

Bronchial hyperresponsiveness to methacholine in patients with primary Sjögren's syndrome

Björn Gudbjörnsson, Hans Hedenström, Gunnemar Stålenheim, Roger Hällgren

Abstract

The prevalence of bronchial hyperresponsiveness (BHR) to methacholine inhalation in a consecutive series of 21 patients with primary Sjögren's syndrome was studied prospectively. Slight to severe BHR was seen in 12/20 (60%) of the patients. Ten of 12 patients with BHR (83%) had a non-productive cough, wheezing, or intermittent breathlessness. Bronchial hyperresponsiveness was more common in patients with extraglandular symptoms (10/14, 71%) than in those with only glandular symptoms (29%). Spirometrically 29% (6/21) of the patients had 'small airways' disease, and all those had BHR. Of 6/21 (29%) who had diffuse interstitial lung disease, two had BHR. Three of the four patients with obstructive lung function were challenged with methacholine and two of them had BHR. Only two patients with BHR had normal spirometry findings. The data showed that respiratory disease—mostly mild or moderate but even severe bronchial hyperresponsiveness—is commonly seen in patients with primary Sjögren's syndrome.

Sjögren's syndrome is a chronic autoimmune inflammatory disease, which mainly affects exocrine glands. Sjögren's syndrome can occur alone—primary Sjögren's syndrome, or in association with other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis—secondary Sjögren's syndrome. Several visceral organs, including the lungs,¹ may be affected in primary Sjögren's syndrome. The respiratory manifestations include among others interstitial pneumonitis, 'small airways' disease, and pleuritis.²⁻⁴ Large airway obstruction has been reported in 8-12% of patients with primary Sjögren's syndrome.^{5,6} In our experience severe obstructive symptoms are attributed to bronchial asthma and the diagnosis of Sjögren's syndrome unfortunately does not become apparent until the patients develop interstitial lung fibrosis. About one third of patients with primary Sjögren's syndrome have a chronic dry non-productive cough and dyspnoea.^{2,3} These symptoms are thought to be due to dryness in the large airways, secondary to a lymphocyte infiltration of the glands of the mucous membrane in the trachea. These so-called xerotrachea symptoms may, however, also imitate the symptoms of mild or moderate bronchial hyper-reactivity. This clinical background induced us to investigate the prevalence of bronchial hyperresponsiveness (BHR) to methacholine

inhalation in a consecutive series of patients with primary Sjögren's syndrome. We found that most patients were hyperreactive in the test, and we correlated the methacholine test findings with clinical features and spirometric findings.

Patients and methods

A consecutive, non-selected series of patients (20 women, one man; aged 22-78 years; mean age 53.6) who were admitted to the section of rheumatology were studied. The diagnosis of primary Sjögren's syndrome was based on the following findings: each patient had keratoconjunctivitis sicca shown by a pathological Schirmer's test (<10 mm/5 min) and positive rose bengal staining,⁷ and xerostomia with a total salivary secretion rate stimulated by chewing of <0.7 ml/min,⁸ in the absence of other rheumatic diseases. The diagnosis was confirmed by a positive lower lip biopsy.⁹ Glandular and extraglandular symptoms of the patients were clinically evaluated. All patients underwent serological examinations with the following tests: Waaler-Rose rheumatoid factor and antinuclear antibodies were measured at the department of clinical bacteriology, University Hospital, Uppsala. Anti-Ro (SS-A) and anti-La (SS-B) were measured by the Western blot technique at the State Bacteriological Laboratory in Stockholm, Sweden.

All subjects underwent plain chest radiography and spirometry. The spirometric test included measurements of the total lung capacity (TLC), residual volume (RV), airways resistance (Raw), and airway conductance (Gaw/V) with a body plethysmograph. Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), FEV₁ as a percentage of VC (FEV₁/VC) and of TLC (FEV₁/TLC), flow volume registrations with maximal expiratory flow $V_{e_{max}}$ and flows measured at 50% ($V_{e_{50}}$) and 25% ($V_{e_{25}}$) of FVC were measured with an Ohio spirometer. The slope of the alveolar plateau (phase III), closing volume (CV) as a percentage of VC (CV/VC), and closing capacity (CC) as percentage of TLC (CC/TLC) were determined with the single breath nitrogen washout test and the transfer factor of the lung for CO (TLCO) was measured with the transfer test. The values obtained were compared with those for healthy controls matched for age and sex, and abnormal values were defined as values outside the 95% confidence intervals.^{10,11}

The methacholine test was modified from Hargreave's method.¹² A hand-held deVilbiss

Rheumatology Section,
Department of
Internal Medicine,
Uppsala University
Hospital, S-751 85
Uppsala, Sweden
B Gudbjörnsson
R Hällgren

Department of
Clinical Physiology,
Uppsala University
Hospital,
Uppsala, Sweden
H Hedenström

Department of
Lung Medicine,
Uppsala University
Hospital, Uppsala,
Sweden
G Ståhlenheim

Correspondence to:
Dr Gudbjörnsson.

Accepted for publication
1 February 1990

Table 1 Sex, age, serology, extraglandular manifestations and respiratory symptoms in 21 patients with primary Sjögren's syndrome

Case No	Sex	Age (years)	Serology		Extraglandular symptoms	Pulmonary symptoms
			RF* titre	ANA* titre, pattern		
1	F	22	— ‡	—	Sun sensitivity	None
2†	F	60	1/125	—	Raynaud's	Dry coughing
3	F	38	1/25	—	Raynaud's	Dry coughing
4	F	78	1/640	1/100 Speckled	Raynaud's	Exertional dyspnoea
5	F	60	—	1/25 Homogeneous	BC,* NEAr,* HTh,* Raynaud's	Dry coughing
6	F	71	—	1/1600 Nucleolar	NEAr, Raynaud's, kidney stone	'Asthma'
7	F	63	—	1/1600 Nucleolar	NEAr, Wmgl,* polyneuropathy, kidney stone	Dry coughing
8	F	62	—	—	None	Exertional dyspnoea
9†	F	55	1/80	1/25 Homogeneous	None	Dry coughing
10	F	55	—	—	None	None
11	F	40	—	1/400 Homogeneous	None	None
12††	F	41	1/80	—	None	'Asthma'
13	F	63	—	—	None	Exertional dyspnoea
14	F	43	—	1/100 Homogeneous	Kidney stone, cutaneous vasculitis	Dry coughing
15	F	51	1/25	—	Sun sensitivity, Raynaud's	Dry coughing
16	F	56	1/25	1/25 Speckled	HTh, NEAr, Raynaud's	None
17†	F	46	—	1/100 Homogeneous	Raynaud's	Dry coughing
18	F	38	—	1/3200 Homogeneous	Kidney stone, non-Hodgkin's lymphoma, leucopenia, neuropathy	Dry coughing
19	M	63	—	—	NEAr, Raynaud's	None
20	F	60	—	—	Raynaud's	Exertional dyspnoea
21	F	50	1/160	1/25 Speckled	None	None

*RF=rheumatoid factor; ANA=antinuclear antibody; BC=biliary cirrhosis; NEAr=non-erosive arthritis; HTh=hypothyroidism; Wmgl=Waldenström's macroglobulinaemia.

†Smokers; ††ex-smoker.

‡—indicates a titre <1/25.

646 nebuliser was used. After an initial test with saline the patients were tested with double dilutions of methacholine, at three minute intervals, starting with 1.2 mg/ml up to a maximum dose of 20 mg/ml. The subject inhaled for two minutes actuating the nebuliser during each inhalation. The nebuliser was weighed before and after each inhalation and the consumed dose calculated. The inhalation was discontinued when there was a fall in the FEV₁ of 20% or more below the lowest post-saline value. The test result was expressed as the provocation dose which caused a fall in FEV₁ of 20% (PD₂₀). The degree of BHR was divided into categories based on the PD₂₀ value: severe (<0.125 mg methacholine), moderate (0.125–1.2), mild (1.3–5.0), and slight (5.1–9.0). Twenty one healthy subjects (19 women, two men; aged 29–63 years; mean age 48 years) served as controls. One was a smoker and three were ex-smokers.

Results

The onset of the Sjögren's disease occurred two to 21 years (mean 9.5) before respiratory evaluation. Seven of 21 patients (33%) had only glandular symptoms, whereas extraglandular symptoms as well were evident in 14 patients (67%) (table 1). Fifteen patients (71%) had positive rheumatoid factor or antinuclear antibody titres, or both (table 1). Only three patients were anti-SSA and anti-SSB positive, however (case nos 14, 15, and 18).

METHACHOLINE CHALLENGE TEST RESULTS

Twenty patients underwent the methacholine inhalation challenge test. One patient (case No 12) had an FEV₁ lower than 1.0 l/min before methacholine inhalation and was therefore not challenged with methacholine. The bronchial response to methacholine inhalation showed that 12/20 (60%) of the patients fulfilled the criteria for BHR. One patient had severe BHR, five moderate, four mild, and two patients had slight BHR (table 2). In the reference group only two subjects had mild BHR (their PD₂₀ values were 3.2 mg and 3.4 mg).

CLINICAL SYMPTOMS AND BRONCHIAL HYPERRESPONSIVENESS

Dry non-productive coughing and foreign body sensation in the pharynx were noted in nine of the 21 patients. No one had productive cough. Exertional dyspnoea was seen in six of the 21 patients; in two of these patients asthma had been diagnosed. They suffered from intermittent wheezing, chest tightness, and breathlessness. Two patients had a history of pleuritis and five patients had frequent respiratory infections. Only four patients had smoked (table 1). Clinical examination showed that two patients had bilateral basal rales and four patients had prolonged expiration, one of whom had forced expiratory, low pitched rhonchi.

Seven patients had no extraglandular symptoms; two of these (29%) had evidence of slight to mild BHR. One patient (case No 12)

Table 2 Results of pulmonary function and methacholine challenge tests in 21 patients with primary Sjögren's syndrome

Case No	VC* (l) (% predicted)	FEV ₁ * (l) (% predicted)	FEV ₁ /VC	TlCO* (% predicted)	Methacholine PD ₂₀ * (mg)
1	4.1 (91)	3.4 (90)	82.9	78.9	4.4
2	2.2 (64)	1.9 (72)	86.4	63.3	0.62
3	4.5 (117)	3.8 (130)	84.4	71.5	1.8
4	2.4 (102)	1.7 (89)	70.8	87.4	0.08
5	3.5 (98)	2.4 (89)	68.6	81.7	3.2
6	3.3 (135)	2.2 (108)	66.7	71.7	0.14
7	3.6 (104)	2.6 (99)	72.2	73.4	0.36
8	3.5 (96)	2.1 (77)	60.0	77.9	1.8
9	3.7 (99)	2.7 (94)	73.0	70.4	6.6
10	2.9 (80)	2.4 (85)	82.8	71.4	>12
11	2.6 (72)	2.2 (73)	84.6	82.8	>9
12	2.3 (56)	0.7 (21)	30.4	51.8	Not done
13	4.1 (107)	3.1 (111)	75.6	100.1	>11.6
14	3.2 (78)	2.7 (84)	84.4	76.7	0.76
15	3.6 (96)	2.7 (92)	75.0	111.0	>9.35
16	3.9 (97)	2.4 (81)	61.5	80.7	0.4
17	2.8 (84)	1.9 (67)	67.9	Not done	7.0
18	3.9 (83)	3.0 (84)	76.9	67.2	>9.3
19	6.5 (149)	4.7 (137)	72.3	128.9	12.1
20	3.4 (100)	2.6 (99)	76.5	51.1	>11.1
21	3.6 (97)	3.0 (102)	83.3	74.0	>9.5

*VC=vital capacity; FEV₁=forced expiratory volume in one second; TlCO=transfer factor of the lung for CO; PD₂₀=provocation dose which caused a fall in FEV₁ of 20%.

without extraglandular symptoms was not tested because of a low postsaline FEV₁ value (FEV₁<1 l/min). Fourteen patients had extraglandular symptoms and 10 (71%) of these had BHR (table 3).

Ten of the 12 patients with BHR had subjective symptoms: dry non-productive cough, wheezing, or intermittent breathlessness. Two patients who had no subjective respiratory symptoms had mild and moderate BHR. Two patients had mild respiratory symptoms; one a non-productive cough and the other a mild exertional dyspnoea. Both displayed normal spirometry and methacholine inhalation tests. Two other patients with mild xerotracheitis and exertional dyspnoea respectively, had spirometrically interstitial lung disease without BHR (tables 1 and 2).

BRONCHIAL HYPERRESPONSIVENESS AND LUNG FUNCTION

The pulmonary functional evaluation showed that 16 of the 21 patients (76%) had abnormal spirometric findings (table 2). Based on these findings the patients were subgrouped into four groups:

Group I: Diffuse interstitial lung disease shown by impaired TlCO and without evidence of central or peripheral obstruction. This group included six patients (29%).

Table 3 Twenty one patients with primary Sjögren's syndrome divided into two groups: patients with glandular and extraglandular symptoms and their response to the methacholine challenge test*

Bronchial responsiveness to methacholine PD ₂₀ † (mg)	No (%) of patients with only glandular symptoms	No (%) of patients with extraglandular symptoms	Total
Normal (>9.0)	4 (57)	4 (29)	8 (38)
Slight (5.1-9.0)	1 (14)	1 (7)	2 (10)
Mild (1.3-5.0)	1 (14)	3 (21)	4 (19)
Moderate (0.125-1.2)	0	5 (36)	5 (24)
Severe (<0.125)	0	1 (7)	1 (5)
Not done (FEV ₁ <1.0 l/min)	1 (14)	0	1 (5)
Total	7	14	21

*The methacholine challenge test was not carried out in one patient (No 12) who had a low postsaline FEV₁ of less than 1.0 l/min.
†For abbreviations see table 2.

Table 4 Respiratory function findings and results of bronchial hyperresponsiveness (BHR) due to methacholine inhalation tests in 21 patients with primary Sjögren's syndrome

BHR (mg/ml methacholine)	Spirometry finding*			
	Normal	DILD	OLD	SAD
Normal (>9.0)	3	4	1	0
Slight (5.1-9.0)	0	1	1	0
Mild (1.3-5.0)	1	1	0	2
Moderate (0.125-1.2)	1	0	1	3
Severe (<0.125)	0	0	0	1
Not done	0	0	1	0

*DILD=diffuse interstitial lung disease; OLD=obstructive lung disease; SAD=small airways disease.

Group II: Obstructive lung disease shown by diminished FEV₁ and sGaw (specific Gaw) with normal VC and TLC. This group included four patients (19%).

Group III: Small airways disease shown by diminished Ve₂₅ and with normal sGaw, FEV₁, FVC, TLC, and TlCO. This group included six patients (29%).

Group IV: Patients with clinical respiratory symptoms of varying intensity with normal chest radiograph and normal spirometric lung function. Two patients (10%) were in this group.

Ten of the 12 patients with BHR (83%) had pathological spirometric findings (table 4). Two of the six patients with spirometrically diffuse interstitial lung disease had evidence of BHR. Four patients had obstructive lung disease and two of three patients challenged with methacholine inhalation had slight or moderate BHR. All patients with spirometrically 'small airways disease' had BHR.

BRONCHIAL HYPERRESPONSIVENESS AND LUNG RADIOGRAPHIC FINDINGS

Five (24%) patients had abnormal radiological findings. Three patients had minimal diffuse interstitial densities in the lungs; two of these patients had moderate BHR. One patient had bilateral nodular intensities in the lungs. This patient was not challenged with methacholine because of a low postsaline FEV₁ (case No 12). One patient had isolated bullae in the right lung and no BHR. No patient had pleural thickenings or effusion.

Discussion

Bronchial hyperresponsiveness is defined as an exaggerated bronchoconstrictive response in smooth muscles with airway narrowing to a small quantity of a non-allergic stimulus that does not provoke such a reaction in normal subjects.¹³ This airway narrowing may manifest itself as episodes of coughing, dyspnoea, and wheezing after exposure to stimuli such as cold air, smoke, exercise, and pharmacological agents such as histamine and methacholine. These symptoms can mimic xerotracheal symptoms in patients with primary Sjögren's syndrome.

Our study of consecutive patients with primary Sjögren's syndrome showed that 12/20

(60%) had BHR of varying severity and that the BHR correlated strongly with their subjective symptoms. In a control population of similar age and sex only 10% had mild BHR. All patients, except two, with a chronic dry cough and exertional dyspnoea had severe, moderate, or mild BHR when challenged with methacholine. The two patients with mild so-called xerotracheitis and exertional dyspnoea and without BHR were spirometrically abnormal with an impaired diffusion capacity. Only two patients with evidence of BHR were without any subjective respiratory symptoms.

In clinical studies the severity of BHR due to histamine or methacholine correlates strongly with the intensity of asthma or with the bronchial obstructive symptoms¹⁴ and remains stable over long periods in asthmatics in the absence of exacerbating factors.¹⁵ The BHR also correlates with the amount of treatment required to control the symptoms of the obstructive lung disease.¹⁶ Asthma may exist without BHR, however,¹⁷ and vice versa, BHR may exist in patients without bronchial asthma—for example, in those with chronic bronchitis or upper respiratory tract infections; patients with atopy or allergy without asthma may also have a mild or slight BHR.^{18–20} None of our patients had an active respiratory infection at the time of evaluation and none had a history of atopy or pollen allergy. Thus it is interesting that all the patients with spirometrically small airways' disease had BHR, while one of three tested patients with spirometrically obstructive lung function had no evidence of BHR.

Several studies have shown that the respiratory system is affected in primary Sjögren's syndrome.^{1–4 21–24} In secondary Sjögren's syndrome lung disease is often dominated by the associated autoimmune disease.^{4 25} Therefore, we studied only patients with primary Sjögren's syndrome, thus avoiding confusion with respiratory manifestations of concomitant autoimmune disorders. Our study showed that 19/21 (91%) of patients with primary Sjögren's syndrome, with or without extraglandular symptoms, had respiratory system disease, in which the major abnormality was a variable BHR response to methacholine in 12/20 (60%), followed by diffuse interstitial lung disease in 6/21 (29%) and small airways' disease in 6/21 (29%) and, finally, obstructive ventilatory function in 4/21 (19%). Previous studies have also reported that diffuse interstitial lung disease and small airways' disease are commonly seen in patients with primary Sjögren's syndrome.^{2 3} Others have described obstructive ventilatory defects as the major abnormality.^{5 6}

The mechanism behind BHR in patients with primary Sjögren's syndrome is not known but may be related to bronchial or tracheal inflammation. Bronchial hyperreactivity in other conditions has been explained as an activation of various cell types in the airways: mast cells, alveolar macrophages, eosinophils, and neutrophils. The release of inflammatory mediators may alter the function of nerves or the response of smooth muscle cells to reflex bronchial constriction.^{26 27} Such postulated mechanisms

may be present in patients with primary Sjögren's syndrome, who may have an inflammatory cell infiltration of the glands in the tracheal and bronchial mucosal membrane. Additionally, increased cell counts in bronchoalveolar lavage fluid are seen in 50% of patients with primary Sjögren's syndrome.²²

Our observations on BHR in primary Sjögren's syndrome seem to have some practical clinical implications. The strong correlation between BHR and symptoms of xerotracheitis sicca suggests that either BHR is secondary to dryness of the bronchial mucus or, alternatively, that symptoms due to BHR contribute to or mimic tracheitis sicca. Studies are in progress to determine whether or not pharmacological bronchodilators or inhaled corticosteroids reduce the troublesome symptoms of tracheitis sicca. Furthermore, the observation that all patients with small airways' disease but not all of the patients with spirometrically obstructive lung function have BHR may reflect the fact that it is the small airways that are affected and hyperresponsive to external stimuli. Thus repeated methacholine testing with progressive increases in BHR may be a better indicator than spirometry of patients at risk for developing progressive small airways' disease. Finally, the high incidence of impaired gas diffusion in primary Sjögren's syndrome might to some extent be influenced by an obstruction of the airways. Airway obstruction may induce an uneven distribution of alveolar ventilation,²⁸ which in turn may contribute to reduced TLCO values.

In conclusion, we have shown that BHR is the major respiratory disease in patients with primary Sjögren's syndrome. The respiratory evaluation of these patients with symptoms of chronic coughing and breathlessness should therefore include not only spirometry and chest radiographs but also a methacholine or histamine challenge test. Furthermore, the presence of primary Sjögren's syndrome should be considered in patients complaining of a chronic cough and obstructive lung symptoms and, in particular, when the lung radiograph is abnormal and pulmonary physiological findings are not fully compatible with the findings in bronchial asthma.

We thank Eva Persson and Sonja Nordström for their excellent technical assistance. This work was supported by grants from the Sättra Brunns Fund, the Swedish Medical Research Council, and the Swedish National Heart and Lung Fund.

- 1 Moutsopoulos H M, Chused T M, Mann D L, *et al*. Sjögren's syndrome (sicca syndrome): current issues. *Ann Intern Med* 1980; 92: 212–26.
- 2 Oxholm P, Bundgaard A, Birk Madsen E, Manthorpe R, Vejlo Rasmussen F. Pulmonary function in patients with primary Sjögren's syndrome. *Rheumatol Int* 1982; 2: 179–81.
- 3 Constantopoulos S H, Drosos A A, Maddison P J, Moutsopoulos H M. Xerotrachea and interstitial lung disease in primary Sjögren's syndrome. *Respiration* 1984; 46: 310–4.
- 4 Constantopoulos S H, Moutsopoulos H M. Respiratory involvement in patients with Sjögren's syndrome: Is it a problem? *Scand J Rheumatol [Suppl]* 1986; 61: 146–50.
- 5 Newball H H, Brahim S A. Chronic obstructive airway disease in patients with Sjögren's syndrome. *Am Rev Respir Dis* 1977; 115: 295–304.
- 6 Segal I, Fink G, Machtey I, Gura V, Spitzer S A. Pulmonary function abnormalities in Sjögren's syndrome and the sicca complex. *Thorax* 1981; 36: 286–9.
- 7 van Bijsterveld van O P. Diagnostic test in the sicca syndrome. *Arch Ophthalmol* 1969; 82: 10–14.

- 8 Heintze U, Birkhed D, Björn H. Secretion rate and buffer affect of resting and stimulated whole saliva as a function of age and sex. *Swed Dent J* 1983; 7: 227-38.
- 9 Chisholm D M, Mason D K. Labial salivary glands biopsy in Sjögren's disease. *J Clin Pathol* 1968; 21: 656-62.
- 10 Hedenström H, Malmberg P, Agarwal K. Reference values for lung function tests in females. Regression equations with smoking variable. *Bull Eur Physiopathol Respir* 1985; 21: 551-7.
- 11 Hedenström H, Malmberg P, Fredriksson H. Reference values for pulmonary function tests in men. Regression equations which include tobacco smoking variable. *Ups J Med Sci* 1986; 91: 299-310.
- 12 Hargreave F E, Ryan G, Thomson N C, O'Byrne P M, Latimer K, Juniper E F. Bronchial responsiveness to histamine or methacholine in asthma: measurement and clinical significance. *Eur J Respir Dis* 1982; 63 (suppl 121): 79-88.
- 13 Curry J J. Comparative action of acetyl-betamethacholine and histamine on respiratory tract in normals, patients with hayfever and subjects with bronchial asthma. *J Clin Invest* 1947; 26: 430-8.
- 14 Cockcroft D W, Killian D N, Mellon J J A, Hargreave F E. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977; 7: 235-43.
- 15 Juniper E F, Frith P A, Hargreave F E. Long-term stability of bronchial responsiveness to histamine. *Thorax* 1982; 37: 288-91.
- 16 Juniper E F, Frith P A, Hargreave F E. Airway responsiveness to histamine and methacholine: relationship to minimum treatment to control symptoms of asthma. *Thorax* 1981; 36: 575-9.
- 17 Giffon E, Orehek J, Vervloet D, Arnaud A, Charpin J. Asthma without airway hyperresponsiveness to carbachol. *Eur J Respir Dis* 1987; 70: 229-33.
- 18 Empey D W, Laitinen L A, Jacobs L, Gold W M, Nadel J A. Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. *Am Rev Respir Dis* 1976; 113: 131-9.
- 19 Mapp C E, Di Giacomo G R, Omini C, Broseghini C, Fabbri L M. Late, but not early, asthmatic reactions induced by toluene-diisocyanate are associated with increased airway responsiveness to methacholine. *Eur J Respir Dis* 1986; 69: 276-84.
- 20 Richardson J B. Airways smooth muscle. *J Allergy Clin Immunol* 1987; 80: 409-11.
- 21 Constantopoulos S H, Papadimitriou C S, Moutsopoulos H M. Respiratory manifestations in primary Sjögren's syndrome. A clinical, functional and histologic study. *Chest* 1985; 88: 226-9.
- 22 Harton P-Y, Wallaert B, Gosset D, et al. Subclinical lung inflammation in primary Sjögren's syndrome. *Arthritis Rheum* 1987; 30: 1226-31.
- 23 Anderson L C, Talal N. The spectrum of benign to malignant lymphoproliferation in Sjögren's syndrome. *Clin Exp Immunol* 1972; 10: 199-221.
- 24 Ziza J M, Kaplan G, Salomon C, Kahn M F. Fibroses pulmonaires graves révélatrices d'un syndrome de Gougerot Sjögren primitif. *Ann Med Interne (Paris)* 1986; 137: 46-50.
- 25 Andonopoulos A P, Constantopoulos S H, Drosos A A, Moutsopoulos H M. Pulmonary function of non-smoking patients with rheumatoid arthritis in presence and absence of secondary Sjögren's syndrome, a controlled study. *Respiration* 1988; 52: 251-8.
- 26 Chung K F. Role of inflammation in the hyperreactivity of the airways in asthma. *Thorax* 1986; 41: 657-62.
- 27 Barnes P J. Asthma as an axon reflex. *Lancet* 1986; i: 242-5.
- 28 Dal Negro R, Turco P, Pomari C, Zaccatelli O, Serra R. Bronchial hyperreactivity to fog challenge checked by a multiple parametrical method in FEV₁ non-responders atopic workers. *Wien Med Wochenschr* 1985; 135 (suppl 92): 20-1.