The Current Clinical Value of Broncho-alveolar Lavage: A Personal View

Broncho-alveolar lavage was first introduced in the mid-1960s to remove tenacious secretions from patients with asthma and cystic fibrosis; it was also developed into a procedure of whole lung lavage in the treatment of alveolar proteinosis.[1]

It was reintroduced in the late 1960s and early 1970s in an attempt to identify cells and products from the lungs that could not be sampled from the blood. The procedure has provided a large amount of exciting material for research fundamental to chronic inflammation at tissue sites and has given much insight about the interaction of individual cell types, since lavage cells are living and can be maintained in tissue culture over considerable periods of time. Lavage has been especially exciting as a tool to evaluate the function and morphology of living alveolar macrophages because these possess properties different from monocytes and cannot, of course, be studied from blood samples.

Some claims have been made for the value of lavage in a clinical context. Some of these have been fulfilled and others not. The purpose of this editorial is to present a personal view of the current position, recognising that it is not possible to do full justice to all the work undertaken, some of which presents conflicting results. Nor is it intended as a final judgement, for much more work still needs to be done.

What are the questions?

The question of what is the "clinical value" of lavage must be stated more precisely because 'clinical value' can be defined under at least three headings:

1. The diagnostic value.
2. The value in indicating the need to initiate therapy.
3. The value in monitoring activity in the titration of drugs during the course of therapy.

Diagnosis

Lavage is of considerable value in diagnosis provided that the specimens are properly evaluated by experienced pathologists and prepared and stained appropriately. Lavage has two orders of diagnostic value: first, through its pathognomonic appearances and, second, by differential counts, suggesting a priority of more probable diagnoses without implying absolute specificity.

Some of the pathognomonic appearances include those of malignant cells in lung cancer or lymphomas; the presence of Langerhans' cells on electron microscopy in eosinophilic granuloma; the presence of iron-laden macrophages in idiopathic pulmonary haemosiderosis; the presence of asbestos bodies in those exposed to asbestos, and other identifiable materials encountered in specific occupations such as those using silica, talc and hard metals. Microprobe analysis will identify these specifically, but the characteristics of the material are often suggested in a routine preparation or under polarised light.

Extracellular eosinophilic material, highly suggestive of alveolar proteinosis, may establish a rare diagnosis, important because of its specific treatment. Other features may strongly support this diagnosis. Electron microscopy will confirm the presence of the whorled lamellar bodies, so characteristic of this condition. In some cases, even the macroscopic appearance of lavage fluid is almost diagnostic and "milky" opaque fluid is highly suggestive of alveolar proteinosis, even on naked eye examination.

Examination of lavage fluid can be extremely valuable in the diagnosis of infection, especially by opportunist organisms, provided that specimens are stained correctly. This usually requires an appropriate index of suspicion by the physician before lavage is undertaken, so that the pathologists may be alerted to process the specimens optimally. For example, *Pneumocystis carinii* cysts can frequently be found if silver stains are used; fungal mycelia may be similarly identified. Cytomegalovirus inclusions may be seen with Giemsa's stains, suggesting this type of specific pneumonia. Culture for bacteria, including *M. tuberculosis*, may yield valuable diagnostic information. Because unusual pneu-

monias are often important, it is wise to include a wide range of culture media appropriate for acid fast bacilli, fungi, *Actinomyces* and *Nocardia*, as well as more common organisms.

Differential counts of inflammatory cells, although far from specific, may have diagnostic value in suggesting a priority of likely possibilities in interstitial lung disease. For example, very high lymphocyte counts of greater than 60 per cent are more likely to indicate a hypersensitivity pneumonitis or tuberculosis than sarcoidosis and one or other of these conditions is far more likely than that of cryptogenic fibrosing alveolitis (synonym: idiopathic pulmonary fibrosis), which very rarely produces a lymphocyte count of this order. On the other hand, high neutrophil counts of greater than 50 per cent may suggest a bronchial component to the lavage material or the presence of a bacterial infection. Moderately raised neutrophil counts are common in fibrosing alveolitis and may occur in the late fibrotic stages of any form of interstitial lung disease, including asbestosis, fibrotic sarcoidosis and late-stage hypersensitivity pneumonitis.

A cell profile may give more information than increases in a single cell type. For example, lymphocytes, together with mast cells, are more characteristic of hypersensitivity pneumonitis than sarcoidosis. The frequency of atypical "activated" lymphocyte is also often greater in hypersensitivity pneumonitis than in sarcoidosis, although occurring in both.

An increase in neutrophils, together with eosinophils, is more characteristic of cryptogenic fibrosing alveolitis with or without associated connective tissue disorders than asbestosis but, in the latter, large numbers of asbestos bodies are almost invariably seen.

Thus, differential counts, interpreted by an experienced pathologist with good preparations, can be of great value. Poor preparations, preparations, viewed by someone unfamiliar with the subtleties of lavage samples, will certainly not provide optimal results and may lead to misleading reports being issued. In particular cell distortion can lead to other cell types, especially macrophages, being counted as lymphocytes with obvious misleading implications.

Sporadic ill-considered lavages, performed and interpeted by non-experts, should not be undertaken. Under these circumstances, it is probably wiser to remain on more secure ground using lung biopsies, remembering that small tissue samples of transbronchial biopsies are, themselves, often misleading in interstitial lung disease, and particularly when examined by a non-specialist pulmonary pathologist. Our current preference is for open biopsy in the diagnosis and staging of interstitial disease, where pathognomonic appearances are less likely, and where other diagnostic procedures have failed.

Lavage as an indicator to initiate therapy

It has been suggested that a high lymphocyte count (greater than 28 per cent T cells) in sarcoidosis[2] indicates the need to start steroid therapy. The basis for this is that a group of patients with high counts showed a greater clinical deterioration over six months compared with those having fewer T lymphocytes. Before this policy is adopted two additional facts need to be considered. First, about 70 per cent of patients with sarcoidosis having parenchymal shadows will resolve spontaneously without treatment. This implies that they may pass through a phase of some physiological and radiographic deterioration but still remit spontaneously and, in the view of many physicians, do not require treatment. High lympocyte counts under these circumstances do not necessarily imply *continuing* progressive disease in the longer term. Second, many patients with more persistent chronic sarcoidosis have normal or only slightly raised lymphocyte counts, but will respond substantially to treatment. To deny these patients the chance of improvement on the basis of the lymphocyte count would not seem to be wise. Absolute statements about which patients require and do not require treatment with steroids are, however, not yet agreed upon and there is a very wide variety of physicians' opinion. Until this metter is clarified, it is wise not to rely on a lymphocyte count alone, which has clear logical and factual limitations, as summarised above. The overall state of the individual patient, using the clinical, physiological and radiographic state and the progress over time, are certainly as important, and perhaps more important, than a single lavage lymphocyte count in indicating progression towards chronicity and a likelihood of developing irreversible fibrosis. Even when the lavage lymphocyte count is combined with a ^{67}gallium scan, there is too great a discordance between these measurements to allow them to be used alone as indicators for treatment.

It has also been suggested that a neutrophil count of 10 per cent and greater and a positive ^{67}gallium scan in IPF distinguishes those with a tendency towards deterioration on steroids, while those with neutrophils of less than 10 per cent do better.[3] The arguments here are somewhat different. The tendency for IPF to progress is very much greater than in sarcoidosis and many series have now shown that about 50 per cent of patients die within four years of first presentation. Moreover, there is now considerable indirect information that a better response to steroids is achieved when the disease is at an earlier stage. Thus, a good case can be made for treating all cases (other clinical factors being acceptable) and not to rely on any arbitrary indicator, be it a physiologic, radiographic or lavage one. Further, while some cases with high neutrophils respond

to corticosteroids, those with a somewhat raised lymphocyte count respond particularly well and the neutrophil count in these is often relatively low. Thus, to depend on the neutrophil count alone is to deny the administration of steroids in perhaps the best (albeit minority) group of all.[4]

Lavage as a tool to monitor activity during treatment and to adjust drug dosage

Lavage in the context of adjusting therapy has, so far, been perhaps the most disappointing aspect of lavage as a clinical tool.

In sarcoidosis and hypersensitivity pneumonitis, lymphocyte counts often remain substantially raised when all other modalities of assessment have returned to normal. Few biopsies are available to establish the meaning of these results. That they do *not* necessarily reflect a consistently more sensitive index of activity is, however, suggested by the not infrequent finding of an improving radiograph and physiology in the presence of a normal lymphocyte count. Under these circumstances, the lymphocyte count appears to be relatively less sensitive.

In one study comparing cell counts in lavage samples before and during treatment of sarcoidosis, there was less discordance of results (i.e. one modality improving while another deteriorated) between the radiograph and gallium scan, the radiograph and angiotensin converting enzyme (ACE), and gallium scan and ACE, than between lavage lymphocytes and any of the other measurements.

Serial lavages in CFA have, with one exception, proved somewhat disappointing in that neutrophils and eosinophils frequently remain persistently raised in both deteriorating as well as stable steroid unresponsive cases. Thus, while deterioration seems to relate to raised neutrophils or eosinophils when patient *groups* are studied, this is not a consistent finding in individual patients, even when followed over several years (mean of four years in the particular study quoted) (personal observation). Of some interest is the observation that, in the small group of patients who responded well to steroids or cyclophosphamide, there was a trend of change towards normal in all types of inflammatory cell. Thus, it may be possible to use normalisation of counts as a marker for continuing remission of the underlying inflammatory process and, thus, allow for a greater reduction of doses of therapeutic agents. If these findings can be confirmed in even longer studies, the question of when drug therapy may be stopped in cases of fibrosing alveolitis may be answered.

Conclusion

The clinical value of bronchoalveolar lavage needs careful specification. In expert hands, and when special preparations or stains are used, it can be of considerable value diagnostically, both in terms of pathognomonic appearances and in suggesting a priority of diagnosis based on differential inflammatory cell counts.

In the author's view, lavage cell counts have not yet been proven to be reliable indicators upon which to make a decision to start treatment in either sarcoidosis or IPF. The frequent lack of concordance between the various modalities to assess "activity" and "progression of disease" make it unwise, at the present time, to rely on lavage lymphocyte counts for this purpose.

Likewise, serial lavage counts have not shown a close correlation with progression of disease when individual patients are studied and, in particular, patients with apparently stable disease may have continually raised neutrophil and eosinophil counts which persist over quite long periods of time. Counts do, however, tend to fall towards normal in those who have responded well and continued monitoring of a *normal* count may, perhaps, provide an additional method to aid monitoring of these patients while drug doses are being reduced. Thus, the value in this particular sub-group of patients, when an equally specific question is being asked, may be considerable.

Overall, alveolar lavage has provided an important new tool in attempting to understand disease. Its use by the clinician has been summarised and it can be extremely valuable, but changes observed in groups of patients cannot always be used to manage individuals. Thus, as indicated, the precise circumstances, in which it has value, have to be recognised. There is now considerable evidence that, over-reliance on particular types of cell count alone in individual patient management, is not justified. We must neither over- nor underestimate the clinical value of lavage, but use it sensibly in individual patients in the context of other information.

Margaret Turner-Warwick, M.A., D.M., FRCP, Ph.D.
Director, Department of Thoracic Medicine, The Cardiothoracic Institute, University of London, U.K.

REFERENCES

1. Ramirez RJ. Bronchopulmonary lavage; new techniques and observations. Dis Chest 1966; 50:581-8.
2. Crystal RG, Roberts WC, Hunninghake GW, Gadek JE, Fulmer JD, Line BR. Pulmonary Sarcoidosis: disease characterized and perpetuated by activated lung T lymphocytes. Ann Int Med 1981; 94:73-94.
3. Keogh BA, Line BR, Rust M, Hunninghake GW, Meier-Sydow J, Crystal RG. Clinical staging of patients with idiopathic pulmonary fibrosis. Am Rev Respir Dis 1981; 123 (Suppl):89.
4. Rudd RM, Haslam PL, Turner-Warwick M. Cryptogenic fibrosing alveolitis; relationships of pulmonary physiology and bronchoalveolar lavage to response to treatment and prognosis. Am Rev Respir Dis 1981; 124:1-8.