Boissard, J. M., and Fry, R. M. (1941). *Publ. Hlth.*, London, **54**, 105.
—— —— (1942). *Lancet*, **1**, 610.
Bourdillon, R. B., and Lidwell, O. M. (1941). Ibid., **2**, 365.
—— —— and Lovelock, J. E. (1942). *British Medical Journal*, **1**, 42.
Brown, W. A., and Allison, V. D. (1937). *J. Hyg.*, Camb., **37**, 1.
Casassa, M. T. (1937). *Gior. Batt. Immun.*, **18**, 381.
Chapin, C. V. (1912). *The Sou ces and Modes of Infection*, New York.
Colebrook, L. (1933). *British Medical Journal*, **2**, 723.
Cornet, G. (1889). *Z. Hyg.*, **5**, 191.
Crosbie, W. E., and Wright, H. D. (1941). *Lancet*, **1**, 656.
Cruickshank, R. (1941). Ibid., **1**, 493.
De Waal, H. L. (1940). *J. Hyg.*, Camb., **40**, 172.
Dold, H., and Weigmann, F. (1935). *Z. Hyg. InfektKr.*, **116**, 158.
Duguid, J. P. (1945). *Edinb. med. J.*, **52**, 385.
—— (1946). In press.
Edward, D. G. ff. (1941). *Lancet*, **2**, 664.
—— (1944). *J. Hyg.*, Camb., **43**, 256.
Gloyne, S. R. (1922). *Tubercle*, **3**, 497.
Gordon, M. H. (1916). *British Medical Journal*, **1**, 849.
Gulbrandsen, L., and Keller, R. (1935). *Illinois med. J.*, **68**, 336.
Hamburger, M. (1944). *J. infect. Dis.*, **75**, 71.
—— Green, M. J., and Hamburger, V. G. (1945). Ibid., **77**, 68, 96.
—— Puck, T. T., Hamburger, V. G., and Johnson, M. A. (1944). Ibid., **75**, 79.
Hare, R. (1940). *Canad. publ. Hlth. J.*, **31**, 539.
—— (1941). *Lancet*, **1**, 85.
—— (1945). *British Medical Journal*, **1**, 383.
Heymann, B. (1901). *Z. Hyg. InfektKr.*, **38**, 21.
Jennison, M. W. (1942). In *Aerobiology*, Amer. Assoc. Adv. Sci. Pub., No. 17, p. 106, Washington, D.C.
Kanter, F., and Appleton, J. L. T. (1940). *J. dent. Res.*, **19**, 279.
Laschtschenko (1899). *Z. Hyg. InfektKr.*, **30**, 125.
Min. Hlth. Rep., 1930, Publ. Hlth. med. Sub., No. 58, London.
Min. Hlth. Rep., 1939, Publ. Hlth. med. Sub., No. 90, London.
Nassau, E. (1941). *Proc. roy. Soc. Med.*, **34**, 397.
Paine, C. G. (1935). *British Medical Journal*, **1**, 243.
Peacock, S., Bigler, J. A., and Werner, M. (1939). *Amer. J. Dis. Child.*, **57**, 759.
Reiche, F. (1915). *Z. klin. Med.*, **81**, 199.
Stillman, E. G. (1917). *J. exp. Med.*, **26**, 513.
Thomas, J. C. (1941). *Lancet*, **1**, 433.
—— and van den Ende, M. (1941). *British Medical Journal*, **1**, 953.
Van den Ende, M., Lush, D., and Edward, D. G. ff. (1940). *Lancet*, **2**, 133.
Wells, W. F. (1934). *Amer. J. Hyg.*, **20**, 611.
—— (1935). *J. industr. Hyg.*, **17**, 253.
—— and Wells, M. W. (1936). *J. Amer. med. Ass.*, **107**, 1698.
White, E. (1936). *Lancet*, **1**, 941.
Williams, R. E. O., and Harper, G. J. (1944). *Mon. Bull. Min. Hlth. and Emerg. publ. Hlth. Lab. Serv.*, **3**, 86.
Winslow, C. E. A., and Robinson, E. A. (1910). *J. infect. Dis.*, **7**, 17.
Wright, J., Cruickshank, R., and Gunn, W. (1944). *British Medical Journal*, **1**, 611.
Ziesché, H. (1907). *Z. Hyg. InfektKr.*, **57**, 50.

PLASMA VISCOSITY: A CLINICAL TEST

BY

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While investigating the mechanics of blood sedimentation one of us (Whittington, 1942) found that if the maximum rate of fall of the cells is plotted against the plasma viscosity a complex pattern is formed. Under strictly controlled conditions this pattern is reproducible in any laboratory. Its somewhat bizarre appearance is shown by Fig. 1, which incorporates the results of our further investigations. Fig. 1 shows, moreover, that if the controlled E.S.R. is even a roughly proportionate index of a patient's pathological condition the plasma viscosity is not. And, of course, vice versa. From 63 cases of pulmonary tuberculosis Miller (Miller and Whittington, 1942) concluded that plasma viscosity was the more significant index. The 645 experiments reported here confirm this finding.

Method

Our technique is given in detail elsewhere (Houston, Harkness, and Whittington). Lack of space prohibits its full reproduction here. It is based on the use of a viscometer* which requires only 0.7 ml. of plasma and which is capable of an accuracy of about 99.8%. A water-bath, centrifuge, and stop-watch are the only other special pieces of apparatus required.

The viscosities quoted here are all "referred to Viscometer No. V5." Individual viscometers, if correctly calibrated, will agree in their results for pure liquids; but the apparent viscosity of a given colloidal solution will differ somewhat from instrument to instrument. Thus every viscometer will give its own characteristic version of Fig. 1. This phenomenon may be made use of to standardize viscometers for plasma: the method is described elsewhere (Houston, Harkness, and Whittington).

A simpler scheme of standardization is as follows: any new viscometer, direct from the glass-blower, may be set up alongside V5 (which is still in existence) and a series of three plasmas (one normal, one medium, and one high-viscosity) run through both instruments. These three double tests provide in themselves enough data for the accurate calibration of the new instrument, which will give plasma viscosities "referred to V5" as in Fig. 1. Those investigators wishing to build up their own version of Fig. 1 for themselves will require to measure maximum sedimentation velocities in the manner described (Houston, Harkness, and Whittington).

Our results are given here for citrate plasma prepared by centrifuging a mixture of one part of 3.8% sodium citrate solution and four parts of venous blood. An empirical correction (Houston, Harkness, and Whittington) has been made for varying plasma dilution due to haematocrit variations.

Material

In all, 645 experiments were carried out; 223 were on cases of pulmonary tuberculosis at the Crossley Sanatorium, and 385 on patients with various pathological conditions encountered in Montrose Asylum (850 beds). These conditions included skin sepsis, gangrene, syphilis, malaria, paratyphoid, rheumatic fever, meningitis, pneumonia, pernicious anaemia, cerebral haemorrhage, carcinoma, and bone and pulmonary tuberculosis. In addition, 37 controls were drawn from radiologically and clinically normal members of the sanatorium staff and from psychotic patients who were physically normal.

Results

Space will not permit the reproduction of our results in detail. It is hoped that the four diagrams will summarize them effectively.

Fig. 1 was prepared by plotting simultaneous measurements of plasma viscosity and maximum sedimentation velocity (under strictly standardized conditions of cell volume, etc.). For convenience in considering the clinical aspect of our results the viscosity range (from roughly 1.4 to 2.1) has been arbitrarily divided into numbered zones by perpendiculars drawn from the "wave-peaks" as shown in Fig. 1. The 37 normal controls had a mean viscosity of 1.546. Of these, 30 (81%) fell in zones 1 to 3, the remainder falling in zone 4, with the highest at 1.626. There is, of course, no clearly defined boundary of normality, and zone 4 may be regarded as a threshold or transition range.

Fig. 2 shows the average viscosities corresponding to normal and Ministry of Health groups "minus," "plus 1," "plus 2," and "plus 3" in pulmonary tuberculosis. These cases were classified at the Crossley Sanatorium.

At Montrose, 177 tests in all were done on 79 patients giving viscosities in zone 6 or higher. These patients were suffering from various diseases. Using the maximum viscosity recorded for each patient, the accompanying Table gives the incidence of deaths among these high-viscosity cases.

Table showing Death Rate in Viscosity Zones

Viscosity Zone (V5)	Number of Cases	Deaths	
		No.	%
6	25	5	20
7	19	7	37
8	9	4	44
9	17	11	65
10	5	3	60
11	4	4	100
Totals ..	79	34	43

Discussion

(a) General

The conclusion to be drawn from Fig. 2 seems inescapable. At least in a chronic disease such as pulmonary tuberculosis, there is an increase of viscosity corresponding on the whole to an increase in the extent and severity of the disease process.

* Supplied (to the design of R. B. W.) by the Scientific Glass-Blowing Company, 12–14, Wright Street, Manchester, 15.

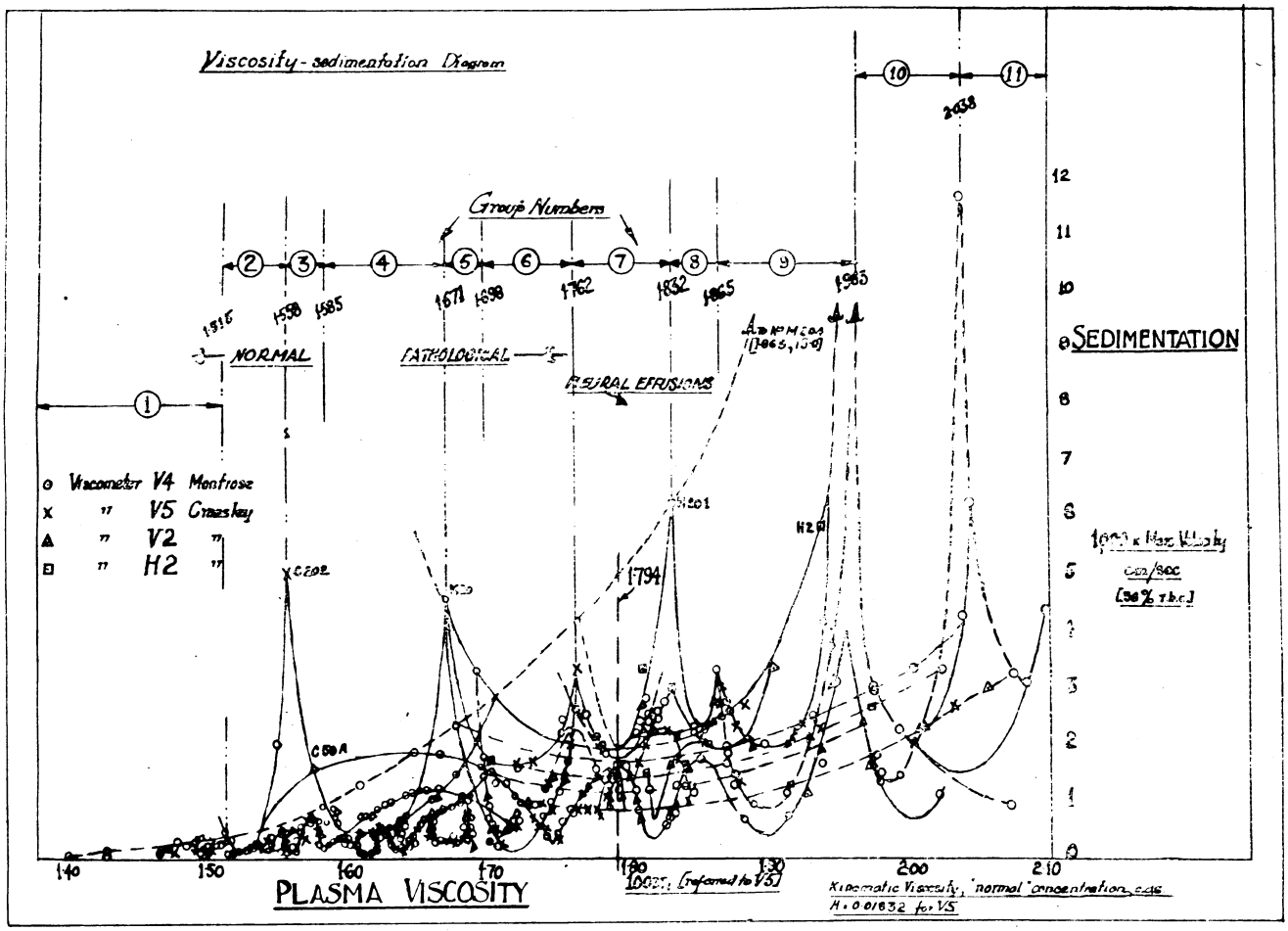

FIG. 1

(Of course, Fig. 2 shows only average results. It would be absurd to claim, for example, that every tuberculous patient with a viscosity of 1.77 must necessarily fall into the Ministry of Health group plus 2: the diagram merely implies that if a large number of patients in group plus 2 be examined the average of their plasma viscosities will be about 1.77—referred to V5.)

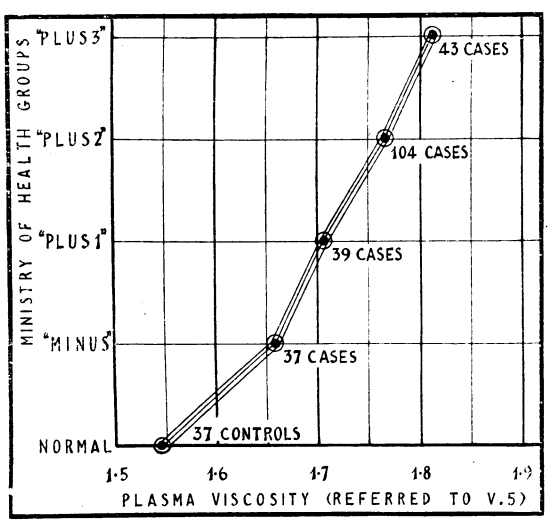

FIG. 2.—Distribution of Ministry of Health groups in pulmonary tuberculosis (223 cases + 37 controls).

But Fig. 2 refers only to pulmonary tuberculosis: from our experience in following the progress of both acute and chronic cases we are of the opinion that in general the viscosity increases (i.e., there is a shift to the right in Fig. 1) as the physical condition worsens; and that with recovery the viscosity decreases again (corresponding to a shift to the left). Intervening complications or intercurrent infections may temporarily reverse the latter movement.

The grave prognosis in general to be associated with very high viscosities is, we feel, an inevitable conclusion to be drawn from the Table. That this, however, *is* only a generalization is shown by the fact that two patients with viscosities in zone 10 did eventually recover. (They were cases of paratyphoid and of rheumatic fever.)

We have mentioned that there is no clearly marked boundary between the normal and the pathological, but that zone 4 may be regarded as a threshold range. Here fall the early and the late results of pathological processes, together with some normals. The finding of a result in zone 4 appears to call for further investigation. This conclusion was brought home to us at Montrose, where two mental patients who were normal to physical examination and picked to act as normal controls gave results high in zone 4. Within six months they both developed definite signs of pulmonary tuberculosis. Further, a member of the staff who gave a high zone 4 viscosity reading, and who was at the same time clinically, radiologically, and bacteriologically negative, developed active pulmonary tuberculosis within three months.

A zone 4 viscosity, then, may be held to call for further investigation; but it need not occasion alarm. Seven of the Crossley staff controls were (low) in zone 4, and have as yet shown no signs of pathological disturbance. We have evidence that the use of the sulphonamide drugs can produce an increase in the plasma viscosity sufficient to shift a physically normal zone 2/3 individual into zone 4: other drugs may have a similar action. Moreover, we have as yet totally insufficient data as to physiological changes—e.g., menstruation; nor do we know

to what extent a trifling infection (such as a common cold) may affect the viscosity.

A glance at Fig. 1 will confirm what we have said already—that viscosity and corrected sedimentation velocities cannot both be accurate indices: in our experience reliability is to be placed on the viscosity test, whatever the sedimentation result may be. Cases will be seen in Fig. 1 with extremely high viscosities but with sedimentation velocities falling within the range of normality. Case C202 is an interesting (though rare) example of the converse phenomenon, occurring in a clinically and radiologically normal female member of the sanatorium staff. Only five higher sedimentation velocities were ever recorded in our whole series. Viscosity was normal (zone 2/3). Repeated after 14 days, both velocity and viscosity results were practically identical. Observation of the sedimentation rate alone would have occasioned great alarm. Seven months after test C202, she is still perfectly healthy.

(b) Terminal Decay

Here we must describe an exception to the foregoing generalizations—a process which by its very exception may be of great importance to prognosis. So far we have in effect described a cycle of viscosity (normal—maximum—normal), a cycle which coincides with the clinical cycle (health—disease—recovery). But in many cases in which the disease process continues without respite to a fatal end the viscosity rises to a maximum value and then gradually falls towards the normal. In this way a value in the range of the normal may be reached in the moribund. We have called this phenomenon "terminal decay." In chronic conditions it may appear months before death, while in acute conditions it may precede death only by a few days or even a few hours. Some examples of this terminal phenomenon are shown in Fig. 3. We cannot state positively that this viscosity cycle (normal—maximum—normal) is invariably followed. It will be appreciated that the necessary evidence is not easily obtained from human subjects; but the general case is illustrated by the curves of Fig. 3.

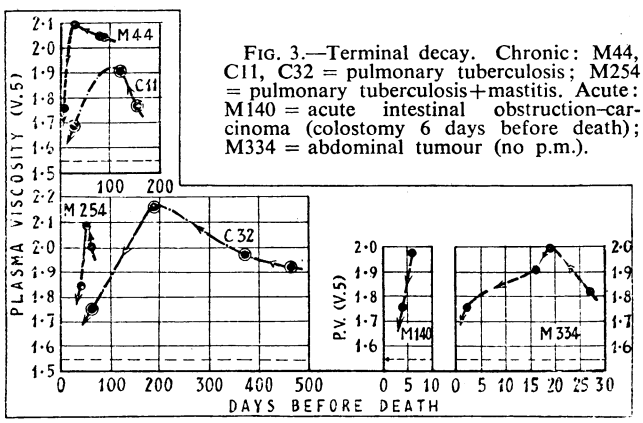

FIG. 3.—Terminal decay. Chronic: M44, C11, C32 = pulmonary tuberculosis; M254 = pulmonary tuberculosis+mastitis. Acute: M140 = acute intestinal obstruction-carcinoma (colostomy 6 days before death); M334 = abdominal tumour (no p.m.).

Thus, before finally accepting any plasma-viscosity measurement as an indication of clinical condition, the possibility of decay must be considered. If this possibility is not out of the question the test should be repeated after a suitable interval. If the viscosity is increasing, decay is not present provided there is no intercurrent disturbance. If the viscosity is falling the plasma is either on the terminal path or is showing recovery. We feel that the clinician will easily decide this point. Sometimes, however, it is clear from a single viscosity reading that a patient is on the terminal path—for example, Case C50A, viscosity 1.576 (zone 3), 21 days before death from pulmonary tuberculosis. Here the viscosity result merely emphasized what was clinically all too obvious.

Fractionation of the plasma proteins is of distinct value in the recognition of terminal decay; but unfortunately any discussion of the serum and plasma proteins is beyond the scope of the present brief report.

(c) Plasma Viscosity and Management of Pleural Effusions

Fig. 4 shows the incidence of pleural effusions in 23 cases. There was definite clinical and radiological evidence pointing to the actual formation of fluid at the time of test in each case. Fifteen (65%) were found to be in viscometric zone 7.

We consider Fig. 4 highly suggestive. It appears to indicate that zone 7 forms a critical region in which the exudation of fluid is highly probable. Of course our present small number of cases does not allow us to lay down definite limits beyond

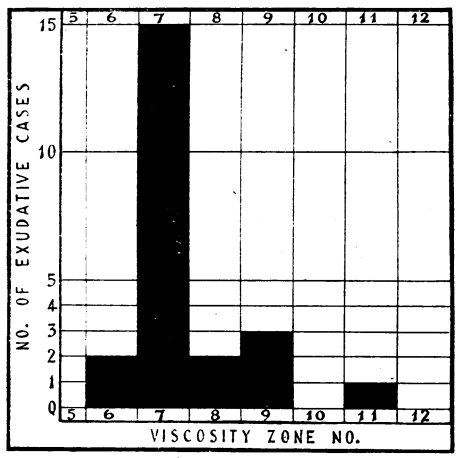

FIG. 4.—Distribution of pleural effusions (23 cases).

which fluid *cannot* be exuded. But our experience indicates that if an effusion be aspirated while the viscosity is in zone 7 the fluid will re-form; recurrence is unusual when aspiration is delayed until the plasma viscosity has shifted either to the right or to the left. We have found, moreover, that a recovering patient sometimes has an effusion as his viscosity passes through zone 7 from right to left.

Viscosity measurements may thus prove of importance in the management of pleural effusions. (We hope to investigate this possibility further.)

Conclusions

Plasma viscosity can be of diagnostic value in revealing otherwise hidden pathological changes, as is emphasized in the Discussion (*a*). As a diagnostic test, however, it seems to be completely non-specific.

The prognostic value of the viscosity test appears to be high.

The viscosity test should be found valuable in the treatment of chronic disease, inasmuch as it provides a good index of deterioration or recovery.

Viscosity estimations may have special value in the management of pleural effusions.

A comparison of the sedimentation velocities in Fig. 1 with our findings for viscosity should show the impossibility of correlating sedimentation rates (even under controlled conditions) with the clinical picture.

These conclusions are drawn from 645 experiments on the plasma viscosity in a wide variety of pathological conditions.

We wish to thank our committees of the Royal Asylum, Montrose, and of the Crossley Sanatorium, Frodsham, for the facilities kindly afforded. Invaluable technical work was done by Miss Norah Brown and Mr. Archibald C. Harris.

REFERENCES

Houston, J.,* Harkness, J., and Whittington, R. B. *Acta tuberc. scand.* (in press).
Miller, A. K., and Whittington, R. B. (1942). *Lancet*, **2**, 510.
Whittington, R. B. (1942). *Proc. roy. Soc.*, B, **131**, 183.

At the annual meeting of the Governors of the Dental Hospital of Manchester it was announced that a department of preventive dentistry and research is to be created. Its work is to be linked with the school health services and maternity welfare centres, and with the new department of child health. Funds for the research to be undertaken have been provided by the Nuffield Trustees, who have made a grant of £30,000 spread over ten years. The University is also expected to provide financial assistance. The team of specialists will include an experimental physiologist, a bacteriologist, and two research fellows, together with the necessary laboratory and technical assistance and clerical staff. The intention is to launch a large-scale clinical study of the causation of dental disease.