SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2000; 17; 174-180

Bronchoalveolar lavage macrophage-lymphocyte clusters in granulomatous disease are linked to lymphocytosis

Roslyn A Bauer[1], Richard T Sawyer[1, 2], Elaine Daniloff[1], Ronald Balkissoon[1, 2], Cecile S Rose[1, 2], Lee S Newman[1, 2, 3]

[1] Division of Environmental and Occupational Health Sciences, Department of Medicine, National Jewish Medical and Research Center
[2] Division of Pulmonary Science and Critical Care Medicine, Department of Medicine, University of Colorado Health Sciences Center
[3] Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver, CO.

Abstract. *Background and aim of the work:* Clusters of macrophages associated with lymphocytes (ML clusters) have been observed among the bronchoalveolar lavage (BAL) cells of patients with pulmonary disease. We tested the hypothesis that ML clusters might be found among the BAL cells from patients with granulomatous disease. *Methods:* We measured the number of ML clusters among the BAL cells from normal controls (n = 13), sarcoidosis patients (n = 18), beryllium-sensitized (BeS) patients (n = 21) and chronic beryllium disease (CBD) patients (n = 15). *Results:* ML clusters were observed in the BAL cells of all groups, but at different frequencies: normal 8.5% (median, range 2-15%); BeS 7% (range 2-31%); sarcoidosis 14% (range 4-50%); and CBD 17% (range 6-73%). This data suggested that ML clusters were increased in granulomatous lung disease. However, the percentage of ML clusters strongly correlated with the BAL lymphocyte percentage (rho = 0.79). Cohort analysis showed that increases in macrophages having 2, 3 or > 3 associated lymphocytes correlated with an increase in lymphocyte percentage. *Conclusions:* An increase in ML clusters in BAL cells is not specific for granulomatous disease and is associated with the increase in BAL lymphocytes. ***(Sarcoidosis Vasc Diffuse Lung Dis 2000; 17: 174-180)***

Key Words. Beryllium. Chronic Beryllium Disease. Sarcoidosis. Granulomatous Disease. Macrophage-Lymphocyte Clusters.

Introduction

Sarcoidosis and Chronic Beryllium Disease (CBD) share in common the formation of non-caseating granulomas, often within the lung [1,2]. Clusters of adherent macrophages and lymphocytes (ML clusters) have been identified in the bronchoalveolar lavage (BAL) of patients with granulomatous lung diseases including sarcoidosis, extrinsic allergic alveolitis, and tuberculosis [3-7]. It has been suggested that ML clustering represents an immune response in these diseases [7-11], although their significance remains uncertain.

ML clusters may be defined as one or more lymphocytes associated with a mononuclear phagocyte in the BAL. ML clusters have been noted in granulomatous diseases, but they are not

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Correspondence: Richard T. Sawyer, Neustadt D-309, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206.
Phone: 303-398-1167
Fax: 303-398-1851
E-mail: sawyerr@njc.org

specific to these disorders. ML clusters have been observed in the BAL from patients with diseases including asbestosis and cancer [4,12]. In addition to BAL, they have been observed in cultured cells from the synovial fluid and peripheral blood of patients with Reiters syndrome and rheumatoid arthritis, and in cultured cells from the synovial fluid and peripheral blood of healthy normal controls [9].

In sarcoidosis and CBD, granuloma formation is preceded by an interstitial and alveolar leukocyte infiltration. Over time the numbers of lymphocytes and macrophages within the BAL cell population may increase [2,5,13]. We hypothesized that ML clusters would be present in the CBD BAL. Furthermore, we speculated that the presence of these clusters is dependent on the lymphocyte predominance of the BAL. We tested our hypotheses by measuring the number of ML clusters in the BAL cell population from normal, Be-sensitized (BeS), sarcoidosis, and CBD patients. To address the clinical relevance of ML clusters, we examined the correlation with clinical disease status and with the specific cell classes represented within the BAL cell population.

Methods

Study Population

Normal controls: The normal controls (n = 13) who participated in this study had no known exposure to beryllium, were free of respiratory symptoms and lung disease, and had normal chest radiographs and spirometry at the time of BAL.

Beryllium Sensitized (BeS): The BeS patients without disease (n = 21) met the following case definition: (1) a history of occupational, or environmental Be exposure; (2) no histologic evidence of non-caseating granulomas on lung biopsy; (3) at least two positive blood beryllium-lymphocyte proliferation tests (BeLPT); (4) a negative BAL BeLPT; and (5) normal chest radiographs and spirometry at the time of BAL.

Sarcoidosis: The sarcoidosis patients (n = 18) who participated in this study had a history, physical examination, radiographic findings, and pulmonary physiology compatible with a diagnosis of sarcoidosis [1]. Granulomatous inflammation was confirmed by either transbronchial biopsy or mediastinal lymph node biopsy. In all cases cultures and smears of bronchoalveolar washing for acid-fast bacilli and fungi were negative. All had negative BAL and blood BeLPTs [14,15].

CBD: The CBD patients (n = 15) met the following case definition: (1) a history of occupational, or environmental, Be exposure; (2) histologic evidence of non-caseating granulomas on lung biopsy; and (3) $BeSO_4$-stimulated blood and/or BAL lymphocyte BeLPT [15,16].

A "never smoker" was defined as having smoked less than 20 packs of cigarettes or 12 ounces of tobacco in a life time, or less than one cigarette per day for one year. A "former smoker" was defined as having exceeded the number of cigarettes in the "never smoker" definition, but having ceased at least one month prior to bronchoscopy. A "current smoker" was defined as having smoked cigarettes within one month of study participation.

A "steriod user" was defined as a subject taking oral steroids at the time of the bronchoscopy

We obtained informed consent from all participants according to the protocol approved by the National Jewish Medical and Research Center Human Subjects Review Board.

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) was performed by standard methods reported previously [17]. In brief, four 60 ml aliquots of room temperature, normal saline were instilled via syringe directly into the subject's lung and lavage fluid was harvested by gentle suction on the instilling syringe. The fractions were pooled and centrifuged at 2,000 rpm for ten minutes to recover BAL cells. Cell viability was evaluated by trypan blue exclusion and ranged from 90 to 97%. Differential white blood cell counts were performed on cells prepared by cytocentrifugation (Shandon Southern, Sewickley, PA), stained with LeucoStat (Fisher Scientific Co., Springfield, NJ), and included macrophages, lymphocytes, eosinophils, and neutrophils. Ciliated epithelial cells and erythrocytes were excluded.

Cell Analysis. Cell differential counts were performed on 400 BAL cells and the relative percentages of macrophages, lymphocytes, neutrophils, and eosinophils determined. The percentage and number of ML clusters was determined by a single blinded observer counting 400 BAL macrophages with or without associated lymphocytes. The percentage of macrophages with 1, 2, 3, or > 3 lymphocytes was determined by counting 200 associated macrophages and ranking them accordingly.

Statistical Analysis

Analysis of variance was performed using the Wilcoxon/Kruskal-Wallis and Student's t-tests. Medians were used for data that was not normally distributed. SAS and JMP software were used and positive values for pairs of means were considered significantly different at a p value of ≤ 0.05. To compare medians we used the Dunn's non-parametric multiple comparison test. Pairs of medians were considered significantly different at a p value of ≤ 0.05. Correlation relationships were determined by the non-parametric Spearman method.

Table I
Demographics, smoking status and steroid use by study participants

	NORMAL n=13	SARCOIDOSIS n=18	BeS n=21	CBD n=15
Mean Age, Yr (SD)	30 (4.8)	48 (11)	53 (12)	57 (10.7)
Gender, n (%)				
Male	7 (54)	11 (61)	17 (81)	10 (67)
Female	6 (46)	7 (39)	4 (19)	5 (33)
Race, n (%)				
Caucasian	13 (100)	16 (89)	21 (100)	14 (93)
Black	0 (0)	2 (11)	0 (0)	1 (7)
Ethnicity, n (%)				
Hispanic	0 (0)	3 (17)	2 (10)	3 (20)
Non-Hispanic	13 (100)	15 (83)	19 (90)	12 (80)
Smoking Status, n (%)				
Never	13 (100)	12 (67)	9 (43)	5 (33)
Former	0 (0)	6 (33)	6 (29)	7 (47)
Current	0 (0)	0 (0)	6 (29)	3 (20)
Steroid Use, n (%)				
Yes	0 (0)	11 (61)	0 (0)	3 (20)
No	13 (100)	7 (39)	21 (100)	12 (80)

Results

Study Population demographics and clinical status

The demographics, smoking, and steroid status of the study population are shown in *Table I*. Six (29%) of the BeS patients and three (20%) of the CBD patients in this study were current smokers. Three (20%) of the CBD patients and eleven (61%) of the sarcoidosis patients were currently using steroids. We found no significant association between race, ethnicity, age, gender, smoking status, or steroid status of our study population and percentage of ML clusters, or with the percentage of lymphocytes in BAL.

BAL Cellularity

As seen in *Table II*, elevated numbers of BAL leukocytes in CBD patients were accompanied by a significant increase in the relative percentage of lymphocytes. Macrophage and lymphocyte numbers as well as relative macrophage and lymphocyte percentages in normal controls were comparable to those found by other investigators for non

Table II
Bronchoalveolar lavage (BAL) cellularity and differential cell count

	NORMAL	BeS	SARCOIDOSIS	CBD
WBC X 10^4/ml	14 (2.1)	32 (5.5)*	34 (5.8)*	32 (5.4)*
LEUKOCYTE CLASS				
Macrophage %	78 (1.7)	83 (2.5)	74 (3.2)	56 (6.0)*
X 10^4/ml	10 (3.6-27)	18 (5.6-90)*	23 (4.8-88)*	12 (7.0-76)
Lymphocyte %	20 (1.7)	16 (2.5)	25 (3.3)	43 (6.1)*
X 10^4/ml	2.4 (0.6-0.5)	2.3 (1.2-19)	5.0 (1.3-24)*	14 (1.8-36)*
Neutrophil %	1.5 (0.3)	0.7 (0.2)*	0.4 (0.1)*	1.0 (0.3)
X 10^4/ml	0.1 (0-5.0)	0.1 (0-1.4)	0 (0-0.5)	0.1 (0-1.0)
Eosinophil %	0.2 (0.2)	0.3 (0.1)	0.4 (0.1)	0.2 (0.1)
X 10^4/ml	0 (0-0.4)	0 (0-0.9)	0 (0-0.6)	0 (0-0.3)

Parenthesis following cell % denote SEM. Parenthesis following cell # denote range (min-max). * Denotes a significant difference from the normal subject group $p \leq 0.05$

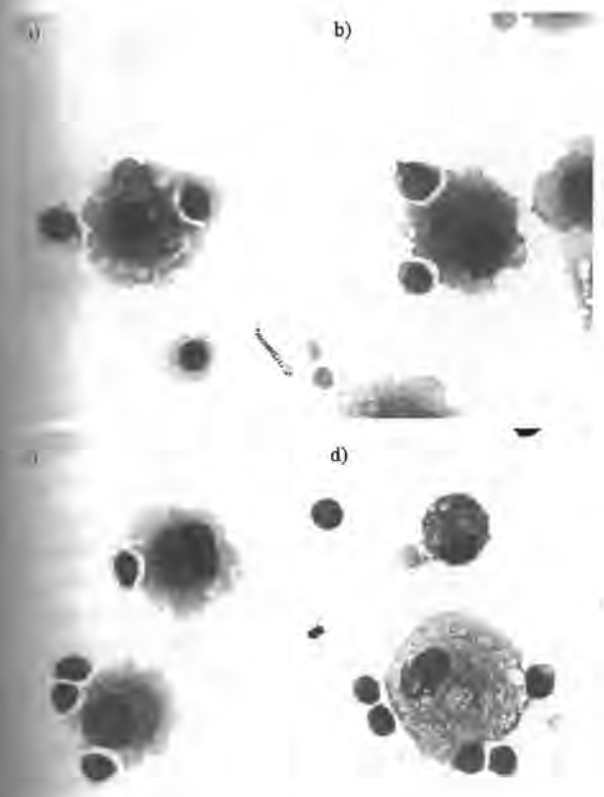

Fig. 1. Photomicrograph (1,000 X) showing differential staining of BAL cells. ML clusters are present among the bronchoalveolar lavage cell population from (a) normal (b) sarcoidosis (c) beryllium-sensitized and (d) chronic beryllium disease patients.

mal, non-smoking individuals [18]. There was a significant correlation between lymphocyte percentage and lymphocyte number/ml BAL for the entire study population (rho = 0.73, p<0.0001).

ML Clusters In Granulomatous Disease

We tested the hypothesis that CBD patients, like sarcoidosis patients, have increased ML clusters among their BAL cells. *Figure 1* shows ML clusters in the BAL of normal, BeS, sarcoidosis, and CBD patients. As shown in *Figure 2*, 8.5% (median, range 2-15%) of normal BAL macrophages and 7% (range 2-31%) BeS BAL macrophages were associated with lymphocytes in ML clusters. Among diseased patients, 14% (range 4-50%) of the BAL macrophages in sarcoidosis patients and 17% (range 6-73%) of the BAL macrophages in CBD patients were associated with lymphocytes.

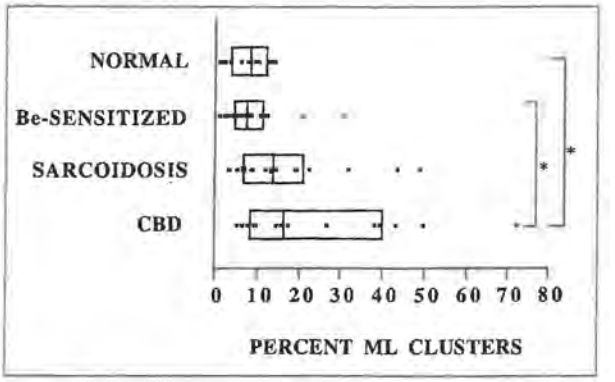

Fig. 2. The median percentage (%) of ML clusters present among the bronchoalveolar lavage cells from normal, beryllium (Be)-sensitized sarcoidosis and chronic beryllium disease (CBD) patients. * $p \leq 0.05$.

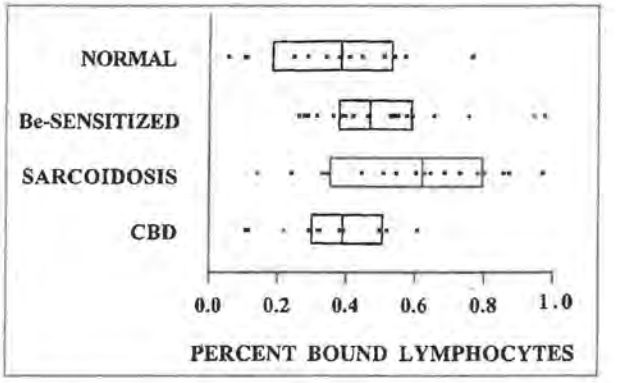

Fig. 3. The median percentage (%) of bound lymphocytes in ML clusters present among the bronchoalveolar lavage cells from normal, beryllium (Be)-sensitized sarcoidosis and chronic beryllium disease (CBD) patients.

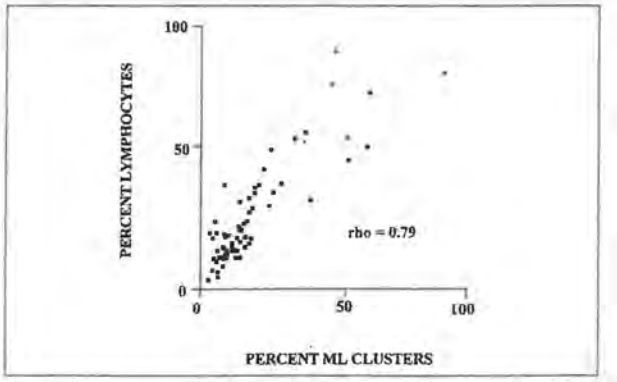

Fig. 4. Scatter plot of the percentage of bronchoalveolar lavage (BAL) lymphocytes as compared to the percent of ML clusters present in the BAL. The correlation coefficient using data for all subjects in this study was rho = 0.79.

Table III
Cohorts of bronchoalveolar lavage (BAL) macrophages with one or more associated lymphocytes.

COHORT	MEDIAN PERCENTAGE MACROPHAGES BOUND NORMAL	SARCOIDOSIS	BeS	CBD
+ 1 lymphocyte	92 (72-97)	85 (48-98)	89 (73-96)	78 (36-93)* [N,Be,S]
+2 lymphocytes	8 (3-24)	14 (2-27)	10 (4-22)	18 (6-40)* [N,Be,S]
+3 lymphocytes	0 (0-4)	2 (0-14)* [N]	1 (0-6)	4 (0-19)* [N]
>3 lymphocytes	0 (0-1)	0 (0-12)	0 (0-1)	0 (0-7)

Parenthesies denote minimum-maximum range of data. * Denotes a significant difference in comparison to the study group in [brackets.]. N = normal [illegible] = beryllium sensitized

The median percentage of lymphocytes involved in ML clusters did not vary significantly among normal, BeS, sarcoidosis, or CBD subjects. As seen in *Figure 3*, there was no significant difference in the percentage of lymphocytes bound to BAL macrophages for either normal or diseased groups.

ML Cluster Formation as a Function of Lymphocyte Percentage

We tested the correlation between the percentage of lymphocytes present in the BAL and the percentage of ML clusters. As seen in *Figure 4*, we observed a significant correlation (rho=0.79, $p<0.0001$) between the percentage of ML clusters and the percent of lymphocytes in the BAL.

Cohort Analysis of ML Clusters in Granulomatous Disease

We tested the hypothesis that patients with granulomatous disease were more likely to have ML clusters containing multiple lymphocytes. *Table III* shows the percentage of associated BAL macrophages having 1, 2, 3 or > 3 attached lymphocytes. Among the cohorts of ML clusters having two associated lymphocytes, there was a significant difference between normal controls and CBD patients. Among the cohorts of ML clusters having three associated lymphocytes, there was a significant difference between normal controls and CBD patients, as well as between normal controls and sarcoidosis patients. We performed simple linear regression analysis to determine if there was a relationship between a higher BAL lymphocyte percentage and a greater number of associated lymphocytes per macrophage. When two or more lymphocytes were associated with a BAL macrophage, the slope of the line was positive. When fewer than two lymphocytes were associated with a BAL macrophage, the slope of the line was negative. (% macrophages with 1 lymphocyte: $y = 99.11 - 0.66\ x$, $r^2 = 0.68$; % macrophages with 2 lymphocytes: $y = 3.64 + 0.42\ x$, $r^2 = 0.68$; % macrophages with 3 lymphocytes: $y = -1.69 + 0.17$ [illegible], $r^2 = 0.57$; % macrophages with >3 lymphocytes: $y = -1.05 + 0.07\ x$, $r^2 = 0.33$). As the percentage lymphocytes increase the percentage of macrophages with one lymphocyte attached decreases (negative slope). As the percentage of lymphocytes increase the percentage of macro-phages with greater than two lymphocytes increases (positive slope). As the percentage lymphocytes in the population increase, the macrophages are more likely to have multiple lymphocytes bound.

Discussion

Macrophage-lymphocyte clusters (ML clusters) occur in the bronchoalveolar lavage (BAL) cells of both normal individuals and individuals with granulomatous lung disease. Our data show that ML cluster formation is linked to an increase in the percentage of lymphocytes in the BAL in all study groups. Therefore, we conclude that the presence of ML clusters in BAL is not a consequence of granulomatous disease.

Consistent with our observation, using an experimental animal model, Lipsky and Rosenthal [19] found that while the formation of ML clusters *in vitro* requires metabolically active macrophages, neither serum nor specific antigen is required. Moreover, ML clusters formed with either heat killed or poisoned lymphocytes. Thus, syngeneic

macrophages were able to recognize and bind lymphocytes in an antigen-independent manner. In a later study Lipsky and Rosenthal [20] demonstrated that ML cluster formation is a function of the number of lymphocytes. Ziprin et al. [21] found that ML clusters are not due to lymphocyte phagocytosis and are not mediated by FC receptors. Our study confirms that the percentage of macrophages that have associated lymphocytes increases with an elevation in lymphocyte percentage in the BAL. Further, the number of lymphocytes bound per macrophage increases with an elevation in lymphocyte percentage . These relationships exist regardless of disease status. ML clusters were observed in the BAL of beryllium sensitized and normal subjects. The BAL cells from beryllium sensitized patients and from normal controls do not proliferate in response to *in vitro* beryllium stimulation [22]. Based on our observations, we suggest that ML clusters form non-specifically, possibly due to interactions between macrophage surface molecules and ligands on the surface of lymphocytes.

Previous studies suggest that ML clusters are associated with granulomatous and other disease states [4,7,23]. However to our knowledge no study has examined the prevalence of these clusters in BAL in relation to lymphocyte percentage. Alternatively, Hepburn et al. [9] identified ML clusters in cultured synovial fluid cells from both normal controls and patients with rheumatoid arthritis. They noted an increase in the number of associated T cells proportional to the number of T cells in the culture. Lyons et al. [4] noted an increase in peripolesis associated with disease status but always accompanied by an increase in lymphocytes. Van Maarseveen et al. [23] noted an increase in ML clusters in sarcoidosis patients undergoing steroid treatment. It was suggested that the increase was due to an association of macrophages with T suppressor lymphocytes. In the present study, we did not determine the phenotype of the lymphocytes present in ML clusters. Thus, our study does not rule out a potential contribution to ML cluster formation based on disease-specific shifts in the ratio of CD4+/CD8+ T cells within the BAL of any individual subject. However, previous studies show that the CBD/BAL lymphocyte population is principally CD4 positive [24,25] suggesting that the ratio of CD4+/CD8+ T cells may not contribute to ML cluster formation.

Numerous studies suggest that in granulomatous disease ML clusters represent an antigen-mediated interaction [7,8,10,11]. Antigen processing macrophages bearing surface major histocompatibility class II molecules bound to antigen-peptide could interact with T cell antigen receptors specific for that antigen-peptide complex. As a result, macrophages and lymphocytes may physically cluster. In support of this notion, ML clusters have been shown to play a role in initiating lymphocyte blastogenesis and increased tritiated thymidine uptake by lymphocytes *in vitro* [8,11,26]. We suggest that ML clustering is not a direct result of disease-specific antigen stimulation. However, our study does not rule out the possibility that ML cluster formation is a consequence of the up-regulation adhesion molecules such as CD11b and ICAM-1 on alveolar macrophages. This up-regulation has been shown in patients with sarcoidosis [27]. Alternatively, ML clustering could result from inhaled stimuli. Thus, ML clusters may have immunologic significance, even if they are not disease specific.

Taken together, our data suggest that ML clusters in the BAL cell population are unrelated to disease status. ML clusters in BAL are proportional to lymphocyte percentages. Their immunological significance warrants future investigation.

Acknowledgements

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Sarcoidosis Factoid: An Almost Forgotten Manuscript

Om P Sharma, MD
USC School of Medicine, Los Angeles, CA 90033, USA


ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 366

STUDIES ON THE CARDIOPULMONARY FUNCTION IN SARCOIDOSIS

Edited by NILS SVANBORG

ACCOMPANIES VOL 170

STOCKHOLM 1961

Four decades ago, Acta Medica Scandinav published a supplement [1] that was edited by Nils Svanborg (*Fig. 1*). This was one of the most complete and authoritative accounts of the cardiopulmonary function in sarcoidosis. It was based on the late Dr. Svanborg's extensive physiological evaluation of 37 patients that were under the care of Dr. Sven Lofgren who at the time had pointed out the association of hilar adenopathy and erythema nodosum in sarcoidosis. The clinical combination is now known as Lofgren's or Lofgren Syndrome. Dr. Svanborg was assisted in his efforts by Dr. A. Holmgren.

Svanborg pointed out the existence of airway obstruction and increased airway resistance in sarcoidosis patients before it was emphasized by other workers. He showed that it was not unusual to have almost normal lung functions in some patients with severe radiographic abnormality. Eight of the thirteen patients with stage III disease had pulmonary hypertension but showed no evidence of right heart failure. One curious finding which remains uninvestigated to this day was the orthostatic reaction in a few patients. It is conceivable that the orthostatic reaction was related to autonomic dysfunction. Perhaps this autonomic dysfunction is manifested as fatigue in some patients with sarcoidosis. Now it is time to dust off the old manuscript, study it, and plan further studies to investigate orthostatic hypotension in sarcoidosis.

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Book Review

Interventional bronchoscopy

Bolliger C, Mathur P
Karger, Basel, 2000, 171 figures, 80 tables, 198 CHF

Among the many areas in pulmonary medicine ... have been revolutionised by technological advances, b... choscopy is one of the most striking examples. This special... state-of-the-art book covers all the aspects of diagnostic ... therapeutic bronchoscopy, which go beyond the technique... of inspection, simple lavage and biopsies of the trache... bronchial tree.

The book is divided in five sections. The first covers the historical aspects and the modern use of both the rigid and flexible instruments, the set-up of a bronchoscopic unit, anaesthetic techniques, and functional evaluation for patients undergoing interventional bronchoscopy. The second section is diagnostic, and covers the transbronchial needel aspiration and the (adveniristic) bronchoscopic ultrasound. The third section describes all the existing therapeutic techniques: foreign body removal, laser resection, electrocautery, argon plasma coagulation, cryotherapy, brachyterapy, photodynamic therapy, stenting, and a chapter on multi-modality treatment of advanced pulmonary malignancies. The fourth section deals with percutaneous image-guided procedures, percutaneous dilational tracheostomy, and transtracheal oxygen therapy. The last section provides an in-depth look at emerging bronchoscopic technology, such as autofluorescence, virtual bronchoscopy, and gene therapy.

Written by the world's leading authorities of both sides of the Atlantic, and beautifully illustrated, with elegant hard cover look, wide subject index and updated references at the end of each chapter, the book is a must for pneumologists, thoracic or ENT surgeons, oncologists and physicians who have interest in bronchoscopy.

Gianfranco Rizzato (Milan)