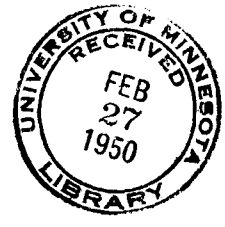
Bulletin of the

University of Minnesota Hospitals
and
Minnesota Medical Foundation



Inhibition of Hyaluronidase by Serum in Skin Diseases

Volume XXI | Friday, February 17, 1950 | Number 17

BULLETIN OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
and
MINNESOTA MEDICAL FOUNDATION

Volume XXI | Friday, February 17, 1950 | Number 17

INDEX

Published weekly during the school year, October to June, inclusive.
Annual Subscription Rate - $3.00

Address communications to: Staff Bulletin, 332M University of Minnesota Hospitals, Minneapolis 14, Minn.

I. INHIBITION OF HYALURONIDASE BY SERUM IN SKIN DISEASES

Melvin L. Grais
David Glick

Introduction

In 1928 Duran Reynals noted that when he injected attenuated vaccinia virus into the skin of rabbits an extremely mild lesion was produced. When he injected the same material into the testicle, severe lesions resulted[9,10] He then made an aqueous extract of testicle, mixed it with the virus, injected it into the skin and severe lesions resulted. He isolated the virus from the enhanced lesion and found that there was no alteration in its infectivity. From this he concluded that the testicular extract enhanced the lesion by some effect on the host tissue rather than on the virus.

In 1930 McClean confirmed these findings and found that testicular extract increased the rate of absorption of fluid injected intracutaneously. This was demonstrated by the rapid disappearance of the bleb of injected fluid, and by the fact that india ink or any other suitable indicator, when injected alone, formed a small pigmented area, but if testicular extract was injected with it, the dye spread through the skin and produced a large pigmented area. McClean therefore ascribed the effect of testicular extract to an immediate increase in tissue permeability and the agent was called a "spreading factor". As work on the "spreading factor" continued, it was shown that it was also produced elsewhere in nature.

In 1934 Meyer and Palmer[44] described a mucopolysaccharide present in vitreous humor of cattle eyes which they called hyaluronic acid. Later it was also found to be present in aqueous humor, and Whartons jelly of the umbilical cord[45,48], synovial fluid from cattle[47], certain tumors[26,38,39], the mucoid phase of group A hemolytic streptococci[28] and pig skin[49].

In 1936 Meyer, Dubos, Smyth and others[42,43,47,48] described an enzyme present in autolysates of certain strains of pneumococcus, and, so they claimed, in rabbit iris, ciliary body and spleen, which was capable of hydrolysing hyaluronic acid.

In 1939 and 1940 Chain and Duthie[2,3] demonstrated that the enzyme which hydrolyses hyaluronic acid was the "spreading factor" of the testis. They found that the testis extract acts as a spreading factor in extremely high dilutions and that it also hydrolyses hyaluronic acid and reduces its viscosity to approximately that of water. This enzyme was called "hyaluronidase".

Recent work in Glick's laboratory makes it doubtful that mammalian tissues other than those associated with spermatogenesis, contain the enzyme. Claims for its occurrence in other tissues may have been based on activity resulting from contamination of the tissue extracts with microorganisms.

Hyaluronic Acid

Hyaluronic acid has been found in vitreous humor[44,45], human umbilical cord[46], bovine aqueous humor, group A and C, hemolytic streptococci[28], synovial fluid[47], in a number of mesenchymal tumors[26,39,49], and in pig skin[38]. Hyaluronic acid is a mucopolysaccharide consisting of large and elongated molecules having a molecular weight of 200,000 to 500,000[27]. It is readily soluble in water producing highly viscous solutions, and on hydrolysis its viscosity is reduced. The polysaccharide is made up of units of glucuronic acid and acetyl N-glucosamine. It is apparently not antigenic.

Hyaluronic acid is believed to be a constituent of the interfibrillar ground or cement substance of the skin[37]. This belief is based on observations of the method of spread of indicators through the skin plus morphological and chemical studies of the ground substance[1,4,5].

The role of the ground substance is

varied and great. It governs the properties of diffusion and permeability. All substances reaching the cells, nutrients, toxins, infectious agents, or products of metabolism must pass through the ground substance. Its role in protection is evidenced by the great resistance connective tissue offers to penetration of foreign substances.

Hyaluronidase

The predatory properties of the enzyme accounts for its wide distribution over the entire evolutionary scale. It has been found in many bacteria, snake venoms, bee sting and leech head extracts[3,8,12,13] and in schistosomes[29]. High concentrations of hyaluronidase are found in mammalian testicular extract[5,25,32] and this is a practical and potent source of the enzyme. The enzyme is believed to be required for the breakdown of the mucoid coating on the ovum in order to allow penetration of the spermatozoa[16,30]. The claim has been made that hyaluronidase is a normal constituent of the skin[41]. As already indicated, our own work has shown that the skin does not contain hyaluronidase and that the method by which it was supposedly demonstrated is unreliable[41,51].

While non-enzymatic spreading factors exist, they do not duplicate the action of hyaluronidase. Among these are ascorbic acid, lecithin and peptones[36] and diazotized proteins[6,7]

The ability of the enzyme to increase spreading in the skin and to enhance infection plus the fact that it is elaborated by many virulent organisms has led to the belief that it is important in the mechanism of invasion of the animal body by bacteria and other toxic agents.

Hyaluronidase Inhibitors

There are many chemical substances and natural products which inhibit hyaluronidase. Among these are rutin, ascorbic acid, dicoumarol[13], heparin[35], partially depolymerized hyaluronic acid[34], hyaluronic acid derivatives[23], salicylates[21], and estrogens[50].

Hyaluronidase, like all enzymes, contains protein and hence is antigenic. Injected into an animal, it will provoke the formation of antibodies which will inhibit the enzyme in vitro. This anti-hyaluronidase is immunologically specific and so it will inactivate only the antigenic hyaluronidase but not the enzyme from any other sourse[11,24,31,34].

There is, in addition to this specific inhibitor, a non-specific inhibitor in the serum of practically all animals. The latter can affect the hyaluronidase from any source[33,24,22].

The present study was instituted after it had been shown by Glick and Golian[17] that the level of the hyaluronidase inhibitor in serum rose in acute poliomyelitis and fell to normal with recovery. We wanted to extend this study to bacterial as well as to other virus diseases, and to observe what effects were produced in a variety of skin diseases. This presentation emphasizes the latter. In some instances it was possible to follow the same patient through different stages of his disease; in others only single samples were obtained at the height of the disease for comparison to normal controls.

Hyaluronidase was assayed by its ability to reduce the viscosity of hyaluronic acid, and the inhibitor was determined by adding the serum to a standard hyaluronidase preparation and then measuring the residual activity as compared to that in the uninhibited material. The hyaluronidase was obtained from bovine testes, the hyaluronic acid from human umbilical cord, and the magnitude of the inhibition was recorded in arbitrary units designated as "A".

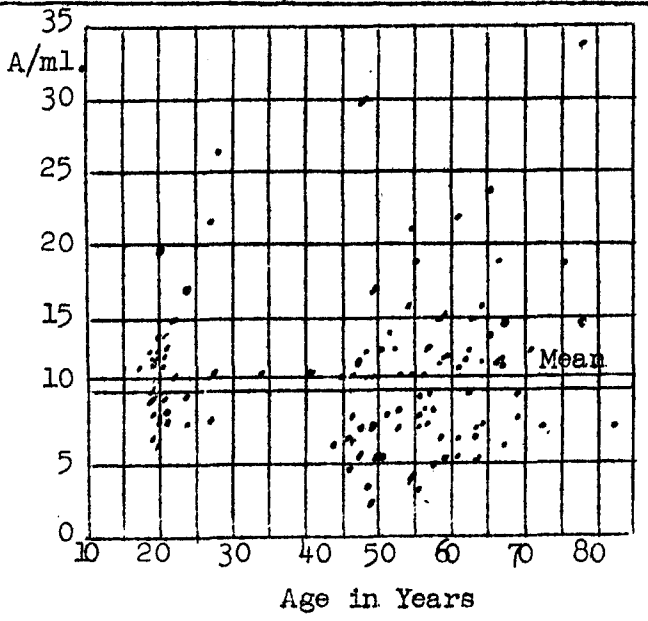
Normal Values

One hundred twenty-one sera from normal people of all ages gave the following (A) values:

RANGE	2 - 34	No relation between age and A value was observed, Fig. 1.
MEAN	11.0	
STANDARD DEVIATION	3.4	

Figure 1

Relationship Between Hyaluronidase Inhibitor Value in Blood Sera and Age in Normal Humans



Pemphigus Vulgaris

Correlation between the inhibitor value, and the total leucocyte count, sedimentation rate, temperature and clinical condition is given in Chart I. It may be seen that the (A) value increased with the severity of the disease and the increase in temperature. No relation between the (A) value and the other laboratory findings can be drawn from the data presented.

Chart I

Mrs. Age 82 - Pemphigus Vulgaris

Day after Admission	2	7	8	12	13	14	17	19	24	26
A per ml.	10	16		31			29	30	44	
Temp. high	99.2	99.6	100.0	100.0	100.0	99.8	100.2		100.6	104.4
Sed. Rate mm. in 60 min.	60				48			11		
Wbc. total	5900		7000	5200						
Clinical condition	G	G	F	F	P	P	P	V.P.	V.P.	E

Code: F - Fair P - Poor V.P. - Very Poor V.G. - Very Good E - Expired D - Discharged G - Good

Similar data for another case are shown in Chart II. There is some correlation with sedimentation rate but the inhibitor value corresponds more closely to the clinical condition. The fall in (A) value on the 33rd day was not accompanied by clinical improvement as is usually the case.

Chart II

Mrs. Age 59 Pemphigus Vulgaris

Day after Admission	2	3	6	8	10	15	19	25	27	30	33	39	46	50
A per ml.		27	60		98	79	84	72		93	57	59	55	
Temp. high	101.6	101.2	101.0	101.6	101.8	102	102.4	101.8	100.8	101.0	102.0	101.4	101.4	
Sed. Rate mm. in 60 min.				70		68			97	107				
Wbc. total	7300					5800			9300	2700				
Clinical condition	F	F	F	P	P	P	P	P	P	P	V.P.	V.P.	V.P.	E

Pemphigus Foliaceous

As seen in Chart III, the (A) value corresponds closely to the patient's clinical condition. The last three values listed were obtained from blood drawn after the patient's discharge from the hospital.

Chart III

Mr. Age 44 Pemphigus Foliaceous

Day after Admission	67	68	79	80	94	95	102	107	108	143	166	198
A per ml.		44		40	50		44			32	28	11
Temp. high		99.8	99.8	100.2	101.0	101.6	98.6	98.6		98.6	98.6	98.6
Sed. Rate mm. in 60 min.			72				51					
Wbc. total	9000		6500			9500						
Clinical condition	P	P	P	P	P	F	F	F	D	G	G	V.G.

A summary of nine cases of pemphigus is given in Table I. The inhibitor value is greatly elevated in each case. In those cases in which serial determinations were done on the same patient a rather striking feature which developed was the direct correlation of the inhibitor value with the clinical condition. This was also noted in other conditions studied as will be presented later.

Bullous fluid from patients with pemphigus was tested for presence of both hyaluronidase and hyaluronidase inhibitor. While none of the three samples tested showed presence of the enzyme the inhibitor values were 22, 38, and 18 corresponding to serum (A) values of 62, 57, and 23 respectively. Thus the (A) value of the bullous fluid varied from 35% to 77% of the serum level.

Table I

DISEASE	PATIENT			A/ml
Pemphigus Vulgaris	H. H.	44	M	50
" "	V. C.	52	M	112
" "	J. J.	64	M	68
" "	G. K.	67	M	57
" "	J. W.	59	M	82
" "	A. P.	82	F	44
" "	I. E.	59	F	98
" "	M. P.	69	F	47
" "	I. B.	32	F	88
			Av.	71.7

Lupus Erythematosus

Chart IV illustrates a severe prolonged case. The last inhibitor value was obtained when the patient returned to the clinic subsequent to discharge from the hospital. At that time she was just beginning to do some of her own housework. Marked correlation of inhibitor value with clinical condition was noted. A less impressive relation to temperature may also be seen in the chart.

Chart IV

Mrs. ____ Age 38 Lupus Erythematosus Acute Disseminated

Day after Admission	26	27	67	72	171	321
A per ml.		136		112	67	31
Temp. high	101.4	100.6	101.4	99.4	98.6	98.6
Sed. Rate mm. in 60 min.	85		111		115	
Wbc. total	3800	4300	1850			
Clinical condition	V.P.	V.P.	V.P.	V.P.	P	F

Cases of lupus erythematosus are summarized in Table 2. The increase in (A) value of the acute type over the subacute and chronic is noteworthy.

Table 2

Lupus Erythematosus			
Acute	38	F	137
Subacute	46	M	22
"	22	F	25
"	23	F	29
			25.3
Chronic	61	F	9.6
"		F	13
"	40	F	16
"		M	15
		Av.	13.4

Syphilis

Chart V illustrates a typical case. Central nervous system syphilis itself causes no elevation of (A) value, however, in malaria treated cases a marked elevation occurs with the onset of the malaria. Good correlation of (A) value with temperature may be noted.

Chart V

Mr. Age 40 C.N.S. Syphilis - Malaria Therapy

Day after Admission	2	4	5	11	14	16	18	21	23	25
A per ml.		13		89		67		55		37
Temp. high	98.0	98.6	102.4	103.6	102.0	105.4	103.5	103.0	106.0	99.4
Sed. Rate mm. in 60 min.	6		16	116	95	60	40		63	
Wbc. total								5800		

Chart VI illustrates the effect of fever per se on the inhibitor value. Serial hematocrits were done as a rough index of possible hemoconcentration. No hemoconcentration occurred and the inhibitor value was not affected by fever per se.

Chart VI

Mr. Age 42 C.N.S. Syphilis - Hypertherm Cabinet Therapy

Time	8:30 a.m.	10:30 a.m.	2:30 p.m.	3:30 p.m.
A per ml.	29	22	24	27
Temp. high	98.6	105.4	104.8	100.2
Sed. Rate mm. in 60 min.	69	67	71	
Hematocrit	41	41	40	41
Wbc. total	6200	4500	6300	5950

Table 3 summarizes findings in syphilis. The single case of primary syphilis permits no conclusions. Secondary and untreated tertiary have average (A) values in the normal range.

Table 3

DISEASE	PATIENT		A/ml
Syphilis			
Primary	18	M	34
Secondary	22	M	14
"	17	F	8.8
"	20	F	7.9
		Av.	10.2
Tertiary	52	M	15
"	48	F	22
"	48	F	25
"	42	M	25
		Av.	21.7
Tertiary (malaria therapy)	39	M	62
" "	40	M	109
" "	39	M	75
" "	55	M	42
" "	42	F	42
		Av.	66

Erythema Multiforme

Patient represented in Chart VIII was extensively involved. Inhibitor value correlated well with clinical condition and temperature.

Chart VIII

Miss Age 24 - Erythema Multiforme

Day after Admission	5	8	12	18
A per ml.	36	36	17	
Temp. high	101.6	99.6	99.4	98.8
Sed. rate mm. in 60 min.	48			
Wbc. total	5950	7050	9250	
Clinical condition	P	F	G	D

Table 4 lists two additional cases.

Erythema Nodosum

A typical case is given in Chart IX. Decline in (A) value was accompanied by a decline in sedimentation rate and temperature, and improvement of clinical condition. One additional case is listed in Table 4.

Chart IX

Mr. Age 8 - Erythema Nodosum

Day after Admission	2	3	7	9	14	21	35
A per ml.		49	67	45	15	19	
Temp. high	101.4	101.0	100.4	98.6			
Sed. rate mm. in 60 min.	101			101	81		39
Wbc. total	8200			7700	9500		
Clinical condition	P	P	P	F	G	V.G.	V.G.

Table 4

Erythema Multiforme	35	M	31
" "	39	F	14
" "	24	F	36
		Av.	27
Erythema Nodosum	44	F	67
" "	8	M	67

Diseases caused by or thought to be caused by a virus

Chart X illustrates increase of inhibitor value during the acute phase of these diseases.

Chart X

Chicken Pox

	Male	Day	2	3
Age	23	A/ml	28	42

Kaposis Varicelliform Eruption

	Female	Day	1	4	53
Age	19	A/ml	43	28	12

Herpes Zoster

	Female	Day	1	3	6
Age	64	A/ml	36	45	22

Diseases caused by a virus but having no systemic manifestations show a different picture. Table 5 includes cases of molloscum contagiosum and verruca vulgaris, these diseases showing normal (A) values. In dermatitis herpetiformis (Table 5) (A) values are within the normal range.

Table 5

DISEASE	PATIENT			A/ml
Chicken Pox	23	M		42
Kaposis Varicelliform Eruption	19	F		43
Herpes Zoster	68	M		33
" "	64	F		45
" "	25	M		14
			Av.	30.6
Dermatitis Herpetiformis	58	M		21
"	67	M		22
Molloscum Contagiosum	27	M		4.6
Verruca Vulgaris	24	M		4.6
" "	18	M		3.7
" "	24	M		6.5
			Av.	4.7

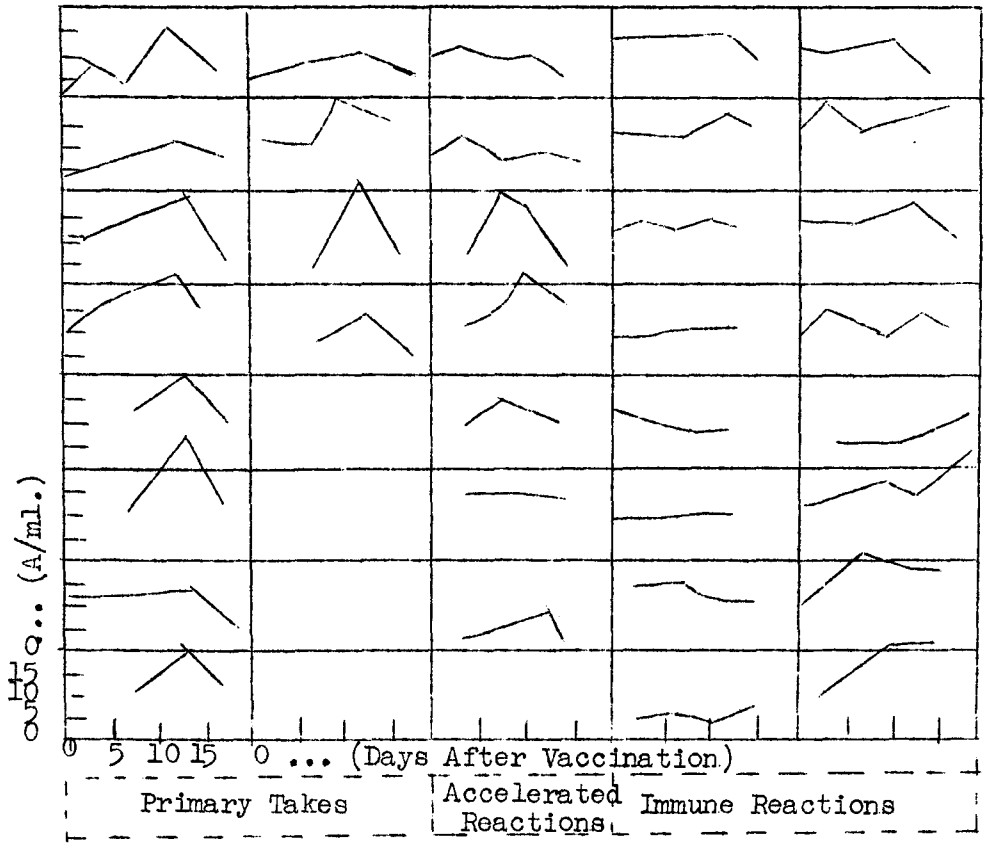
Smallpox Vaccination (Vaccinia)

Normal males ranging in age from 17 to 29 were studied. The only element of selection introduced was that individuals who gave no history of previous vaccination were purposely included in order that the number of primary takes be as great as possible. In every one of the twelve primary takes the hyaluronidase inhibitor level in the serum rose between the tenth and thirteenth day after vaccination. It will be recalled that the maximum reaction in primary takes in vaccination occurs in this period. In most cases this rise was at least double the normal value as measured by either prevaccination level or that to which the value fell after the reaction subsided. Accelerated reactors showed varied responses and in the immune reactors the trend was toward no significant change. Fig. 2.

The responses obtained in individuals showing accelerated reactions reached a maximum in most cases earlier than the tenth to thirteenth day period of the primary takes. It is known that the maximum response in individuals showing accelerated reactions usually occurs before the tenth day and it will be seen in Fig. 2 that in only one instance did the maximum response come later than 10 days after vaccination. The majority of individuals with immune reactions showed no significant change in hyaluronidase inhibitor level after vaccination and those cases in which changes were observed they followed no consistent pattern.

Fig. 2

The response of the hyaluronidase inhibitor level in human blood serum to vaccinia vaccination



Effect of Drugs

The following drugs were tested for their effect on both hyaluronidase and hyaluronidase inhibitor: penicillin, streptomycin, sulfanilamide, sulfapyridine, pyribenzamine, mapharsen, gold sodium thiosulfate and thiobismol.

The tests were in vitro and a variety of concentrations were tested for each drug. Within, and exceeding the therapeutic range by a wide margin, no effect by any of the above drugs on either hyaluronidase or the inhibitor was observed.

Chart XI

Drug Tested	Therapeutic Concentration	Highest concentration tested of drug in serum with no effect on inhibitor	Highest concentration tested of drug in hyaluronidase solution with no effect on the enzyme activity
Penicillin	30 U/ml. serum	500 U/ml.	100 U/ml.
Streptomycin	20 U-60 U/ml. blood	250 U/ml.	100 U/ml.
Sulfanilamide	10 mgm. % in blood	20 mgm. %	50 mgm. %
Sulfapyridine	4-6 mgm. % in blood	50 mgm. %	20 mgm. %
Pyribenzamine		50 mgm. %	10 mgm. %
Mapharsen (30% arsenic)	0.1 mgm. % As. in blood	30 mgm. % As.	0.6 mgm. % As.
Gold Sodium Thiosulfate (37% gold)		3.7 mgm. % Au.	0.74 mgm. % Au.
Thiobismol (38% bismuth)	0.0057 mg. % $Bi._{blood}$ in	19 mgm. % Bi	3.8 mgm. % Bi

Discussion

A high degree of correlation exists between the clinical condition in certain skin diseases and the serum hyaluronidase inhibitor value. A calculation of the co-efficient of correlation for the hyaluronidase inhibitor in the serum compared to sedimentation rate, temperature, and total leucocyte count is given in Table 6. This statistical treatment was applied to all of the data obtained.

A positive correlation with the sedimentation rate and temperature, which is significant as indicated by the data, and no significant correlation with the total leucocyte count was found (Table 6). This fits well with the normal response of these factors in infection. Sedimentation rate and temperature almost always rise while leucocyte count may vary considerably in either direction.

Table 6

Correlation of the hyaluronidase inhibitor values in blood serum with values of other measurements on the same patients.

Measurement	Number of Cases	Coefficient of Correlation	K	P
Erythrocyte sedimentation rate	129	0.4	4.5	0.001
Temperature	414	0.3	6.1	0.001
Total leucocyte count	104	0.1	1.0	0.317

In general it has been noted, with a high degree of consistency, that skin diseases of a systemic rather than localized nature, result in an elevation of the hyaluronidase inhibitor in the blood serum in a manner which seems to be a function of the severity of the involvement. On recovery the values drop to the normal range. This response is entirely non-specific with respect to the nature of the infecting agent. A variety of both viruses and bacteria elicit the effect. It is to be noted that fever per se as produced by mechanical means does not cause the inhibitor titer to rise.

The pattern of the responses of the serum inhibitor levels to vaccinia vaccination is largely that expected in the light of the other findings. The individuals exhibiting primary takes showed elevated levels whose magnitude paralleled the vaccination reaction itself. Varied responses were obtained with accelerated reactors and little if any change occurred in the immune reactors. Again, a correspondence was noted between the height of the reaction and the extent of the inhibitor elevation in those accelerated reactors with the more pronounced reactions.

One can speculate that this increase in the serum inhibitor may be a general non-specific defensive response of the body to counteract the invasiveness of hyaluronidase bearing organisms. That the response occurs in infections by organisms not containing hyaluronidase would seem to be contradictory. It must be remembered, however, that infective agents which do not in themselves contain hyaluronidase, are none-the-less rendered more invasive by the enzyme which might arise from secondary sources.

References

1. Bensley, S. H.
On the presence, properties and distribution of the intercellular ground substance of loose connective tissue.
Anat.Rec.60:93-108, '34.
2. Chain, E. and Duthie, E. S.
A mycolytic enzyme in testis extracts.
Nature, 133:977-978, '39.
3. Chain, E. and Duthie, E. S.
Identity of hyaluronidase and spreading factor.
Brit.J.Exptl.Path.,23:324-338, '40.
4. Chambers, R. and Zweifach, B. W.
Capillary endothelial cement in relation to permeability.
J.Cell.Comp.Physiol.,15:255-271, '40.
5. Clark E. R.
Intercellar substance in relation to tissue growth.
Ann.New York Acad.Sci.,46:733-740,'46.
6. Claude, A.
A group of chemicals active in increasing tissue permeability and enhancing certain infectious processes.
Science, 78:151-152, '33.

7. Claude, A.
Spreading property of azoproteins in the dermis.
J.Exptl.Med.,62:229-244, '35.

8. Claude, A.
Spreading properties and mycolytic activity of leech extracts.
Proc.Soc.Exptl.Biol.Med.,43: 684-689, '40.

9. Duran-Reynals, F.
Exaltation de l' activite' du virus vaccinal par les extraits des certains organes.
Compt.rend.soc.biol.,99:6-7, '28.

10. Duran-Reynals, F.
The effect of extracts of certain organs from normal and immunized animals on the infecting power of vaccine virus.
J.Exptl.Med.,50:327-340, '29.

11. Duran-Reynals, F.
The effect of antitesticular serum on the enhancement value of testicle extract.
J.Exptl.Med.,55:703-712, '32.

12. Duran-Reynals, F.
Studies on a certain spreading factor existing in bacteria and its significance for bacterial invasiveness.
J.Exper.Med.,58:161-181, '33.

13. Duran-Reynals, F.
A spreading factor in certain snake venoms and its relation to their mode of action.
J.Exptl.Med.,69:69-81, '39.

14. Elson, L. A. and Morgan, N. T. G.
A colorimetric method for the determination of glucosamine and chondrosamine.
Biochem.J.,27:1824, '33.

15. Favilli, G.
Mucolytic effects of natural and artificial spreading factors.
Nature, 145:866, '40.

16. Fekete, E. and Duran-Reynals, F.
Hyaluronidase in fertilization of mammalian ova.
Proc.Soc.Exper.Biol.Med.,52:119-121, '43.

17. Glick, D., and Gollan, F.
Mycolytic enzyme systems. I. Inhibition of hyaluronidase by serum in poliomyelitis.
J.Infect.Dis.,83:200-206, '48.

18. Glick D. and Grais, M. L.
Concerning the alleged occurrence of hyaluronidase in skin.
Arch.Biochem.,18:3,511, '48.

19. Grais, M. L. and Glick, D.
Mycolytic enzyme systems. II. Inhibition of hyaluronidase by serum in skin disease.
J.Inves.Derm.,11:No.4, 259-273, '48.

20. Grais, M. L. and Glick,D.
Mycolytic enzyme systems. Inhibition of hyaluronidase by serum in infectious diseases.
J.Infect. Dis.,85:101-106, '49.

21. Guerra, F.
Hyaluronidase inhibition by sodium salicylate in rheumatic fever.
Science, 103:686-687, '46.

22. Haas, E.
On the mechanism of invasion. I Antivasin I, an enzyme in the plasma.
J.Biol.Chem.,163:63-87, '46.

23. Hadidian, Z., and Pirie, N. M.
The effects of serum and of hyaluronic acid derivatives on the action of hyaluronidase.
Biochem.J.42:266-274, '48.

24. Hobby, G. L., Dawson, M. H., and Meyer, K.
The relationship between spreading factor and hyaluronidase.
J.Exp.Mer.,73:109-122, '41.

25. Hoffman, D. C. and Duran-Reynals, F.
The influence of testicle extract on the intradermal spread of injected fluids and particles.
J.Exper.Med.,53:387-398, '31.

26. Kabat, E. A.
A polysaccharide in tumors due to a virus of leucosis and sarcoma of fowls.
J.Biol.Chem.,130:143-147, '39.

27. Kass, E. H., and Seastone, C. V.
The role of the mucoid polysaccharide (hyaluronic acid) in the virulence of group A hemolytic streptococci.
J.Exptl.Med.,79:319, '44.

28. Kendall, F. E., Heidelberger, M., and Dawson, M. H.
A serologically inactive polysaccharide elaborated by mucoid strains of group A hemolytic streptococcus.
J.Biol.Chem., 118:61-69, '37.

29. Levine, M.D., Garzoli, R.F., Kuntz, R.E. and Killough, J.H.
On the demonstration of hyaluronidase in cercariae of schistosoma mansoni.
Federation Proc., 7:274, '48.

30. Leonard, S. L., and Kurzok, R.
A study of hyaluronidase effects on the follicle cells of ovulated rat ova.
Endocrin. 37:171-176, '45.

31. Madinaveitia, J.
A factor in culture filtrates of certain pathogenic bacteria which increases the permeability of the tissues.
J.Path.Bact.,42:477-511, '36.

32. Madinaveitia, J.
Studies on diffusing factors. Active preparations from mammalian testicle and their biological assay.
Biochem.J.32:1806-1813, '38.

33. Madinaveitia, J.
The in-vivo decapsulation of streptococci by hyaluronidase.
J.Path.Bact. 54:284-286, '42.

34. Madinaveitia, J. and Hale, C. W.
Studies on diffusing factors. The hyaluronidase activity of testicular extracts, culture filtrates and other agents that increase tissue permeability.
Biochem.J.,35:159-183, '41.

35. McClean, D.
The in-vivo decapsulation of streptococci by hyaluronidase.
J.Path.& Bact.,54:284, '42.

36. McClean, D., and Hale, C. W.
Studies on diffusing factors. The hyaluronidase activity of testicular extracts. Bacterial culture filtrates and other agents that increase tissue permeability.
Biochem. J. 35:159-183, '41.

37. Meyer, K.
The biological significance of hyaluronic acid and hyaluronidase.
Phy.Rev.,27:3, '47.

38. Meyer, K. and Chaffee, E.
Hyaluronic acid in pleural fluid associated with malignant tumor involving pleura and peritoneum.
Proc.Soc.Exptl.Biol.Med.,42:797-800, '39.

39. Meyer, K. and Chaffee, K.
Hyaluronic acid in the pleural fluid associated with a malignant tumor involving the pleura and peritoneum.
J.Biol.Chem.,133:83-91, '40.

40. Meyer, K. and Chaffee, E.
The mucopolysaccharides of skin.
J.Biol.Chem.,138:491-499, '41.

41. Meyer, K., Chaffe, E., Hobby, G. L., and Dawson, M. H.
Hyaluronidases of bacterial and animal origin.
J.Exptl.Med., 73:309, '41.

42. Meyer, K., Dubos, R. and Smyth, E.M.
Action of a lytic principle of pneumococcus on certain tissue polysaccharides.
Proc.Soc.,Exptl.Biol.Med., 34:816-818, '36.

43. Meyer, K., Dubos, R. and Smyth, E. M.
The hydrolysis of the polysaccharide acids of vitreous humor, of umbilical cord, and of streptococcus by the autolytic enzyme of pneumococcus.
J.Biol.Chem.,118:71-78, '37.

44. Meyer, K. and Palmer, J. W.
The polysaccharide of the vitreous humor.
J.Biol.Chem.,107:629-634, '34.

45. Meyer, K. and Palmer, J. W.
On the nature of ocular fluids.
Am.J.Ophthal.19:859-865, '36.

46. Meyer, K. and Palmer, J. W.
On glycoproteins, polysaccharides of vitreous humor and of umbilical cord.
J.Biol.Chem.,114:689, '36.

47. Meyer, K., Smyth, E. M. and Dawson, M. H.
The isolation of a mucopolysaccharide from synovial fluid.
J.Biol.Chem.,128:319-327, '39.

48. Meyer, K., Smyth, E. M. and Gallardo, E.
On the nature of ocular fluids. II. The hexosamine content.
Am.J.Ophthal.21:1083-1090,'38.

49. Pirie, A.
A hyaluronidase and a polysaccharide from tumors.
Brit.J.Exptl.Path.,23:277, '42.

50. Sprunt, D. H. and McDearman, S.
A study of the dispersion or concentration of india ink by certain sex hormones.
Endocrin. 27:893-898, '40.

51. Wattenberg, L. W. and Glick D.
Mucolytic Enzyme Systems VII. Effects of tissue extracts and body fluids, certain steroids, and hemoglobin derivatives on hyaluronidase activity.
J.Biol.Chem.,179, No. 3, 1213-1228, '49.

II. MEDICAL SCHOOL NEWS

Coming Events

February 21 - The Minnesota Pathological Society - "The Implications of a Study of Poliomyelitis" - Dr. James Watt; Medical Science Amphitheater, 8:00 p.m.

March 6-8 - Continuation course in Gastro-Intestinal Diseases for General Physicians.

March 27-29 - Continuation course in Dermatology for General Physicians.

* * *

Progress Note

On Thursday of this week bids were received for the construction of the fourth floor of the Variety Club Heart Hospital. The third floor is closed in now, and work on the fourth floor will be started soon.

The new hospital will be the first hospital in the United States devoted exclusively to the treatment and study of heart disease. It is a chronic hospital and is designed for long-term care and study of cardiac patients.

Original plans called for a three-story building. However, a grant to the University from the National Heart Foundation made possible the building of an additional floor which will be used chiefly for laboratories and research in cardiovascular disease. If construction continues as planned, the hospital will be completed and ready to receive patients by July 1.

Faculty News

Dr. Gaylord W. Anderson, Director of the School of Public Health and Mayo Professor of Preventive Medicine in Public Health, has been invited to be a member of the World Health Organization Expert Committee on Professional Technical Education, Medical and Auxiliary Personnel. Dr. Anderson will attend the February session of the committee when it meets in Geneva, Switzerland.

* * *

Dr. Homer Smith Visits University

Dr. Homer W. Smith, Director of the Physiological Laboratory, New York University College of Medicine, was a visitor on our medical school campus this past week. Dr. Smith is known throughout the medical world for his outstanding contributions to our knowledge of the physiology of the kidney. His work has been widely applied to the studies of problems concerning the kidney function in human disease, particularly in hypertension.

While he was on our campus, Dr. Smith delivered a special lecture, "The Evolution of the Kidney", before students and faculty of the medical school and other guests.

* * *

New Minnesota Medical Found. Member

Dr. Ruth I. Lundberg, Minneapolis, Minnesota.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

February 19 - February 25, 1950

No. 278

Sunday, February 19

9:00 - 10:00 Surgery Grand Rounds; Station 22, U. H.

10:30 - 11:00 Surgical Conference; X-ray Diagnosis in Intestinal Obstruction; Francis F. Ruzicka; Rm. M-109, U. H.

Monday, February 20

8:00 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - Pediatric Rounds; Erling Platou; Sta. I, General Hospital.

11:00 - 11:50 Physical Medicine Seminar; E-101, U. H.

11:00 - 11:50 Roentgenology-Medicine Conference; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.

12:00 - 1:00 Physiology Seminar; Cardiac Catheterization Studies in Humans; Drs. John LaBree and Forrest Adams; 214 M. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:20 Pathology Seminar; Histological Differentiation of Psoriasis Lichen-planus and Lupus Erythematosis; 104 I. A.

12:30 - 1:30 Surgery Problem Case Conference; A. A. Zierold, C. Dennis and Staff; Small Classroom, Minneapolis General Hospital.

1:30 - 2:30 Surgery Grand Rounds; A. A. Zierold, C. Dennis and Staff; Minneapolis General Hospital.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - Medical-Surgical Conference; Deep Phlebitis; C. V. Kusz; Bldg. I, Main Conference Room, Veterans Hospital.

4:00 - Public Health Seminar; Subject to be announced; 113 Medical Sciences.

4:00 - Pediatric Seminar; The Cerebral Palsy Patient in Pediatrics; Dr. Lund; 6th Floor West, Child Psychiatry, University Hospitals.

Monday, February 20 (Cont.)

5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.

5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy, O. J. Baggenstoss and Staffs; M-109, U. H.

Tuesday, February 21

8:00 - 9:00 Fracture Conference; Auditorium, Ancker Hospital.

8:15 - 9:00 Roentgenology-Surgical-Pathological Conference; Craig Freeman and L. G. Rigler; M-109, U. H.

8:30 - 10:20 Surgery Seminar; Small Conference Room, Bldg. I, Veterans Hospital.

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staffs; Todd Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and E. T. Bell; Veterans Hospital.

11:00 - Contagion Rounds; Forrest Adams; Sta. L, General Hospital.

12:30 - Pediatric-Surgery Rounds; Drs. Stoesser, Wyatt, Chisholm, McNelson and Dennis; Sta. I, Minneapolis General Hospital.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

1:30 - 2:30 Pediatric Psychiatry Conference; R. A. Jensen and Staff; 6th Floor, West Wing, U. H.

1:00 - 2:30 X-ray Surgery Conference; Auditorium, Ancker Hospital.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans Hospital.

4:00 - 5:00 Physiology-Surgery Conference; The Composition of Intestinal Gases; Bob Halberg and B. Zimmerman; Eustis Amphitheater.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 6:00 Prophyrin Seminar; C. J. Watson, Samuel Schwartz, et al; Powell Hall Amphitheater.

5:00 - 6:00 X-ray Conference; Presentation of Cases by University Hospitals Staff; Todd Amphitheater; U. H.

8:00 - Minnesota Pathological Society Meeting; The Implications of a Study of Poliomyelitis; James Watt; Medical Science Amphitheater.

Wednesday, February 22 -- H O L I D A Y

Thursday, February 23

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

11:30 - Pathology Conference Clinic; Main Classroom; General Hospital.

11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Classroom, Minneapolis General Hospital.

12:00 - 1:00 Physiological Chemistry Seminar; Ascorbic Acid in Relation to Amino Acid Metabolism; A. B. Falcone; 214 M. H.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

2:00 - 3:00 Errors Conference; A. A. Zierold, C. Dennis and Staff; Large Classroom, Minneapolis General Hospital.

4:15 - 5:00 Bacteriology and Immunology Seminar; Hypersensitivity in Disease; W. J. Cromartie; 214 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 X-ray Seminar; The Ileo-cecal Valve; Elliott Lasser; Todd Amphitheater, U. H.

7:30 - 9:30 Pediatrics Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hours; 206 Temporary West Hospital.

Friday, February 24

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Veterans Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - Pediatric Rounds; Erling Platou; Sta. I, General Hospital.

Friday, February 24 (Cont.)

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, O. S. Wyatt, A. V. Stoesser, and Staffs; Minneapolis General Hospital.

11:45 - 12:50 University of Minnesota Hospitals General Staff Meeting; Subarachnoid Hemorrhages and Intercranial Aneurysms; Lyle A. French and Paul S. Blake; Powell Hall Amphitheater.

12:00 - 1:00 Surgery Clinical Pathological Conference; Clarence Dennis and Staff; Large Classroom, Minneapolis General Hospital.

1:00 - 1:50 Dermatology and Syphilology Conference; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 3:00 Pathology-Surgery Conference; Auditorium, Ancker Hospital.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 4:00 Neuropathology Conference; F. Tichy; Todd Amphitheater, U. H.

3:00 - 6:00 Demonstrations in Cardiovascular Physiology; M. B. Visscher, et al; 301 M. H.

4:00 - 5:00 Clinical Pathological Conference; A. B. Baker; Todd Amphitheater, U. H.

4:15 - 5:15 Electrocardiographic Conference; Demonstration; G. N. Aagaard; 106 Temp. Bldg., Hospital Court, U. H.

5:00 - 6:00 Otolaryngology Seminar; Review of Current Literature; Dr. Younger; Discussor, H. V. Hanson; Todd Memorial Room, U. H.

Saturday, February 25

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; M-109, U. H.

8:00 - 9:00 Surgery Literature Conference; Clarence Dennis and Staff; Small Classroom, Minneapolis General Hospital.

8:30 - 9:30 Surgery Conference; Auditorium, Ancker Hospital.

9:00 - 11:30 Neurology Conference; Pyramidal and General Cerebral Degenerative Diseases; Powell Hall Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-221, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 11:30 Surgery-Roentgenology Conference; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

Saturday, February 25 (Cont.)

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - Contagion Rounds; Forrest Adams; Sta. L, General Hospital.

11:00 - 12:00 Anatomy Seminar; Jost's Study of Differentiation of the Urogenital Tract; Lemen J. Wells; Biliary Obstruction in the Vitamin A Deficient Albino Rat; Harry Monsen; 226 I. A.