Four papers delivered at the 2006 annual IAACI Meeting were selected for publication. They follow the overview of the Meeting, presented below by Z.T. Handzel

The 2006 Annual Meeting of the Israel Association of Allergy and Clinical Immunology (IAACI)

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The annual meeting of the IAACI took place on 26-28 November 2006 in Safed in northern Israel. Invited lectures by numerous eminent scientists from abroad and from Israel contributed to an especially high professional level. Many subjects within the field of allergy and clinical immunology were discussed.

- Asthma and clinical aspects of allergic conditions were debated at large. William Silver from Denver, USA, spoke on behalf of the Allergists for Israel and described various exercise-induced allergies, such as: anaphylaxis, which may be food-specific or not, may be associated with urticaria and cold or cholinergic stimuli; non-immunoglobulin E-induced mast cell activation may result in generalized urticaria, which is aggravated by exposure to cold; rhinitis, which again may be conditioned by changes in temperature; sinusitis which may be caused by barotrauma during swimming or diving, and the well-described association with asthma which should be differentiated from vocal cord dysfunction. Zev Sthoeger reported the results of the 33 patients enrolled in the Israeli arm of the INNOVATE study, which assessed in a double-blind protocol the efficacy of an anti-IgE monoclonal antibody (omalizumab, Xolair®) in 419 patients in 14 countries with severe allergic asthma (GINA 4). This was part of a larger worldwide cohort of 6363 patients suffering also from food allergy and allergic rhinitis. The clinical score, spirometry values, and the numbers of asthma exacerbations and hospitalizations were significantly reduced in the Xolair® arm. Thus, this novel, albeit expensive, treatment modality gives new hope to severe asthma patients who are non-responsive to conventional therapies.

  Ruth Soferman and colleagues demonstrated the value of measuring serum C-reactive protein levels in pediatric asthma exacerbations to assess airway inflammation, correlating reciprocally with the forced expiratory volume in the first second. Interestingly, the CRP levels correlated positively with body mass index, adding evidence to the detrimental effect of obesity on asthma. Yael Graif found an intriguing association between psychological conditions, such as hypochondriasis and somatic awareness, and the severity of allergic rhinitis symptoms, the latter not correlating with the magnitude of the skin prick test response to aeroallergens. Nili Mazur and team documented the severity, clinical course and management of 46 patients with anaphylactic reactions among 173,864 admissions to the emergency department of the Sheba Medical Center. Only 13% of the anaphylactic reaction cases were diagnosed correctly on site and an additional 24% after discharge. Epinephrine auto-injectors were rarely dispensed. These findings underscore the need for educating emergency department personnel about the diagnosis and management of this life-threatening condition. Yael Levy and associates showed that, contrary to common belief, supplementing soy-based formulas in nursing infants does not elicit soy hypersensitivity. These results are in accordance with other reports of low soy allergy prevalence in children.

- Some lectures were devoted to the elucidation of mechanisms of the immune response and of allergic reactions. Dr. Chiorazzi from New York dwelt on the characteristics of the B cell in chronic lymphatic leukemia, which belongs to the CD5+ subgroup and produces mainly the IgM immunoglobulin isotype. It retains the polyreactivity to multiple microbes and autoantigens due to a failure of the apoptotic mechanism, which normally eliminates such clones during terminal maturation. This results in chronic overstimulation, leading to an increased incidence of mutations during the V_HDJ_H rearrangement. Interestingly, the mutated cells lose some of their poly- and autoreactivity, therefore a high incidence of mutated cells leads to a better prognosis.

  Alon Y. Hershko and co-workers characterized three motifs in a novel regulatory element in the 3′ region of the human interleukin 10 promoter, specifically recognized by a protein

Ig = immunoglobulin
CRP = C-reactive protein

factor, resulting in a reduction in the promoter activity. The 3' segment is preserved in several mammalian species and a CTTGC motif is found also in promoters of other cytokines, such as IL-2 and IL-15. Mona Kidon, Kobi Sade and teams evaluated the prevalence of sensitization to various dust mite species in adults and children in Israel, in two separate studies. Surprisingly, many were found to respond to other species, besides the "classic" D*ermatophagoides pteronissimus* and D. *farinae*, especially to B*lomia tropicalis*. The positive responses correlated with an allergic phenotype and were epitope-specific. Thus, recognition of some specific mite epitopes may hallmark the development of clinic allergy. Michael R. Goldberg and group demonstrated that it is possible to switch the predominant neonatal Th-2 response to Th-1, by stimulating cord blood mononuclear cells with bacterial lipopolysaccharide and/or with immobilized anti-human CD3 monoclonal antibody. These stimuli synergized in activating the T cell receptor of the cord blood mononuclear cells, while failing to do so in the maternal cells. These findings may demonstrate a critical link between the innate and adaptive immune systems and may add support to the molecular mechanism of the "hygiene hypothesis," which claims that the infantile immune system is primed towards a Th-1 response by exposure to environmental microbes.

- Eosinophil-driven disorders were discussed by Marc Rothenberg and Miguel L. Stein from Cincinnati, USA. Eosinophilic esophagitis and gastritis are characterized by a massive submucosal eosinophilic infiltration, mediated by eotaxin 3 and CCR3 and causing chronic inflammation. Eosinophilic esophagitis presents as dysphagia, epigastric pain and food impaction. It is often associated with atopy and causes 30% of pediatric reflux. Treatment includes an elemental diet, and the administration of steroids and imatinib (Glivec®)). Potential new therapies are monoclonal anti-IL-5, anti-IL-13 and anti-CCR3 antibodies. Recently, a beneficial effect of mepolizumab, a monoclonal antibody preparation against the eosinophilopoietic cytokine IL-5, was demonstrated by M. Stein et al. on the clinical outcome. It caused a reduction in blood eosinophilia and CCR3+ cells in patients with eosinophilic esophagitis, without affecting plasma IL-5 or eotaxin-3 levels. This novel approach may signify a much needed improvement in the treatment of this disease.

  The latest developments in the hypereosinophilic syndrome were described by M. Rothenberg. This disorder of unknown etiology is characterized by massive peripheral blood eosinophilia, causing organ infiltration and damage. A subset of patients demonstrate a deletion in chromosome 4q12, which results in the generation of a fusion protein between the platelet-derived growth factor receptor alpha with the Fip1-like1 (*FIP1L1*) gene, resulting in a dysregulated tyrosine kinase activity associated with chronic eosinophilic leukemia. These patients benefit from imatinib therapy, which inhibits tyrosine kinase. A murine model has demonstrated that this disease variant is probably caused by overexpression of IL-5, in addition to the fusion gene. The mainstay of current treatment in most patients with hypereosinophilic syndrome is corticosteroids, to which may be added hydroxyurea, vincristin or methotrexate and cyclophosphamide. Also interferon alpha, intravenous immunoglobulin, and bone marrow transplant may be of benefit. Both fusion gene-positive and negative patients respond well to mepolizumab, which has a steroid-sparing effect.

- Mast cell physiology was discussed at length. Ronit Sagi-Eisenberg from Tel Aviv University described a novel approach of targeting allergic and inflammatory diseases by transducible anti-MC signaling peptides. Mast cells may be activated both by IgE-dependent and IgE-independent mechanisms, via class I, II and III histocompatibility antigens, all through G-proteins. Some pertussis toxin fragments inhibit G-proteins in gastrointestinal mast cells, blocking intracellular signaling and activation. A C-terminus decapeptide of the toxin, designated Gi3, was found to inhibit secretagogue, non-IgE mediated activation and IgE-mediated MC activation via phosphokinase signaling activation. However, this molecule does not penetrate the cell membrane, therefore a chimeric peptide of the Gi3-C-terminal decamer, designated ALL1, has been constructed. It was demonstrated to effectively inhibit phosphokinase and to be beneficial in a rat model of allergic conjunctivitis and asthma. Calcium-binding proteins also regulate MC activity. One of those proteins, neuronal calcium-sensor-1, induces MC exocytosis (degranulation) through the FcεR1 receptor, thereby activating the ERK-MAPK signaling pathway, which results in enhancing the production of arachidonic acid metabolites. Therefore, ERK inhibition may be a therapeutic target in allergic inflammation.

  Israel Pecht from the Weizmann Institute, Rehovot, discussed means of MC desensitization and suppression of secretory responses. Excessive antigen and IgE binding to the FcεR1 reduces the clustering of these receptors and diminishes MC responses as measured by β-hexosaminidase and leukotriene B4 secretion. This phenomenon may be exploited for therapeutic desensitization of MC. It has been shown that two MC subpopulations – mucosal (MMC) and connective tissue (CTMC) – are activated via IgE or secretagogues, such as neuropeptides, mellitin, morphin, dextran and others. The complement fragment C3a has activating and inhibitory elements, acting on MMC and on bone marrow mast cells. Some synthetic peptides of this fragment have been selected for their capacity to bind to the β-subunit of the FcεR1 receptor, thereby inhibiting early, calcium-dependent and also late-phase MC responses. Trials in guinea-pig and rat asthma models have been promising.

  Ehud Razin and his group from the Hadassah-Hebrew University Medical School have demonstrated that the anti-

IL = interleukin

MC = mast cell

apoptotic function of the Bcl-2 in mast cells is dependent on the heat shock protein 90β (Hsp90β), and their dissociation, or the knocking-out of Hsp90β, leads to MC apoptosis by increasing the activity of caspases 3 & 7. Other proteins in the Bcl gene family, such as B*ax*, have an opposite effect to Bcl-2, directly causing cell apoptosis. These findings may point to a new therapeutic strategy in MC-associated conditions, such as mastocytosis.

- In the field of Autoimmunity, interesting advances were reported. Yehuda Shoenfeld from Sheba Medical Center described the newly discovered participation of the olfactory system in immune-mediated central nervous system disorders, such as systemic lupus erythematosus encephalopathy and multiple sclerosis, and also in Alzheimer's and Parkinson's diseases. Anti-P ribosomal antibodies (aPrAb), which are associated with lupus psychosis, bind to the limbic system, which is linked to the olfactory system. In all these diseases progression is associated with loss of olfaction, which recovers in remissions. Even depression may be induced by the same mechanism, as demonstrated in rodent models, and abolished by anti-idiotypic aPrAb. Successful treatment of depression by prozac is also associated with recovery of diminished olfaction. Possibly, this could become the basis of treatment of depression by aromatherapy.

  The pathogenic role of anti-cardiolipin antibodies was discussed by Yaniv Sherer, Ilan Asher and others from the same group. These antibodies are known to be associated with thromboembolic events, fetal loss and thrombocytopenia. However, in 33/64 patients' serum ACL became negative during a 5 year follow-up. Almost all the remaining patients demonstrated some clinical pathology, including death. In addition, a pro-atherogenic association with ACL was found in animal models and in humans, both in autoimmune conditions and in the general population. Therefore, the use of statins and anti-aggregants is warranted in conditions associated with ACL positivity. Furthermore, Miri Blank and collaborators demonstrated the efficacy of a fraction of intravenous immunoglobulin, containing anti-idiotypic antibodies to beta-2-glycoprotein-1 (β2GP1), in reducing fetal loss in a murine model of antiphospholipid syndrome and in inhibiting human trophoblast cell invasion *in vitro*. This effect was attributed to the Fab portion of the anti-β2GP1 antibody.

  N. Chiorazzi, in his second presentation, summarized evidence that diet may affect the outcome of clinical autoimmunity, such as in an animal model of SLE. It has been shown that indole-3-carbinol (I-3-C), which is present in cruciferous vegetables, is beneficial in estrogen-dependent tumors. Estrogen's link to murine SLE has been demonstrated. A diet rich in I-3-C slowed significantly the development of glomerulonephritis, decreased the level of anti-DNA antibodies and excessive B cell maturation, and prolonged survival in NZBxNZW-F mice with SLE. Also the naïve T cell subpopulation was increased, at the expense of memory T cells, and the high CD4/CD8 ratio was reduced. It remains to be demonstrated whether diet may similarly benefit human SLE.

- Ysrael Yust summarized the current situation of the fight against human immunodeficiency virus and AIDS. About 40 million people worldwide live with an HIV infection, 25.8 million of those in sub-Saharan Africa, 7.4 million in Asia, 1.8 million in Latin America, approximately 1 million in North America and 1 million in Europe. So far 2.8 million patients with AIDS, which is the advanced form of the infection, have died. Only 24% of HIV patients receive appropriate antiviral treatment, mostly in industrialized countries. The global funding allocation for prevention and treatment in 2006 was $US 8.9 billion, while the World Health Organization's estimate for the real need is $14.9 billion and will climb to $22 billion in 2008. In Israel a total of 4662 people with HIV have been reported, of whom 3547 are alive residents and 1115 have died or left the country. Because the virus directly attacks the central cells of the immune system, no effective vaccine has yet been developed. Heterosexual transmission being the main route of infection, "safe" sex is still recommended as the major preventive measure. In addition to the male condom, other "barrier" measures are available, such as female cervical "condoms" and microbicides. Male circumcision has been shown to significantly reduce transmission to female partners. Also, pre- and post-exposure antiretroviral prophylaxis is recommended. A wide armamentarium of antiretroviral drugs is now available, attacking the fusion and intracellular enzyme machinery used by the virus. Treatments are now condensed in a few pills/day, facilitating compliance. Treatment success may be monitored by measuring plasma viral load and levels of CD4 lymphocytes. Therefore, this deadly infection has been converted into a chronic disease, with long symptom-free spans. However, drug treatment is plagued by side effects and the development of viral resistance. Clearly, the global fight against HIV is far from over.

ACL = anticardiolipin antibodies
SLE = systemic lupus erythematosus
HIV = human immunodericiency virus

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Let proportion be found not only in numbers and measure, but also in sounds, weights, times, and positons, and whatever force there is

Leonardo Da Vinci (1452-1519), Italian painter, engineer, musician and scientist