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CONFERENCE REPORT

From alveoli back to bronchi: new perspectives of bronchoalveolar lavage

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The Bronchoalveolar Lavage Conference 1989 investigated the possible uses of the technique and applications were define in obstructive airways disease, the diagnosis of pulmonary infection, particularly in immunocompromised patients, the investigation of malignancy and lung toxicity. This year, the discussions were focused more on asthma, bronchitis and cancer. This restriction is testimony to the increasing scientific application of the technique evident during the two day proceedings.

BAL and asthma

Inflammation of the airways has long been accepted as a fundamental part of the asthma mechanism, but to those not closely involved with bronchoalveolar lavage (BAL) continuing inflammation of small airways has not been an appreciated feature of bronchitis. This inflammation contrasts with the clinical manifestations of occasional attacks of green sputum and pyrexia which are quickly controlled with antibiotics. In a number of patients a more sinister long-term inflammation of the bronchioles continues, causing progressive tissue destruction. It is here that the contrasts with bronchial asthma are marked, where despire years of florid inflammation few patients proceed to destructive and permanent airway change. In bronchitis a proportion of hospital patients seem to undergo a progressive decline, as judged by spirometry, which is given no more than temporary relief by current therapeutic applications. FLETCHER *et al.* (1976) [1] studied early bronchitis in postmen and found it to be largely related to smoking, and to subside after cessation of the habit. This suggests that bronchial inflammation in bronchitis, like that in asthma, need not necessarily lead to destructive disease. What is it that triggers airway destruction in bronchitis and to a lesser extent in bronchial asthma? We know of a number of trigger factors, viral infection, perhaps also bacterial infection, tobacco smoke in susceptible persons and damaging fume of an overwhelming nature. The Bhopal disaster in India is a good example of the latter and there must be others.

Therefore, airway inflammation was appropriately considered in more detail. In the first paper by Foresi (Italy), remarkable concordance was observed between cells produced by bronchoalveolar lavage (BAL) and cells in biopsy specimens found in the wall of inflamed bronchi. It has always been worrying that bronchoalveolar lavage does not reliably reflect the happenings in the adjacent airway. Reassurance was evident in this paper. Bronchial hyperresponsiveness is also associated with an inflammatory reaction, but it must be different from that associated with bronchial asthma as the asthmatic expression has still not occurred.

Many technical problems remain in the BAL procedure. Walters (UK) and Klech (Austria) reminded us of the difficulties of dilution, the treatment of cells and the sequence and volume of lavages. Whilst it is accepted that many studies employ techniques developed in individual departments a plea was made for adherence to the standardization of techniques already printed through the auspices of the SEP Bronchoalveolar Lavage Working Party [2]. This will make it easier to compare the work of different departments.

The importance of high dose aerosolized steroid treatment of bronchial asthma was emphasized by Walters (UK). Interestingly, the good clinical response was not mirrored by a concurrent reduction of inflammatory cells and other measurements in BAL. There were questions as to the relevance of the florid manifestations of airway inflammation in bronchial asthma to the associated bronchoconstriction.

BAL in bronchial asthma is associated with increasing numbers of neutrophils, eosinophils, lymphocytes and macrophages. There seem to be different patterns, different sorts of asthma and differences at various stage of the disease. Godard (France) felt that the macrophage was the central cell to which the induction and activities of the other cells relate. This was not

universally agreed, others pointed to the respective importance of the other cells. G. Rossi (Italy) examined inflammatory cells and their activity in small airways and alveoli. He questioned whether low aliquot BAL truly reflects airway pathology alone. However, the idea that inflammation at the two sites, bronchi and alveoli, might be different was well accepted. He suggested an early release of eosinophils with production of specific immunoglobulin E (IgE) as a first phase in the asthmatic reaction.

Chronic bronchitis

Jeffery (UK) outlined the pathological differences in the airway of the asthmatic and the bronchitic. He considered morphological, microscopic and cellular changes. There were marked differences between bronchitis in asthma and chronic bronchitis in terms of airway size, mucosal disruption, smooth muscle hypertrophy, characteristics of mucus and the pattern of inflammatory cells. Such differences must point to differences in consequence of the inflammatory reaction.

A number of papers looked at the components of airway destruction in bronchitis. Costabel (FDR) described a suppression of immune response of alveolar macrophages in smokers and pointed to increased levels of oxidized methionine in bronchitics with airway obstruction, noting no differences in this measurement between smokers and nonsmokers in the absence of airways obstruction. This was interesting, as it suggested that some specific change had occurred in those patients reacting adversely to the smoking habit.

In subsequent papers the mechanisms of oxidant-antioxidant balance, protease-antiprotease balance and deficiency of surfactant were considered. All may contribute to progressive airways destruction. Oxidants were classified as either endogenous or exogenous in origin. Therapeutic intervention might stimulate, respectively, the patients endogenous antioxidant sources or add exogenous therapy by means of tablets or aerosols, preferably the latter.

Similar discussion reviewed the concept of excess alveolar protease, which was thought to contribute to destructive emphysema. The principle consequence is a deficiency of alpha$_1$-antitrypsin (α_1-AT) in epithelial lining fluid, allowing digestive destruction of small airways and alveolar walls. In a masterly exposition, the work of the National Institute of Health in Bethesda, Maryland, on alpha$_1$-antitrypsin substitution therapy was detailed by Hubbard (USA). Intravenous weekly or monthly injections of human α_1-AT or inhalation of recombinant α_1-AT through aerosols were considered. The prospects for the therapeutic use of recombinant α_1-AT are increasing. It is possible to achieve adequate blood levels and, therefore, to replace α_1-AT deficiency in patients with congenital defects and cystic fibrosis, the latter having an overwhelming neutrophil load with consequent protease excess in small airways and alveoli. It has not, as yet, been possible to translate α_1-AT replacement to undoubted evidence of clinical benefit, but hopes are high for current trials. These are being conducted in congenital α_1-AT cystic fibrosis and chronic obstructive pulmonary disease.

Lusuardi (Italy) reviewed the role of surfactant on maintenance of airway integrity, airway defence, control of small airway infection and inhibition of tissue destruction. Two therapeutic applications should be considered: replacement of lost surfactant in chronic obstructive pulmonary disease (COPD) and related conditions and stimulation of natural surfactant production by drugs such as Ambroxol. In the first studies of Ambroxol, no clear ability to increase the phospholipid pool in the lung was realized but these are early investigations. Both the dose and the dosage schedules might be incorrect, and work must continue in this important area.

BAL and cancer

Three aspects of this topic were considered: detection of cancer with a view to prevention, investigation of carcinogenic mechanisms, and monitoring of therapy through adjustment of manipulation of the function of recovered BAL cells.

Izzotti (Italy) described a fascinating investigation of the attachment of carcinogens to nuclear material of pulmonary alveolar macrophages (PAM). It is possible to detect benzpyrene attached to deoxyribonucleic acid (DNA) in smokers. This is an exciting discovery as it suggests detection of cancer prone persons might be possible, opening the way to preventive chemotherapy. Questions were raised as to how long the carcinogen might stay attached to the nuclear material of PAM's why some heavy smokers succeeded in avoiding such DNA attachment, and the mechanism by which PAM carcinogen affected tumour formation in neighbouring epithelial or glandular cells.

A discussion of the importance of epithelial metaplasia as a pre-cancerous lesion in the lung followed. Metaplasia was found to be associated with airway inflammation from a wide range of trigger factors. Airway inflammation has carcinogenic potential. Cellular function associated with this type of airway inflammation appeared to be slightly different from that associated with bronchial asthma and the destructive lesions of bronchitis. The consequences of the functions of inflammatory cells will differ quite markedly from one situation of inflammation to another. BAL has a major potential to examine the function of individual cells and provide a new horizon for the method. Investigation of these functions is less dependent on the details of technique necessary for counting cells.

The diagnostic value of BAL was reviewed. In conjunction with skilled cytology it is now possible to achieve 60–70% positive diagnostic yield for lung

cancer. Further work needs to be undertaken to define the precise use of BAL in cancer diagnosis. When bronchoscopy reveals an obvious tumour in the main airways for which biopsy is performed or an obvious peripheral lesion in which it is easy to place a needle, BAL is less important. For diffuse lesions of doubtful aetiology there is an important and developing application.

More detailed examinations of lymphocyte and macrophage function yielded complex and disparate findings. It is difficult, as yet, to identify a clear channel through which these studies might contribute to the therapy or diagnosis of cancer except to re-emphasize that cancer associated cells are functionally different from those in the inflammation associated with bronchitis and asthma. An investigation of tumour necrosis factor, produced by pulmonary alveolar macrophages, showed this substance to be reduced by prostaglandin E_2. Prostaglandin E_2 was found to be in high concentration in a number of lung cancers. Perhaps the tumour cells can turn-off one of their destructive opponents. Investigation of cellular function, by use of BAL, after cancer chemotherapy or cancer immunotherapy has started.

Conclusion

In summary, this Conference showed that the scientific aspects of BAL are being focused on aspects of inflammation in asthma, bronchitis and cancer. Inflammation is clearly not a uniform condition and cellular function within it is variable. We are reminded that twenty years ago, at the birth of modern immunology, lymphocyte function remained an enigma as all of the cells looked alike. Measurement of subset function is now common-place. The same process, it would seem, will develop for inflammatory cells. BAL is ideally placed to be the modern tool of this new science.

References

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