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HYALUONIC ACID - HYALURONIDASE IN RELATIONSHIP
TO THE RHEUMATIC DISEASES

by

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HYALURONIC ACID-HYALURONIDASE

IN RELATIONSHIP TO THE RHEUMATIC DISEASES

Rheumatic fever ranks among our most important chronic diseases. About 2.5 per cent of the total number of patients admitted to general hospitals in this country have rheumatic fever, and in children's hospitals the rate is 5.6 per cent (1). Cardiac involvement probably strikes 95 per cent of those afflicted with rheumatic fever.

Rheumatic fever is most common in children from five to fifteen years. It has been reported (2) that during this age period rheumatic fever with heart disease is the leading cause of death in the United States, and at ages 15 to 24 it is second only to tuberculosis. Rheumatic heart disease is serious in the fact that it is particularly a disease of youth, crippling and killing many children and adults. Research is under way on many phases of this disease, the cause of which is still unknown.

In the following treatise the hyaluronic acid-hyaluronidase system will be presented as a possible mechanism for the production of the rheumatic mesenchymal diseases, which include rheumatic fever, rheumatoid arthritis, periarteritis nodosa, lupus erythematosis, nephritis, etc.

Evidence is increasing in amount linking the connective in general and the fibrillar tissue in particular with rheumatic diseases. Histologically and chemically the connective tissue consists of two components, the fibrillar material and the interfibrillar substances (3). The two components belong to quite different classes of chemical substances, the fibrous elements being denatured, insoluble, fibrous proteins of very high molecular weight; whereas the cement substances are compounds or complexes of protein with highly polymerized mucopolysaccharide acids.

The interfirbrillar or cement substances seem to be of considerable importance in the mechanism of rheumatic diseases. The interfibrillar substances consist of the amorphous and viscous ground substances proper. The primary lesions of rheumatic fever and rheumatoid arthritis are located in the interfibrillar spaces, while the swelling, fragmentation and finally lysis is a secondary phenomenon (4). The chemical nature of the proteins in the cement substance is unknown. The mucopolysaccharides which are more or less loosely bound to the proteins have been studied more extensively. Up to the present time four mucopoly-saccharides have been identified as components of cement substance, (1) hyaluronic acid, (2) chondroitin sulfuric acid, (3) hyaluronosulfuric acid, which has been found

only in cornea, and (4) the sulfuric acid ester occurring
in amyloid. Hyaluronic acid and chondroitin sulfate probably
occur singly or together in varying proportions in all connec-
tive tissue.

HYALURONIC ACID

The exact chemical structure of hyaluronic acid
like that of other mucopolysaccharides is still unknown.
Equimolar quantities of N-acetyl hexoseamine and hexuronic
(glucuronic) acid have been found on analysis (5).
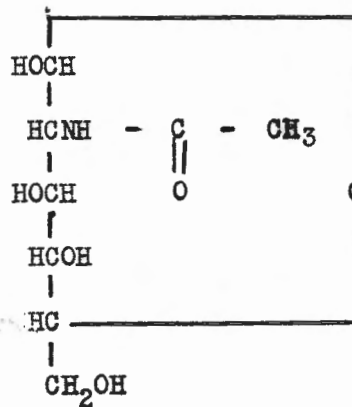
β-N-acetylglucosamine
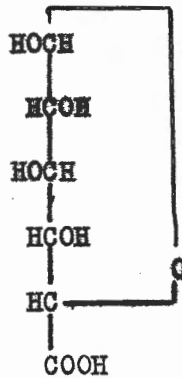
β-d-glucuronic acid

Hyaluronic acid in contrast to chondroitin sulfuric acid probably contains little or no branched chains. The basic unit is a disaccharide with a free aldehyde group present in the acetyl glucoseamine moiety.

The molecular weight of hyaluronic acid varies according to the source from which it is obtained; it has been estimated as between 200,000 and 500,000 and may be higher. It is viscid, soluble in water and precipitable by acetic acid. It occurs free or in salt linkage and is not chemically bound to proteins but will stoicometrically combine with the free amino groups of the proteins to form salts. The so-called mucins or mucoids prepared by acidifying the diluted solutions of such fluids as synovial fluids or vitreous humor are such salts. In all fluids so far investigated hyaluronic acid migrates in an electric field at pH 7.6 or 7.8.

Hyaluronic acid is not antigenic. The same compound, although serologically inactive, has been isolated from mucoid strains of groups A and C hemolytic streptococcus (7).

It is not known with certainty which cells produce the acid but it appears that young fibroblasts in undifferentiated connective tissue may produce it in large quantities. Young callus in experimental fractures is being

studied in this regard (8). The synovioblast of Vaubel
has been found to secrete mucin as well as proteolytic
enzymes (9). Mucin production is a sign of cell activity
rather than cell death, and, in inflammation, the number
of cytoplasmic granules and mucin increases greatly (10).
When synovioblasts change into fibroblasts there is diminution
of mucin secretion.

Highest concentrations of hyaluronic acid in the mammalian
body are found in synovial fluid (11) and skin (12) and next
in vitreous humor (13). It has also been isolated from
Wharton's jelly in human umbilical cord (14), from certain
mesodermal tumor fluids, eg., mesenthioloma (15), synovioma
(16) and chicken tumor (17, 18). It probably occurs in
nucleus pulposus of intervertebral disc (19) and in small
concentrations in connective tissue, although it has not
been isolated from these sources.

<div align="center">HYALURONIDASE</div>

Hyaluronic acid is depolymerized and hydrolyzed by
specific enzymes called hyaluronidases. Hyaluronidase has
been found in smooth and rough forms of types I, II, III,
and VI pneumococcus, groups A and C hemolytic streptococci
(20), staphylococci and in gas forming anerobes (21). It
has also been reported as occurring in snake venoms (22),

in leech extract (23), in mature mammalian spermatozoa (24), in extracts of spleen, ciliary body and iris (25). The greatest store of hyaluronidase appears to be in the skin where, however, it appears to be largely in an inactive form (26,27).

A very interesting property of hyaluronidases is their effect on dermal effusion, the so-called spreading reaction of Duran-Reynals (28). This reaction is usually carried out in guinea pigs or rabbits,but also has been observed in man. On intradermal injection of an indicator, usually T1824, together with suitable concentrations of enzyme, the indicator diffuses in the skin over a wide area as compared to the localized bleb in control injections without hyaluronidase. The reaction has been demonstrated also in the wall of stomach and intestine, in muscle, fasciae and tendon (29). However, in contrast to skin no hyaluronic acid has been obtained from these sources. The spreading reaction cannot be considered an accurate assay of hyaluronidase because mechanical pressure can aid the spreading activity of hyaluronidase in intradermal injections of fluids (30).

Consideration of the spreading activity of hyaluronidase has been applied clinically as an aid in fluid

and drug administration by the subcutaneous or intramuscular routes where the volume of fluid administered is large, relative to tissue spaces available. Since the enzyme causes rapid spreading, pain resulting from tissue distention produced by large volumes of fluid should be prevented or reduced. Hyaluronidase should increase the rate of fluid administration since the fluid does not remain at the site of injection. The rate of circulatory absorption of injected fluid should be increased by hyaluronidas, since the injected material is in contact with greater numbers of absorptive channels by virtue of the spreading effect of the enzyme. Hechter (31) found that swellings produced by clinical hypodermoclydid in enzyme treated areas disappeared within ten to twenty minutes after cessation of the injection, while in the absence of hyaluronidase sixty to ninety minutes were required. The amount of pain in the local swellings was less in the hyaluronidase areas than in those areas without the enzyme. Schwartzmann (32) obtained similar results without any untoward reactions. He recommended that hyaluronidase be added to the medical armamentarium in treatment of dehydration by hypodermoclysis.

Biological, chemical and physico-chemical methods have been used for the determination of hyaluronidases. Biological methods include the spreading reaction of Duran-

Reynals and the decapsulation of mucoid hemolytic strepto-
cocci of groups A and C by hyaluronidase. The physico-chemical
methods employed are the mucin clot prevention test, the
viscosity reducing method and the turbidimetric method.
Chemically, hyaluronidase has been determined by measuring
the increase in reducing sugar, or by the increase in
liberated N-acetyl glucosamine.

Hyaluronidases of various origins undoubtedly
contain different enzymes. On examination of various
experiments (33,34,35,36) there is marked discrepancy
in the activity of the enzyme, which varies according to
its source. The mode of action and the number of enzymes
acting in the activity of hyaluronidase is not known.

Inhibitors to hyaluronidase have been reported to
be present in sera (37). Inhibitory reaction of heparin
and chondroitin sulfate and sera from guinea pig, rabbit,
sheep, horse, mouse and human serum on hyaluronidase has
been reported (38,39). The inhibitory reaction of the
sera from different species against any one enzyme showed
considerable variation. Haas (40) has made extensive
reports on the presence of two enzymes in the blood plasma
which he states are part of the defense mechanism of the
body. He describes a third enzyme which promoted the

invasion of tissues. He further suggests evidence of two
additional enzymes; one in plasma, the other in the
invading organism. According to Haas, the invasive agent,
hyaluronidase, is counteracted by enzymes of sera of
different species, ranging from man to carp, which were
said to destroy hyaluronidase. Crude bacterial and some
anomal hyaluronidases in turn counteracted by another serum
enzyme and so forth. In reviewing the work of Haas, Meyer
(41) states that the data do not seem essentially different
than that presented by inhibition of heparin and other
substances, except that the inhibitors in serum are more
thermolabile.

CHONDROITIN SULFATE

Chondroitin sulfates, though known much longer than
hyaluronic acid, have been studied much less extensively.
They are compounds of high molecular weight similar to that
of hyaluronic acid, composed of equimolar concentrations
of acetyl galactose, glucuronic acid and sulfuric acid,
apparently in the C_6 position of the gaglctoseamine.
Chondroitin sulfuric acid has been isolated from hyaline
cartilage, umbilical cord and skin (42). A fraction
recently isolated from calves tendon (43) is probably also
chondroitin sulfate. It appears from histochemical studies
that chondroitin sulfate appears in the intima of arteries (44).

This layer may continue to the precapillaries and capillaries. That this layer does exist in the capillary wall is suggested by the increase in capillary permeability caused by hyaluronidase injected into connective tissue, whereas intravenous injection had no effect (45). The enzyme in vitro attacked chondroitin sulfate.

$$
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\text{HCNH---C---CH}_3 \\
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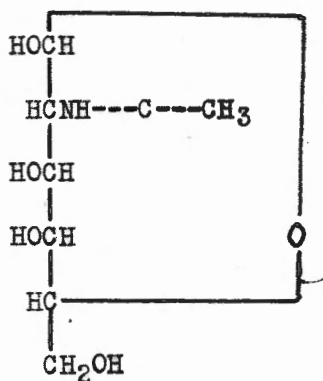
β -N-acetylgalactosamine

It should be noted that two tissues contain hyaluronate and chondroitin sulfate in about equal concentrations, namely, skin and umbilical cord. Synovial fluid, vitreous humor and the tumor fluids contain only hyaluronate, while cartilage contains only chondroitin sulfate.

Chondroitin sulfates probably are mixtures of similar but not identical compounds, some of which are hydrolyzed by hyaluronidases or by enzymes associated with hyaluronidases. The spreading effect in some tissues thus may be due to the hydrolysis of chondroitin sulfate rather than to that of hyaluronate. The metachromasia of

some dyes (such as toluidine blue) shown by connective
tissue and cartilage appears to be caused by chondroitin
sulfate (46). Hyaluronate does not seem to be stained by
any of the usual methods.

The known data of the chemistry of the connective
tissue, when considered in relation to what has been
learned by histological and tissue culture studies,
suggest the following mechanism in the development of
connective tissue (47). The young, growing fibroblasts
secrete hyaluonic acid, which is followed by the secretion
of chondroitin sulfate and of a precursor of collagen,
the latter a fibrous and non-soluble protein. By
local acidification in the immediate neighborhood of
the fibroblasts, the precursor is denatured by the
polysaccharides, the latter acting as anionic detergents
rolling up the peptide chains along the acidic groups of
the fibrous polysaccharide molecules. Most of the hyaluronate
is removed enzymatically, leaving the more firmly bound
chondroitin sulfates as a network on the surface
of the fibers. The latter by cross linking grows
into the mature insoluble fibers. Only in metabolically
very active connective tissue like that of skin,
does hyaluronic acid production continues in appreciable
quantities. The role of ascorbic acid (48,49)
is that it may be a component of chondroitin sulfate,

replacing in the chain so$_m$e of the glucuronic acid
molecules.

HYALURONIC ACID AND HYALURONIDASE
IN SYNOVIAL FLUID

The pathological chemistry of connective tissue is
still in an embryonal state. Synovial fluid is embryo-
logically, and to some extent physiologically, related to
connective tissue. Ragan and DeLameter (50) attempted to
determine the activity of hyaluronidase in vivo. Fluid
was removed from the knees of four patients and an
aqueous solution of the enzyme was immediately injected
into the joint space. At varying times, thereafter, the
fluid was again removed from the knees of four patients
and aqueous solution of the enzyme was immediately
injected into the joint space. At varying times thereafter
the fluid was again removed from the knee. The viscosity
of the fluid was determined. In all instances in which
the potent enzyme hyaluronidase was injected, there was
a marked reduction in the viscosity of the joint fluid.
In instances in which an enzyme was injected which had
become inactive as measured by in vitro hydrolysis no
significant change in viscosity occurred. Another
experiment was done to show that the change in visdosity
was brought about by the enzyme itself. Fluid was with-
drawn from the knee at hourly intervals. After the first

hour 2.5 cc. sterile water was injected into the joint
space. An hour later there was a small reduction in
viscosity of the same order of magnitude as the fall in
total protein. At this point a similar amount of water
in which 3.4 mg. of testicular enzyme had been dissolved
was injected into the joint. There was again a slight
fall intotal protein, but with the addition of the
enzyme, a marked fall in viscosity occurred.

There was no significant change in the underlying
disease leading to hydarthrosis. There was no marked
change in erythrocyte sedimentation rate, agglutination
with the group A and C hemolytic streptococcus, or in the
general course of the disease. There was no change in
the tendency of the fluid to reaccumulate in the joint.

Recent studies have been made by Meyer and Ragan
(51,52). Hyaluronic acid has been isolated from synovial
fluids in man. The concentration of hyaluronate was
measured by the turbidimetric method in both normal and
pathological synovial fluids. Pathological fluids in
this reaction appear as a stable colloidal turbidity,
while normal fluids of man and cattle precipitate as a
fibrous clot containing the polysaccharide. This clot
formation is prevented by 0.01 unit of hyaluronidase, an
amount too small to decrease measurably the hyaluronate

concentration and the colloidal turbidity seen in
pathological fluids. With normal vitreous humor
a colloidal precipitate is obtained, while in aqueous
humor 95 per cent of the total hyaluronate is found in
the depolymerized, non-precipitable form. This depoly-
merization is due to the co-presence of hyaluronidase
which was demonstrated in a concentration of about 0.4
u/cc. in ocular fluid.

In synovial fluid no measurable amount of hyaluronidase
could be demonstrated, unless the colloidal precipitation
is taken as an indication of the presence of the enzyme
in low concentration. The viscosities of over thirty
synovial fluids examined were not directly proportional
to the hyaluronate concentrations, the viscosities being
higher and the hyaluronate concentrations lower in normal
fluids as compared with pathological synovial fluids,
obtained from patients who had rheumatoid arthritis and
rheumatic fever. In view of the increased volume of
fluid in these joints, they contain a considerably larger
total amount of hyaluronic acid. Meyer and Ragan conclude
that the injured synovial cells produce an excess of the
acid, which may be followed by a compensatory increase of
hyaluronidase, the source of which is undetermined. They
feel that similar changes may occur in the mesenchymal
tissue spaces leading to an increase in interfibrillar

cement substances. Such an increased concentration of
highly viscous material would presumably slow down meta-
bolic processes.

HYALURONIC ACID AND HYALURONIDASE
AND THE B-HEMOLYTIC STREPTOCOCCUS

The only micro-organisms known to produce hyaluronic
acid are groups A and C hemolytic streptococci in the
mucoid phase. Non-mucoid hemolytic streptococci may pro-
duce hyaluronidase. The relationship to beta hemolytic
streptococci to the etiology of rheumatic has long been
a controversial subject. There are many who are of the
opinion that the initial attack and subsequent recurrences
of rheumatic fever are usually preceded by streptococcal
upper respiratory infections, others believe this
association to be merely accidental. Much of the
difficulty in studying rheumatic disease has been the
failure to reproduce the disorder in experimental animals.

Over a three year period in a convalescent home
for rheumatic fever Kuttner (53) observed the effect of
streptococcal upper respiratory infections on rheumatic
fever children. It is observed from the experimental data
that following outbreaks of sore throat due to group A
type 4 hemolytic streptococci there was no recrudescence
of rheumatic fever, while sore throat due to other types

of hemolytic streptococci chiefly types 27 and 51, there was a definite number of recurrences.

Later Crowley (54) tested 376 strains of hemolytic streptococci for hyaluronidase activity and for the presence of capsules. He found that only groups A types 4 and 22 produced hyaluronidase in demonstrable quantities. All attempts to grow type 4 in the mucoid phase have failed. Group C hemolytic streptococci also produce hyaluronic acid and many strains produce hyaluronidase. No data has been found which links group C streptococci with any particular type of infection, nor with virulence for man.

The antistreptolysin titer is used in many clinics to follow patients with rheumatic disease. The titer of the streptococcus antibody is elevated following acute hemolytic streptococci infections, nephritis, rheumatic fever and occasionally in the early stages of rheumatoid arthritis. It appears significant that "false positives" obtained by the antistreptolysin titer occur in those with mesenchymal disease. It has also been shown recently by Wallia (55) that serum of some of these patients will agglutinate unsensitized collodion particles as well as group A hemolytic streptococci.

There has been suggested that rheumatic diseases
are allergic in nature. Rich (56) has reported he was
able to produce lesions of periarteritis nodosa in rabbits
by injecting horse serum. The Caveltis (57) recently
have prepared an antigen from ground up human heart sus-
pension which was used to coat collodion particles. A
positive streptococcus agglutination response with the
sera of approximately 75 per cent of rheumatic fever
patients was found when tested against this antigen. They
previously demonstrated that auto-antibodies to kidney can
be produced by immunization of animals with mixtures of
group A hemolytic streptococci and kidneys of the same
species. Further investigation along these lines should
prove interesting.

ANTIRHEUMATIC DRUGS
AND HYALURONIDASE

Some information about the rheumatic process may
be obtained from the effects of antirheumatic drugs, A
possible relationship between the salicylates and hyaluronic
acid and hyaluronidase system was suggested by Fuerra (58) who
reported on the inhibition by salicylates of the spreading
reaction of testicular hyaluronidase in animals and in
man. Guerra demonstrated that hyaluronidase from bacterial

origin or from testicular extract in a 1 per cent solution

of Evans blue in humans or India Ink 1:2 for rabbits

increased the spread of the dyes. In a total of 96

experiments on 24 albino rabbits the spread of India Ink

with hyaluronidase was six times greater than with saline.

Oral or intravenous administration of sodium salicylate

inhibited 57 to 66 per cent the spreading effect of

hyaluronidase. The degree of inhibition varied with the

dose administered. Sulfadiazine did not reduce the

activity of hyaluronidase but appeared to enhance its

effect with inflammatory reactions in the area in several

groups.

Results were also reproduced in a total of 144

experiments on 36 normal males and females, adults and

children. Intradermal injections on individuals either

with active rheumatic fever or having suffered it gave

unique reactions with enormous diffusion of the dye and

local edema that sometimes occupied the entire arm injected

with hyaluronidase. Salicylates also inhibited the

enzyme in those cases and reduced the spreading effect in the

connective tissue. These types of allergic reactions to

hyaluronidase were also observed in one male who suffered

exanthemic typhus. This observation was confirmed by Meyer and

others. Meyer and others (59,60),61) demonstrated that

in vitro salicylate in therapeutic levels had

no effect on hyaluronidase activity but did inhibit in
concentrations which denatured the protein.

The cause of the interference with the spreading
reaction was conjectured to be due to interference with
the substrates or interference of a metabolic product of
salicylate with the enzyme. Interference with the sub-
strate may be suggested from the strong influence of
salicylate feeding on excretion of glucuronic acid (62).
The biosynthesis of chondroitin sulfate and hyaluronic
acid from glucuronic acid and acetylhexoseamines is
unknown. The inhibitory action of a biological derivative
of salicylate on hyaluronidase has been definitely estab-
lished by Meyer and others (63). The urine of patients on
salicylate therapy was fractionated and the fractions
tested for inhibition of hyaluronidase. A potent
inhibitor was found in the recrystallized salicyluric acid
fractions but synthetic salicyluric acid had no effect.
The inhibition proved to be due to gentisic acid and is
apparent only when the acid and enzyme are incubated
together while the copresence of the substrate prevents
this inactivation. Lowenthal and Gagnon (64) reported that
2-5 benzoquinone carboxylic acid (quinone of gentisic acid)
inhibits hyaluronidase.

Meyer and Ragan (65) also found water soluble
quinones and hydroquinones to be strong inhibitors of

hyaluronidase, among them were homogentisic quinone,
1,4 naphthoquinone-2-sulfonic acid and polyporic acid.
Cysteine, ascorbic acid, acetyl-glucosamine and
glucuronic acid could not replace hyaluronic acid in the
prevention of the inactivation.

The antirheumatic effect of sodium gentisate was
investigated by Meyer and Ragan (66) in a small number of
patients. They found that gentisate had the same anti-
rheumatic effect as salicylate without some of its
disadvantages. Five patients with acute rheumatic fever
were given sodium gentisate which was followed by disap-
pearance of pain, swelling and heat in the joints, by
fall of temperature to normal, and by fall in sedimentation
rate. In one patient, withdrawal of gentisate after
three days of administration was followed within 44 hours
by a return of acute joint symptoms, which promptly
responded to renewed administration of gentisate. Seven
patients with rheumatoid arthritis responded similarly
to gentisate as to equivalent amounts of salicylate. In
one patient, the salicylate was not tolerated because of
a co-existent duodenal ulcer, whereas gentisate caused
no gastric irritation. Four patients with persistently
active rheumatic fever responded similarly to gentisate
and salicylate.

Dosages as high as 10 gm./day of sodium gentisate
were given without untoward effects, although one patient
developed epigastric distress on 8 gm./day which subsided
immediately on withdrawal of the gentisate. No significant
increase in prothrombin time, no tinnitus or aural symptoms
developed; no sign of methemoglobinemia or liver damage
was observed. The increase in urinary glucuronic acid
excretion with salicylate ingestion did not occur with
gentisate. Only one quarter of the gentisate ingested
was recovered in the urine as gentisic acid.

ANTIHISTAMINES AND HYALURONIDASE

There is some experimental evidence that indicates
that the so-called antihistamines are also inhibitory to
hyaluronidase. Mayer and Kull (67) have found that
hyaluronidase markedly influences certain non-bacterial
allergic inflammation as it does in certain bacterial
processes; however, it has not been shown that hyaluronidase
is liberated during allergic inflammation of the skin and
other organs. Pyribenzamine and antistine prevented and
suppressed the allergic reaction of antigens with or with-
out hyaluronidase when injected intradermally in rabbits and
guinea pigs. It appears that the antihistamines act by
a similar mechanism as the salicylates in rheumatics

diseases. However, there is no record of antihistamines used in the treatment of rheumatic diseases per se.

Swyer (68) failed to demonstrate in vitro inhibition of hyaluronidase by salicylates as previously described by Guerra. Swyer concludes that Guerra's hyaluronidase preparations contained histamine and that salicylates inhibited the histamine effect. Since streptococci of the type responsible for rheumatic fever produce hyaluronidase the author suggests sensitivity to hyaluronidase as commonly occurring in rheumatic fever. He suggested that if the interstitial fluid pressure is increased or maintained by capillary damage produced by histamine, a substance known to play a part in hypersensitivity reactions, results of Guerra can be explained as being due to inhibition of histamine effect.

SUMMARY

Rheumatic diseases are common, of unknown etiology, subject to remission and exacerbations characterized clinically principally by cardiac and/or joint involvement and to a varying degree of other systems, and demonstrated pathologically to be a disorder of connective tissue. Rheumatic fever, rheumatoid arthritis, serum sickness,

disseminated lupus erythematosus, periarteritis nodosa
and scleroderma all present certain common features and it
is convenient to attempt to explain etiology on a common or
similar basis.

Because the connective tissue appears to be the common
denominator in all these diseases, the nature of its two
main subdivisions are considered in this paper. The three
types of fibrous elements, collagenous, reticulin and
elastic fibers are known to be denatured, insoluble proteins
of high molecular weight. The cement substances on the
other hand are made up of compounds or complexes of proteins
with highly polymerized mucopolysaccharides. Only four
polysaccharides have been identified: hyaluronic acid,
hyaluronosulfuric acid, chondroitin sulfuric acid and the
amyloid sulfuric acid ester. Specific enzymes called
hyaluronidases exist in the mammalian body, as well as
in many other natural sources, which possess the specific
power of depolymerizing and hydrolyzing hyaluronic acid
and perhaps other polysaccharides. While all these
substances are presumably concerned with the rheumatic
diseases, their normal physiology and pathological
variations have not yet been worked out.

In some patients with rheumatoid arthritis and
rheumatic fever, hyaluronate is increased in the synovial fluid

but what significance this observation has remains to be determined.

At the present time no etiological agent or mechanism is know for these diseases. Klinge has postulated that the initial lesion of rheumatoid arthritis and rheumatic fever involved the connective tissue cement substance. The hemolytic streptococcus theory has as yet resulted only in the diagnostic group A streptococcus agglutination reaction which is positive in about one half of cases, and it may be a non-specific reaction. The possibilities of virus, bacterial and allergy have offered possibilities but have not been placed on tenable grounds.

There have been some promising results indicating that antirheumatic drugs are inhibitory to hyaluronidase. Guerra described inhibition by salicylates of the spreading reaction due to hyaluronidase in animals and in humans with rheumatic fever.

Meyer and others found that gentisic acid a metabolic product of salicylate was inhibitory to hyaluronidase. The inhibition is present only when the acid and enzyme are incubated together. This work led to the discovery that quinones and hydroquinones are also strong inhibitors of hyaluronidase. In view of these findings sodium gentisate was used in a small number of patients with rheumatic fever.

and rheumatoid arthritis. Results obtained with sodium

gentisate therapy were comparable to that of the salicylates

without many of the toxic results of salicylates, eg.,

tinnitus, epigastric distress, etc. That the antirheumatic

effects of salicylates is due solely to the inhibition of

hyaluronidase does not seem likely, and other enzyme systems

are probably involved. However, the hyaluronic acid in

the synovial fluid is influenced by oral administration

of salicylates. Salicylates and other antirheumatic

drugs may act by influencing the synthesis of normally

occurring quinones.

In this paper, the emphasis has been placed on

hyaluronic acid, while changes in the chondroitin sulfates

and their enzymatic breakdown have been hardly mentioned.

It may be that the changes in chondroitin sulfates and in

their protein complexes are of greater importance for the

rheumatic processes than those related to hyaluronic acid.

It has been suggested that the feature distinguishing one

rheumatic disease from another is the mucopolysaccharide-

enzyme system which is primarily involved in a particular

disease.

A study of the interstitial mucopolysaccharides and

their relation to animal physiology and pathology is

necessary before a relationship can be established between

bacterial infection and the hyaluronidase system. From the
scanty data available it seems obvious that the function
of the skin, of ocular fluids, of synovial fluid and of con-
nective tissue in general must depend in part on the
quantity and degree of aggregation of hyaluronic acid. Gels
formed by the acid serve as the cement which holds cells
together. In other structures as in the joint they protect
internal surfaces, or they are part of the viscous barriers
as in some connective tissue, which regulate the exchange
of metabolites and water. Thus the physiological aspects
of hyaluronic acid as well as of the other mesodermal
cement substances seem to be of ever greater importance
than their role in infection.

The study of the interstitial mucopolysaccharides
and their relation to growth and differentiation of aging
and malignancy as well as its role in mesenchymal diseases
promises to be a rewarding field of investigation.

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