SYNOVIAL FLUID MUCIN*

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Synovial mucin, the characteristic component of synovial fluid, was first isolated in 1846 by Frerichs (1846), who precipitated it from joint fluid by addition of acetic acid. Its high viscosity and peculiar chemical composition made it a subject of much interest. Frerichs realized that it was a complex of protein and carbohydrate components, but little additional information was added until the 1930's, when hyaluronic acid, the carbohydrate component, was isolated and more closely studied. Even so, much confusion still exists concerning both the constitution of hyaluronic acid and the type of linkage by which it can unite with protein. The question is still unsettled whether connective tissue mucins found in different situations in the body are all similar or whether there are a great variety of mucins differing one from another in the character of their protein groups or even also in the hyaluronic acids they contain.

With regard to the physiological role of the mucins, we have hardly got beyond the realm of speculation, and their actual relation to disease processes is therefore equally obscure.

Within recent years several different lines of approach have been made towards these various problems, particularly as regards the synovial mucin of joints, and it is my intention to describe to you briefly what progress has been made towards an understanding of the chemical and physiological fields.

Distribution of Mucins

The mucins are very widely distributed in the animal kingdom and throughout the different parts of the human body. They are acido-glycoproteins, that is to say, complexes of protein united to a polysaccharide which possesses acidic characteristics, but a subdivision is possible according to whether the carbohydrate is rendered acid by virtue of sulphuric acid groups—as in the chondroitin sulphuric acid of cartilage—or of uronic acid units as in synovial mucin and vitreous humour. In either case they appear to act as cementing substances or extra-cellular ground substance in the connective tissues.

Most tissues of mesenchymal origin appear to produce the uronic acid type of mucin, collectively termed hyaluronate or hyaluronic acid mucin, and as examples may be cited synovial fluid, umbilical cord, lung, malignant tumours of the pleura, aqueous and vitreous humours, connective tissue generally, and skin connective tissue. It is also produced in abnormal quantities in myxoedema (Ord, 1878, Halliburton, 1888; Ropes and others, 1947; Martin and Hynes, 1948).

Either the acid polysaccharide, hyaluronic acid, or mucin can be isolated from these sources, and it is often difficult to say whether in the tissues the polysaccharide is free or actually bound to protein. In the case of synovial fluid the evidence is conflicting, but since the synovial cavity can be rightly regarded as a tissue space, it is not surprising to find within it a mesenchymal type of mucin. Destruction of hyaluronic acid by the enzyme hyaluronidase or other "spreading factors" loosens the intracellular cement and permits an abnormal diffusion of substances into and from the tissues (Duran-Reynals, 1942).

Mucins of epithelial origin differ from the hyaluronic acid mucins in their chemical composition and reaction to enzymes. Very frequently they contain, not sugar acids, but sulphuric acid in ester linkage which confers upon them the property of staining metachromatically.

Properties of Hyaluronic Acid and of Mucins

I do not propose to deal further with the sulphuric-acid-containing mucins or chondroitin sulphuric acids, but to turn now to a more detailed consideration of hyaluronic acid itself.

This substance was first isolated from vitreous humour and then from umbilical cord by Meyer and Palmer (1934, 1936) and found to be built up from units of glucuronic acid, glucosamine, and acetic acid, the whole molecule being a high polymer of this comparatively simple structure.

Solutions of hyaluronic acid were extremely viscous, and from physical measurements of diffusion coefficient, sedimentation velocity, etc., it appears that the molecule consists of long chains having a molecular weight of at least 200,000 to 500,000.

* A Lecture delivered to the Heberden Society on Oct. 16, 1948.

By taking precautions to avoid degradation of the substance during preparation, Hadidian and Pirie (1948) have obtained hyaluronic acid preparations with viscosities nearly twice as great as the highest hitherto recorded, so the true molecular weight of the native substance may well be several millions. Hyaluronic acid is very easily degraded by oxidation, by ascorbic acid, probably on account of hydrogen peroxide formed during the autoxidation of the latter (Madina-veitia and Quibell, 1941; Robertson and others, 1941; Pirie, 1942), and by serum rich in phosphatase (Robertson and others, 1940) in addition to the various enzymes termed hyaluronidases acting specifically upon it. Even slight degradation is revealed by a pronounced drop in viscosity.

Solutions of hyaluronic acid form mucins when soluble protein is added and then dilute acetic acid. The mucin separates as a tough, ropy mass leaving any excess of protein in solution; it can be redissolved, affording solutions of viscosity approximately equal to that of the original hyaluronic acid. It is the polysaccharide, therefore, that is responsible for the high viscosity of mucins. Removal of mucin by acetic acid precipitation reduces the viscosity of synovial fluid to approximately that of water (Cajori and Pemberton, 1928).

Viscosity.—The property of viscosity depends upon many factors, which will be considered in turn, such as: (1) the concentration of the solution; (2) the presence of inorganic salts; (3) the hydrogen ion concentration; (4) the temperature.

Viscosity is a manifestation of the mutual inter-

FIG. 1.—Relationship between the logarithm of the viscosity and the square root of the concentration of mucin-glucosamine in synovial fluid and in mucin and polysaccharide solutions. Viscosity measurements were made at 38° C. (After Ropes and others, 1947.) This, and Figs. 2, 3, and 5, are reproduced by kind permission of the authors and of the *Acta Medica Scandinavica*.)

Key

- * Bursal fluid (human) in 0.9 per cent. NaCl.
- Carpo-metacarpal and astragalo-tibial joint fluid (bovine).
- ◻ Mucin (bovine) in $\frac{M}{15}$ Na_2PHO_4 .
- ◻ Mucin (bovine) in 0.5 per cent. NaHCO_3 .
- Mucin (bovine) in joint fluid (bovine).
- ▽ Mucin (bovine) in 0.5 per cent. Na_2CO_3 .
- Astragalo-tibial joint fluid (bovine) in 0.9 per cent. NaCl.
- Mucin (bovine) in serum (human) diluted with Ringer's phosphate solution.
- ▲ Mucin (bovine) in $\frac{M}{15}$ Na acetate.
- ◇ Polysaccharide (bovine) in 0.9 per cent. NaCl.

action between particles in solution and the relation between concentration and viscosity is not a linear one. However, a simple empirical relation has been found to hold between the logarithm of the viscosity and the square root of the mucin concentration, such plots affording a straight line; at relative

FIG. 2.—The effect of hydrogen ion concentration on the relative viscosity of polysaccharide solutions. The open circle indicates a sample which formed a gel on shaking. To 5 c.cm. of polysaccharide solution dialyzed against 0.2 N NaCl was added 0.5 c.cm. of 0.2 N NaOH or 0.2 N HCl. (After Ropes and others, 1947.)

viscosities >20 the slope changes (Ropes and others, 1947) (Fig. 1).

An interesting illustration of the dependence of viscosity upon chain length in the polysaccharide is seen in an experiment in which mucinase was allowed to act for varying periods of time upon a mucin preparation, and then a graph was made, as above, between the log viscosity and the square root of the time of action of the enzyme, the assumption being that the enzyme caused a regularly progressive diminution in mean chain length as it acted on the mucin. The result was an excellent straight line relationship, supporting the assumption. It is of interest that a similar relationship between viscosity and the chain length of molten polyesters has been found recently by Flory (1940). The experiment also indicates that we can use the viscosity/concentration relationship to compare mucins obtained from normal and diseased joint fluids. Whilst traumatic fluids have a viscosity little if anything different from normal, in rheumatoid arthritis and in specific infectious arthritis the degeneration of mucin is more marked and increases proportionally with the severity of the joint involvement (Ropes and others, 1947).

Salts.—The viscosity of mucin or hyaluronic acid solutions is markedly reduced by the presence of salts, the effect being more marked with divalent than with monovalent ions at equimolar concentration. Taking any one salt, the depression of

viscosity of mucin or hyaluronic acid increases with increasing concentration of salt up to about 0.1 M. after which there is little or no increment. This effect of salts is completely reversible by dialysis.

pH.—In considering the effect of pH upon viscosity, mucin and hyaluronic acid must be dealt with separately. Hyaluronate is little affected over a range from pH 10.0 to 4.0; beyond these limits viscosity falls rapidly and irreversibly (Fig. 2). In the case of mucin there is a gradual increase in viscosity from pH 10 to 4, at which latter point the substance precipitates. It redissolves in more acid solutions, but with a greatly diminished viscosity (Fig. 3).

Temperature.—Rise in temperature causes a reversible decrease in the viscosity of both mucin and polysaccharide solutions.

Other Properties of Mucin; Base Binding.—The isoelectric point of mucin is about pH 4.0 and it has a base-binding power at pH 7.4 of 6.4 meq./g. N. (Ropes and others, 1947). This high value is supported by calculations based on the distribution of electrolytes between serum and synovial fluid, from which it appears that synovial mucin binds about ten times the amount of calcium per gramme as do the serum proteins (McLean and Hastings, 1935).

Analytical comparison of synovial fluid with the plasma accords with the view that the former is a dialysate of blood plasma containing some protein and to which hyaluronic acid has been added by the

FIG. 3.—The effect of hydrogen ion concentration on the relative viscosity of normal cattle synovial fluid. Fluid A is indicated by the symbol O, fluid B by X, and fluid C by ■. The open square and the solid circle indicate samples which formed gels on shaking. To 5 c.cm. of synovial fluid was added 0.5 c.cm. of 0.2 N NaCl containing 0.2 N NaOH or 0.2 N HCl. Viscosity measurements were made at 38° C. (After Ropes and others, 1947.)

secretory activity of modified connective-tissue cells of the synovial membrane (Bauer and others, 1940).

Osmotic Properties.—Another important property of mucin is its contribution to the osmotic pressure. This has been determined indirectly by measuring the osmotic pressure of synovial fluid and comparing the figure obtained with that expected from its protein content. It transpires that the osmotic effect of mucin per gramme is nine times that of serum albumin. This is no doubt of great importance in achieving a fluid circulation through the joint in spite of the relatively low protein content of the fluid in the joint space (Ropes and others, 1939). Another illustration of the osmotic effect of mucin is seen in the swelling of the sexual skin of monkeys treated by injections of oestrogen. This causes an increase in mucin, and consequently the cells of the tissue become turgid (Ogston and others, 1939).

The State of Hyaluronic Acid in Synovial Fluid

Since both protein and hyaluronic acid are constituents of synovial fluid, it is pertinent to enquire whether they exist free or mutually associated. Acidification, as we know, leads to the precipitation of the hyaluronic acid and some of the protein as mucin, the rest of the protein remaining in the filtrate. More sensitive and discriminating methods must be used to solve the problem. Of these, electrophoresis has given what appeared to be a decisive answer. Both Hesselvik (1940) and Blix (1940) found, on subjecting synovial fluids to electrophoresis, the presence of a fast-moving component having the same glucosamine/nitrogen ratio as has hyaluronic acid, which was therefore thought to exist in the fluid free from any combination with protein.

Other physical methods such as ultra-filtration, precipitation by salts, and, in particular, viscosity

TABLE I
VOLUME OF SYNOVIAL FLUID AND MUCIN CONCENTRATION IN JOINTS OF
VARIOUS SPECIES (Ropes and others, 1947)

Species	Author	Joint	Volume of fluid (c.cm.)	Mucin (g. per 100 c.cm.)
Human	Cajori and Pemberton (1928)	Knee	—	0.42 ³
	Fisher (1929)	—	—	1.95
	Achard and Piettre (1930)	Knee	—	3.0 ²
	Ropes, Rossmeisl, Peabody, and Bauer (1940)	Knee	0.13-3.5	0.85
		Knee	0.25-40.0	0.50 ³
Cattle	Frerichs (1946)			
	Newborn calves		—	0.33
	Oxen in stalls		—	0.24
	Oxen in pastures		—	0.56
	von Holst (1944)		15-20	0.5
	Fisher (1923)		—	0.13
	Ropes, Bennett, and Bauer (1939)			
	Steer	Astragalo-tibial	20-100	0.14
	Steer	Carpo-metacarpal	5-15	0.60
	Zeller, Bywaters, and Bauer (1941)			
	Calves	Astragalo-tibial	6-8	0.28
	Calves	Carpal	3.5	0.75 ¹
	Davies (1944)	Hip	3.27	—
		Knee	0.42	—
Astragalo-tibial		5-65	—	
Carpo-metacarpal		3-7	—	
Carpal		—	0.47	
Horse	Bywaters (1937)	Astragalo-tibial	12	0.35 ¹
	Unpublished	Carpo-metacarpal	7	0.46 ¹
Rabbit	Unpublished	Knee	0.1-0.3	—
Dog	Unpublished	Knee	0.1-0.3	—
Pig	Unpublished	—	4	0.81 ¹

¹ Result based on the analysis of one fluid only.

² Result obtained by acetone precipitation of one fluid from a patient with oedema.

³ Fluids obtained from patients with oedema.

FIG. 4.—Demonstration of the “stick-slip” motion (A), and the effect of lubrication (B), the upper block of radio-active lead being caused to slide upon a lower normal block. (After Gregory, 1946, by kind permission of the author and of the Editor of *Nature*.)

studies at different pH , have led, however, to an exactly opposite conclusion (Ropes and others, 1947).

The viscosity of normal synovial fluid increases from pH 9 to 7 this behaviour being comparable with that of mucin rather than of free polysaccharide. Below pH 7 the viscosity falls rapidly.

It would seem that in normal synovial fluids the hyaluronic acid is probably combined with protein, although in some bursal fluids, it must be noted, hyaluronic acid alone without protein is to be found.

Physiology

The volume of synovial fluid and the concentration of mucin which it contains vary from joint to joint and also in the same joint in different animal species; but, in general, the content of mucin lies between 0.3 and 0.8 g. per 100 ml. (Table 1).

The normal human knee contains about 0.5 ml. of fluid. The astragalo-tibial joint of cattle is remarkable in containing as much as 40 ml. or more of fluid, and this source has been much used for experimental studies.

The mechanism by which mucin is catabolized is not understood, but since large molecules can only with great difficulty leave the joint cavity, it would appear that breakdown must occur in the fluid itself or in the accessory structures.

No hyaluronidase can be detected in normal synovial fluid or tissues, but both ascorbic acid and phosphatase are present and both cause degradation of mucin *in vitro* (Ropes and others, 1947).

Joint disease may affect both the formation and destruction of mucin. In traumatic lesions the volume of synovial fluid may be very greatly increased but the mucin concentration remains normal, either due to enhanced formation of mucin, or to an increase in the amount carried into the joint. At the same time the viscosity per unit concentration and the glucosamine/nitrogen ratio are so nearly normal as to indicate only slight degradation of the polysaccharide.

In rheumatoid arthritis and infectious arthritis of known origin, the joint fluid tends to be poorer in mucin, less viscous, and to give a haziness or soft mass on acidification instead of a ropy precipitate, thus indicating degradative changes in the mucin. It is noteworthy that free hexosamine can never be detected in

FIG. 5.—Diagrammatic presentation of the apparatus employed to study the lubricating properties of synovial fluid and mucin solutions. (a) lead weights of approximately 5 kg. each used to load the joint; (b) iron frame into which the rods carrying the weights are incorporated; (c) copper pan containing fluid to be tested—glass beads are used when necessary, to raise the level of fluid above the joint line; (d) larger copper pan containing water to regulate the temperature—the experiments were run at $38^{\circ}C$.; (e) articulating surfaces of lucite “joint”; (f) wooden stand supporting the entire apparatus; (g) beaker to which mercury is added in sufficient quantity to overcome friction at articulating surfaces and move joint. (After Ropes and others, 1947.)

such fluids so that the pathological breakdown is comparable only with the first stages of *in vitro* enzymatic hydrolysis.

An exceptionally high concentration of mucin is found in the synovial fluid in osteochondromatosis and also in myxoedematous patients, suggesting that the thyroid hormone plays a role in the normal regulation of mucin metabolism. The increase in mucin following administration of oestrogens has already been referred to.

Table 2, taken from Ropes and others (1947) collects some of the data relating to concentration and viscosity of synovial mucin in various types of joint disease.

TABLE 2
CHANGES IN CONCENTRATION AND STATE OF MUCIN IN VARIOUS TYPES OF JOINT DISEASE, ARRANGED IN ORDER OF INCREASING VISCOSITY (Ropes and others, 1947)

Disease	Relative Viscosity 38°	Mucin N (g. per 100 c.cm.)	Type of mucin Ppt. ²	Nitrogen: Glucosamine
Pulmonary osteo-arthropathy ..	3.21	0.0141	PI	1.001
Syphilitic arthritis ..	6.3	0.038	VP	1.06
Tuberculous arthritis ..	7.5	0.021	F	0.80
Gouty arthritis ..	12.0	0.041	F	0.94
Probable rheumatoid arthritis ..	12.9	0.041	F	0.82
Rheumatoid arthritis ..	13.1	0.067	P	1.30
Infectious arthritis ..	14.6	0.062	F	1.69
Reiter's Syndrome ..	14.9	0.074	F	1.35
Rheumatic fever ..	15.5	0.101	G	1.54
Haemophilia ..	17.4	0.0481	F	0.49
Lupus erythematosus disseminatus ..	25.5	0.048	G	1.37
Neuro-arthropathy ..	29.6	0.054	G	1.32
Traumatic arthritis ..	31.1	0.058	F	0.631
Degenerative joint disease ..	45.9	0.099	F	1.04
Osteochondromatosis ..	137.0	0.108	G	1.41
Normal human knee joints ³ ..	208.0	0.066	G	1.16
Myxoedema ..	361.0	0.1921	G	—

¹ Results based on the analysis of only one fluid.

² The type of precipitate is expressed in symbols having the following significance: VP=few or no flecks in a cloudy solution; P=small, friable masses in a cloudy solution; F=soft mass in a clear or slightly cloudy solution; G=tight, ropey clump in a clear solution.

³ These fluids were obtained post mortem.

Bearing on this discussion is the apparent inverse relationship between viscosity and phosphatase concentration in various joints and species (see Table 3 from Ropes and others, 1947). Phosphatase determinations in pathological joint fluids might afford some interesting data.

Lubricating Action of Synovial Mucin

The high viscosity of mucin in solution immediately suggests its possible function as a lubricating agent in the movement of the joints and the increased mucin content of joint fluid in some cases of degenerative joint disease might argue for an attempt to provide better lubrication for the damaged surfaces of the articular cartilage.

The physical phenomena of friction and lubrication are not at all simple, and I feel that it might be some help to attempt a brief analysis of these problems.

When two solid surfaces such as blocks of wood or metal are in contact it is found that a definite force is necessary to induce one to move relative to the other. This minimum force bears a linear relation to the load upon the upper block, and their ratio is known as the coefficient of static friction $\left(\frac{W}{W}\right)$. The magnitude of the coefficient of friction depends greatly upon the nature of the materials in contact, and the frictional resistance is considered to be due to an interlocking of the unevennesses forming the boundaries of the two layers in contact.

When motion takes place in the absence of any lubricant, there is jerking or tearing apart of the surfaces which is described as "clutching" or "stick-slip" motion and which rapidly leads to erosion and wear. Very beautiful pictures have been taken by Gregory (1946) of this stick-slip motion by sliding a block of radio-active lead upon a normal block and then photographing the deposit of radiant lead left upon the latter (Fig. 4).

The action of a lubricant is to separate the two sliding solid surfaces from each other by the interposition of a film or layer of liquid. A good lubricant must act so that when motion occurs the sliding which takes place is that of one liquid layer over another—in other words, a shearing effect. Our most familiar example of liquid shear is the flow of water or oil from a pipe, and it is well known that one can consider the liquid in contact with the inner surface of the pipe to be at rest while the velocity of the liquid stream increases progressively from the periphery to the centre. The rate of flow, other things being equal, depends upon the viscosity of the liquid or mutual attraction of the molecular surfaces slipping over each other.

In the case of articular surfaces bathed in a relatively deep layer of synovial fluid, we may consider the centre of the fluid to be at rest whilst the solid surfaces confining it are in motion so that the problem becomes analogous. Now in ordinary engineering practice the same set of conditions present themselves in the lubrication of a shaft and journal bearing, and a great deal of research has been applied to their investigation.

Engineers distinguish two types of lubrication, the one in which the film of oil separating the metal surfaces is extremely thin—even approaching a monomolecular layer; this is spoken of as "boundary lubrication". Such thin films acquire properties, such as abnormally high viscosity

differing from the liquid in bulk, but the conditions of boundary lubrication are not likely to occur in joints except possibly for a short time at the commencement of movement. The other case is that in which the surfaces are separated by a relatively thick layer of lubricant as normally in the joint space. Here the frictional resistance is proportional to the viscosity of the liquid and the rate of shear. The falling-sphere method of measuring viscosity makes use of this principle for, as is well known, the velocity of fall reaches a steady value related to the viscosity of the medium by Stokes's equation.

Ropes and others (1947) have designed an artificial joint for the study of the lubricating efficiency of various materials. This apparatus is shown in Fig. 5. It consists of a ball-and-socket bearing made out of the plastic substance lucite, which is weighted by lead weights on a heavy iron frame. By swinging the frame, a pendulum or circular motion may be imparted which causes the lucite surfaces to slide over each other.

With this apparatus the coefficient of static friction was measured under different loads and shown to obey the usual law. Synovial fluid was then compared with other substances such as saline or serum by introducing it between the sliding surfaces. A similar type of apparatus, but employing a human proximal interphalangeal joint, has been used by Jones (1934, 1936), and also made possible a test of the load necessary to cause a breakdown of the layer of synovial fluid separating the articular surfaces. Such a film withstood the great pressure of 900 lb. per sq. inch, more than that which is sufficient to crush bone itself.

Yet another function of the viscous layer of synovial fluid in the joint may be the provision of a damping or shock-absorbing mechanism for which a viscous material is admirably suited. The jarring and vibration associated with limb movements such as walking would thereby be taken up by the cushion of fluid and the articulating surfaces would be protected from damage. It is quite certain that cartilage, once injured, shows little or no tendency to regenerate and when repair takes place it does so by the invasion of fibrous tissue through marginal or subchondral proliferation.

When we consider the pathological changes in an arthritic joint, it may well be wondered whether lowering of the viscosity of the synovial mucin due to chemical degradation of the hyaluronic acid precedes any structural damage to the articulating surfaces or whether such damage caused by an infective or other type of agent so alters the permeability of the joint tissues that substances enter the cavity which may prove deleterious to the

chemical integrity of the mucin. I am thinking, for example, here, of the possible role of phosphatase or the enzyme accompanying phosphatase which attacks mucin. Only further experiment and investigation will place these occurrences in their right relationship.

Concluding Remarks

It will be noted that I have made no reference to the passage of large molecular substances into or out of the joint cavity. We are, as yet, only at the very beginning of our knowledge on this topic. Rather, have I tried to review the physical and chemical characteristics of synovial mucin, an important constituent of the joint fluid, and in such a way that the physiological importance of this substance might be illuminated and its relation to the pathology of joint diseases be rendered at any rate suggestive.

Mucin is a normal product of connective tissue, where no doubt it subserves several functions. It appears to be an intercellular cement, to regulate ionic distribution and osmotic equilibria, and to impart resiliency to the subcutaneous matrix. Its abundance appears to be affected to some extent by hormonal influences, and it is an intriguing possibility that the loss of resilience and the relative dehydration of the subcutaneous tissues which occur in old age are associated with a decrease in mucin content. Halliburton found in 1888 that the concentration of mucin is higher in the skin of children than of adults. If such changes take place with age in the subcutaneous connective tissues, is it not possible also that the degenerative changes which unhappily occur so frequently in the joints in old age may be related to changes in the quantity or quality of the synovial mucin which lubricates them?

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La Mucine dans le Liquide Synovial

RÉSUMÉ

L'auteur tente de passer en revue les caractères physiques et chimiques de la mucine synoviale, constituant important du liquide articulaire, dans le but de mettre en lumière son importance physiologique, et il suggère une relation entre cette mucine et la pathologie articulaire. La mucine est un produit normal du tissu conjonctif dans lequel ses fonctions sont certainement multiples. Elle paraît constituer un ciment intercellulaire, contrôler la distribution des ions et les équilibres osmotiques, et donner de l'élasticité à la matrice sous-cutanée. Son abondance semble être influencée par les hormones, et il est possible que la perte d'élasticité et la déshydratation relative des tissus sous-cutanés présentes chez les vieillards soient en relation avec une diminution de la quantité de mucine.