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CONFERENCE REPORT

The aetiology of bronchial asthma and critical assesment of therapy

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The aims of the meeting were to clarify the conditions and mechanisms involved in bronchial asthma and to critically assess therapy.

S. Romagnani (Italy) stressed that in the past few years great progress has been made in the knowledge of the cellular and molecular signals responsible for the regulation of human immunoglobulin E (IgE) synthesis. Interleukin-4 (IL-4) and interferon-gamma (IFN-γ) are the main regulatory cytokines of IgE production, with opposite effects. T helper (TH) cells producing IL-4 and IL-5, but no, or limited IFN-γ, that resemble murine TH2 cells, accumulate in the blood and/or target organs of patients with helminthic infections or atopic disorders. These cells account for both IgE antibody formation and eosinophilia. The preferential differentiation of naive TH cells into the TH2 subset in patients with helminthic infection or atopic disorders seems to depend, at least in part, on the nature of antigens involved. Most T-cell clones specific for allergens or helminthic components have a TH2 profile of cytokine secretion, whereas the majority of T-cell clones specific for bacterial antigens established from the same donors exhibit a TH1 profile. However, T-cell clones derived from atopic donors show enhanced ability to produce IL-4 and IL-5 in comparison with T-cell clones specific for the same antigens derived from non-atopic donors. These data provide evidence for a deregulation of IL-4 (and IL-5) production in atopic patients.

G. Marone (Italy) reviewed human basophil/mast cell release in response to IgE- and non-IgE-mediated stimuli. No correlation between serum IgE level, skin reactivity, and IgE-mediated basophil release has been found, suggesting that these parameters are independently controlled. IgE-mediated basophil release is influenced by genetic factors. The histamine release induced by anti-IgE in patients with extrinsic asthma increases significantly compared to controls. Bronchoalveolar lavage (BAL) mast cells from asthmatics are exquisitely sensitive to anti-IgE in terms of release. The greater histamine concentration in BAL of asthmatics compared to non-asthmatics suggests that the increased releasability of mast cells in BAL is at least in part responsible for the higher level of histamine found in asthmatic patients.

B. Kay (UK) discussed the role of T-lymphocytes and cytokines in bronchial asthma. Increased numbers of eosinophils and activated T-lymphocytes are prominent in mucosal biopsies from atopic asthma even in a mild disease. All forms of asthma have a common immunopathology. The disease can be regarded as a cell-mediated hypersensitivity involving specialized T-lymphocyte subsets and eosinophils. Activated T-cells associated with the asthmatic process elaborate cytokines of the IL-3, IL-4, IL-5 and granulocyte macrophage colony stimulating factor (GM-CSF) gene cluster. IL-2, tumour necrosis factor (TNF) and IFN-γ are also involved with the severity and length of the disease possibly reflecting the ultimate cytokine profile. Thus, mild asthma is associated with a TH3-type cytokine profile but as the disease progresses in severity there is a concomitant TH1-type involvement.

J. Blenenstock (Canada) discussed the implication of inflammation, mast cells and nerves to the understanding of asthma. In a variety of *in vivo* and *ex vivo* situations, a physiological unit of mast cells, nerves and epithelium is involved in homeostasis. Eosinophils and enteric nerves are linked much as mast cells with these structures. Mast cells or other cells capable of interacting with antigen to release mediators may then influence local nerves which in turn influence either the inflammatory event or other structures such as epithelium, endothelium or blood vessels, fibroblasts or smooth muscle. In this way, using the mast cells as a model, it may be possible to explore new methods of preventing the amplification of events occurring in a mucosal site to involve the nervous system.

S. Holgate (UK) reviewed the pharmacological modulation of bronchial hyperresponsiveness (BHR). Pharmacological agents with well-defined antagonist action on specific receptors will protect the airways against specific stimuli, *e.g.* histamine (H_1), prostaglandin D_2 (PGD_2) (TP_1), acetylcholine (M_3), leukotrienes (LTs) (LTD_4), which provides a rational basis for their use as therapeutic agents. Examples

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include the inhibitory action of LTD_4 and H_1 antagonist against allergen and exercise induced bronchoconstriction. Through their direct effects or in down-regulating cytokine release by T-cells and other cells, cromoglycate-like compounds and topical corticosteroids reduce the mast cell and eosinophil components of mucosal inflammation with a consequent reduction in BHR. Drugs which reduce the clinical expression of BHR are likely to be of clinical benefit.

L. Fabbri (Italy) discussed the relationships between pathological changes in airway mucosa, and the sensitization to toluene diisocyanate (TDI). In patients with occupational asthma to TDI the bronchial mucosa shows inflammatory cells infiltrating both the epithelium and lamina propria, as well as increased thickness of the reticular basement membrane. Cessation of exposure to TDI for 7–12 months is associated with reduction in the reticular basement membrane thickness and in the inflammatory cell infiltration. Specific sensitivity to TDI and non-specific sensitivity may persist. In contrast to subjects with an early asthmatic reaction and a normal cell count, subjects with a late asthmatic reaction have a significant increase in neutrophils and a slight increase in eosinophils. Pretreatment with steroids either orally or inhaled, completely prevents the late reaction and the associated increase in responsiveness.

M. Belvisi (UK) discussed the role of neuropeptides, neurotransmitters and airway hyperresponsiveness. Neural control of the airways is abnormal in asthma. Autonomic nerves may influence the chronic inflammatory process in asthmatic airways. M_2-receptors on cholinergic nerves which inhibit acetylcholine release may be defective in asthma, tending to increase reflex cholinergic bronchoconstriction. Inhibitory non-adrenergic non-cholinergic nerves are the only bronchodilator pathway in human airways and may function abnormally in asthma. One of the proposed transmitters is vasoactive intestinal peptide (VIP), which is degraded in asthmatic airways by the action of mast cell tryptase, and another, nitric oxide, is degraded by oxygen-derived radicals. Chronic inflammation may lead to sensitization of airway sensory nerves.

G.U. Di Maria (Italy) summarized the role of endothelium and endothelin in airway responsiveness. Cultured endothelial cells produce a 21-residue peptide called endothelin (ET) responsible for a potent and long-lasting contraction of both vascular and airway smooth muscle in several species including humans. The contractile responses of guinea-pig airway smooth muscle to ET-1 is modulated by neutral endopeptidase (NEP). Although the exact role of endothelium and endothelin in healthy or diseased airways is unclear, these experimental observations and the occurrence of a rich venular plexus just below the airway epithelium might have important implications for the pathogenesis of bronchial asthma and airway hyperreactivity.

G.W. Canonica (Italy) reviewed adhesion molecules on epithelial cells. Cell adhesion molecules (CAMs) have been detected on epithelial cells of different pathological conditions. The CAMs expression on the cell membrane is enhanced by exogenous stimulation such as phorbol myristate acetate (PMA). The expression of CAMs is also enhanced by supernatants of PMA-triggered peripheral mononuclear cells (PMNC): preliminary experiments show that IFN-γ induces the expression of CAMs on epithelial cells. IFN-γ and other pro-inflammatory cytokines capable of inducing intercellular cell adhesion molecules (ICAM) expression on fibroblasts, fibrosarcoma, chondrosarcoma and adenocarcinoma cell lines have already been described. Steroids inhibit these phenomena.

J.A. Nadel (USA) reviewed modulation of neurogenic inflammation by neural endopeptidase. Stimulation of sensory nerves in airways causes release of substance P and other neuropeptides. An enzyme, neutral endopeptidase (NEP), cleaves and inactivates these neuropeptides. NEP is located on basal cells in the epithelium, where it is in close contact with the sensory nerve vesicles (the sites of neuropeptide release). NEP also exists on the surface of all airway cells that contain receptors for these neuropeptides. As the neuropeptide diffuses from sites for neural release to target cells, NEP on the surfaces of the cells competes with the receptor for the neuropeptide. Because of cleavage of the neuropeptides neurogenic inflammatory responses are normally mild and presumably protective in nature. NEP inhibition by cigarette smoke, toluene diisocyanate, or respiratory virus infection results in exaggerated neurogenic responses. Conversely, exogenous recombinant human NEP may provide a new strategy for the treatment of these inflammatory manifestations.

D. Olivieri (Italy) reviewed BAL in asthma. In asthmatics during clinical remission the increase in eosinophils and mast cells is significant. T-lymphocytes and macrophage subsets are different from those found in healthy control subjects. Mobilization of CD8 lymphocytes and monocytes within the airways may determine and maintain bronchial inflammation in asthma. In most cases epithelial shedding, epithelial metaplasia, basal membrane thickness, oedema and neutrophil infiltration in the submucosa have been found. The increase in intraepithelial and submucosal cells is consistently associated with a thickened basal membrane.

J. Milic-Emili (Canada) commented that asthma is characterized by an increased airway flow resistance and dynamic pulmonary elastance (Edyn). Pulmonary tissue resistance (Rti) is also increased in asthma, both as a result of enhanced time constant inequalities within the lungs and of changes in viscoelastic behaviour of the pulmonary tissues. The same mechanisms should also result in increased Edyn. Furthermore both Edyn and Rti should exhibit marked flow, volume and frequency dependence.

sleep patterns, causing daytime sleepiness and loss of cognitive function. It possibly makes daytime asthma worse and may be responsible for a proportion of the sudden deaths that occur in this disease. Nocturnal asthma and disorders of sleep may coincide. Some asthmatics snore and a proportion will have obstructive sleep apnoea.

Measurement of nocturnal asthma is difficult without aggravating the disturbances of sleep. There are three main methods. Firstly, the study of ventilatory sleep patterns with non-invasive devices such as Respitrace or inductance plethysmography, secondly, physiological tests which may be of an invasive or a non-invasive type and, thirdly, an experimental method of analysis of tracheal sounds by placing a detector in the supra-sternal notch.

The study of the sleep patterns measures respiratory frequency, tidal volume and minute ventilation in and out of acute exacerbations. Some patients maintain ventilation as obstruction develops, while others have a fall in ventilation and become hypoxaemic. The simplest of the non-invasive tests is to measure spirometry or peak flow rate before retiring to bed, immediately on waking in the morning, and particularly if wheeze develops and awakens the individual from sleep. Bracketing the morning dip with simple function tests may be one of the best indicators of severity of nocturnal asthma. The most important physiological tests amongst the invasive methods is to measure airway resistance, thoracic compliance and airflow. These measurements require the insertion of an oesophageal ballon and flow measuring equipment at the mouth. They can precisely monitor the mechanics of the morning dip. The use of tracheal sounds is an ingenious method which measures total wheeze time in the respiratory cycle. It is simple and non-invasive, but at present there are problems of sensitivity and specificity. However, the method warrants further study.

Treatment has to be directed at nocturnal asthma. Not all patients can be fully controlled. There is a sequence to be followed: firstly, ensure that optimum daytime therapy is achieved; good control of daytime therapy lessens the severity of nocturnal asthma. Secondly, if full control is not achieved add nocturnal therapy, which means slow release β_2-agonists or theophyllines immediately before going to bed. Theophyllines have the disadvantage of further disturbing sleep patterns. If control is still elusive oral corticosteroids during the day may be necessary and, as a last resort, intravenous salbutamol through constant infusion during acute exacerbations.

A new long-acting β_2-agonist, salmeterol, is an interesting compound with a duration of action sufficient to extend through the night. Already improvement of daytime symptoms has been achieved with the drug and preliminary studies suggest that it may be effective in the treatment of nocturnal asthma. It is such a new compound, however, that caution must be exercised in its use. Obstructive sleep apnoea syndromes coinciding with nocturnal asthma are not uncommon in asthmatics. Nocturnal asthma may masquerade as obstructive sleep apnoea. Benefit can be achieved with the use of CPAP.