asthma, Macrophages, Dendritic cells, T.Reg Fox p3. TGF β. IL 10 lymphocytes, Sunshine. Diet

A dozen recent publications have been dedicated to this theme, following the French *Académie de Médecine's* full report on vitamin D (*B.Salles, JF Duhamel et JC Suberbielle Juin 2012*). It appears that if 25 OHD (hydroxy derivative and vitamin stock marker) *levels were measured, half the French population would be found to be suffering from either insufficiency (between 30 and 10 ng/ml) or deficiency (under 10 ng/ml). Admittedly there are regional disparities linked to sunshine, but some subject categories are more affected (the elderly, the obese, those with kidney failure, or immigrant or black-skinned populations, and veiled women). Allergists may be confronted with variations in their patients' vitamin status.*

1.1 In asthmatics

Low levels are often associated with child asthma and its severity (*J.M.Brehm et al AJRCCM July 15 186 2 140-146*). The authors studied 560 Puerto Rican children aged 6-14 (287 asthmatics and 270 controls, where 25 OHD blood levels were measured, and they investigated atopy, asthma evolution, lung function and genotypic data (search for African ancestry). Vitamin D insufficiency is statistically associated with severe, atopic asthma, (with markedly lower FEV1, and severe exacerbation the previous year) and independently of racial ancestry.

Another publication (*A.C.Wu et al AJRCCM 2012 published online July 12*) concerns a cohort of 1024 US children, participating in an asthma research programme, and divided into 3 groups according to their vitamin status : 65% normal (>30 ng/ml), 25% insufficient (30 to 20 ng/ml) and 10% deficient (<20 ng/ml). All subjects underwent FEV1 measurement and metacholine tests, before inhaled corticosteroid treatment. The detailed statistical study shows that deficient subjects are older, more often African-American, have a higher BMI and a much poorer lung function compared to the other two groups. In the same cohort (*SM.Tse et al AJRCCM 2012 130 1 53-60*) of 780 children aged 5-12, vitamin D intake at the same time treats the vitamin deficiency, enhances the anti-inflammatory effect of inhaled corticoids and minimises its adverse effects on children's bone metabolism and growth velocity.

1.2 Vitamin D and immunology

It has been established that vitamin D modulates the way the immune system functions. As for innate immunity, it plays a stimulating role on macrophages and dendritic cells, which has above all been proven in experimentally but is becoming more and more obvious in children and adults as a preventive factor against viral or bacterial infections, be it among normal subjects or asthmatic children.

As for adaptive immunity, vitamin D may induce several types of T regulator Fox p3 TGFβ - or IL10- secretor cells. Thus, in corticosteroid-resistant adult poorly-controlled asthmatics, T.reg Fox p3+ levels are lower in the serum, in correlation with vitamin D deficiency and a low serum IL10 level, but vitamin D intake restores both the IL10 level and the efficacy of the response to corticosteroids (*Chambers et al JACI 2012 1302 542-544*).

It has also been shown that vitamin D has a protective role by preventing or postponing lung function decline in smokers (*N.E.Lange et al AJRCCM July 2012 on line*).

Even food allergy appears to be involved, depending on certain genotypes (*KS Wimaleswaran et al Allergy 2012 in press*). Thus, in carriers of IL4 gene C allele (present in 86% of Europeans, 26% of Chinese and less than 20% of Africans), vitamin D deficiency is associated with high levels of serum IgE and risks of food allergy for children.

1.3 The therapy

What results from all these data is that a vitamin status check appears necessary in a large number of our patients, with 3 possible treatments for deficiency: sunshine, diet and medication.

- Sunshine brings vitamin D without causing over dosage, thanks to auto-regulation, as shown by the Tanzanian example, the average level of the population of which being 46 ng/ml (or 115 mol/l).
- Diet: an intake of 400 to 600 UI/d (800 to 4000 for children) is advised. It can be found in oily fish (salmon, cod, halibut) but also in eggs, milk, oysters, veal liver. JM.Bourre's book (*La chrono-diététique I vol O.Jacob 2012*) provides a series of comparative tables of vitamin D content of foodstuffs.
- Medication: 1 vitamin D dose = 1 mg = 40000 U, its frequency depending on test results, but above all patients under corticosteroid treatment.

31. Is an explosion in food allergy cases to be feared?

Theme: Epidemiology, Food allergy
Key words: Food allergy, Genetics, Environment, Public health, Food industry

This is the crucial question to which the Australian authors (*S.Prescott et al Ped.Allergy.Immunol 2011 22 155-160*) give a positive answer, in a historical epidemiological paper.

Firstly, they draw our attention to the fact that during the last 50 years of the 20th century they were the first to point to the "epidemiologic wave" which swept the Western world in the form of respiratory allergies: rhinitis, asthma, sinusitis.

Much research has been undertaken to try to explain this outbreak, successively and/or jointly incriminating the Western way of life, the diet and changes in intestinal bacterial flora, vehicular urban pollution, and above all environmental aeroallergens (dusts, dust mites, pollens, etc.) sensitising genetically-prone organisms (atopy).

This wave seems to have reached its peak around the year 2000 whereas it now affects emerging and developing countries, which are increasing adopting a Western lifestyle.

The authors point then to a second wave which is looming: that of food allergy which was relatively rare in Australia, but which now affects more than 10% of children and may turn into a real 'tsunami' flooding countries which already suffered from the first wave, i.e. Australia, the USA, Europe.

Researchers must concentrate on identifying the etiological factors responsible, particularly genetic or environmental, and on discovering whether they are the same as in the first wave. However, for the governments of those countries concerned, these allergies are already the cause of a number of problems in public health and hygiene but also regarding the food industry which is required to identify the most frequent allergens such as milk, eggs or peanuts in everyday food products.

32. Egg allergy (E.A.)

Theme: Food allergy
Key words: Egg, Desensitisation

This is, in terms of frequency, the second food allergy after cow's milk. It is known to affect infants as early as one year of age, with manifestations that may be cutaneous (urticaria), digestive, even respiratory or anaphylactic. Treatment is uncertain and avoidance is difficult to enforce and control.

Thus, a group of paediatricians from Madrid have recently analysed the circumstances of accidental reactions, 50% moderate and 8% severe, observed in 92 children of an average age of 4 and a half years, between 2004 and 2005: ingestion of egg often hidden in cakes, sweets, mayonnaise. Besides, high IgE levels seem to be one of the risk factors. Finally, spontaneous regression of the allergy is observed with age: 26% at 8 years, 48% at 12, 68% at 16.

Two new publications are dedicated, each with its own protocol, to *per os* desensitisation, in a progressive manner and for several months.

The first one uses egg white powder, administered in 3 steps: the first, daily, taken in small but increasing doses, followed by a maintenance phase leading to the tolerance of 2g of powder (i.e. 1/3 of an egg) then a challenge at 10 and 22 months, confirming the desensitization and allowing the consumption of one whole egg (*A.W.Burks et al NEJM 2012 19 July 233-243*). This is a randomised survey, conducted in the USA over 5 different sites, and with 55 children aged 5-11, 40 active and 15 placebo. After 10 months of treatment, 55% of the active (*vs* none of the placebo) could be considered as desensitized. This proportion reached 75% at 22 months. A decrease, even a disappearance extinction, of positive of skin prick-tests was observed with them, reflecting the deactivation of mast cells and basophiles and the significant serous increase in IgG4s. The same subjects, examined again at 30 and 36 months, confirmed their egg tolerance.

The other publication, by Spanish authors, uses a liquid mixture of egg yolk and egg white: 1 drop at a 1:100 dilution, equivalent to 0.27 mg of egg protein, administered at home daily, the dose being doubled every 8 days, to reach in 6 months the dose of 25 ml corresponding to 3 hen's eggs weekly (*P.Meglio et al Ped.Allerg.Immunol 2012 september early view*). 20 children (half with placebo) were treated that way, 8 out of 10 successfully and without adverse reaction. A very similar technique of oral specific tolerance-induction (*Iride Dello-Iacono et al Ped All.Immun2012 September early view*) in 20 Italian children, of an average age of 8 years, using egg in the form of emulsion led to similar results and equally conclusive immunologic tests.

33. Tiotropium and poorly controlled asthma with standard treatment

Theme: Asthma
Key words: Tiotropium, non-controlled asthma

Tiotropium (T), a long action cholinergic bronchodilator mostly indicated in COLDs, has not yet acquired full recognition in the treatment of asthma (A), although some studies, of limited duration, already mentioned in these pages, have revealed an indisputable efficacy in some, more or less resistant cases of A.

The colossal survey which was recently reported to us (*H. MKerstjens et al NEJM 2012 3 Septembre*) concerns more than one thousand patients spread over 15 countries (except France) and several continents, and aims to associate T (Spiriva ®) with the standard treatment of severe A (inhaled corticosteroids and LABA of the Salmeterol type) in order to improve lung function and prevent exacerbations.

Two similar randomized studies, performed between 2008 and 2011, concern cases of A which have been known and treated for more than 5 years, in patients aged 18-75 (average 53) with FEV1 of 80% or less of the predicted value. Usual questionnaires on the quality of life and the satisfaction felt by the patient (7 or 32 questions) were handed out. All these subjects received the standard treatment plus T (two 2.5 µg/d puffs, i.e. 5 µg/d) through a soft-mist inhalator, Respimat. This treatment lasted 48 weeks interspersed with 9 visits and, after 11 months, a complete check up. The results were as follows:

In both trials a statistically significant FEV1 improvement is observed in the patients treated, of 86ml and 154ml respectively, that is to say a modest bronchodilation (less than 10%), but a sustained one which is appreciable in severe cases of asthma, and above all a decrease in exacerbations or a delay in their appearance (282 days *vs* 226) as well as a 21% reduction in the risk of a severe exacerbation.

As to the questionnaires' scores, they did not reach the significance threshold, not surprising given the geographic spread of the surveys. The secondary effects were limited to some cases of mouth dryness. There were no deaths.

On the whole, T appears to be a non-negligible complement to the treatment of severe A, all the more that the possible alternatives are limited: theophylline or the modestly efficacious anti-leucotrienes, or omalizumab (limited to certain forms of A with high IgE levels)

or else thermoplasty, an invasive method, not easy to apply to fragile subjects.

34. Asthma and Hollywood

Theme: Asthma
Key words: Asthma, Cinema, Inhaler, Stress, Will power

In a major paper (*Asthma episodes, Stigma, Children and Hollywood. Med. Anthropol. Quarterly 2012 26 1 92-115*) an anthropologist (from Chicago USA), C.D. Clark, addressed this issue by viewing 66 films up to 2008 that contained one or several asthma-related scenes, then by interviewing a dozen asthmatic boys and girls of 9-12 who had watched the most representative scenes, in order to record their reactions as well as those of non-asthmatic children of their age, generally their best friends. Since children in the USA spend an average 8 hours a day in front of a screen, 3 of those hours watching TV, it is easy to grasp the interest of such a psycho-sociological study.

The first notion that asthmatic children get from these images is that of stigmatisation; asthmatics in fact almost never inhabit the hero role, being rather relegated to secondary characters, often socially outcast. The second notion is the importance of the inhaler as a technological symbol of the disease, sometimes regarded as a way of safety but also as a social exclusion factor.

A deeper analysis of the films leads the author to distinguish 4 types of asthma-related episodes:

1) Asthmatics are weak, set-aside characters; in *Toy Story 2*, *Wheezy* the asthmatic penguin which has a broken squeaker, seems destined for an imminent yard sale, before being rescued by *Woody* the hero.
2) Asthma is a stress response (47% of cases); in *Goonies*, a teenage favourite, *Mikey*, one of the 4 boys in search of treasure, suffers an attack after an intense encounter with pirates and has to use his inhaler; many 'suspense' scenes confirm this notion.
3) Asthmatics show their will power by overcoming their crises and rejecting their inhalers (3% of cases), a sign of protest against the usual stereotype.
4) More rarely, asthma is used as an offensive medium; in *Jimmy Neutron* the young asthmatic uses his inhaler as a weapon to scare off the enemy.

Generally speaking, Hollywood does not have a glorious history of social responsibility vis-à-vis asthmatic children, who are often victims of mockery and/or marginalisation, something they are find unacceptable and call upon filmmakers to present positive connotations when filming their handicap.

35. Periostin: a systemic biomarker of eosinophilic asthma

Theme: Asthma
Key words: Steroid-resistant asthma, Eosinophilia, Periostin, IL13

Eosinophilic (E) asthma (A) is a particular phenotype of A, often severe, but sometimes responsive to inhaled corticosteroids (ICs). It is difficult to diagnose because neither blood nor sputum eosinophilia are reliable enough, and the invasive procedures of pulmonary aspiration or lavage are not easy to perform under normal conditions. Thus, clinicians are looking for a non-invasive, if possible blood-based test. Dosing serum Periostin seems to be the answer (*G.Jia et al JACI 2012 August on line*).

It should be recalled that EA results from Th2 type airway inflammation, induced by IL4, IL5 and IL13 cytokines. While the role of IL4 is well known in atopic asthma, that of IL5 and IL13 are not and anti-IL5 medications have not established their efficacy. But higher levels of IL13 have been observed in the airways of an EA sub-type and the authors have shown that 3 genes are clearly expressed in the lung epithelium and induced by IL13: Periostin, the secondary protein of CLCA1 chlorinated canals, and Serpine B2. In doing so, they define a type of asthmatic population characterised by eosinophilia, lung remodelage, and sensitivity to ICs, but with no connection to atopy.

Periostin (P) is a matri-cellular protein, secreted and detected in the sub-epithelial layer of the bronchial mucosa and correlated to the thickening of the basement membrane; it is also overexpressed in nasal polyps and in allergic oesophagitis. It can be measured in serum.

The authors then followed 67 IC refractory (+1000 µg/j) adult asthmatics with FEV1≤60% of the predicted value, for 5 weeks. At the same time, they measured eosinophilia of blood sputum and broncho-alveolar lavage, as well as blood markers (P. IgE, YKL-40, a Th2 marker) and FE NO. It appears that P. is the best indicator of airway eosinophilia, and its high level (over 25 ng/m) is statistically correlated to the severity of eosinophilia and resistance to ICs.

Admittedly, in moderate As, ICs do bring down the expression of the whole set of Th2 markers, but they prove insufficient in severe A. On the contrary, the monoclonal antibody Lebrikizumab, specifically anti IL13, as tested with 218 EA, has shown efficacy, particularly in high serum P. level Asthma: QED.

What is happening is a differentiation of EA with an IL13 induced sub-type. This is a typical example, and an important step in the ever more accurate profiling of A treatment.

36. Latex immunotherapy

Theme: Specific immunotherapy, Allergens
Key words: Immunotherapy, Sublingual immunotherapy, Latex

A general overview of this theme has just been conducted, based on all the publications in English of the past 12 years (*E.Nettis et al Annals of Allergy, Asthma, Immunol 2012 160-165*).

It should be remembered that this allergy does not only concern healthcare workers using latex articles (gloves, catheters, among others) but also hairdressers, gardeners, patients undergoing multiple surgery (spina bifida or other congenital malformations), as well as users of everyday products such as teats for baby bottles and sports equipment.

The principal allergen is derived from *Hevea Brasilensis*: *Hev bl*, followed by 13 other minor allergens, the clinical manifestations concerning mainly the skin (urticaria or contact dermatitis), more rarely the airways or the eyes, and total avoidance is difficult.

The immunotherapy trials, strictly selected according to a number of validity criteria (double blind trials with placebo controls), included 3 subcutaneous (SCI) and 8 sublingual (SLI), of which 1 by the authors themselves.

The first serious study was that by Leynadier and colleagues (in 2000) among 17 doctors and nurses, treated with Stallergen ® extracts, progressively reaching a maximum tolerated dose of 1 to 2 µg kept constant for 1 year. The comparison of the beneficial effect among the Placebo group is clearly in favour of the treated group, but there are more local and general side-effects.

Two other studies, one Spanish (Sastre) and one Italian (Tabar), both carried out in 2006, end up with similar conclusions, but the risks incurred have led the allergists to virtually abandon this type of administration.

The sublingual route (SLI) is also justified by the fact that the oral mucosa, highly vascularised, contains a large number of antigen-bearing cells and few inflammatory ones, which establishes its innocuousness.

Finally, the whole set of trials only concerns 200 patients treated with Stallergen extracts or ALK Abello, among them twenty children aged 4 to 15. With the latter, the use of 2 drops/day of a 40 µg solution for one year, has been remarkably successful, with no side-effects over the next 3 years. This dosage is insufficient for adults, for whom the beneficial effect appears with a maintenance dose of 300 to 500 µg/week, producing some benign local or general reactions. Very long-term effects remain to be investigated, but SLI is still a possible alternative, albeit to be used with caution, and pending new approaches to immunotherapy (recombinant allergens).

37. Sublingual immunotherapy (SLI) and cow's milk allergy

Theme: Immunotherapy, Food allergy
Key words: Sublingual immunotherapy, Cow's milk, Specific IgE, Prick tests

Cows' milk allergy (CMA) is the most frequent food allergy in children, and strict avoidance is for the time being the only method advised, before spontaneous regression in 70% of cases at the age of 3. SLI is currently under investigation.

Between 2006 and 2011 the Barcelona team of paediatricians (*M.Vazquez- Ortiz et al: Clin.Exp.Allergy 2012 September on line Accepted articles*) therefore undertookon a study of 81 children aged 5 to 18, all suffering from clinically-confirmed CMA (Sampson severity score), skin prick-tests, specific IgEs and prick tests. The Committee of Ethics-approved technique included an induction period of 16-week in hospital, with hourly administration of 1, 2, 4, 8, 16 ml of milk (diluted 1:100 on the first day, then 1:10 + 2.5 ml non-diluted on day 2) and every day for one week, then with progressively increasing doses, in consultation every week, reaching the tolerated dose of 200 ml cow's milk. All these subjects were followed up over an average 2 years.

• 60 of then (75%) were considered as desensitised (1 case in 5 still presenting some minor temporary reactions)

• 20 others had more or less severe and unpredictable reactions which persisted in spite of the treatment and have driven 6 of them to stop the immunotherapy.

The authors mainly focused on these latter cases in order to try, through probability statistics (Kaplan-Meier), to define their profile in order to detect the factors responsible. Over and above a number of co-factors (exercise, emotion, NSAI intake, infection), it appears that 3 main bio-clinical, independent factors emerge from the multiple regression statistical models, i.e.:

1) The persistence of IgE ≥50 UI,
2) The size of prick-tests ≥9 mm, and
3) The baseline clinical severity, broken down into 5 grades.
   The combination of 2 or 3 of these factors induce a risk of reactions, of 2.26 (95% CI, 1.14-4.46 p=0.019) and 6.06 (95% CI, 2.7-13.7 p=0.001) respectively.

The authors can conclude that SLI, still an experimental method, is efficient and harmless in 75% of the subjects. Nevertheless, before undertaking it is necessary careful analysis of the predictive factors of hazardous side effects, in order to detect from the start the subjects for whom SLI is contra-indicated. The absence of a control group in this study must not obliterate the sound personal clinical experience of these paediatricians and the large number of statistics presented in their research.

Finally it seems worth noting the possible interest of measuring MIP-1α and MCP-1 chemokines as efficacy markers of the desensitisation to cows' milk (*P.Poza.R.Glez NEJM 2012 367 282-284*).

38. Antioxidant (AO) diet and allergy

Theme: Physiotherapy, Atopy
Key words: Diet, Antioxidants, Allergy, Magnesium

Since the hygiene hypothesis, the role played by the Western way of life, and particularly its diet, has often been pinpointed.

It is well known that immunological surveillance of the organism resorts to a defence system using oxygenated radicals which destroy foreign cells. Adopting an antioxidant diet to strengthen the natural AO system seems all the more logical since the latter is based on the type Th1 immune response, itself being likely to foster a chronic inflammatory process through NF-κB et du TNFα.

Major AOs are found in fruits and vegetables (which contain β-carotene, α-tocopherol and vitamin C) as well as in meat and milk (where magnesium and zinc predominate).

The Swedish authors (*H.Rosenlud et al Clin.Exp.Allergy 2012 42 1491-1500*) wanted to study the relationship between AO intake and allergy by using the data from a cohort of 4489 children followed since birth.

2242 of these, boys and girls of an average age of 8, were enrolled in this study, which included a personal and parental questionnaire (2614 families answered) as well as a dosage of common allergen IgEs. The questionnaires were very detailed and precise as regards food intake frequency (taking into account the basic data of the National Food Agency and also the qualification of allergic diseases) and contained 98 items. Their validity was confirmed by Spearman correlation consisting in comparing answers after several (up to 14) repeated questions.

Gross results show a statistically significant, inverse association between intake of β-carotene and **rhinitis** and between asthma and magnesium, and also between magnesium and atopy. Continuing their survey, they excluded 285 children who had mentioned previous signs of allergies (including cross-allergies, such as apple and birch pollen), and results become less significant with only the inverse association between asthma and magnesium remaining. Despite the large number of participants, which lends indisputable weight to this study, it has been the target of some criticism, mentioned in the editorial of the same journal (*D.Fuchs 1491-1500*) and above all the unexpected lesser role played by AO intake in the epidemiology of **allergic diseases**. Besides, the food industry by adding - without informing the consumers - vitamins such as vitamin C, preservatives such as sulphites, and colouring agents, all of which are AOs, is likely to provoke an inverse consequence: “antioxidant stress”. Which means that, in terms of diet, common sense must be the rule.

39. A new approach to Immunotherapy: the intradermal injection?

Theme: Treatment, Immunotherapy
Key words: Immunotherapy, Intradermal injection, Cutaneous late response, Grass pollen

While traditional specific immunotherapy (IT) uses allergens administered subcutaneously or sublingually, at high and progressively increasing doses, a group of English

researchers at Brompton Hospital (*G.Rotiroti et al..JACI 2012 October 130 4 918-924*) tried to understand what would happen with low-dose allergens administered less frequently, and by intradermal injection, the dermis being an immunologically active zone, rich in dendritic cells and lymphatics. They were surprised to discover that this mode of IT suppressed cutaneous late response.

To confirm this discovery, they selected 30 adults sensitized to grass pollen (*Phl p 5*) but not to birch pollen (*Betula*), and divided them into 3 categories:

A. receiving 6 repeat intradermal injections at 2-week intervals of low-dose pollen extracts (10 BU corresponding to 7 ng),
B. receiving the same dose twice with an interval of 10 weeks, and
C. a control group with a single injection at the end of the test.

The size of the papules occurring after prick-tests on the forearm or the back, at each visit, was measured very accurately (blind), at the same time as grass-specific total IgE (all isotypes) were measured.

Whereas a similar injection of birch pollen carried out for comparison had no effect, the authors observed with group A at the 10th week a 90% suppression of cutaneous late response (after 24h) to grass pollen with a significant increase in specific IgG, unlike groups B and C where a comparable impact on early response was observed, whereas impact was negative on late response.

So, repeated and spaced out intradermal injections of low-dose grass allergens, 1000 times lower than the usual total dose classically injected, induces a suppression of cutaneous late response.

Can this phenomenon of tolerance be transposed in clinical settings? The authors refer to Rinkel's unsuccessful clinical trials using intradermal injection, albeit with a different methodology. Trials are underway.

40. Unexplained chronic cough and old remedies

Theme: Asthma
Key words: Unexplained chronic cough, Vanilloid receptors, Vagal afferents, Camphor, Menthol

Physicians (particularly allergists) are more and more often confronted with symptoms of Unexplained Chronic Cough (UCC) which occur in adults and do not result from allergic etiology, nor from gastro-oesophageal reflux, nor from upper airway infection (with post-nasal drip), nor from use of angiotensin converting enzyme inhibitor type medications. The common feature is an upper airway heightened reflex sensitivity favoured by air pollution or smoking (active or passive).

At a time when some retired colleagues, fishing for notoriety, are casting suspicion on a large number of drugs, it is worth reminding of the therapeutic value of old remedies whose modes of action are better known.

Indeed, this cough reflex could be caused by the hyper-expression of receptors named vanilloid (*Transient receptor potential vanilloid* or TPRV1) located on the vagal afferents which

are inhibited by camphor. K.W.Patberg et al (*AJRCCM 2011 184 382*) recall an old US children's song: *John Brown's baby had a cough upon his chest and they rubbed it with camphorated oil*.

But another type of receptors may be involved (*P.Geppetti et al AJRCCM 2012 185 342*): TRP A1 (ankyrin) inhibited by menthol, an agonist to the cold receptor (TRPM8), responsible from the fresh sensation associated with mint. This receptor is thought to sense a series of endogenous or exogenous irritant molecules.

So, these recent pharmacological advances about the blocking properties of these old remedies seem to open the way for future challenges in drug discovery for the treatment of this heightened cough sensitivity of individuals with UCC.

A more radical approach, but not without many side effects, is presented by an Australian team (*N.M.Ryan et al Lancet 2012 Nov. 380 9853 1583-1589*) who, in a randomised trial, did successfully treat 32 patients with UCCs which persisted beyond 2 months (30 placebo) with Gabapentin ®, an anti-epileptic medication, also successful in peripheral neuropathic pain. This effect would suggest, for the authors, a central reflex sensitisation.

On a practical level, the recent development of automated cough monitors had enable to objectively assess the cough frequency and therefore its severity, as their 4-hour recordings could be a practical tool to validate response to trials of therapy in clinical settings (*KK Lee1 et al Chest 2012 on line*).

Finally, it should be remembered that coughing is a defence reflex, to be respected as much as possible, and the UCC should essentially remain an elimination diagnosis.

41. Effect of Inhaled Glucocorticoids (ICs) in childhood on adult height

Theme: Asthma, Treatment
Key words: Inhaled glucocorticoids, Height, Reduction in growth velocity

We know that the glucocorticoids inhaled by asthmatic children cause a reduction in their growth velocity. The US authors (*H.W.Kellyet al NEJM September 2012 904-912*) in charge of the well-known Childhood Asthma Management Program wanted to know whether in the long run IC treatment had an influence on the children's attained adult height.

To that end, they studied the development of 942 children (of 1041 participants) aged 5 to 13, who could be re-examined at an average age of 25. These subjects had been randomised between 1993 and 1995 to receive:

- Group 1 (311 cases): 400 µg/day of budesonide (Pulmicort ® with Turbuhaler) in 2 doses for at least 2 years; 281 of them were re-examined.
- Group 2 (312 cases): 16 mg/day of nedocromil (Tilade ®), an anti-allergic medication, not in use any longer, in 2 doses; 285 subjects were re-examined.
- Group 3 (418 cases): the placebo group, 377 were seen again.

The accurate statistical studies (multiple linear regression with adjustment for demographic characteristics, children's age and height at trial entry) produced the following results:

- In Group 1 (ICs), adult height was significantly lower (1.02 cm) than in the placebo group.
- In Group 2, it was 0.2 cm lower.

Depending on the IC dose received by the child, it appears that the higher the dose, the greater the impact on adult height. However, treatment duration had no long-term influence, beyond 2 years of treatment. The authors therefore concluded that this decrease in height was neither progressive nor cumulative. Finally, it was primarily when these ICs were administered to pre-pubertal children that the impact on growth was the most marked.

On the whole, in answer to the question of whether ICs are the cause of a simple delay or a complete stop in growth, the authors choose the latter, pointing out that the efficacy of treatment must always be compared with the risks of side effects, which are relatively moderate in these cases.

42. Fish and shellfish allergy in children

Theme: Food allergy
Key words: Fish, Shellfish, Gad c 1, Parvalbumin, Tropomyosin, Toxins, Anisiakis, Sulfites

Frequent in countries with a high consumption of fish and shellfish, the adverse reactions to their ingestion do not all result from allergy. True allergies are relatively rare in children, but they can trigger anaphylactic reactions and, when they settle, they are long-lasting, unlike milk or egg allergies which generally decrease with age.

A group of Greek researchers (*S.Tsabouri et al Ped.Allergy Immunol 2012 23 608-615*), having in a very well documented review compiled 32 studies between 1985 and 2011, distinguish 2 main types of allergy:

1. Allergy to fish: tuna, cod, salmon, and hake, whose major allergen is *Gad c 1*. The common chemical content consists of 12kDa of parvalbumin (P), a calcium-linked sarcoplasmic protein;
2. Allergy to shellfish (molluscs and crustaceans): shrimps, lobster, scampi, mussels, whose chemical composition is based on tropomyosin (T).

There is no standard cross reactivity between P and T. However, shellfish T has a homology with that of invertebrates such as arachnids and cockroaches, so that positive skin reactions to shellfish can be found in religiously abstinent subjects like orthodox Jews (*Fernandes et al Clin. Exp. Allergy 2003 33 956-61*) who are also allergic to dust mite.

In diagnosis, it is first necessary to eliminate non-allergic adverse reactions due to:
- either toxins: the most frequent are due to anisiakis, a fish parasite nematode common in Spain (killed by 20-minute cooking at 60°)
- or sulfites, used for canning the fish, often the cause of severe clinical manifestations.

The simplest positive diagnostic is the skin prick-test using commercial extracts, but which are not very specific, so that it is preferable to use raw extracts of each variety of fish or shellfish. For shrimps, for example, it has been observed that cooked extracts were more allergenic than raw ones.

As to specific IgE, these are reliable in the case of allergy to fish like cod or hake but less so for shellfish.

Proof is provided by means of a Double-Blind Placebo Control Food Challenge (DBPCFC), but it must not be performed on children under 3 and is useless when symptoms are obvious. It can be used, in Open Food Challenge (OPC) without placebo, for elimination diagnosis. The only proved therapy is a strict avoidance, but it is important, in children not to introduce an unjustified restriction diet.

Vaccination with hypoallergenic fish proteins may constitute a promising therapy in the future.

43. The metabolomics of asthma

Theme: Asthma, Physiopathology
Key words: Asthma, Metabolism, Inflammation, Mass spectrometry, Bromo-tyrosin, Electronic nose, Volatile Organic Compounds (VOC), Nuclear Magnetic Resonance.

A few months ago, we mentioned the studies carried out by paediatrician and biochemical teams at Canadian universities (Edmonton, Alberta and Saskatoon) on this theme, i.e. the study of small molecules generated by metabolic activity, due, in asthma, to upper airway inflammation. The idea of studying the metabolic profile of a disease, *a priori* different from that of a normal subject, is not new: glucose surveillance in diabetics is one of the most common examples. Besides, diagnosing asthma is sometimes difficult in children when one is always looking for non-invasive procedures. True, the study of urinary leucotrienes or blood ECP are possible but they are not commonly practiced.

In an general review dedicated to the different modern techniques for detecting the main markers, three are explained in detail (D.J.Adamko et al Chest 2012 141 5 1295_1302):
- Mass spectrometry (MS), applicable on airway and urine biofluids: compounds are of the order of a pico mole. These are delicate and tedious techniques, the results of which are so far not specific enough, except the urine analysis where over 1000 metabolites have been identified and where it appears that the level of Bromo-tyrosin, a marker of eosinophilic peroxydase activity, is statistically high in the case of risk of asthma exacerbation.

- The Electronic nose was developed to measure the different fractions of VOC (Volatile Organic Compounds) in expired air. For some, it may differentiate asthma from COPD, but results are still to be validated.

- Nuclear Magnetic Resonance (NMR), which identifies atomic nuclei inside a biofluid. Its advantage is a more rapid diagnosis than with MS but it is less sensitive and the measured compounds are of the order of a micro mole.

The Canadian authors' studies have enabled the differentiation in children between stable and severe asthma requiring emergency admission to hospital, with an accuracy rate over 90% (*Saude et al JACI 2011 127 3 757-764*). Admittedly, few hospitals have the

sophisticated equipment necessary for regular use of such methods. But this research pathway is promising.

To prove this point, a very recent experimental study (*W.E.HO et al AJRCMB2012 on line*) has shown through MS that an allergic lung was the centre of intense metabolic activity, concerning carbohydrates (increase in mannose, galactose, arabinose) non-affected by corticosteroids, lipids (decrease in phosphatidylcholine, sterols) and amino acids. It remains to develop the metabolomic profile of different phenotypes of Asthma in children and adults.

44. Allergies and mental disorders (anxiety and mood disorders)

Theme: Psycho allergology
Key words: Allergy, Mental disorders, Anxiety, Mood disorders, Desensitization

An US-German group of Psychologists and Psychiatrists (*R.D. Goodwin et al. Clin.Exp.Allergy December 2012 42 12 1765-1771*) has investigated this association, using the data from interviews and examinations of a German cohort of 4181 adults aged 18 to 65. As concerns the definition of mental disorders they referred to the Munich CIDI (*Composite International Diagnostic Interview*). In order to cover the whole range of symptoms and criteria, this CIDI was complemented by the DSM-IV world classification (*Diagnostic and Statistical Manual Revision N°4*) which includes mood disorders (major unipolar depression), anxiety (panic with or without agoraphobia), social and specific phobia, and generalised anxiety. All the symptoms observed in the 12 previous months were taken into account. For allergy (A), the physician-led interview covered clinical signs (hay fever, eczema, food allergy), possible laboratory tests and the desensitization treatment, completed or not.

The statistical analyses of multiple logistic regression between allergy and each mental symptom, after adjusting for age, gender, socio-economic status, then according to treatment, revealed in allergic patients a significantly higher prevalence of each mental symptom: anxiety, panic attacks, mood disorders, depression. However, the adjustment for desensitization treatment (D) made these relationships no longer significant, as if D had had a positive effect on mental disorders. Indeed, those treated for allergy had statistically less anxiety and mood disorders than those non-treated, and amongst the former those who had completed the treatment were suffering less from mental disorders than those whose treatment was incomplete.

While admitting the lacunae of this survey (absence of A objective tests or other anti-allergic treatments than D), the authors provide us the first evidence of a link between A and anxiety and mood disorders and emphasize the impact of desensitization on these typical DSM-IV disorders.

Similarly, as concerns the asthma-anxiety relationship in teenagers, Y.Lu from Singapore (*Y.Lu et al. Ped.Allergy Immunol 2012 23 707-715*), after a randomised meta-analysis of 8 published studies, found a significantly higher risk of depression and anxiety in

3546 asthmatic teenagers as compared to 24884 controls, and suggested the need of early psychological intervention.

45. Chronic urticaria (CU) and psycho-sociological factors

Theme: Psycho-allergology
Key words: Chronic urticaria, Psycho-social factors

A team of Canadian researchers (*Benshoshan et al Allergy 12 Nov 2012 online*) undertook a considerable meta-analysis of English, Spanish and French publications--covering a period from 1st January 1935 to 1st January 2012, i.e. 77 years, and aiming to assess the contribution of psycho-social factors (PSFs) to the development and/or exacerbation of CU.

Two investigators independently reviewed all the titles and abstracts which appeared relevant, following the so-called Newcastle-Ottawa scale and, after discussion and arbitration of a third reviewer, they were able to identify 114 original studies and 17 general reviews, 67 studies with no relation to CU serving as controls. In addition, they interviewed all Canadian allergists.

There are evident lacunae in CU pathogenesis. Allergic origin is sometimes inferred from positive prick-tests and IgE in a number of cases but, generally, elimination of suspected allergen(s) does not improve the patient. Moreover, 80% of the Canadian allergists believe that these psycho-social factors are decisive and consider like the majority of publications, that the inflammatory event is more important than the allergic element. Auto-immunity is also mentioned, from the observation of auto-antibodies against IgE and Fcα RIα but without correlation to clinical symptoms.

Finally, an interaction between the neuro-endocrine and the immune systems, are evoked that could be triggered by stress and all psycho-social factors (anxiety, quality of life, alexithymie, depression). Pooling effect sizes using random effects, analyses revealed that despite large heterogeneity, PSFs had significant overall prevalence of 46, 9 % i.e. nearly half the cases.

On the therapeutic point of view, psychotherapy, relaxation with or without hypnosis, and behavioural interventions did cause some improvement and a reduction in drug therapy to treat CU or depression. But the problem remains: are PSFs a cause or a consequence of CU? As the authors say, it's just like the old 'chicken and egg' paradigm.

46. Ocular allergy (OA): recent data

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Theme: Ocular allergy
Key words: Conjunctivitis, Seasonal conjunctivitis, Kerato-conjunctivitis, Springtime kerato-conjunctivitis, Blepharo-conjunctivitis, Giant papillary conjunctivitis

A group of French-Italian-Polish-Portuguese experts (*A.Leonardi et al Allergy 2012 67 1327-1337*) has just finalised a review on ocular surface hypersensitivity reactions concerning conjunctiva and cornea, requiring a close collaboration between ophthalmologists and allergists. To simplify the classification of these often-complex lesions, it should be remembered that conjunctivitis may be isolated or very often associated with rhinitis: this is the hay-fever seasonal conjunctivitis, frequent, atopic, and well known. When associated with a corneal involvement, it is known as kerato-conjunctivitis (KC). This severe form usually evolves in spring and summer (spring KC, sometimes called Vernal keratoconjunctivitis, VKC). It is associated in approximately half the cases with a sensitivity, to perennial allergens, mostly domestic, sometimes seasonal. It normally disappears with puberty. However, some forms interfere with atopic keratoconjunctivitis (AKC), the other severe form which strikes teenagers or young adults and is always accompanied by eczema. Blepharo conjunctivitis (BC) presents a different clinical aspect. It can be complicated by staphylococci infection, herpes, even cataract or vision disorders if it becomes chronic. Generally, it diminishes with age. Non-atopic OA is most often represented by the giant papillary conjunctivitis (GPC), which follows an ocular surface irritation due to contact lenses or ocular prosthesis or after surgical sutures.

Ocular examination of the eyelid and above all the tarsal or limbic conjunctiva reveals either oedema, hyperaemia, follicles or papules, even erosions or fibrosis. This manage both diagnosis and aetiology. Allergy will be confirmed by the usual blood and skin tests or, in doubtful cases, by cytobiological examination of tears (eosinophils, IgE, ECP), or even, more rarely, by a conjunctival provocation test. In non IgE-dependant (BC) forms, patch tests for suspected cosmetics can be useful.

In addition to avoidance of possible allergens and immunotherapy, treatment includes protective sunglasses, cold compresses or instillation of artificial tears to reduce pruritus. Antihistamines (AHs) and over-the-counter local vasoconstrictors (naphtazoline type), Mastocyte stabilisators (nedocromil or pemirolast non-authorised in Europe) are sometimes useful. Association of local anti-H1 and anti-degranulation effects such olopatadine brings about some improvement for the most common forms. Drugs without preservatives are in development (levocabastine: or ketotifen): Oral antiH1 (usually 2nd generation) are sometimes associated. In seasonal or perennial conjunctivitis, local corticosteroids (fluorometholone or prednisone acetate) should be avoided whenever possible. Their use, reserved to ophthalmologists, and restricted to corneal involvement, must be short and moderate.

Finally, it should be recalled that, in general, the allergist is only consulted in second line (except in case of associated rhinitis).

47. Hand eczema (HE)

Theme: Dermato-allergy
Key words: Eczema, Irritating contact dermatitis, Allergic contact dermatitis, Atopic dermatitis

Based on a clinical case of recurring HE on the palm and dorsal sides of her hands in a young atopic nurse, a mother of 2, the author, a Dutch dermatologist, presents a complete review of this both varied and complex entity (*P.J.Conrads NEJM 8 Nov 2012 367 19 1829-1837*).

The thorough patient history is essential for the diagnosis, but it appears that HE is often multifactorial.

The etiological classification, which comes in a detailed table, includes:

- Irritating contact dermatitis (ICD), due to repeated contact with detergents, soaps, at home or at work, or after wearing occlusive gloves;

- Allergic Contact Dermatitis, is a delayed-type reaction to a chemical substance: nickel: jewels or instruments, coins, (English dermatologists have recently protested to Royal Mint which has introduced nickel coins to cut costs) but also chromates (leather or cement), preservatives (creams or cosmetics), rubber, glues; Standard patch tests are recommended and prove 25-50% positive;

- Protein CD, in early reaction to a protein substance (health professions: latex, or food professions: fish), often preceded by urticaria, the only case when prick tests and IgE can be useful;

- Atopic dermatitis, due to persisting or recurring childhood eczema, and often associated with the other forms (hybrid HE).

HE may be confused with other skin conditions such psoriasis (but without pruritus or vesicles) or mycosis, which is most often unilateral.

As to the morphological classification, HE is typically vesicular and recurrent, primarily affecting of palm and lateral sides fingers, hyper-keratosic in elderly subjects, or nummular or dry and fissured on fingertips (pulpitis) but with no obvious relation to aetiology. Prompt intervention is required to avoid chronicity.

Eviction of irritants and allergens, and application of emollients (ointments are preferred over creams) are the first indications. Wearing gloves is controversial (cotton-lined if indispensable).

Local corticosteroids are first-line pharmacologic treatments although their efficacy has not been statistically established (mometasone furoate 2 to 3 times a week is recommended). Tacrolimus and Pimecrolimus do not seem very efficacious. As second line, phototherapy either with psoralen and UVA, or preferably with UVB, can give good results.

Retinoids which are useful in severe forms, hyperkeratosic, either *per os* (in capsules) or locally, are preferable to immunosuppressive (cyclosporine type) which confer a risk of adverse events (skin dryness, increase in serum lipids, teratogenesis).

48. Gluten: Intolerance, Sensitivity or Food Allergy

Theme: Food allergy
Key words: Gluten, Celiac disease, Irritable bowel, False food allergy

Gluten (G), the major constituent of cereal flour (wheat, barley, rye) is composed of proteins (gliadin and glutenin) which may cause a range of adverse reactions. An Italian physician (*L.Elli BMJ 2 November 2012 online*) and more recently several British gastroenterologists (*BMJ 6 December 2012*) have noticed a huge increase in the use of the term of Gluten Sensitivity (S) which is alleged to cause non specific gastro-intestinal symptoms.

In fact, all these authors consider that the only true Intolerance to gluten, and hence justifying a gluten-free diet, is the auto-immune Coeliac disease, characterised by: histological villous atrophy of the duodenal mucosa with crypt hyperplasia, biologically, by the presence of anti-transglutaminase type 2 IgA, and genetically, by the HLA-DQ2-DQ8 haplotype.

The term, 'S' must be restricted to a set of digestive symptoms (abdominal pains, bloating, meteorism) often spoken of as irritable bowel syndrome. There is no anatomic or biological substratum nor objective findings to support a diagnosis of gluten susceptibility. True, this syndrome could be caused by a stimulation of the immune system (increase in IL 17) and could, in some cases, benefit from a gluten-free diet. But this type of diet, sometimes misguidedly prescribed, constitutes a profitable market for the food industry, is not risk free and often reduces the quality of life. 'False food allergies' (due to additives and preservatives such as metabisulfites or glutamates) are similar but should be differentiated from real food allergy.

Gluten Food allergy, well-described and diagnosed by A.Moneret-Vautrin's Nancy team (*S. Denery-Papini et al. Allergy 2012 67 1023-1032*) can be caused by either wheat proteins, or gluten proteins modified by removal of the amide group (deamidated G, DG) that can be found, in food industry (cereal flours, pork sausages, soups, industrial biscuits) but also, because of their solubility, in cosmetics (creams, shampoos) responsible for contact urticaria. All the Symptoms of this Food Allergy range from urticaria to anaphylactic shock and include exercise-induced anaphylaxis.

It should be noted that some patients, while tolerant to wheat flour, may present allergic reactions to DG whose allergenicity is due to different epitopes (omega 2, gliadine) having a strong affinity to IgE. Hence, we should take this particular entity into account for the diagnosis and before proceeding with any food eviction.

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