

Bronchorrhoea

M. LOPEZ-VIDRIERO, JANET CHARMAN¹, E. KEAL,
and LYNNE REID

Department of Experimental Pathology, Cardiothoracic Institute, Brompton Hospital, London SW3

Lopez-Vidriero, M., Charman, Janet, Keal, E., and Reid, Lynne (1975). *Thorax*, 30, 624–630. **Bronchorrhoea.** Bronchorrhoea has been defined as a condition in which more than 100 ml of sputum is produced within 24 hours, an amount in excess of that seen in chronic lung diseases. The rheological and chemical characteristics of the sputum are here described.

Levels of viscosity, dry weight, N-acetyl neuraminic acid (NANA), fucose, and sulphate fall between those in saliva and mucoid sputum from chronic lung diseases. These levels were always higher in bronchorrhoea sputum than in saliva and therefore may be used in the differential diagnosis of bronchorrhoea and hypersalivation.

Bronchorrhoea sputum has the constituents of a bronchial secretion but is low in acid glycoprotein. Certain other features are commonly found—a large amount of froth, increase in viscosity with time, and separation into two phases.

Some cases respond to steroids, particularly when the levels of NANA in the sputum are low.

Keal (1971) defined bronchorrhoea as the production of amounts of sputum in excess of 100 ml per day, an arbitrary figure chosen as being well above the average (25 ml) produced by patients with chronic bronchitis (Ashcroft, 1965; Miller, Tinker and Fletcher, 1965). Bronchorrhoea may be idiopathic (Hartley and Davies, 1923) or associated with lung diseases, such as tuberculosis (Gee, 1902), alveolar-cell carcinoma (Wood, 1943; Kennamer, 1951; Storey, Knudtson, and Lawrence, 1953; Schools and Ray, 1961), chronic bronchitis (Kourilski, 1960; Calin, 1972) or asthma (Keal, 1971).

In the present study of patients with bronchorrhoea measurements of the rheological properties and the chemical constituents of sputum are described. Sputum results were compared with those obtained for saliva and for mucoid sputum from diseases not complicated by bronchorrhoea. The effect of steroid treatment is also described.

MATERIAL AND METHODS

Sputum from 39 patients with bronchorrhoea as defined by Keal (1971) was studied. The patients were divided into two groups according to the type and number of tests performed.

GROUP I Thirteen patients had their sputum studied both rheologically and chemically, seven of these

serially before and during steroid treatment. A total of 210 specimens was studied.

GROUP II Twenty-six patients had only chemical analysis of their sputum; 23 of these were studied serially for response to steroids. In this group 238 sputa were examined.

Clinical details of the patients and main diagnoses are given in Table I. Diagnosis of the primary disease (chronic bronchitis, asthma, bronchiectasis, etc) was based on the medical history of the patients before the disease was complicated by bronchorrhoea. Diagnosis of chronic bronchitis was based on the Medical Research Council definition (1965), that of asthma on the CIBA Guest Symposium (1959). Bronchiectasis was diagnosed if persistent sputum production was associated with bronchographic evidence of airway dilatation and obliteration. The two cases of alveolar-cell carcinoma were diagnosed by the presence of malignant cells in the sputum. Cases with no evidence of previous lung diseases were regarded as idiopathic.

In all cases, the daily sputum volume was assessed. For rheological and chemical examination sputum specimens representing only one to three hours' production were collected in sterile polythene containers and, within an hour, viscosity measurements were made, using either a Ferranti-Shirley cone-plate viscometer in combination with a Bryans X-Y recorder (Palmer *et al.*, 1970; Charman and Reid, 1972) or a Weissenberg rheogoniometer (Platens 7.5 cm in diameter and a 6/65 torsion bar

¹ We regret to announce the sudden death of Mrs. J. Charman before this paper was published

TABLE I
PATIENTS STUDIED

Group	Primary Diagnosis	No. of Patients	Sex		Age (yr)	
			M	F	Mean	Range
I	Chronic bronchitis	3	3	0	50	48-52
	Intrinsic asthma	3	3	0	39	24-50
	Extrinsic asthma	1	1	0	44	—
	Bronchiectasis	1	1	0	36	—
	Scleroderma	1	1	0	43	—
	Alveolar-cell carcinoma	2	2	0	65	58-72
	Idiopathic	2	1	1	41	37-45
II	Chronic bronchitis	9	7	3	55	26-68
	Intrinsic asthma	13	10	3	40	22-58
	Extrinsic asthma	2	1	1	17	13-22
	Carcinoma	1	1	0	69	—
	Idiopathic	1	1	0		Not available

(Weissenberg, 1964). It is important to test sputum fresh as degradation occurs with time (Woodcraft *et al.*, 1974), and alteration in rheological properties occurs after some methods of freezing (Charman and Reid, 1973).

The Ferranti-Shirley viscometer tests were made over a shear rate range of 0-1800 sec⁻¹. With the Weissenberg rheogoniometer oscillation frequencies between 0.01 and 0.791 c/sec were used and both viscosity and elasticity were determined according to the formulae of Weissenberg (1964). Testing was carried out at room temperature. The remainder of the specimen was stored at -20°C for chemical studies.

For chemical analysis samples of sputum were coughed into a sterile glass jar kept at -70°C on cardice. Each three-hour collection was then stored at -20°C. Estimations were made of total macromolecular dry weight and concentration of N-acetyl neuraminic acid (NANA) (Warren, 1959) and in some cases of methylpentose-fucose (Gibbons, 1955) and sulphate (Antonopoulos, 1962).

CONTROLS Healthy subjects were asked to produce between 5 and 10 ml of saliva. Viscosity measurements, storage, and chemical constituents were carried out as on the sputum.

RESULTS

GENERAL PROPERTIES OF SPUTUM The sputum produced by patients with bronchorrhoea is transparent, mucoid, resembles uncooked egg-white, and is often topped by a large frothy layer. Most patients consistently produced more than 100 ml of sputum per day while others sometimes produced less. All patients usually produced mucoid sputum although an occasional specimen appeared purulent. Sometimes after standing on the bench the sputum seemed to gel spontaneously. Separation into two layers may occur, particularly after freezing and thawing, a

thicker more opaque fluid floating on a thin, clear, watery fluid. For certain tests each layer was studied separately.

VISCOSITY STUDIES

Ferranti-Shirley viscometer In all 13 cases from group I viscosity was measured by the Ferranti-Shirley viscometer and in five by the Weissenberg rheogoniometer also. Twenty-four samples of normal saliva were tested with the Ferranti-Shirley viscometer and two with the Weissenberg rheogoniometer.

Levels of apparent viscosity using the Ferranti-Shirley viscometer and a shear rate of 1350 sec⁻¹ are shown in Table II. Where more than one sample was obtained from a patient the mean and standard error are given. The range of viscosity for saliva was between 0.02 and 0.07 poise. With a range of 0.10-0.52 poise, bronchorrhoea sputum was always above this save for the sputum from one patient with alveolar-cell carcinoma (case 10). One layer of this patient's sputum was less viscous than saliva but more viscous than serum.

In no sputum or saliva sample was a yield point evident, as found in some bronchitic sputum (Elmes and White, 1953; Palmer *et al.*, 1970).

The rate of change of viscosity was calculated as the 'slope' over the last half of the 0-1800 sec⁻¹ run, the most reliable part (Charman and Reid, 1972); only one sputum from each patient or saliva specimen was studied in this way (Table II). For saliva the range was between 0.01 and 0.06 × 10⁻³ poise/sec⁻¹, for sputum values between 0.4 and 6.4 × 10⁻³ poise/sec⁻¹ save that the watery layer in case 10 was within the saliva range. This means that shearing produced a relatively greater fall in viscosity of sputum than saliva.

Weissenberg rheogoniometer For five cases, levels of viscosity and elasticity estimated at the lower shear rate available with the Weissenberg rheogoniometer

TABLE II
RHEOLOGICAL MEASUREMENTS USING THE FERRANTI-SHIRLEY VISCOMETER
ON BRONCHORRHOEA PATIENTS FROM GROUP I

Case	Associated Disease	Viscosity at 1350 sec ⁻¹ (poise)	'Slope' at 900-1800 sec ⁻¹ × 10 ⁻³ (poise/sec ⁻¹)	Increase in Viscosity on standing
1	Chronic bronchitis	0.268 (0.030) ¹	3.0	±
2	Chronic bronchitis	0.100	0.6	-
3	Chronic bronchitis	0.280	2.0	+
4	Intrinsic asthma	0.335 (0.029)	2.2	-
5	Intrinsic asthma	0.143 (0.028)	0.4	-
6	Intrinsic asthma	0.147 (0.037)	6.0	-
7	Extrinsic asthma	0.403 (0.142)	3.0	-
8	Bronchiectasis	0.039 (0.010)	1.3	-
		0.267 (0.060)	1.8	-
9	Scleroderma	0.316 (0.040)	6.0	-
10	Alveolar-cell carcinoma	0.012	0.01	-
		0.103 (0.055)	0.6	-
11	Alveolar-cell carcinoma	0.150 (0.013)	2.0	-
12	Idiopathic	0.160	6.4	+
		0.520		-
13	Idiopathic	0.300	1.7	-
	Saliva	0.029 (0.002)	0.01-0.06	-

¹Standard error of mean.

Where two results are given for one case the first is the thin layer and the second the thick.

TABLE III
RHEOLOGICAL MEASUREMENTS USING THE WEISSENBERG RHEOGONIOMETER
ON BRONCHORRHOEA PATIENTS FROM GROUP I

Case	Associated Disease	Viscosity at 0.791 c/sec (poise)	Elasticity at 0.791 c/sec (dyne cm ⁻²)	Plateau	Notching
1	Chronic bronchitis	6.90	0.12	+	-
2	Chronic bronchitis	15.71	0.95	+	+
3	Chronic bronchitis	2.05	0.12	+	+
7	Extrinsic asthma	3.90	1.41	+	-
12	Idiopathic	3.68	0.22	+	+

at 0.791 c/sec are given in Table III. At this shear rate for both features overlap occurred between saliva and sputum. For bronchorrhoea sputum the viscosity range was 2.05-15.71 poise, and for saliva 6.28-18.4 poise. The elasticity range was also similar for both bronchorrhoea sputum and saliva, 0.12-1.41 dyne cm⁻².

Sputum viscosity decreases with increasing shear rate but between 0.06 sec⁻¹ and 0.15 sec⁻¹ there is no change in viscosity and this region is referred to as the 'plateau region' (Sturgess, Palfrey, and Reid, 1970). A plateau region was found in sputum from all five bronchorrhoea cases, three of which were notched or fluctuating; the other two were smooth. A plateau region was also found in some specimens of saliva.

Effect of time The viscosity of certain samples was tested immediately on production and then again after being left in sealed containers at room temperature for several hours. The results are included in Table II. From two cases all sputum samples tested showed increases in viscosity with time, while from one patient this was seen in only some specimens. A single sample from this patient was tested with the Weissenberg rheogoniometer and showed a smooth plateau.

In contrast, saliva and sputum in diseases not associated with bronchorrhoea degrade with time due to enzymic action (Leach, 1963; Woodcraft *et al.*, 1974). The increase in viscosity seen in some of these bronchorrhoea specimens far exceeds any increase which would be expected from drying. Drying in an incubator at 37°C for an hour, to evaporate water to half the weight, results in only a twofold increase in viscosity (Reid, 1971).

Intraspecimen variation in viscosity The intraspecimen variation for bronchorrhoea sputum ranged from 11% to 70% with a mean value of 35.4% although in seven out of the nine cases studied the coefficient of variation fell within the range of 8-30% found for chronic bronchitis, asthma, and bronchiectasis (Charman and Reid, 1972). The high value of 70% found in one of the cases was due primarily to the presence of pus in some aliquots. The other case (61%) was an extrinsic asthma, and asthmatic sputum typically shows a higher variance (Charman and Reid, 1972).

Diurnal variation in viscosity None of the cases studied showed the diurnal variation pattern described in chronic bronchitis, of a high morning

TABLE IV

CHEMICAL CONSTITUENTS OF SPUTUM IN BRONCHORRHOEA, SALIVA AND IN MUCOID SPUTUM FROM CHRONIC BRONCHITIS, EXTRINSIC AND INTRINSIC ASTHMA: MEAN VALUES AND SE OF MEAN

Associated Diagnosis	No. Patients	No. Samples	Day Weight (mg/ml)	NANA ($\mu\text{mol/ml}$)	Fucose ($\mu\text{mol/ml}$)	NANA/Fucose (molar ratio)	Sulphate ($\mu\text{mol/ml}$)
Chronic bronchitis	12	52	13.66 (1.14)	1.73 (0.11)	2.86 (0.17)	0.82 (0.083)	
Intrinsic asthma	14	58	11.65 (0.83)	1.45 (0.13)	2.28 (0.16)	0.77 (0.05)	0.92 (0.17)
Extrinsic asthma	3	25	7.16 (0.51)	0.59 (0.05)	1.51 (0.12)	0.34 (0.03)	
Alveolar-cell carcinoma	3	17	13.35 (2.35)	0.92 (0.15)	0.95 (0.18)	0.71 (0.13)	0.52 (0.23)
Bronchiectasis	1	6	7.85 (0.99)	1.11 (0.16)	1.68 (0.29)	0.73 (0.13)	
Scleroderma	1	9	14.27 (1.54)	1.75 (0.15)	2.58 (0.14)	0.67 (0.002)	
Idiopathic	2	2	8.69 (0.09)	0.81 (0.187)	3.19 (1.23)	0.29 (0.08)	
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Saliva	6	10	2.90 (0.20)	0.08 (0.02)	0.38	0.14	0.13 (0.04)
Chronic bronchitis	15	25	15.90 (0.90)	2.50 (0.30)	5.30 (0.30)	0.40 (0.03)	1.84 (0.45)
Extrinsic asthma	6	18	14.30 (1.70)	2.60 (0.20)	4.90 (0.60)	0.60 (0.08)	1.34 (0.30)
Intrinsic asthma	4	8	13.10 (5.10)	2.50 (0.60)	5.00 (0.60)	0.50 (0.08)	

viscosity with a gradual fall during the day and an increase late in the afternoon (Lopez-Vidriero, 1974.)

CHEMICAL CONSTITUENTS OF SPUTUM Concentration and standard errors were calculated for the various chemical constituents of all sputum specimens studied and were grouped according to the primary diagnosis. The results are shown in Table IV and include all samples from groups I and II, excluding only sputum collected during steroid treatment. By reference to the concentration of any one constituent, saliva could be distinguished from sputum.

Separation into two layers Two specimens separated on standing into two layers—an upper opaque fluid floating on a watery clear fluid. The results of chemical analysis of the two layers, which were even more definite after storage at -20°C and thawing, are shown in Table V. In each case, the upper layer, as

CORRELATION BETWEEN VISCOSITY AND CHEMISTRY Correlation between viscosity and chemical constituents was possible in group I; samples collected during steroid treatment were excluded from this analysis.

No significant correlation was found between viscosity and chemical constituents for bronchorrhoea associated with chronic bronchitis, bronchiectasis or scleroderma. For patients with intrinsic asthma, significant direct correlations were found between viscosity and dry weight yield, NANA, and fucose ($p < 0.05$ respectively). The case of alveolar-cell carcinoma showed a significant direct correlation between viscosity and dry weight and fucose ($p < 0.05$ respectively).

RESPONSE TO DRUGS Table VI shows the primary diagnosis of 30 patients treated with steroids. The

TABLE V

DIFFERENCE IN CHEMICAL COMPOSITION OF TWO DISTINCT LAYERS

Case	Layer	Dry Weight (mg ml^{-1})	NANA ($\mu\text{mol/ml}$)	Fucose ($\mu\text{mol/ml}$)
8	Upper	13.08	2.62	4.14
	Lower	4.7	0.71	1.09
10	Upper	23.9	1.74	2.31
	Lower	8.04	0.45	0.97

well as having a higher viscosity (see Table II), had a higher dry yield and a higher concentration of NANA and fucose. The tertiary structure of the macromolecular glycoprotein in the top layer evidently confers buoyancy.

TABLE VI

RESPONSE TO STEROID TREATMENT

Primary Diagnosis	No. Treated	No. Positive	No. Negative
Chronic bronchitis	10 (1)	2 (1)	8
Intrinsic asthma	15 (3)	8 (1)	7 (2)
Extrinsic asthma	3 (1)	2	1 (1)
Alveolar-cell carcinoma	1 (1)	0	1 (1)
Scleroderma	1 (1)	0	1 (1)

¹Number from Group I.

drug was considered to be effective if the sputum volume dropped to levels usually found in the primary disease. Of the 30 patients, 12 responded; two were chronic bronchitics, eight had intrinsic asthma, and

two extrinsic asthma. All the cases from group II who improved with steroids had low initial NANA concentrations in the sputum.

DISCUSSION

All patients reported here were producing large volumes of sputum which is rare in chronic bronchitis (Ashcroft, 1965; Miller *et al.*, 1965) or asthma, although it has been found in alveolar-cell carcinoma (Storey *et al.*, 1953).

Levels of apparent viscosity, as measured with the Ferranti-Shirley viscometer, were all above saliva levels, and bronchorrhoea sputum can therefore be distinguished from hypersalivation as already described by Keal (1971). However, there is some overlap with the lower end of the ranges for mucoid sputum in diseases without bronchorrhoea, and rheological testing alone is not sufficient to distinguish bronchorrhoea sputum from other types of sputum.

The slope of the plot of viscosity against shear rate is similar to that found in other diseases (Charman and Reid, 1972), a shallow slope or relatively small effect of shearing being typical of a secretion of low viscosity. What is not typical is that the low shear rate used with the Weissenberg was less discriminating than the higher ones of the Ferranti-Shirley in distinguishing saliva from sputum. No sample exhibited a yield point, and although in other types of sputum this feature has been considered common (Palmer *et al.*, 1970), we have been unable to confirm this (Charman and Reid, 1972).

Sputum from patients with diseases not complicated by bronchorrhoea never increases in viscosity after production (Sturgess, Palfrey, and Reid, 1971), but several specimens in the present series increased in viscosity over some hours. Specimens which showed this increase were not necessarily those without notched plateaux. These two features might be expected to be linked since absence of notching probably indicates incomplete bonding (Sturgess *et al.*, 1970). These large amounts of secretion may be produced so quickly that polymerization is incomplete and proceeds even after the secretion has left the bronchial tree, which may also explain the separation into two layers: as the molecules become polymerized their buoyancy increases, causing them to float. The upper layer of the specimens which showed this phenomenon had a higher dry weight yield and a higher concentration of NANA and fucose, that is, it contained more acid glycoprotein than the lower layer.

Another unusual finding in bronchorrhoea is that the sputum is commonly very frothy and the froth is stable. This is not usual in chronic bronchitis sputum and suggests the presence of surfactant in the large

amounts of fluid which may arise from the alveoli or airways. The presence of surfactant has been looked for, and then it was found in one case of alveolar cell carcinoma described elsewhere (Spiro *et al.*, 1975).

The low viscosity of the bronchorrhoea sputum would mean that it is an entirely different secretion from a different source or that it is produced in a more hydrated form from the same source as in diseases not complicated by bronchorrhoea.

CHEMISTRY Chemical distinction of saliva from bronchorrhoea sputum was very clear. Dry weight, NANA, fucose, and sulphate levels of saliva were well below the sputum values. This has been reported previously for NANA (Anzai, Barker, and Stacey, 1957; Atassi *et al.*, 1959) in saliva and sputum from patients with chronic bronchitis.

Levels of dry weight, NANA, fucose, and sulphate were all lower than for either chronic bronchitis or asthma (Lopez-Vidriero and Reid, 1974). However, there is some overlap between the bronchorrhoea patients reported here and the lower values obtained for mucoid sputum in chronic bronchitis, asthma, and bronchiectasis.

Neither rheological nor chemical estimation can therefore be used alone as a diagnostic tool but must be used in combination with measurements of volume, macroscopic appearance, and behaviour with time.

CORRELATION OF VISCOSITY AND CHEMICAL CONSTITUENTS A significant correlation between viscosity and chemical constituents has been reported in mucoid chronic bronchitis and in purulent bronchiectasis (Lopez-Vidriero and Reid, 1974). The lack of correlation between viscosity and chemical constituents found in bronchorrhoea associated with chronic bronchitis or bronchiectasis may be due to the nature of the bronchial fluid produced in bronchorrhoea.

The amount of fucose and NANA in bronchorrhoea is about half that found in chronic bronchitis and bronchiectasis, while the NANA/fucose ratio is similar. This suggests that the secretion in bronchorrhoea is diluted rather than of different composition. There may be in addition incomplete polymerization.

Fucose is present in considerable amount in bronchial mucus and is negligible in serum while NANA is present in both; the NANA/fucose ratio could therefore give us an indication of the relative proportions of bronchial mucus and serum transudate. The high correlation between fucose and NANA reported in mucoid sputum suggests that

there is a high degree of predictability of viscosity from the concentration of either of these substances.

In the three patients with intrinsic asthma the viscosity showed a significant correlation with dry weight, NANA, and fucose in that order. The trends in correlation for mucoid intrinsic asthma without bronchorrhoea were different in that the highest correlation was with fucose followed by NANA and dry weight (Lopez-Vidriero and Reid, 1974), suggesting that in this group mucus contributed to the viscosity while when bronchorrhoea was also present the serum contribution was responsible, perhaps because of interaction of serum proteins with bronchial glycoproteins (Puchelle, Zohm, and Havez, 1973). This is supported by the fact that in intrinsic asthma associated with bronchorrhoea the NANA/fucose ratio was considerably higher than in asthma alone, that is, the serum contribution was relatively increased.

The alveolar-cell carcinoma showed the highest correlation between viscosity and fucose, which indicates that for this secretion the mucus was important in determining viscosity. It may be that the large volume of sputum produced in bronchorrhoea is due to a change of the secretion from the mucus-secreting cells or to an increase in serum transudate or a combination of these two.

STEROID TREATMENT Steroids have been used successfully in bronchorrhoea associated with extrinsic and intrinsic asthma, especially where low levels of NANA are found in sputum (Keal, 1970; 1971). The cases reported here confirm these findings. Sputum from chronic bronchitis associated with bronchorrhoea usually has a high NANA concentration and responds poorly to steroids, but some improvement was achieved in two cases of chronic bronchitis, one of which had a high sputum NANA content.

Two cases with very low NANA levels however failed to respond to steroids. One was a man with extrinsic asthma and the other had an alveolar-cell carcinoma. It is probable that the excess secretion from the latter was autonomous and not under nervous control since the volume did not alter with either atropine injections or fluid deprivation (Spiro *et al.*, 1974). This agrees with the findings of Rubinstein and Pilheu (1954), Turiaf, Marland, and Sors (1957), and Gernez-Rieux *et al.* (1964). However, Siltzbach, L. E. (personal communication) achieved a sharp reduction in sputum volume in four cases of alveolar-cell carcinoma after ACTH therapy.

It is known that steroids alter the permeability of membrane but whether they have an effect on the blood vessels or the cells in bronchorrhoea is not known.

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Requests for reprints to: Professor Lynne Reid, Department of Experimental Pathology, Cardiothoracic Institute, Brompton Hospital, London SW3.