THE PLASMA VISCOSITY IN RHEUMATIC DISEASES

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In 1942 on a series of 63 tuberculous patients Miller and Whittington (1942) introduced the estimation of the plasma viscosity as a clinical test. They showed that there was a close correlation between the clinical condition and the viscosity value.

In the course of some 650 determinations which included non-tuberculous conditions the usefulness of the viscosity test was confirmed (Houston *et al.*, 1945; Harkness *et al.*, 1946). These experiments also demonstrated the complex "periodic" relationship between the plasma viscosity and the maximum erythrocyte sedimentation rate (Whittington, 1942), showing that if the viscosity is a reliable quantitative index of the clinical state then the E.S.R. is not. The conclusion drawn from that series of experiments was that the viscosity is to be preferred to the E.S.R. as an index.

While the only rheumatic condition in the series was a single case of rheumatic fever, Whittington (1946) suggested the application of the test in rheumatic diseases generally. It has recently been possible for us to apply the test in a series of patients suffering from all types of rheumatic conditions. In doing this we had as our objective the evaluation of the plasma viscosity test as an aid to the clinician in the handling of these rheumatic conditions. At this stage it may be said that the test has proved to be so useful that it is now included in the routine assessment of new patients and in following the progress of others in response to treatment.

The establishment of new treatment centres and research units indicates that rheumatic disease is at present the subject of considerable interest: this preliminary report is presented so that other workers in this field may consider including the plasma viscosity estimation among their laboratory methods.

Technique and Material

The technique of the method is discussed in the Technical Appendix (see p. 688).

The tests were performed chiefly on patients attending the physiotherapy department of Sunderland Royal Infirmary.

Table Showing Plasma Viscosity Findings in Various Conditions

Condition	No. of Tests	Plasma Viscosity*		Average Packed Cell Volume (%)	Average Wintrobe E.S.R. (mm./1 hr.)	Average Total Plasma Protein (g.%)
		Usual Range	Average of Series			
Normal	43	1.700-1.950	1.853	42.9	—	7.15
Fibrositis; myositis	10	1.725-1.950	1.896	46.3	6.7	7.34
Chronic hypertrophic osteoarthritis	17	1.875-2.075	1.921	44.1	8.5	7.31
Rheumatoid arthritis:						
Residual deformity only	8	1.740-1.990	1.909	41.8	19.8	7.40
Chronic	154	1.950-2.300	2.121	42.6	25.2	7.80
Subacute	22	2.300-2.550	2.512	40.8	36.1	8.50
Acute	16	2.500-3.400	2.897	38.8	38.8	9.54

* The plasma viscosity is the kinematic viscosity measured at 20° C. and expressed in terms of the calibration of Viscometer V5 as centipoises per g. per c.cm. or cm.² per sec. $\times 10^{-1}$.

In the past nine months 320* tests were carried out on cases of rheumatic disease, 200 being cases of rheumatoid arthritis. In addition there were 43 normal controls. In all cases a thorough general medical examination was made to exclude any other pathological process apart from the rheumatic condition.

The diagnosis is the final evaluation of the findings of a team of investigators consisting of a physician, surgeon, radiologist, clinical pathologist, physiotherapist, and biochemist.

Results

In the absence of an agreed scheme of classification which would allow of statistical comparison we have grouped our cases into the crude groups of (A) rheumatoid arthritis, (i) acute, (ii) subacute, (iii) chronic, (iv) residual deformity only; (B) chronic hypertrophic osteoarthritis; (C) fibrositis and myositis. (Our results for Still's disease, rheumatic fever, etc., have been omitted from the accompanying Table and from the discussion.)

We give a few representative cases in detail while outlining our findings for the series as a whole in the following general terms (see also Table):

(a) In the early stages of rheumatoid arthritis the plasma viscosity value may still be within range of normality; normal values may be obtained in cases which have responded to therapy.

(b) Progress of the disease processes is usually accompanied by an increase in viscosity, improvement by a decrease; the rate of change in viscosity parallels the rate of change in the clinical condition.

(c) In chronic conditions there may be no change in the viscosity for several months, although the E.S.R. shows large variations.

(d) There is good correlation between the plasma viscosity value and the clinical picture in rheumatoid arthritis.

(e) The viscosity values for acute, subacute, and chronic rheumatoid arthritis tend to fall, on an average, into distinct zones of the viscosity range (see Table).

(f) Cases of chronic hypertrophic osteoarthritis have viscosity values in the upper range of normality and the lower part of the abnormal range (see Table).

(g) In fibrositis and myositis the viscosity is within normal limits.

(h) Our results appear to confirm that the viscosity is a more reliable index of clinical condition than the E.S.R.

Case Histories

Case 1: Chronic Rheumatoid Arthritis.—Female aged 32. Eight years' history of pain and swelling of both knees and the proximal interphalangeal joints of the fingers, and pain and limitation of movement of shoulders. Both knee-joints were active, with effusion and increased heat. There was gross limitation of movement of the right shoulder. Medical examination revealed no other pathology. Skiagrams of the involved joints showed an atrophic arthritis and those of the chest and sinuses were negative. A catheter specimen of urine was negative on culture. Haemoglobin, 82%; W.B.C., 9,600 per c.mm.; Wintrobe E.S.R., 2 mm. in first hour; P.C.V., 45.7%; total protein, 7.81 g.; plasma viscosity, 2.045.

Case 2: Chronic Rheumatoid Arthritis.—Female aged 38. In 1944 she had pain and swelling of the right elbow-joint and the proximal interphalangeal joints of fingers which lasted for six weeks and subsided after a course of physical therapy. In November, 1946, she had another attack of pain and swelling of the interphalangeal joints of the fingers, right elbow, and shoulder-joint. Examination revealed typical fusiform swelling

* The number of cases has now reached 450 without any alteration of the opinions expressed.

of the interphalangeal joints of the fingers, with wasting of the interossei. The elbow-joint was swollen, and movement was painful but full. There was limitation of external rotation and abduction of the right shoulder-joint. Skiagrams of the involved joints showed a typical atrophic arthritis. No focus of infection was found. Hb., 88% ; W.B.C., 7,600 per c.mm. ; Wintrobe E.S.R., 6 mm. in first hour ; P.C.V., 44.8% ; total plasma protein, 7.85 g. ; plasma viscosity, 2.034.

Case 3: Chronic Rheumatoid Arthritis.—Male aged 43. General condition very poor. Pain, swelling, and deformity of small joints of hands ; swelling and increased local heat in right knee-joint ; progressive loss of weight and secondary anaemia. Radiography of chest and sinuses was negative. No focus of infection or any other pathological condition was discovered on medical examination. Feb. 23, 1947: Hb., 75% ; W.B.C., 10,600 per c.mm. ; Wintrobe E.S.R., 5 mm. in first hour ; P.C.V., 41% ; total plasma protein, 8.13 g. ; plasma viscosity, 2.270. March 25, 1947: Hb., 80% ; W.B.C., 8,500 per c.mm. ; E.S.R., 12 mm. in first hour ; P.C.V., 43% ; total plasma protein, 8.0 g. ; plasma viscosity, 2.280.

Case 4: Chronic Rheumatoid Arthritis.—Female aged 32. Pain and fusiform swelling of proximal interphalangeal joints of fingers ; both wrists ankylosed ; pain and limitation of movement of right shoulder. The patient had been losing weight rapidly and said the pain was getting worse. Skiagrams of the involved joints showed a typical atrophic arthritis. No focus of infection was found on routine medical examination. Clinically the disease was active, and this finding was supported by a Wintrobe E.S.R. of 35 mm., total plasma protein amounting to 8.1 g. %, and a plasma viscosity of 2.095. Four months later, after a period of complete rest in bed, a course of physical therapy, and 0.12 g. of "myocrisin" in weekly injections of 0.01 g., the patient had put on weight, the pain in the joints had greatly diminished, and there was increased movement in the shoulder. The plasma viscosity had now fallen to 1.935, with a total protein of 7.8 g. %. The E.S.R. was still 40 mm.

Case 5: Chronic Rheumatoid Arthritis.—Female aged 58. Twelve years' history of pain and stiffness in joints. The patient now had flexion deformities of both knee-joints and was unable to walk. She no longer had pain in the joints. Clinically the disease had died out, leaving residual deformities. E.S.R., 20 mm. in first hour ; P.C.V., 44.0% ; total plasma protein, 7.6 g. ; plasma viscosity, 1.995.

Case 6: Subacute Rheumatoid Arthritis.—Female aged 35, Dec. 9, 1946: General condition very poor ; signs of activity in small joints of fingers, in knees, and in shoulders. Skiagrams of joints revealed an atrophic arthritis ; no focus of infection could be found on routine medical examination. Hb., 65% ; W.B.C., 10,600 per c.mm. ; Wintrobe E.S.R., 39 mm. in first hour ; P.C.V., 39.0% ; total plasma protein, 8.5 g. ; plasma viscosity, 2.199. Jan. 21, 1947: After five weeks of treatment, which included three weeks' rest in bed with physical therapy and five weekly injections of 0.01 g. of myocrisin, the E.S.R. was 40 mm. ; the P.C.V. 40.5% ; the total plasma protein 8.8 g. ; and the plasma viscosity 2.210. On April 30 the condition was still active and there was marked pain in knees and shoulders. E.S.R., 49 mm. ; total plasma protein, 8.9 g. ; plasma viscosity, 2.259. The myocrisin was stopped after a total of 0.12 g. On May 19 the pain was subsiding and in the joints the condition was less active. E.S.R., 40 mm. ; total plasma protein, 8.9 g. ; plasma viscosity, 2.250. Here the plasma viscosity increased gradually just as the clinical condition deteriorated. The E.S.R. showed similar changes, but this finding was exceptional.

Case 7: Chronic Osteoarthritis (Hypertrophic).—Male aged 50. Complained of pain in both knees ; no effusion ; marked crepitus in the joints ; full but painful movement. Skiagrams showed the changes typical of chronic hypertrophic osteoarthritis. E.S.R., 8 mm. in first hour ; P.C.V., 44.4% ; total plasma protein, 7.20 g. ; plasma viscosity, 1.979.

Case 8: Chronic Osteoarthritis (Hypertrophic).—Male aged 45. In 1938 he sustained a fracture of the upper third of the right tibia involving the knee-joint. Now complaining of aching pain in the joint. No effusion ; marked periarticular thickening ; crepitus present ; movement full, but painful on full flexion ;

gross wasting of quadriceps muscle. Skiagrams showed chronic hypertrophic arthritis. E.S.R., 6 mm. in first hour ; P.C.V., 45.0% ; total plasma protein, 7.40 g. ; plasma viscosity, 1.920.

Case 9: Acute Fibrositis.—Female aged 32. Trapezius muscle very tender and painful, with tender nodules present. Skiagrams of cervical and thoracic spine negative. Responded to five treatments with infra-red radiation. E.S.R., 10 mm. in first hour ; P.C.V., 44.6% ; total plasma protein, 7.8 g. ; plasma viscosity, 1.820.

Case 10: Atrophic Spondylitis.—Male aged 34. Complained of low back pain for several years. There was tenderness over both sacro-iliac joints and marked rigidity of the lumbar spine. Skiagrams showed an atrophic spondylitis. E.S.R., 15 mm. in first hour ; total plasma protein, 8.0 g. ; plasma viscosity, 2.184.

Discussion

The plasma viscosity test is non-specific. It depends entirely upon the plasma proteins, ultra-filtrate experiments having shown the effect of variations in the non-protein constituents to be negligible.

With regard to solutions of the purified protein fractions, in equal concentrations the large molecules of fibrinogen have a proportionately greater effect on the viscosity than those of globulin, and the globulin in turn has a greater effect than the albumin. On the other hand, the three purified fractions appear to affect the specific gravity equally (Nugent and Towle, 1934). Thus a dual test consisting of plasma viscosity and plasma specific gravity frequently suggests which fraction, if any, is markedly increased. Accurate quantitative results cannot, of course, be inferred, for we are now dealing with the highly complex molecular interrelation of native plasma protein (Harkness and Whittington, 1947a), and at present there is no exact knowledge of the physical effects in these circumstances.

While it is not definitely known, it is believed that the liver is the organ which is chiefly responsible for these changes in the plasma proteins—i.e., the plasma viscosity test is a measure of a change in a liver function. The plasma viscosity is a measure of the change in plasma protein which occurs as part of a general systemic reaction to the disease processes in the body: the changes in the joints and soft tissues in rheumatoid arthritis are roughly paralleled by the plasma viscosity changes, indicating that there is a similar parallel systemic upset. We therefore arrive at the conclusion of earlier workers that rheumatoid arthritis is a disease of the whole organism and not merely an affection of the joints.

In striking contrast are the findings in osteoarthritis, where marked changes may occur in a joint without altering the plasma viscosity. Osteoarthritis would thus appear to be a local affection which produces little or no systemic reaction.

As results accumulated, the manner in which similar types of cases gave comparable viscosity results became striking. An apparent paradox arose with a typical osteoarthritis case whose plasma viscosity was 2.535, which was far higher than the expected value (see Table). Clinical re-assessment led to the discovery of an early apical tuberculous focus. The necessity of eliminating other possible known causes of disturbance in this non-specific test is obvious.

The variation of serial results in individual cases has proved very useful in estimating progress, and it has been the means of detecting flare-up in chronic conditions. Particularly in the serial tests, the viscosity test is more reliable than the E.S.R.

The plasma viscosity test, on the basis of these first 320 results, would appear to be a promising method of investigation in rheumatic diseases. When further results are

obtained and when serial testing has been carried out for longer periods a more critical evaluation of the method will be possible.

Summary

The plasma viscosity has been estimated in 320 tests in cases of rheumatic disease and in 43 tests in normal controls. The results of these have been considered generally and some representative cases have been presented in detail.

The plasma viscosity increases with progressive disease in rheumatoid arthritis and decreases with improvement; the increase is roughly proportional to the severity of the disease process; on the whole, the viscosity values for acute, subacute, and chronic conditions tend to fall into distinct zones of the viscosity range.

In osteoarthritis the plasma viscosity values tend towards high normal and low abnormal zones.

Cases of fibrositis and myositis present normal viscosity values.

The general nature of rheumatoid arthritis as contrasted with the local nature of osteoarthritis is discussed.

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TECHNICAL APPENDIX

In the estimation of the kinematic viscosity of plasma it is essential that the viscometer be accurate (at least to the second place of decimals) and that the viscometer be calibrated for colloidal solutions. The high degree of accuracy is necessary because changes of the order of 0.01–0.02 centipoise are clinically significant in the lower range of viscosity values.

Viscometers which measure viscosity by comparison of the time taken by fluids to flow through a capillary will give identical results for monophasic liquids such as water or benzene: with colloidal solutions such as plasma proteins, however, each instrument will give its own characteristic value, depending upon the "shear" of the capillary. In the range of viscosity usually measured in plasma viscosity tests two similar instruments may give results on the same plasma which differ by 0.3 centipoise.

Thus if the significance of viscosity values is to be general and not localized to individual hospitals some method of correlating instruments is necessary. Such correlation has been made successfully (a) by simultaneous estimation of the viscosity of a few plasmas in several instruments, (b) by the comparison of characteristic points of the individual periodic relationships between the plasma viscosity and the maximum E.S.R., as described in detail previously (Houston *et al.*, 1945), and (c) by comparison of the viscosity/concentration line for a solution of a pure protein with the sucrose viscosity/concentration line (Harkness and Whittington, 1947c). Methods (a) and (b) have proved satisfactory for the small number of instruments at present in use, but method (c) will be necessary if this test is used more widely.

All estimations here were made at 20° C. in a Whittington-type viscometer (V6). The results are expressed in terms of instrument V5, the viscometer to which all our instruments are correlated. This modification of the Ostwald viscometer requires only 0.7 ml. fluid and has an experimental error of about 0.2% only. The details of the construction, calibration, and use of this viscometer have been given previously (Houston *et al.*, 1945).

In our original technique sodium citrate solution was used as the anticoagulant, but in the present series it was more convenient to use the potassium and ammonium oxalate mixture of Heller and Paul (1934). This produces no effect on the ratio of cells to plasma as measured by the

haematocrit. This anticoagulant was later recommended for E.S.R. estimations (Wintrobe and Landsberg, 1935) and for the estimation of the plasma specific gravity (Phillips *et al.*, 1945). With this solid anticoagulant fewer laboratory manipulations are required and twice as many tests can be handled daily as with the original method. Owing to the diluting effect of the anticoagulant solution the plasma viscosities of citrate plasma are all much lower than the corresponding viscosities of oxalate plasmas.

Method

Quarter-ounce (7-ml.) capped bottles are prepared for 5 ml. of blood by evaporating in an incubator 0.2 ml. of a solution containing 2% potassium oxalate and 3% ammonium oxalate. To such a tube is added 5 ml. (± 0.5 ml.) of venous blood, drawn without stasis. The contents are mixed by gentle rocking so as to avoid the formation of froth. In the laboratory this blood is centrifuged in a graduated tube for half an hour at 3,000 r.p.m. The viscosity estimations on this plasma can be delayed up to about four hours without error.

(a) *Haematocrit: Packed Cell Volume (P.C.V.)*.—While the packing in the wide tube is not maximal an approximate packed cell volume can be calculated from the levels in the graduated centrifuge tube. In dealing with large numbers of tests it was found that the above standardized conditions allowed satisfactory comparison of serial results in the individual cases.

(b) *Plasma Viscosity*.—About 1 ml. of plasma is pipetted out and the viscosity estimation completed. This plasma can be recovered for further chemical tests.

(c) *Total Plasma Protein*.—This is estimated by the copper sulphate specific gravity method of Phillips *et al.* (1945). From the total blood volume as measured in the centrifuge tube the concentration of the anticoagulant can be calculated and allowed for. The plasma protein results so obtained were considered only in the full realization of the possible gross errors of the method, as we have reported elsewhere (Harkness, 1947; Harkness and Whittington, 1947b).

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Reading a paper on "Smoke and the Public Health" at the Annual Conference of the National Smoke Abatement Society held at Edinburgh on Oct. 1–4, Sir Alexander Macgregor said that further progress towards a cleaner atmosphere might be expected as a result of the increasing application of fuel efficiency methods in industry and in housing. In 1938, 232 tons of smoke were precipitated upon Glasgow as compared with 5 tons at Loch Katrine, and the figure for Glasgow was half of what it had been 30 years ago. In England as much as 500 tons and even 1,000 tons in one place had been recorded as falling on towns. People who worked under a smoke screen suffered in two main ways: (a) the direct ill effects of breathing smoke-laden air, and (b) the effects of being deprived of sunshine. Smoke had been held to account for some part at least of the higher mortality rates of children under 5 years from pneumonia and bronchitis in the Midland industrial area. He drew attention particularly to the screening off of ultra-violet light by smoke palis, and the necessity for offsetting this effect by adding vitamin D to children's food.