# Chemical Balance as a Rheometer for Biological Fluids

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**Abstract** □ The chemical balance provides a simple, cheap, and readily available method of assessing the consistency of biological fluids such as sputum. Scale reading at an arbitrary time provides a useful empirical parameter that can be employed in routine testing of clinical samples and in the assessment of mucolytic agents. It also correlates well with data obtained using a conventional cone and plate viscometer. The change of scale reading with time can be analyzed in a fundamental rheological manner using the linear viscoelastic model. The method of measurement is nondestructive and allows repeated measurements to be made on the same sample.

**Keyphrases** □ Chemical balance—used as rheometer □ Rheometer—chemical balance use □ Sputum—rheological measurements □ Viscosity measurements—viscometer, chemical balance comparison □ Mucolytic agent effect—sputum viscosity

In the past, many attempts have been made to obtain some form of "viscosity" or consistency measurement for complex biological fluids such as sputum and to correlate this with variables such as state of disease, biochemistry, and the action of mucolytic agents. Unfortunately, sputum is not a simple Newtonian fluid, and its rheological evaluation is beset with many difficulties. These can be summarized as follows (1, 2): (*a*) limited sample size; (*b*) highly shear-sensitive structure which is easily destroyed in sample collection or in its preparation for examination; (*c*) inhomogeneity; (*d*) material cannot be frozen or homogenized without greatly altering its structure; (*e*) complex nature of material makes it difficult to obtain fundamental rheological parameters; (*f*) *in vitro* rheological measurements must be representative of the conditions that exist *in vivo;* and (*g*) material changes rapidly in consistency after collection due to loss of water and biodegradation.

Using sputum as the representative biological fluid, the authors examined some of the previous attempts to measure consistency (Table I). It is clear that many of the difficulties listed have not been given proper consideration; it is, therefore, not surprising that few reasonable consistency correlations have been obtained. Only in the more recent studies of Hwang *et al.* (1), Denton *et al.* (22), Davis and Dippy (24), and Sturgess *et al.* (25) have fundamental rheological param-

**Table I**—Rheological Evaluation of Sputum

| Method and References | Advantages | Disadvantages |
|---|---|---|
| 1. U-tube viscometer (3–9) | Simple and inexpensive | Variable shear rate; single-point method; destructive; data of doubtful significance; often impossible to obtain meaningful results |
| 2. Falling-sphere viscometer (10) | Same as for No. 1 | Same as for No. 1 |
| 3. Concentric-cylinder viscometer (5, 6, 8, 11–14) | Different shear rates can be studied (hysteresis effects); non-Newtonian behavior; can be used effectively as comparative method | Destructive; high shear rates that are almost impossible to correlate with *in vivo* conditions; some instruments only single point; automatic recording instruments are expensive; often impossible to obtain meaningful results |
| 4. Cone and plate viscometer (15–19) | Small sample size; same as for No. 3 | Material can be expelled from measuring surface; evaporation; same as for No. 3 |
| 5. Perforated disk (2, 8, 20, 21) | Simple and inexpensive; yield effects can be measured | Destructive; measured parameter difficult to interpret in fundamental manner; poorly reproducible |
| 6. Magnetic rheometer (1, 22, 23) | Provides fundamental viscoelastic data, elasticities, viscosities, *etc.*, which can be correlated with *in vivo* conditions and molecular structure | Complex experimentally; not suitable for routine testing; complex mathematical analysis requiring digital computer |
| 7. Rheogoniometer (oscillation) (24, 25) | Wide frequency range; same as for No. 6 | Very expensive, especially when using automatic data-collection method; same as for No. 6 |
| 8. Rheogoniometer (creep testing) (24) | Same as for No. 6 | Not suitable for samples of low consistency; same as for No. 6 |

eters been obtained that can be correlated sensibly with mucus structure and cilia transport. In these cases, the linear viscoelastic model was employed as a convenient starting point and the experimental results were interpreted in terms of viscosities, elasticities, and relaxation or retardation times.

In some cases, such as the assessment of mucolytic agents or the routine examination of clinical samples in the clinical laboratory, a detailed viscoelastic treatment is time consuming and probably unnecessary (16). It would rarely warrant the considerable capital outlay needed for setting up the experimental and data analysis procedures. Therefore, an instrument is needed that will satisfy the necessary conditions without being unduly expensive. The basic requirements for this instrument are:

1. It must be capable of dealing with a small sample size, a maximum of a few milliliters.
2. It must be robust and cheap.
3. It must be simple to operate in routine tests by unskilled technical staff.
4. The measurement should be reasonably quick to perform so that large numbers of samples can be examined without delay.
5. It should provide some easily calculated, empirical parameter that will characterize consistency in a rheologically sound manner.
6. The data obtained should also be amenable to further treatment to obtain fundamental quantities such as viscosities and elasticities, should these be required.
7. The test should be nondestructive to enable repetition with the same sample in storage or kinetic experiments.
8. The conditions of test should be such that the derived data describes as well as possible the conditions *in vivo*.

Fortunately, a minor adaptation of the modern chemical balance is suitable for this purpose. This, of course, is standard equipment in nearly all laboratories.

## APPARATUS

A conventional chemical balance (Stanton A.D.3) forms the main part of the apparatus (Fig. 1). The essential requirement is some type of illuminated scale that gives readings over the range 0–100 mg. A small glass plate (microscope cover slip) is suspended from one side of the balance and is immersed in the test fluid, which can be conveniently contained in a spectrophotometer cell. The latter is adjusted using a rack and pinion movement, and the whole assembly is enclosed in a thermostated glove-box at required temperature. The final setup is similar in a number of ways to the rising sphere viscometer described by McVean and Mattocks (26) and the commercial Haake Viskowaage viscometer (27).

**Operation of the Balance**—The glass plate is counterbalanced so that the reading on the illuminated scale is at the 100-mg. mark. The material under test is placed in the cell, and the plate is carefully immersed so that it is in the center of the cell and well below the surface. The vertical position of the cell is then adjusted, if necessary, to correct for buoyancy and to ensure that the balance is once again "zeroed" at the 100-mg. position. A 100-mg. weight is added carefully to the right-hand scale pan, and the change in scale reading with time is followed with a stopwatch.

**Theoretical Considerations**—From an analysis of the principle of the chemical balance, one can easily show that in the absence of a sample in the cell the balance system can be represented by a mechanical model (Fig. 2A), consisting of a spring (elastic) element and a dashpot (viscous) element arranged in parallel. The spring $G_b$ represents the movement of the balance in response to a weight

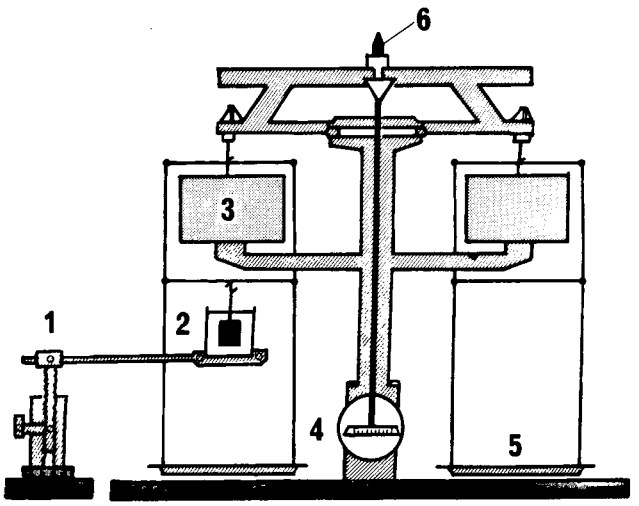


**Figure 1**—*Diagram of apparatus. Key: 1, rack and pinion stand; 2, cell and glass plate; 3, mechanical damper of balance; 4, illuminated scale; 5, weight added to this scale pan; and 6, counterbalance arrangement.*

placed on the scale pan, and the dashpot $\eta_b$ represents the mechanical damping of the balance together with friction in the knife edges, *etc.* $G_b$ will be directly proportional to the sensitivity of the balance. The ratio $\eta_b/G_b$ is called the retardation time ($\tau_b$).

In rheological terms, this representation is equivalent to a Voigt (Kelvin) solid (28). Material placed in the cell will naturally change the situation, as shown in Fig. 2B–E. The Newtonian fluid (Fig. 2B) and the Voigt solid (Fig. 2D) are trivial cases since similar models in parallel are additive (29); however, the Maxwell

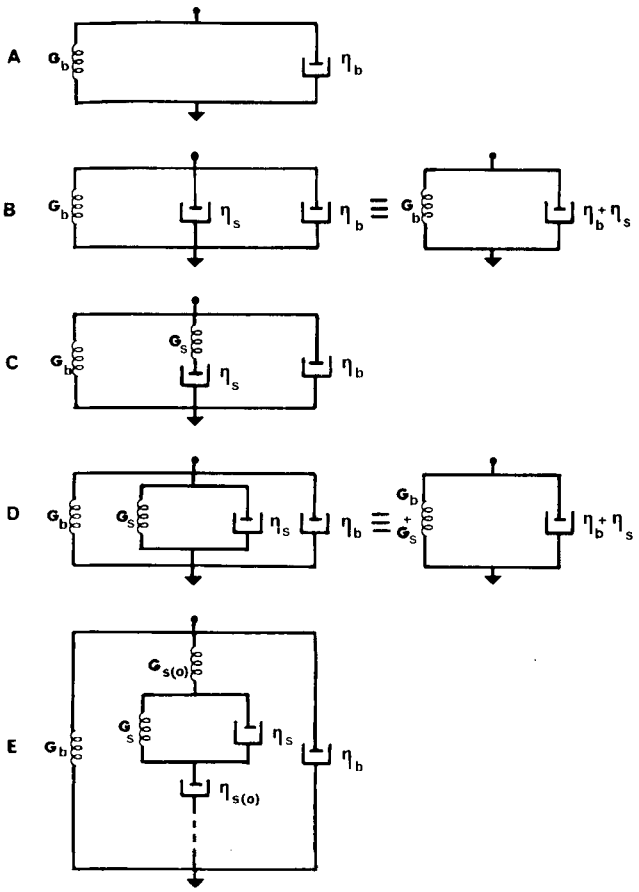


**Figure 2**—*Model representation. Key: A, balance alone; B, Newtonian fluid in cell; C, Maxwell fluid in cell; D, Voigt material in cell; and E, generalized viscoelastic material in cell.*

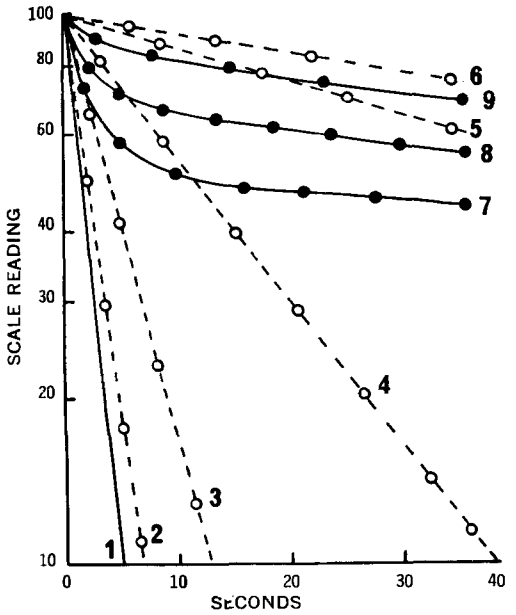


**Figure 3**—*Change in balance scale reading with time for different materials. Key: balance without sample (——), 1. Newtonian fluids (- - O - -): caster oil ($\eta_s$ = 8.0 P), 2; silicone oils—($\eta_s$ = 1250cS), 3; ($\eta_s$ = 3000cS), 4; ($\eta_s$ = 60,000cS), 5; and ($\eta_s$ = 100,000cS), 6. Complex materials (—●—●): egg white, 7; sputum, 8; and tragacanth mucilage, 9.*

liquid (Fig. 2C) and the generalized viscoelastic material (Fig. 2E) provide rather complex models. Nevertheless, it is possible to analyze these, subtract out the inherent contribution of the balance, and thereby represent the behavior of the material in the conventional viscoelastic manner (see *Appendix*). However, as neither stress nor strain is held constant during an experiment, this is not a simple process and, in routine testing, little is to be gained. The change in scale reading (equivalent to a change of strain) with time is an extremely useful, albeit empirical, parameter for studying rheological behavior.

**The Newtonian Fluid**—The Newtonian fluid (Fig. 2B) provides the simplest possible condition for rheological testing, and it is instructive to examine this in detail. When the 100-mg. weight is placed on the right-hand scale pan, the plate will be moved upward through the test fluid, and the change in strain will be proportional to the reading on the illuminated scale. The strain–time response for a Voigt model can be represented by Eq. 1 (30):

$$\gamma_t = \gamma^{\infty}(1 - e^{-t/\tau}) \qquad \text{(Eq. 1)}$$

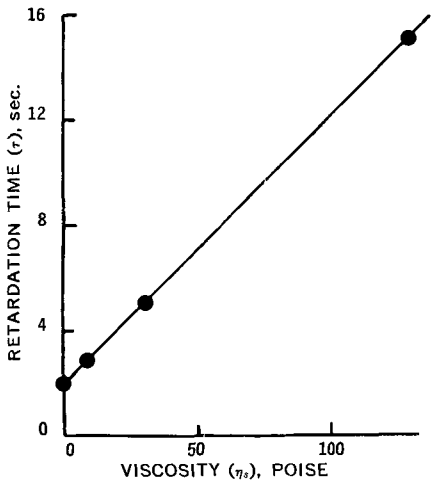


**Figure 4**—*Calibration of balance viscometer with Newtonian fluids (25°). Viscosity standards: mineral oil ($\eta_s$ = 14.5 P); and silicone oils ($\eta_s$ = 30.9 P) and ($\eta_s$ = 129 P).*

where $\gamma_t$ is the strain at time $t$, and $\gamma^{\infty}$ is the total strain at infinite time. Or, in terms of scale readings, $S$, and 100 mg. as the zero:

$$100 - S_t = 100(1 - e^{-t/\tau}) \qquad \text{(Eq. 2)}$$

which, on rearranging:

$$S_t/100 = e^{-t/\tau} \qquad \text{(Eq. 3)}$$

Taking logs:

$$2.303 \log S_t - 4.606 = -t/\tau \qquad \text{(Eq. 4)}$$

$$\log S_t = 2 - t/2.303\tau \qquad \text{(Eq. 5)}$$

The retardation time will be made up from two contributions, a retardation time associated with the balance ($\tau_b$) and one with the Newtonian sample ($\tau_s$):

$$\tau = \tau_b + \tau_s \qquad \text{(Eq. 6)}$$

A graph of scale reading against time, in semilog form (Fig. 3), for a Newtonian fluid will be linear with gradient $-1/(2.303\tau)$ and the intercept at the 100-mg. unstressed position. The combined retardation time can easily be calculated.

The $\tau$ is defined as the ratio of viscosity to spring modulus for the Voigt model. For the Newtonian fluid in the cell,

$$\tau_s = K_1\eta_s/G_b \qquad \text{(Eq. 7)}$$

where $K_1$ is an apparatus constant that will depend on the geometry of the plate and the cell. Substituting in Eq. 6:

$$\tau = \tau_b + K_2\eta_s \qquad \text{(Eq. 8)}$$

where $K_2 = K_1/G_b$. A graph of $\tau$ *versus* $\eta_s$ will be linear with gradient $K_2$ and intercept $\tau_b$. The latter can be obtained by following the movement of the balance when there is no sample in the cell. A calibration curve can thus be obtained using Newtonian fluids of known $\eta_s$ (Fig. 4).

The viscosity term ($\eta_s$) is defined from Newton's law as the ratio of shear stress to shear rate. Shear stress will be directly related to the apparatus geometry. Changing the size of the plate will have a direct effect on the shear stress through an area relationship, and one can write

$$\tau = \tau_b + AK_3 \qquad \text{(Eq. 9)}$$

where $A$ is the surface area of the plate and $K_3 = K_2\eta_s$.

For a given Newtonian oil, $\tau$ will be linearly related to plate area with intercept $\tau_b$ and gradient $K_3$. However, experimental data plotted in this manner do not pass through the expected intercept, and an end-correction term is evident such that

$$\tau = \tau_b + (A + Ae)K_3 \qquad \text{(Eq. 10)}$$

It is to be expected that this end-correction value will vary to some extent with the viscosity of the test fluid (31).

Similar experiments with polystyrene spheres also give a linear

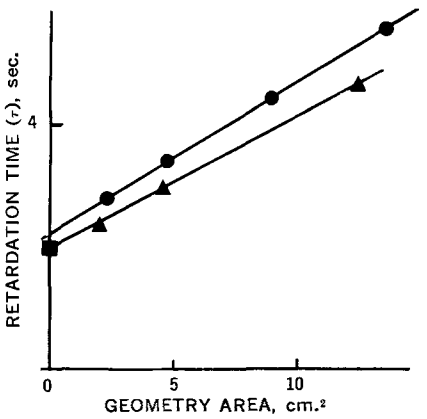


**Figure 5**—*Change in retardation time with apparatus geometry. Key: —●—, glass plates; and —▲—, polystyrene spheres.*

Table II—Comparison of Balance Method and Ferranti-Shirley Viscometer for the Effect of Water and Mucolytic Agent[a] on the Consistency of Sputum (Contact Time = 20 min.)

| Viscometer | Measured Parameter | Percent Reduction in Parameter Compared to Untreated Sputum (Mean & *SD*) | | No. Experiments |
|---|---|---|---|---|
| Balance | Scale reading at 60 sec. | Water | 22.5 ± 12.9 | 20 |
| | | Mucolytic agent | 54.3 ± 11.1 | 20 |
| Ferranti-Shirley | Static yield value | Water | 26.2 ± 14.8 | 10 |
| | | Mucolytic agent | 55.6 ± 11.1 | 10 |
| | Dynamic yield value | Water | 25.0 ± 12.6 | 10 |
| | | Mucolytic agent | 56.1 ± 16.5 | 10 |
| | Apparent viscosity | Water | 22.1 ± 12.4 | 10 |
| | | Mucolytic agent | 61.0 ± 14.6 | 10 |
| | Limiting viscosity | Water | 22.8 ± 12.6 | 10 |
| | | Mucolytic agent | 60.9 ± 13.7 | 10 |

[a] Ascoxal–ascorbic acid–hydrogen peroxide–cupric-ion system.

plot between $\tau$ and $A$ but without an end correction. This is as expected from theoretical considerations (32, 33) (Fig. 5).

## SOME PRACTICAL SYSTEMS

Experiments with a range of Newtonian fluids (Figs. 3 and 4) show that the instrument can be used without modification for viscosities in the range 1–1000 P. Complex non-Newtonian fluids such as sputum do not give linear relations between log $S$ and time. Instead, the scale reading changes rapidly at short times and then more slowly at long times until it reaches an almost constant value. The same sample of biological fluid can be subjected to repeated measurements with little or no change in the measured log $S$ *versus* $t$ curve. The movement of the plate (*i.e.*, the strain) is small and, therefore, the method is essentially a nondestructive test. In practice the sample is usually examined a number of times, and a mean or self-consistent curve is taken as being representative. In repeated measurements the variation in measured scale readings is in the region of 10%, provided that care is taken in centering the plate in the cell well below the surface.

The sensitivity of the balance can be controlled by the counterbalance arrangement above the fulcrum of the balance. Theoretically, there is no reason why the counterbalance should not be set so that the fulcrum and center of gravity are coincident to provide the experimental conditions for pure creep (constant stress). However, experimentally the system would be mechanically unstable. The retardation time of the balance is directly related to the sensitivity, and the range on the illuminated scale can be changed if required using the counterbalance arrangement.

As an alternative to the full viscoelastic treatment for complex materials (see *Appendix*), the scale reading at an arbitrary time or the limiting scale reading as $t$ becomes large is a suitable parameter for use in comparative experiments. For linear viscoelastic materials, the former is very similar to a compliance at arbitrary time measured from a creep curve. This is a popular approach in studies on polymer solutions and pharmaceutical systems (34, 35). In many cases, little difference exists between the two suggested parameters at times greater than 40 sec.

## COMPARISON OF BALANCE METHOD WITH FERRANTI-SHIRLEY VISCOMETER

The results obtained with the balance were compared with those from the conventional Ferranti-Shirley cone and plate viscometer (28) for measurements on the consistency of sputum (Table II). The scale readings at an arbitrary time of 60 sec. were chosen for the balance experiments and compared with four rheological parameters obtained from the sputum rheogram off the Ferranti-Shirley viscometer. The rheological parameters were: (*a*) static yield value—minimum shear stress necessary to cause the unsheared material to flow (dyne cm.$^{-2}$); (*b*) dynamic yield value—minimum shear stress required to keep the sample in flow once it has been sheared (dyne cm.$^{-2}$); (*c*) apparent viscosity—ratio of shear stress to shear rate at the highest shear rate (poise); and (*d*) limiting viscosity—reciprocal of the gradient of the down-curve of the hysteresis loop (poise).

The comparison was made on the basis of percent reduction in rheological parameter upon addition of water or a mucolytic agent[1] as compared to an untreated sample. In all cases, the standard deviations about the mean are large due to considerable biological variation. Nevertheless, statistical analysis (16) shows that the results are valid and can be used in a comparative manner. The agreement between the two methods, balance and Ferranti-Shirley viscometer, is extremely satisfactory, especially when one considers that two different measurement principles are used. There is a slightly better correlation between the balance method and the two yield values from rheograms than with viscosities. This is as expected, because yield values can be considered as an estimate of solidlike structure in a material and will, therefore, be closer in physical nature to scale readings obtained in a nondestructive test than viscosity values calculated after a material has been broken down by shear.

## KINETIC EXPERIMENTS

Besides having the great advantage of inexpensiveness, the balance method is also almost nondestructive and the same sample can be examined a number of times. Therefore, kinetic experiments can be performed, provided that the kinetic process proceeds at a rate whereby little change occurs in the consistency of the sample during the period of measurement. Figure 6 shows the effect of contact time for the mucolytic agent on the log $S$ *versus* $t$ curves of sputum. To obtain similar information with the Ferranti-Shirley viscometer, fresh samples have to be loaded for each measurement. This introduces sampling errors. The percentage reduction in consistency with mucolytic contact time is shown in Fig. 7. Once again the agreement between the two different methods of evaluation is satisfactory.

## APPENDIX

**Calculation of Viscoelastic Parameters**—The rheological behavior of biological fluids can often be examined in a fundamental manner, using the linear viscoelastic model as a convenient starting point (1, 24). It can be used effectively in the present case, provided the strain response of the material is small and it is behaving in a linear viscoelastic manner (37). The behavior of the balance system will be superimposed upon the model and will contribute $G_b$ and $\eta_b$, respectively, to the elasticity and viscosity of the total system (Fig. 8, System I). The material under examination can be represented by a subsystem consisting of a series of Voigt elements ($G_{sr}$, $\eta_{sr}$) with or without a final series viscosity ($\eta_{s(0)}$). Moreover, the total combined system can be represented by the series Voigt system in Fig. 8, System II; in general, Systems I and II are entirely equivalent over a wide range of time (in creep testing) or frequency (in oscillatory testing) (29).

The problem is to evaluate the material subsystem in System I. This may be achieved by employing an intermediate hypothetical

[1] Ascoxal, Astra-Hewlett Ltd., Watford, England.

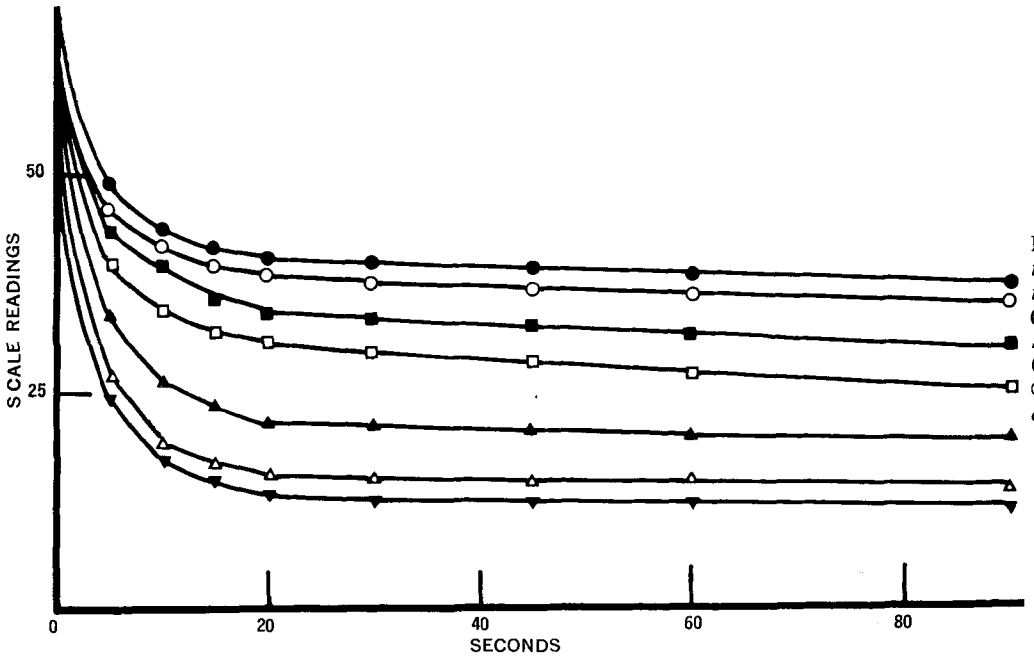


**Figure 6**—*Effect of contact time of the mucolytic agent on the consistency curves for sputum (repeated measurements on same sample). Mucolytic contact time (min.): ●, 0 (control with water); ○, 5; ■, 10; □, 15; ▲, 20; △, 30; and ▼, 40.*

oscillatory experiment of wide frequency range. The steps in the analysis are as follows:

1. Conventional creep curve analysis is used to evaluate the viscoelastic models in System II (30, 38).

2. From the models produced by this procedure, the frequency response over a wide range of frequency is then evaluated using the following equations (29):

$$J'(\omega) = \sum_{r=1}^{n} J_r\left(\frac{1}{1 + \omega^2\tau_r^2}\right) \qquad \text{(Eq. A1)}$$

$$J''(\omega) = \sum_{r=1}^{n} J_r\left(\frac{\omega\tau_r}{1 + \omega^2\tau_r^2}\right) \qquad \text{(Eq. A2)}$$

3. The complex modulus is then computed from the complex compliance over a similarly wide frequency range. Since

$$G^*(\omega) = 1/J^*(\omega) \qquad \text{(Eq. A3)}$$

$$G^*(\omega) = G'(\omega) + iG''(\omega) = 1/[J'(\omega) + iJ''(\omega)] = \frac{J'(\omega) - iJ''(\omega)}{[J'(\omega)]^2 + [J''(\omega)]^2} \qquad \text{(Eq. A4)}$$

4. After Step 3 is completed, the total arrangement can be considered equivalent to System I. The contribution of the balance $G_b' + iG_b''$ is known:

$$G_b' = G_b \qquad \text{(Eq. A5)}$$

$$G_b'' = \omega\eta_b \qquad \text{(Eq. A6)}$$

and, therefore, can be subtracted from the total complex modulus to give that of the subsystem in System I, using Eqs. A5 and A6:

$$G_s'(\omega) = G'(\omega) - G_b'(\omega) \qquad \text{(Eq. A7)}$$

$$G_s''(\omega) = G''(\omega) - G_b''(\omega) \qquad \text{(Eq. A8)}$$

5. The complex compliance of the subsystem can then be calculated:

$$J_s'(\omega) + iJ_s''(\omega) = \frac{G_s'(\omega) - iG_s''(\omega)}{[G_s'(\omega)]^2 + [G_s''(\omega)]^2} \qquad \text{(Eq. A9)}$$

6. The values of $J_s'(\omega)$ and $J_s''(\omega)$ can finally be used to calculate either a line spectrum or continuous spectrum of viscoelastic behavior for the material (37).

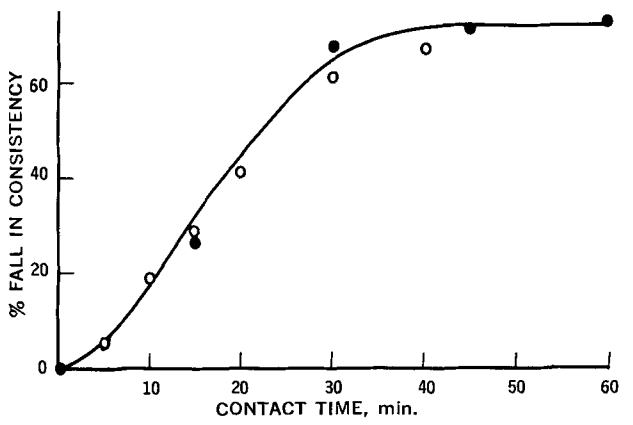


**Figure 7**—*Change in consistency with contact time for the action of the mucolytic agent on sputum. Comparison of balance rheometer and Ferranti-Shirley viscometer. Key: ○, balance (calculated from scale reading at 60 sec.); and ●, Ferranti-Shirley viscometer [mean value from change in four rheological parameters (Table II)].*

## SYMBOLS

$A$ = surface area, cm.$^2$
$Ae$ = end correction, cm.$^2$
$G_b$ = elastic contribution (shear modulus) associated with balance, dyne cm.$^{-2}$

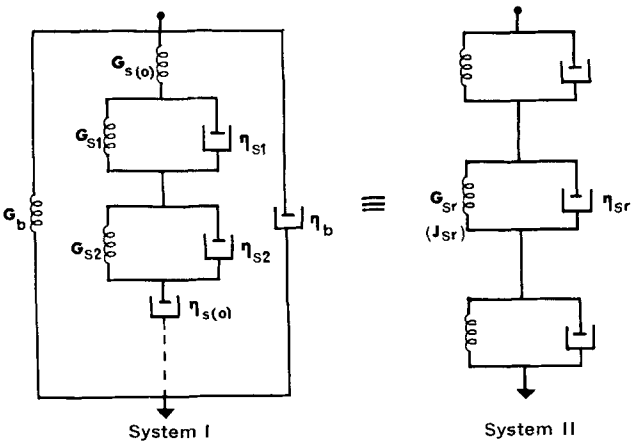


**Figure 8**—*Models for calculating viscoelastic data.*

$G_{sr}$ = shear modulus of test sample, Voigt unit $r$, dyne cm.$^{-2}$
$G'(\omega)$ = real part of total complex modulus, at frequency $\omega$ rad. sec.$^{-1}$
$G''(\omega)$ = imaginary part of total complex modulus, at frequency $\omega$ rad. sec.$^{-1}$
$G^*(\omega)$ = complex modulus [$= G'(\omega) + iG''(\omega)$]
$J_{sr}$ = compliance of test sample, Voigt unit $r$, cm.$^2$ dyne$^{-1}$
$J'(\omega)$ = real part of complex compliance, at frequency $\omega$ rad. sec.$^{-1}$
$J''(\omega)$ = imaginary part of complex compliance, at frequency $\omega$ rad. sec.$^{-1}$
$J^*(\omega)$ = complex compliance [$= J'(\omega) + iJ''(\omega)$]
$K_n$ = apparatus constants
$S$ = scale reading
$i$ = $\sqrt{-1}$
$t$ = time
$\gamma$ = strain
$\eta_s$ = viscosity of Newtonian fluid, poise
$\eta_b$ = viscous contribution associated with balance, poise
$\eta_{sr}$ = viscosity of test sample, Voigt unit $r$
$\eta_{s(0)}$ = viscosity of uncoupled Newtonian dashpot in viscoelastic model
$\tau$ = total retardation time, sec.
$\tau_b$ = retardation time of balance, sec.
$\tau_s$ = retardation time for Newtonian fluid in apparatus
$\tau_r$ = retardation time for Voigt unit $r$ ($= \eta_r/G_r$)
$\omega$ = frequency, rad. sec.$^{-1}$

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