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Bulletin of the

University of Minnesota Hospitals
and
Minnesota Medical Foundation

Fibrinoid Disease

Volume XXVI | Friday, April 22, 1955 | Number 25

BULLETIN OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
and
MINNESOTA MEDICAL FOUNDATION

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CONTENTS

Published weekly during the school year, October to June, inclusive.

The Bulletin is sent to members of the Minnesota Medical Foundation. Annual membership fee - $10.00.

Address communications to: Staff Bulletin, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minn.

I. EXPERIMENTAL AND CLINICAL STUDIES OF FIBRINOGEN AND HEPARIN PRECIPITABLE FIBRINOGEN, PARTICULARLY AS RELATED TO FIBRINOID DISEASE

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Intravenous injection of two appropriately spaced doses of gram-negative bacterial endotoxin into the young rabbit results in a catastrophic reaction of hemorrhage and necrosis in almost every organ - the generalized Shwartzman phenomenon.[1,2] The underlying histopathological lesion in this experimental model has been shown to consist of occlusion of small blood vessels by intravascular and perivascular deposits of a homogeneous pink-staining material with the tinctorial qualities of fibrinoid.[3,4,5,6] These experimental fibrinoid lesions have attracted particular interest because of their striking resemblance to the lesions found in certain human diffuse vascular diseases[7] and infections.[8] Several lines of indirect evidence suggest that the fibrinoid deposits in the experimental animal originate in the fibrinogen component of the circulating blood.[9,10,11] Moreover, direct immunological identification of fibrin in the fibrinoid deposits from human pathologic material has been recently achieved.[12]

It was of interest, therefore, to examine the blood of the experimental animal, as well as human patients, for changes in fibrinogen which might be related to these pathologic deposits. It is the purpose of this presentation to review the available evidence pertaining to origin and nature of fibrinoid and to present the results of recent studies of quantitative and qualitative alterations of circulating fibrinogen in the experimental model, and in various human diseases, which appear to be related to fibrinoid deposition.

These studies were supported in part by grants from the National Heart Institute of the National Institutes of Health, The Helen Hay Whitney Foundation, The Minnesota Heart Association, The American Heart Association, and the Graduate School of Research Fund.

Review of evidence for origin of fibrinoid from the circulating blood - The perivascular and intravascular eosinophilic deposits in both the generalized Shwartzman reaction and human "fibrinoid disease" demonstrate all of the special tinctorial qualities which differentiate them from fibrin.[6,7,13] On the other hand, it is difficult to reconcile this histochemical evidence that fibrin and fibrinoid are significantly different with the considerable body of indirect evidence that fibrinoid originates in the circulating blood. Some items of evidence for origin in the circulating blood of fibrinoid, and more specifically, fibrinogen, are as follows:

1. The earliest visible microscopic change in the generalized Shwartzman reaction is deposition of layers of fibrinoid along the renal glomerular endothelium. This progresses to complete occlusion; occasionally clumps are seen backing up into the afferent arteriole, indicating its intravascular origin.[1,4,6]

2. Glomeruli may be isolated by differential sedimentation of a mash of kidney from a rabbit with the generalized Shwartzman reaction.[14] The fibrinoid in these glomeruli is dissolved by proteolytic enzymes, and is birefringent in polarized light, suggesting a protein with highly organized molecular configuration, similar to polymerized fibrinogen.

3. Doses of heparin sufficient to render the blood incoagulable for 2 - 3 hours after the provoking injection of endotoxin protect rabbits against the generalized as well as the dermal Shwartzman reaction.[15] This suggests that some alteration in blood coagulation, prevented or reversed by heparin, is related to fibrinoid deposition.

4. Fibrinoid deposits identical to those of the generalized Shwartzman reaction can be produced by intravenous injection of any of several large-molecule acid polysaccharide sulfates in combination with a single injection of small amounts of endotoxin,[9,16] or by direct renal perfusion of polymer-endotoxin prepared donor blood.[11] No reaction occurs with these doses of the polymer alone or with endotoxin alone. These substances, including polyanethol sulfonate ("Liquoid"), polyvinylalcohol sulfate (PVAS), and dextran sulfate, share the heavy charge, anticoagulant, and combining properties of heparin. Anticoagulant doses of heparin were found to prevent completely the endotoxin polymer reaction providing heparin was given before the polymer. Walton and co-workers[17] have found that dextran sulfate precipitates fibrinogen *in vitro*, and that precipitation is blocked by prior exposure to heparin. It seems reasonable, therefore, to postulate that polymers produce *in vivo* precipitation of fibrinogen and that these precipitates are in turn responsible for the endotoxin-polymer reaction. The first section of this presentation is concerned with showing evidence of fibrinogen depletion by the acidic polymers, and with a qualitative change in fibrinogen occurring after endotoxin in rabbits. These studies are being reported in detail elsewhere.[10]

Materials and Methods - Rabbits of a hybrid albino stock, weighing approximately one kilogram, were used for all experiments. Blood specimens were obtained by heart puncture with a 22-gauge needle. Blood was always withdrawn rapidly and mixed with the anticoagulant. If any technical difficulty in obtaining blood specimens was encountered, the animal was discarded. Meningococcal endotoxin, prepared as previously described,[1] was diluted in sterile pyrogen-free saline, and injected intravenously in a 2.0 ml. volume. Na Polyanethol sulfonate, "Liquoid", obtained from Hoffman-LaRoche, Nutley, N. J., was prepared in sterile pyrogen-free saline in a 10 mg./ml. concentration. Fibrinogen determinations were made on plasma samples, using ACD anticoagulant, by a modification of the method of Morrison,[18] described elsewhere.[10] A correction factor for "occlusion" of other proteins[18] was made and the result expressed as Gm. per 100 ml. The procedure for measuring heparin-precipitable fraction is outlined in the text. Heparin employed for these experiments included a pure sodium heparin preparation (129 USP units per mg., lot DX-629) generously supplied by Dr. James Dugger of the Upjohn Company, Kalamazoo, Michigan, and commercial heparin solutions containing 10 mg. per ml., prepared by The Upjohn Company, Vitarine Company, and Hoffman-LaRoche.

Changes in circulating fibrinogen during the generalized Shwartzman reaction produced by endotoxin in combination with "Liquoid" - If a relationship between circulating fibrinogen and fibrinoid deposition is postulated on the basis of various items of indirect evidence, it follows that an alteration in the blood level of fibrinogen should be demonstrable at the time these deposits are being laid down. Accumulation of fibrinoid in the blood vessels is known to begin within one hour of the provoking injection of endotoxin, and earlier in the case of the endotoxin-polymer reaction. Therefore, groups of rabbits were given a single intravenous injection of 1-200 endotoxin. Two hours later, after a base line bleeding, 8 mg. of "Liquoid" was injected intravenously and a second blood specimen obtained one hour later.

Results of this experiment are shown in Table I. It will be seen that significant reductions in fibrinogen levels occurred in the endotoxin-treated rabbits given "Liquoid", while animals receiving "Liquoid" alone showed no significant change in fibrinogen. Fibrinogen depletion occurred within 10 minutes and lasted up to 6 hours in other experiments in which 8 mg. of "Liquoid" was given. Significant depletion of fibrinogen in blood specimens taken one hour after "Liquoid" were found after 10.0, 8.0, 4.8, and 2.4 mg.

Table I

Fibrinogen Depletion by Liquoid in Rabbits Given Meningococcal Endotoxin

Group	Rabbit Number	Fibrinogen Grams Percent	
		Before Liquoid	One hour after Liquoid
Endotoxin* followed in two hours by intravenous Liquoid**	1	.22	.06
	2	.24	.07
	3	.17	.03
	4	.27	.03
	5	.15	.00
	6	.20	.09
	Average	.208	.047
Intravenous Liquoid alone	1	0.21	.17
	2	.29	.26
	3	.27	.24
	4	.26	.20
	5	.22	.17
	6	.24	.16
	Average	.24	.20

* 2.0 ml. 1 - 200 meningococcal endotoxin given intravenously

** 8.0 mg. Liquoid in 2.0 ml. saline

"Liquoid" were injected after endotoxin, but not after 1.2 mg. This range of "Liquoid" dosage producing fibrinogen depletion corresponds roughly to those producing the generalized Shwartzman reaction with "Liquoid"-endotoxin combinations.

Similar experiments have been conducted with the conventional two-dose Shwartzman reaction. However, no significant change in fibrinogen level could be demonstrated using various amounts of endotoxin and taking blood specimens at varying times after provocation. Since fibrinogen turnover takes place at an extremely high rate,[20] it seems possible that the slower rate at which deposition

occurs in the conventional reaction could be compensated for by rapid replacement into the circulation.

Prevention of fibrinogen depletion by "Liquoid" with anticoagulant doses of heparin - Deposition of glomerular fibrinoid in the glomerular capillaries of rabbits treated with endotoxin and polymer is completely prevented by prior injection of anticoagulant doses of heparin. Experiments were therefore designed to determine if similar amounts of heparin prevent fibrinogen depletion by "Liquoid". Table II gives the results of an experiment in which groups of rabbits were given intravenous injections of 1-200 endotoxin, followed in two hours by 8 mg. of "Liquoid" intravenously. Twenty-five mg. of heparin were injected immediately before "Liquoid." Blood specimens were taken before and one hour after "Liquoid" administration. Appropriate controls which received endotoxin followed by "Liquoid" and endotoxin followed by heparin were included. No significant difference was found between the fibrinogen levels of the heparin-treated endotoxin-"Liquoid" group and the controls receiving only endotoxin and heparin. Again, marked depletion of fibrinogen was observed in the group receiving endotoxin and "Liquoid" without heparin.

These experiments indicate that fibrinogen depletion of the circulating blood by "Liquoid" parallels in timing the appearance of fibrinoid deposits in the kidneys and other vessels, and that heparin in dosage sufficient to prevent fibrinoid deposits also prevents fibrinogen depletion.

Demonstration of a heparin-precipitable fraction in the plasma of endotoxin-treated rabbits - Assuming that fibrinoid is somehow derived from fibrinogen, it may be inferred that an alteration in this component of circulating blood must occur following endotoxin injection, which renders it more susceptible in vivo to precipitation by "Liquoid" and other polymers. Attempts were therefore made to demonstrate a qualitative in vitro change in the blood of rabbits given endotoxins which would result in increased precipitability by polymers. A component of the heparinized plasma of endotoxin-treated rabbits was found which would precipitate reversibly at 4°C.[21]

This heparin-precipitable fraction (HPF) is demonstrated by taking blood samples into heparin in a final dilution of 1 mg. per ml., then centrifuging at 2600 r.p.m. for 15 minutes, separating the plasma, and cooling it to 4°C. The precipitation first appears about 30 minutes after placing in the cold as a visible opalescence with gradual opacification. Soon the precipitate collects as fine, then coarse, floccules, and within two hours a dense, opaque, flocculant precipitate has formed in the tube. This precipitate redissolves on warming to 37°C. No precipitation occurs in serum or in freshly obtained oxalated or citrated plasma. Addition of heparin to oxalated or citrated plasma, but not to serum, causes cold-precipitation similar to that in heparinized plasma.

In an experiment designed to estimate quantitatively the HPF appearing after a single endotoxin injection, rabbits were given 1-200 endotoxin intravenously and bled two hours later. The heparinized plasmas were chilled for six hours, the precipitate collected by centrifugation at 4°C, and washed twice with cold phosphate buffer pH 7.4, M/20. The protein content of the precipitates was then measured by the biuret method. Data from this experiment are presented in Table III. The average precipitate in this experiment represented 0.043 Gm. % of protein, while the range was from 0.03 to 0.06 Gm.%. In other experiments values as high as 0.20 Gm.% have been observed.

The time of appearance and duration of presence of HPF is shown by the data in Table IV. In this experiment groups of rabbits were given an intravenous injection of 1-200 endotoxin, bled at various times afterward. The plasma was

Table II

Heparin Prevention of Fibrinogen Depletion by "Liquoid" in Rabbits Given Meningococcal Endotoxin

Group	Rabbit Number	Fibrinogen Grams Percent	
		Before Liquoid	One hour after Liquoid
Endotoxin* followed in two hours by intravenous "Liquoid."** Heparin*** before "Liquoid."	1	.22	.16
	2	.43	.37
	3	.20	.17
	4	.17	.13
	5	.20	.16
	6	.17	.14
	Average	.232	.188
Endotoxin followed in two hours by intravenous "Liquoid" No heparin.	1	.20	.09
	2	.17	.03
	3	.17	.02
	4	.20	.00
	5	.17	.00
	6	.31	.14
	Average	.220	.046
Endotoxin followed in two hours by Heparin. Bleedings before and one hour after Heparin.	1	.18	.17
	2	.39	.27
	3	.25	.22
	4	.18	.17
	5	.25	.21
	6	.19	.17
	Average	.240	.201

* 2.0 ml. 1 - 200 meningococcal endotoxin intravenously
** 8.0 mgm. "Liquoid" in 2.0 ml. saline
*** Heparin, 25 mgm. injected intravenously immediately before "Liquoid."

Table III

Amount of Heparin-Precipitable Fraction Present in Plasma of Rabbits Two Hours after Intravenous Meningococcal Endotoxin*

Rabbit Number	Heparin Precipitable fraction Grams Percent
1	0.06
2	0.03
3	0.04
4	0.04
5	0.03
6	0.06
Average	0.043

* Rabbits given 2.0 ml. 1 - 200 meningococcal endotoxin intravenously, bled two hours later.

Table IV

Time of Appearance of Heparin-Precipitable Fraction in Rabbit Plasma after an Intravenous Injection of Meningococcal Endotoxin*

Time of Bleeding	Number of Rabbits Injected	Number with HPF
Before endotoxin	20	1
15 minutes after endotoxin	10	0
30 minutes after endotoxin	10	1
1 hour after endotoxin	20	16
2 hours after endotoxin	20	20
4 hours after endotoxin	20	19
6 hours after endotoxin	10	8
24 hours after endotoxin	20	5

* Rabbits given 2.0 ml. 1 - 200 meningococcal endotoxin. At the time intervals indicated, the animals were bled, and the heparinized plasma chilled to 4° for two hours. The number showing a precipitate at this time is indicated.

chilled to 4°C and observed after two hours for the presence of precipitate. HPF was absent at thirty minutes, but had appeared in the plasma of most rabbits by one hour, and all rabbits by two hours after injection. It was gone in 75% of rabbits 24 hours after injection.

Studies attempting to determine the composition of HPF in the experimental animal indicate strongly that it is closely related to, if not identical, with fibrinogen. For example, it migrates with fibrinogen on paper electrophoresis at 37°C, it is partially clottable by thrombin, it is absent from serum, and it gradually takes on the appearance and consistency of a clot, being no longer completely soluble at 37°C if allowed to remain in plasma more than 24 hours at 4°C.

Further evidence of the identity of HPF and fibrinogen was obtained in experiments which showed that HPF, like fibrinogen, was abruptly depleted in the endotoxin treated animal given an intravenous injection of "Liquoid."

The appearance of HPF in plasma following an injection of endotoxin can be completely prevented by prior intravenous injection of anticoagulant doses of heparin. Table V shows an experiment in which a group of twelve rabbits were given 1-200 endotoxin, bled two hours later, and the plasma observed for the appearance of HPF. The precipitates appearing after two hours at 4°C were compared with those from an identical group of rabbits receiving 20 mg. heparin immediately before, one hour and three hours after endotoxin. It will be seen that HPF appeared in no group receiving

Table V

Prevention of Appearance of Heparin-Precipitable Fraction in Plasma of Rabbits after Intravenous Meningococcal Endotoxin by Prior Heparin Treatment

Procedure	Number of Rabbits	Number with HPF
Intravenous endotoxin.* Bled two hours later.	12	11
20 mgm. Heparin intravenously immediately before endotoxin. Bled two hours later.	12	0
20 mgm. Heparin intravenously one hour after endotoxin. Bled two hours after endotoxin	12	5
20 mgm. Heparin intravenously three hours after endotoxin. Bled one hour later.	12	12

* 2.0 ml. 1 - 200 meningococcal endotoxin

heparin before endotoxin, in five of twelve receiving it one hour later, and in all receiving heparin three hours later. Eleven out of twelve rabbits in the control group showed precipitates. In other experiments it has been found that the appearance of HPF after endotoxin injection is not prevented by nitrogen mustard in a leucopenia-inducing dose, or by prior treatment with cortisone.

Studies of a Heparin-Precipitable Fraction Occurring in the Plasma in Various Human Disease States

The studies cited above in experimental animals prompted examinations of human plasma for a similar qualitative fibrinogen alteration, particularly in disease states characterized histopathologically by fibrinoid deposition. A heparin-precipitable, cold-insoluble protein, similar to that produced in experimental animals, was found to be present in large quantity in the plasma of patients with acute rheumatic fever, rheumatoid arthritis, periarteritis nodosa, and other vascular diseases. However, further studies demonstrated clearly that HPF occurs in similarly large amounts in a variety of other diseases, including meningitis, Group A, hemolytic streptococcal pharyngitis, disseminated neoplasms, hypersensitivity states, and in smaller quantity in normal persons. The results of serial quantitative estimations of fibrinogen and heparin-precipitable fibrinogen in various disease states, and studies of the properties of HPF are presented in this section.

Methods and techniques - Blood specimens were obtained from patients with various diseases and from normal volunteers in the fasting state and immediately mixed with the appropriate anticoagulant. At each bleeding, samples were taken in heparin, 1-50 final dilution, for HPF determination, into "double oxalate" for erythrocyte sedimentation rate and fibrinogen determination, and into a sterile tube for serum mucoprotein, C-reactive protein, and other studies.

HPF was determined by measuring the protein content of the precipitates formed in heparinized plasma, after 18 hours at 4°C. The precipitates were washed twice with pH7.4 M/20 Sorensen phosphate buffer by centrifugation at 2600 r.p.m. in the International refrigerated centrifuge at 4°C. The precipitate was then dissolved in buffer at 37°C for 30 minutes, whereupon the precipitate would go back into solution. The protein content of the resultant solution was determined by the biuret technique employing a Coleman, Jr. spectrophotometer. The resultant value was expressed as grams per 100 cc. plasma. The method produces results, in replicate samples, from patients with varying HPF levels, which vary within 0.010 Gm.%. The conditions chosen for the determination were found to be optimal for maintaining insolubility at 4°C during washes, and at the same time maximum solubility on rewarming to 37°C. Details concerning the effects of pH and ionic strength on solubility will be reported later.

In experiments in which electrophoretic patterns were obtained, or clottability by thrombin estimated, HPF was prepared as described above.

Fibrinogen was determined by a modification[10] of the method of Morrison.[18] The results, expressed in grams per 100 ml., include the correction factor. Erythrocyte sedimentation rates were determined by the Westergren method; the numerical result refers to the fall in millimeters in one hour.

C-reactive protein was estimated using the capillary tube technique and Schiefflin "C.R.P.A." rabbit anti-C-reactive protein. Results are given from 0 to 4+ depending on measurements of the column of precipitate present after 18 hours of refrigeration.

Result of Clinical Studies - Approximately 1600 determinations of HPF have been performed since July, 1954, on normal adults and children, and in patients of all ages with a variety of disease states. Attempts were made to study selected patients serially with a

group of determinations rather than to include all possible varieties of disease. Most experience has been gained to date in patients with rheumatic fever, rheumatoid arthritis, lupus erythematosus, meningitis, nephrosis, malignancy, and various acute infectious diseases.

Normal values for HPF and fibrinogen have been determined on a group of 100 apparently healthy adults. Figure 1 depicts the distribution of these HPF values. It will be seen that the normal adult values ranged from 0.01 to 0.13 gm.%, the mean value being 0.056 gm.%.

Summary graphic charts depicting clinical progress correlated with HPF, fibrinogen and other determinations have been prepared for representative cases and will be presented. Data sheets on groups of patients with various diseases, showing HPF values in relation to the clinical state, and other simultaneous laboratory determinations corresponding to that value, are presented in Tables VI, VII, VIII, IX, X, XI.

Figure I

Heparin-Precipitable Values on 100 Apparently Healthy Adults

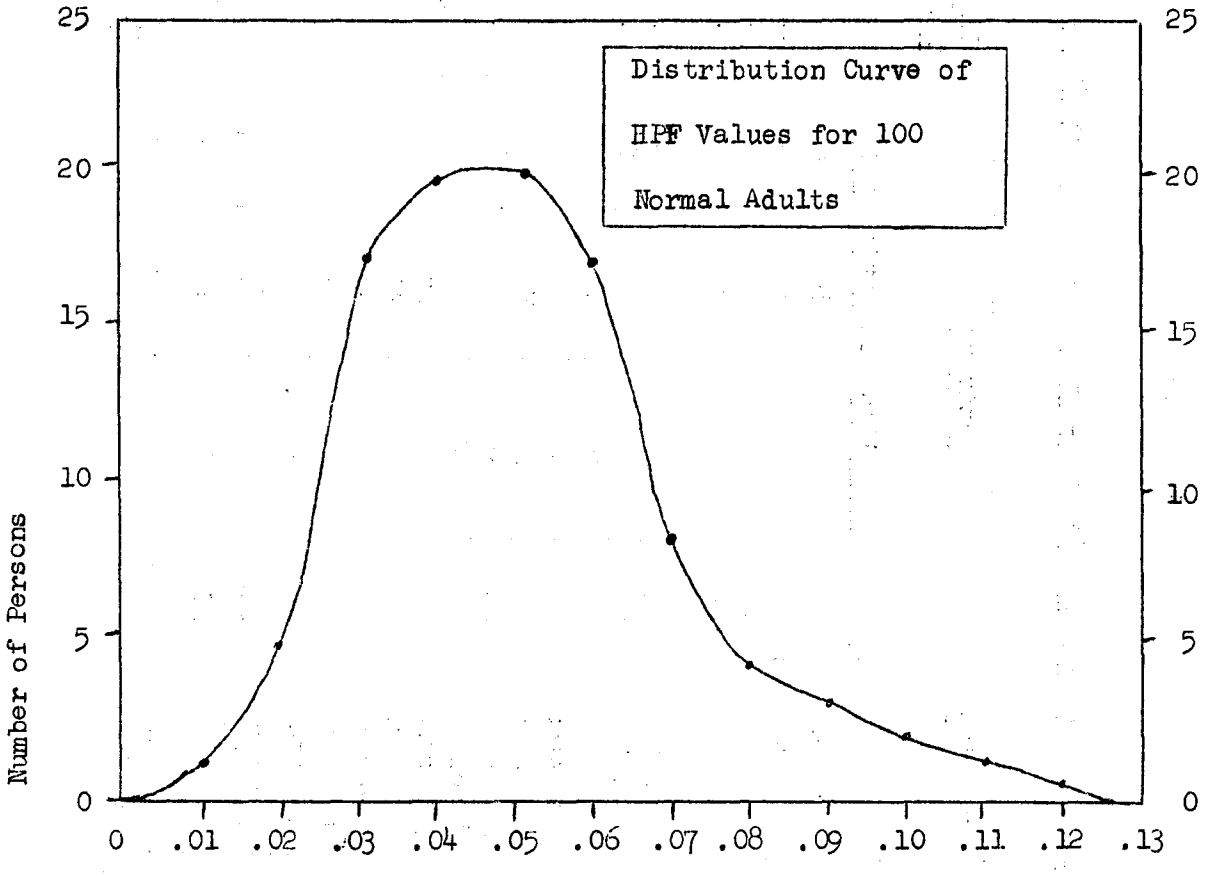

Table VI shows that most patients with acute rheumatic fever were found to have HPF values well above normal, in two instances exceeding 1.0 gm.%. No consistent correlation of HPF level with any single feature of the clinical condition of the patient was found; however, it tended to be highest in the most

Table VI

Relation between Clinical Activity and Heparin-Precipitable Values in Patients with Rheumatic Fever

Initials	Age	Duration	Activity				HPF Gm.%	Fibrinogen Gm.%	HPF/ Fib.	ESR	CRP
			Fever	Arthritis	Carditis	Failure					
.	12 yrs.	2 weeks	103	0	5+	4+	1.38	0.68	2.01	114	6+
.	8 yrs.	1 week	101	0	4+	1+	1.10			120	6+
.	8 yrs.	1 week	102	2+	4+	0	.67	.51	1.30	75	3+
.	16 yrs.	1 month	102	0	0	0	.65	.46	1.41	96	2+
.	14 yrs.	3 weeks		1+	4+	0	.59	.57	1.03	108	5+
.	9 yrs.	1 week	103	4+	3+	0	.57	.64	.88	121	4+
.	7 yrs.	2 weeks	102	1+	0	0	.56	.49	1.14	45	3+
.	30 yrs.	2 weeks	100	0	1+	0	.42			65	1+
.	24 yrs.	5 months		1+	2+	0	.40	.42	.95	62	2+
.	13 yrs.	8 months		3+	2+	0	.40	.40	1.00	46	-
.	7 yrs.	2 weeks	102	4+	4+	1+	.30	.29	1.03	49	2+
.	7 yrs.	1 month	101	1+	3+	1+	.27	.49	.55	68	4+
.	9 yrs.	3 months		3+	3+	0	.26	.74	.35	93	4+
.	12 yrs.	3 months		0	1+	0	.26	.37	.70	36	-
.	10 yrs.	1 month		0	1+	0	.24	.36	.67	46	-
.	38 yrs.	4 weeks		2+	1+	0	.23	.19	1.21	22	1+
.	5 yrs.	1 month	100	0	2+	0	.17	.42	.40	62	2+
.	12 yrs.	1 month		0	2+	0	.17	.38	.45	89	-
.	13 yrs.	3 months	101	0	2+	4+	.16	.21	.76	9	2+
.	12 yrs.	3 weeks	100	0	2+	0	.14	.31	.45	67	1+
Mean Values for 20 Patients							0.447	0.397	0.815		

Table VII

Relation between Clinical Activity and Heparin Precipitable Fraction in Patients with Rheumatoid Arthritis

Initials	Age	Treatment	Duration	Fever	Active Joint Disease	HPF Gm.%	Fibrinogen Gm.%	HPF/ Fib.	ESR	CRP
.	5 yrs.	none	5 weeks	101	1+	0.73	0.66	1.10	91	3+
.	9 yrs.	aspirin	6½ years	101	3+	0.52	.39	1.33	84	4+
.	50 yrs.				3+	0.44	0.71	.62	113	4+
.	22 yrs.	hydrocortisone	3½ years	100	4+	0.38	0.42	.90	104	3+
.	6 yrs.	Na salicylate	3 years	104	4+	0.33	0.64	.52	54	4+
.	45 yrs.	none	12 years	98	1+	0.25	0.25	1.00	91	5+
.	14 yrs.	none	3 weeks	100	1+	.24	.28	.86	39	-
.	31 yrs.	ACTH	7 years	98	1+	.11	.27	.41	10	1+
Mean Values for 8 Patients						0.375	0.453	0.843		

Table VIII

Heparin Precipitable Fraction Values in Patients with "Fibrinoid" Diseases

Initials	Age	Fever	Rash	LE Cells	Joints	HPF Gm.%	Fibrinogen Gm.%	HPF/ Fib.	ESR	CRP
.	15 yrs.	+	+	+	+	.32	.64	.50	142	4+
.	12 yrs.	0	0	+	+	.16	.51	.32	123	4+
.	70 yrs.	+	0	+	+	.08	.32	.24	96	1+
.	9 yrs.	+	+	0	+	.04	.32	.11	103	2+

Table IX

Heparin-Precipitable Fraction in Patients with Meningitis

Initials	Age	Type	Duration	Severity	Septicemia	HPF Gm.%	Fibrinogen Gm.%	HPF/ Fib.	ESR	CRP
	3 yrs.	H. influenza	1 day	severe	yes	1.08	0.88	1.23	104	4+
	10 yrs.	Meningococcal	3 days	severe	yes	.69	.54	1.28	53	3+
	14 yrs.	Pneumococcus	1 week	severe	no	.40	.53	.75	71	5+
	3 yrs.	Meningococcal	1 week	severe	yes	.38	.51	.75	109	3+
	6 mos.	H. influenza	10 days	severe	yes	.36	.48	.75	108	3+
	3 yrs.	Meningococcal	24 hours	expired one hour later	yes	.33	.78	.42	-	5+
	1 yr.	H. influenza	6 days	moderate	yes	.31	.35	.88	33	3+
	1 yr.	H. influenza	6 days	moderate	yes	.31	.38	.55	81	+
	8 mos.	Tuberculous	1 week	moderate	no	.26	.35	.74	25	3+
Mean Values for 9 Patients						0.458	0.533	0.817		

severely ill patients with high fever and pericarditis. Treatments of the patients showing high HPF levels with salicylates or steroids resulted in a rapid fall of the value to within the normal range, paralleling or anticipating reduction in fever, joint manifestations, or pericarditis. Values remained low as long as treatment was successful in suppressing the disease, but when inadequate dosage was given, or when therapy was stopped abruptly, the values usually rose again to higher levels. Patients receiving no suppressive therapy were found to have prolonged elevation of HPF. Recovery was reflected in the HPF values obtained by return to within the normal range.

Fibrinogen values were also elevated in acute rheumatic fever, as has been reported by others.[19] It is of interest that HPF equalled or exceeded the clottable fibrinogen value in 8 of 20 patients studied. In only 6 was the HPF fibrinogen ratio under 0.40.

Patients with active rheumatoid arthritis had similarly high levels of HPF, corresponding roughly to the degree of activity. Return to normal of these values marked periods of quiescence of the disease or use of steroid therapy. These data are summarized in Table VII.

Four patients with "fibrinoid" disease[7] have also been studied serially. (Table VIII) Three of these had clinical lupus erythematosus and the fourth, J.S., generalized vascular disease characterized histopathologically by widespread deposition of fibrinoid in and around vessels of the kidney, heart, liver, pancreas, lung, and adrenal gland. Histopathological studies of this patient were presented previously by Bronson and Gamble.[7] It will be seen that these four patients had particularly low HPF values, and low HPF/fibrinogen ratios, considering their high fever, skin rash, and joint manifestations. The last patient, J.S., showed a rapid fall in HPF level to 0.01 Gm.% terminally.

The data on patients with meningitis,

Table X

Heparin-Precipitable Fraction Values in Patients with Various Neoplastic Diseases

Initials	Age	Type Tumor	HPF Gm.%	Fibrinogen Gm.%	HPF/ Fib.	ESR	CRP
	7 yrs.	Hodgkins Disease, grade 4	0.83	0.67	1.24	74	4+
	7 mos.	Massive cavernous hemangioma	.66	.35	1.88	49	-
	7 yrs.	Hodgkins Disease, grade 4	.61	.52	1.17	106	3+
	54 yrs.	Carcinoma of the lung with metastases	.55	.58	.95	29	3+
	68 yrs.	Carcinoma of the lung inoperable	.37	.30	1.23	22	
	10 yrs.	Leukemia, acute	.31	.32	.97	78	-
	9 yrs.	Leukemia, acute	.29	.37	.18	40	1+
	4 yrs.	Wilms - metastatic	.23	.25	.92	26	-
	13 yrs.	Myelogenous leukemia	.19	.27	.70	22	+
	7 yrs.	Lymphoma, disseminated	.18	.28	.64	40	6+
	8 mos.	Neuroblastoma - metastatic	.13	.32	.41	42	-
	28 yrs.	Lymphoma, disseminated	.11	.29	.38	5	-
	67 yrs.	Carcinoma of the lung operable	.13	.41	.33	46	1+
	5 yrs.	Lymphatic leukemia - in remission	.11	.14	.79	2	-
	65 yrs.	Multiple myeloma	.02	.34	.59	10	-

Table XI

Heparin-Precipitable Fraction in Patients with Nephrosis

Initials	Age	Clinical				HPF	Fibrinogen	HPF/	ESR	CRP
		Edema	Albuminuria	Hypoproteinemia	Hypertension	Gm.%	Gm.%	Fib.		
. .	2 mos.	+	+	+	0	.40	.31	1.29	-	-
	7 yrs.	+	+	+	+	.35	.90	.39	140	1+
	3 yrs.	+	+	+	0	.25	.32	.78	43	-
. . . . .	4 yrs.	+	+	+	0	.13	.51	.25	124	+
	13 yrs.	+	+	+	+	.11	.34	.32	68	3+
	9 yrs.	+	+	+	0	.09	.50	.18	109	+
	14 yrs.	0	+	+	+	.08	.35	.22	62	-
. .	24 yrs.	+	+	+	+	.07	.36	.20	155	+
.	2 yrs.	+	+	+	0	.06	.66	.10	121	+

shown in Table IX, indicate that this severe inflammatory disease is also associated in its acute stages with high HPF levels and high HPF/fibrinogen ratios. As fever, central nervous system signs, and spinal fluid findings showed improvement under specific antibiotic therapy, the high HPF values fell quickly. However, in most patients these values remained persistently above the normal limits for up to three weeks after apparent clinical recovery had occurred. In two patients with persistently elevated levels, D.O. and I.Q., subdural empyema and cerebritis, respectively, were demonstrated. The patients with meningococcemia accompanying meningitis held special interest for the authors, but did not show a pattern of HPF response differing from patients similarly ill without bacteremia.

Patients having neoplastic diseases, particularly Hodgkins disease, had in many instances high HPF levels (Table X) Wide dissemination of the disease was apparently the single clinical correlate of a high HPF level; no consistent correlation with tumor type was observed. Nephrotic patients (Table XI) on the other hand, were found to have exceptional patterns of normal or only slightly elevated HPF levels associated with high fibrinogen values, thus a low ratio. Elevated fibrinogen levels returned to normal as diuresis occurred.

From these clinical studies it seems apparent that elevated HPF levels occur in a wide variety of diseases in amount roughly in proportion to the degree of illness of the patient. High values were generally associated with a correspondingly elevated fibrinogen level and a high HPF fibrinogen ratio. Exception to this generalization was noted in patients with diffuse vascular disease and nephrosis. Erythrocyte sedimentation rates were almost invariably high in patients with high HPF levels; however, serial changes in these values failed to show significant or regular correlation with HPF. The ESR remained elevated longer than HPF after recovery, and returned to normal more slowly with treatment. As has been well established,

fairly consistent ESR-fibrinogen correlation was observed. Of the acute phase reactants studied, C-reactive protein level most nearly followed HPF changes in the serial studies. These changed in parallel in rapid return to normal following treatment or spontaneous recovery, and were equally sensitive to reappearance of activity in a disease state.

Relation of human HPF to fibrinogen - In the experimental studies it was shown that the heparin-precipitable fraction appearing in rabbit plasma after endotoxin injection was closely related to fibrinogen. Similar, somewhat more extensive investigations of the properties of this substance in various patients have been conducted. It has been found that human HPF, like that obtained from the experimental model, is not present in serum or in unheparinized, oxalated, or citrated plasma. However, on occasion oxalated plasmas from very acutely or severely ill patients have been observed which demonstrate cold-precipitation similar to that with heparin, but in much smaller quantity. This finding is of interest in view of the studies on a patient with carcinoma of the lung and multiple thrombotic episodes reported by Korsh and Kratochil.[22] These authors demonstrated in the patients citrated plasma a cold-insoluble protein similar to fibrinogen in sedimentation constant and electrophoretic mobility, which they termed "cryofibrinogen."

HPF from patients with several diseases has been studied by paper electrophoresis and compared with simultaneously run heparinized serum and plasma. Because of the tendency of HPF to become less soluble at room temperature, all runs were made at 37°C in a Spinco (Model L) paper electrophoresis apparatus. Most runs were made in pH 8.6 veronal buffer at 5 amps., 110 V, for 8 - 12 hours to avoid excessive diffusion which occurred at the high temperature. These studies have shown that HPF migrates primarily as a single peak, paralleling fibrinogen of heparinized plasma and a partially purified heparinized fibrinogen of human origin run simultaneously. Contamination of the twice-washed precipitates with gamma and beta globulins was commonly observed, but not in quantitatively significant amounts. Similar studies of more purified HPF are in progress.

Another indication that HPF and fibrinogen are closely related is the finding that both are partially clottable by thrombin. Table XII depicts the results of an experiment in which HPF from three patients with different levels was examined for clottability. An optimal concentration of thrombin was added to the HPF, and the resultant clots washed, dried, and weighed as in the fibrinogen procedure. The clottable material was compared with the total HPF and the percentage figure indicated in the table

Table XII

Clottability of Heparin-Precipitable Fraction

Patient Initials	Total HPF Gm.%	Clottable HPF* Gm.%	Percent Clottability
	0.57	0.21	37
----	0.27	0.14	52
	0.04	0.02	50

* For method see text.

obtained. It will be seen that 37-52% of HPF from these three patients was clottable.

These studies indicate strongly that HPF from human plasma is closely related to fibrinogen; indeed, at least 50% of it is unequivocally, if this protein is defined by its clottability. On the other hand, a significant proportion of HPF has the characteristics of fibrinogen but is non-clottable. This would be predicted from the clinical studies which showed, in a number of very ill patients, HPF values exceeding significantly the values for clottable protein. These findings raise the question of a correct definition of fibrinogen; i.e., whether it should be limited to clottable protein, or whether it should be defined by its other characteristics including electrophoretic migration, sedimentation constant, double refraction of flow, isoelectric point, intrinsic viscosity, or salt and alcohol-low temperature precipitation characteristics.

Detailed studies of a non-clottable, cold-insoluble globulin obtained from Cohn plasma fraction I and shown to be very closely related to fibrinogen, has been reported recently by Edsall and co-workers.[23] Preliminary studies in our laboratory have indicated that cold-precipitation of similarly prepared bovine non-clottable fraction is considerably augmented by addition of heparin, and that removal of the cold insoluble fraction by the procedure of Laki removes most heparin precipitable material. It seems possible, therefore, that HPF, particularly in the acutely ill patient, may be very closely related to this non-clotting fraction of fibrinogen.

Discussion

The experimental studies outlined in this report show that fibrinogen disappears from the circulation of the endotoxin-treated rabbit shortly after the administration of a high molecular weight, acidic polymer. This occurs during a time when intravascular fibrinoid is known to be deposited. Fibrinogen depletion was prevented by prior injection of the rabbits with heparin. These items of evidence, considered with the points cited previously, suggest strongly that intravascular fibrinoid deposits characteristic of the endotoxin-polymer analogue of the generalized Shwartzman reaction consist in part of fibrinogen or fibrin.

It has been recently observed in our laboratories that "Liquoid" combines in vitro with fibrinogen and fibrin to yield precipitates with the appearance and staining characteristics of fibrinoid.[24] This observation may provide an explanation for the dilemma posed earlier --that in spite of evidence that fibrinoid should contain fibrinogen, it does not have the staining reactions and appearance of this protein.

The evidence available seems to permit the tentative conclusion that fibrinoid deposits in the experimental animal have resulted from agglomeration in vivo of polymer-fibrinogen precipitates. This explanation fails to account satisfactorily for the occurrence of subintimal and perivascular collections of fibrinoid observed commonly in the coronary arteries and other vessels during the reaction.[6] A possible mechanism by which this might occur that fibrinogen present normally in the tissue spaces[25] is precipitated by polymer in perivascular locations. It is, perhaps, more plausible to account for this localization of fibrinoid on a basis of accellerated transudation of plasma proteins through endotoxin-damaged endothelium.[26] This would explain the extravascular location either of fibrinogen-polymer complexes, or of fibrinogen susceptible to polymer precipitation.

In addition to quantitative depletion of fibrinogen during fibrinoid deposition in the experimental animal, a qualitative alteration of circulating fibrinogen--cold precipitation by heparin--has been observed. The precipitable material, designated HPF for convenience, appears in the plasma of animals given endotoxin intravenously after a one hour

interval, reaches a maximum level in two to three hours, and is gone in 80% of animals after 24 hours. HPF did not appear if anticoagulant doses of heparin were given prior to endotoxin injection. Studies of HPF from the experimental animal indicate that it consists mostly, if not entirely, of fibrinogen.

No satisfactory explanation of the origin or role of HPF in the animal model has been established. The cold-insoluble, non-clottable globulin (fraction I-1) was thought by Edsall, et al,[23] possibly to represent a dimer of fibrinogen molecules. Demonstration that heparin accellerates cold-precipitation of fraction I-1 has suggested its possible relationship to the heparin-precipitable fraction under study. HPF might represent, then, a partially polymerized form of fibrinogen. The observation that its appearance following endotoxin administration is prevented by prior treatment with heparin then raises the possibility that such partial polymerization could occur as a result of *in vivo* initiation of incomplete clotting.

There is a striking coincidence of timing in the appearance of HPF in the rabbit given endotoxin, and susceptibility of its fibrinogen to *in vivo* depletion by polymers. It might be postulated, therefore, that the same alteration of fibrinogen resulting in enhanced cold-precipitability by one acidic polymer -- heparin -- also results in increased precipitability *in vivo* by polymers such as "Liquoid." By this reasoning, heparin prevents *in vivo* precipitation, as has been shown *in vitro*,[17] by successful competition with the other polymers for a combining site on the altered fibrinogen molecule. Whether heparin-precipitability signifies in this experimental circumstance a general alteration of polymer-combining properties of fibrinogen and is the form of this protein representing the circulating precursor of fibrinoid is not as yet established.

Heparin-precipitation has been demonstrated also in the plasma of normal humans and found in greatly increased quantities in persons with a variety of diseases. As in the experimental situation, HPF isolated from such patients has been shown to consist mostly of fibrinogen. Whether reasoning developed from the experimental data is applicable to HPF derived from human patients is not clear at this time. The possibility that precipitation of fibrinogen or an altered form of fibrinogen - HPF - by naturally produced polymers may be responsible for fibrinoid deposits observed in certain human diseases is currently under study.

Acknowledgment: The author wishes to express appreciation to Dr. Robert Good for constructive advice and helpful suggestions during the course of the study, and to acknowledge with gratitude the able assistance of Mrs. Donna Gellerman, Mr. Don Olmanson, and Mr. Neil Priske in various phases of the work.

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II. MEDICAL SCHOOL NEWS

Coming Events

April 26	Minnesota Pathological Society Meeting; "Anginoid Chest Pain. An Inquiry into the Causes of Pain in the Left Chest;" Dr. Asher A. White; Owre Amphitheater; 8:00 p.m.
April 27	Special Lecture; "Medical and Surgical Implications of Liver Regeneration;" Dr. L. Schalm, Director, Municipal Hospital, Arnhem, Holland; Todd Amphitheater, University Hospitals; 12:45 p.m.
April 28	Phi Delta Epsilon Lectureship; "Newer Concepts in Psychosomatic Disease;" Dr. Adelaide M. Johnson, Professor of Psychiatry, Mayo Foundation, Rochester, Minnesota; Mayo Memorial Auditorium; 8:15 p.m.
May 9 - 14	Continuation Course in Electrocardiography for General Physicians
May 10	Duluth Clinic Lectureship; "The Relationship of Achylia Gastrica to Pernicious Anemia;" Dr. William B. Castle, Professor of Medicine, Harvard University Medical School, Boston; Mayo Memorial Auditorium; 8:15 p.m.
May 16 - 21	Continuation Course in Proctology for General Physicians

* * *

Continuation Course

The University of Minnesota announces a continuation course, An Introduction to Electrocardiography, which will be held at the Center for Continuation Study from May 9 to 13, 1955. As its name implies, this year's course is intended only for those with very little or no previous experience in electrocardiographic interpretation. The first morning will be devoted to the consideration of introductory material. During the remainder of the week, instruction will be tutorial in type. Registrants, meeting in small groups with individual instructors, will have an opportunity to interpret more than 200 tracings during the course. The instructors will supervise the interpretation and will discuss in informal fashion the various electrocardiographic abnormalities. Faculty for the course will include Doctors Arthur C. Kerkhof, Alan P. Rusterholz, Ben Sommers, and Paul Winchell.

* * *

Special Lectures Held

Dr. Michael E. DeBakey, Professor of Surgery, Baylor University, Houston, Texas, presented the Annual George E. Fahr Lecture on Thursday evening, April 14, in the Mayo Auditorium. A large and interested audience heard Dr. DeBakey speak on "Surgical Management of Aortic Disease."

The Annual Clarence M. Jackson Lecture was presented by Dr. Leslie N. Gay, Associate Professor of Medicine, Johns Hopkins University, Baltimore, Maryland, on Tuesday, April 19. Dr. Gay's talk, "A History of the Treatment of Bronchial Asthma," was well received by an enthusiastic audience.

* * *

Dr. Keys Receives Award

Dr. Ancel Keys, Professor and Director, Laboratory of Physiological Hygiene,

has been named recipient of one of the Minneapolis Awards, an award made annually by the Minneapolis Chamber of Commerce. Dr. Keys was recognized for his pioneering research in the field of human nutrition.

* * *

Faculty News

The Division of Anesthesiology was represented at the Biennial Western Conference on Anesthesiology, held in San Francisco on March 21-23, by Doctors Frederick H. Van Bergen and James H. Matthews. Dr. Van Bergen served as moderator for a panel on the subject of "Problems in Anesthesia for Surgery on the Ductless Glands", and delivered an address entitled, "The Effects and Use of Chlorpromazene in Anesthesia."

Dr. Ivan D. Frantz, George S. Clark Research Professor of Medicine, attended the recent meeting of the Federation of American Societies for Experimental Biology which was held in San Francisco from April 11 to 15.

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Publications of the Medical School Faculty

Garabedian, G. A. and Syverton, J. T.: Studies on Herpes Simplex Virus. I. An Antigenic Analysis of Four Strains of Virus Isolated From a Human Subject. J. Inf. Dis., 96: 1, 1955.

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III.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

April 25 - 30, 1955

Monday, April 25

Medical School and University Hospitals

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; W-612, U. H.

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

11:30 - Tumor Conference; Doctors Hitchcock, Zimmermann, and Stenstrom; Todd Amphitheater, U. H.

11:30 - 12:30 Physical Medicine and Rehabilitation Staff Seminar; Evaluation of Range of Motion of the Hip; Martin Mundale; Heart Hospital Theater.

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

12:30 - Physiology Seminar; Studies of the Arterial Wall in Experimental Hypertension; Louis Tobian; 214 Millard Hall.

1:00 - 2:00 Roentgenology-Surgical-Pathological Conference; Paul Lober and L. G. Rigler; Todd Amphitheater, U. H.

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

1:30 - 3:30 Dermatology Hospital Rounds; H. E. Michelson and Staff; Dermatology-Histopathology Room, C-394, Mayo Memorial.

4:00 - 6:00 Anesthesiology Conference; F. H. Van Bergen and Staff; Todd Amphitheater, U. H.

4:30 - Public Health Seminar; Polio, Is It Conquered? Gaylord W. Anderson; 100 Mayo Memorial.

4:30 - Pediatric-Medicine Infectious Disease Rounds; Station 33, U. H.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Ancker Hospital

8:00 - 9:00 Pediatric Contagion Rounds; Richard Lein; Contagion 5.

8:30 - 10:30 Medical and Surgical Chest Conference; Dr. Gehlen and Staff; Auditorium.

9:30 - 12:00 Visiting Staff Rounds.

10:00 - 12:00 Surgery Grand Rounds; Begin Floor E4.

11:00 - 12:00 Pediatric Rounds; Harry Orme; Contagion 1.

12:30 - 2:30 Surgery Out-Patient Clinic; Room 8.

Monday, April 25 (Cont.)

Ancker Hospital (Cont.)

2:00 - 3:00 Routine EKG Interpretation; Dr. Sommers and House Staff; Medical Record Library.

2:30 - 3:00 Discussion of Problem Case; Auditorium.

3:00 - 4:00 Surgery Journal Club; Classroom.

3:00 - 4:00 Lectures on Electrocardiography; Ben Sommers; Auditorium.

4:00 - 5:00 Medical Clerk Journal Club; Auditorium.

Minneapolis General Hospital

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station 11.

10:30 - Orthopedic and Fracture Rounds; Drs. John Moe and O. J. Campbell; Station 20.

11:00 - Pediatric Case Discussions; Erling Platou; Station 8.

12:30 - Surgery Grand Rounds; O. J. Campbell, Station 21.

1:30 - 2:30 Tuberculosis Conference; J. A. Myers; Station 8.

2:00 - Pediatric Rounds; William Krivit; Stations 4, 5, & 6.

Veterans Administration Hospital

9:30 - Infectious Disease Rounds; Drs. Hall, Zinnemann, and Doe.

1:30 - Cardiac Conference; Drs. Smith, J. Brown, Hoseth, Simonson, and Farquhar; Conference Room, Bldg. I; Rounds immediately following conference.

Tuesday, April 26

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Pediatric Conference; Samuel Feinberg, John A. Anderson and Staffs, Eustis Amphitheater, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 104 Jackson Hall.

12:30 - 1:30 Physiological Chemistry Seminar; Determination of Inulin and Evans Blue in Tissue; Donald Clausen; 214 Millard Hall.

12:30 - Anatomy Seminar; Concepts of the Golgi Apparatus; 226 Jackson Hall.

3:30 - General Physiology Seminar; 323 Zoology Building.

3:30 - Pediatric Seminar; Subject to be announced; Richard B. Raile; 1450 Mayo Memorial.

4:00 - 5:00 Pediatric Rounds on Wards; John A. Anderson and Staff; U. H.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

Tuesday, April 26 (Cont.)

Medical School and University Hospitals (Cont.)

5:00 - 6:00 X-ray Conference; Presentation of Cases by Veterans Hospital Staff; Eustis Amphitheater, U. H.

*8:00 p.m. Minnesota Pathological Society Meeting; "Anginoid Chest Pain. An Inquiry into the Causes of Pain in the Left Chest;" Dr. Asher White; Owre Amphitheater.

Ancker Hospital

8:00 - 9:00 Pediatric Rounds; Dale Cumming; Contagion 1.

9:00 - 10:30 Visiting Staff Rounds.

9:00 - 12:00 Practical Diagnostic Clinic; Harry Orme; Out-Patient Department.

11:00 - 12:00 Medical X-ray Conference; J. R. Aurelius; Auditorium.

2:30 - 4:00 Routine EKG Interpretations; Resident Staff.

4:00 - 5:00 Medical-Pathological Conference; W. F. Mazzitello, Auditorium.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Elizabeth Lowry and A. Bridge; Station 5.

10:00 - Cardiac Rounds; Paul F. Dwan; Classroom, Station 4.

10:00 - Psychiatry Grand Rounds; R. W. Anderson, Station 3.

11:30 - 12:30 Neurology-Neurosurgery Conference; Classroom, Station 8.

12:30 - 2:30 Dermatology Rounds on Clinic; Carl W. Laymon and Staff.

1:00 - Tumor Clinic; Drs. Eder, Coe, and Lipschultz; Classroom.

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Surgical Conference Room, Bldg. 43.

8:30 - Hematology Rounds; Drs. Hagen and Wexler.

8:30 - Surgery Journal Club; Conference Room, Bldg. I.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery-Tumor Conference D. Ferguson and J. Jorgens.

1:00 - Review of Non-TBC Chest Pathology Conference; E. T. Bell; Conference Room, Bldg. I.

2:00 - Combined Medical-Surgical Chest Conference; Conference Room, Bldg. I.

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

4:00 - Thoracic Surgical Problems; Conference Room, Bldg. I.

5:00 - Fluid Balance Conference; Conference Room, Bldg. I.

5:30 - Physiology Seminar; Surgical Conference Room, Bldg. 43.

Wednesday, April 27

Medical School and University Hospitals

11:00 - 12:00 Pathology-Medicine-Surgery-Pediatrics Conference; Todd Amphitheater, U. H.

12:30 - 1:30 Radioisotope Seminar; Francis Spurrell; Betatron Room in Cobalt Underground Section, U. H.

*12:45 p.m. Special Lecture; "Medical and Surgical Implications of Liver Regeneration;" Dr. L. Schalm, Director, Municipal Hospital, Arnhem, Holland; Todd Amphitheater, U. H.

1:00 - 2:00 Dermatology Clinical Seminar; F. W. Lynch; 300 North Clinic.

1:30 - 3:00 Pediatrics Allergy Clinic; Albert V. Stoesser and Lloyd Nelson; W-211, U. H.

3:30 - 4:30 Dermatology-Pharmacology Seminar; 3rd Floor Conference Room, Heart Hospital.

4:30 - 5:50 Dermatology-Infectious Disease Seminar; 3rd Floor, Conference Room, Heart Hospital.

5:00 - 6:00 Radiology Residents' Lecture; Orthopedics; Kenath Sponsel; Todd Amphitheater, U. H.

5:00 - 5:50 Urological-Pathological Conference; C. D. Creevy and Staff; A503, Mayo Memorial.

5:30 - 7:30 Dermatology Journal Club and Discussion Group; Hospital Dining Room.

7:30 - 9:30 Dermatology Seminar; Review of Interesting Slides of the Week; Robert W. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; J. Noble; Auditorium.

11:00 - 12:00 Pediatric and Contagion Rounds; Harry Orme; Contagion 1.

11:00 - 12:00 Medicine Resident Rounds; W. F. Mazzitello.

3:30 - 4:30 Pediatric Surgery Conference; Harry Orme; Auditorium.

Minneapolis General Hospital

8:30 - 9:30 Obstetrical and Gynecological Grand Rounds; William P. Sadler and Staff; Station 30.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station 31.

11:00 - Pediatric Rounds; Erling Platou and Richard Raile; Station 6.

12:30 - Pediatrics Staff Meeting; Classroom, Station 4.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; E. T. Evans and Staff; Surgical Conference Room, Bldg. 43.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

9:00 - Gastro-Intestinal Rounds; Drs. Wilson, Zieve, Ferguson, Brakel, Vennes, Nesbitt and Sadoff.

Wednesday, April 27 (Cont.)

Veterans Administration Hospital (Cont.)

10:30 - Psychosomatic Conference; C. K. Aldrich; 7th Floor, Bldg. 43.

12:30 - Medical Journal Club; Doctors' Dining Room.

12:30 - X-ray Conference; J. Jorgens; Conference, Bldg. I.

1:30 - 3:00 Metabolic Disease Conference; Drs. Flink and Shapiro.

3:30 - Urology Pathology Slide Conference; Dr. Gleason; Conference Room, Bldg. I.

7:00 - Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, April 28

Medical School and University Hospitals

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Room 3.148 Mayo Memorial.

11:00 - 12:00 Cancer Clinic; K. Stenstrom, B. Zimmermann; Todd Amphitheater, U. H.

12:30 - 1:55 Physiology Seminar 210; Transport; Selected Topics in Advanced Permeability; Nathan Lifson; 214 Millard Hall.

12:30 - 1:30 Endocrine Seminar; Neurosecretory Systems; Dr. Stephens; 271 Lyon Laboratories.

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.

4:00 - 5:00 Anesthesiology Seminar; F. H. Van Bergen and Staff; Room 100, Mayo Memorial.

5:00 - 6:00 Radiology Seminar; Porphyrins and Radiation Therapy; Karel Absolon and Merle K. Loken; Eustis Amphitheater, U. H.

7:30 - 9:30 Physiology 211 Seminar; Selected Topics in Heart and Circulation; Hemodynamics; M. B. Visscher and Robert Evans; 271 Lyon Laboratories.

*8:15 p.m. Phi Delta Epsilon Lectureship; "Newer Concepts in Psychosomatic Disease;" Dr. Adelaide M. Johnson, Professor of Psychiatry, Mayo Clinic, Rochester; Mayo Auditorium.

Ancker Hospital

8:00 - 9:00 Pediatric Clinical Staff Conference; Contagion Classroom.

9:00 - 10:00 Pediatric Contagion Rounds; Alexander Stewart, Contagion 5.

9:30 - 10:30 Medical Grand Rounds; Auditorium; Visiting Staff Rounds immediately following Grand Rounds.

11:00 - 12:00 Pediatric X-ray Conference.

11:00 - 12:00 Medicine Resident Rounds; W. F. Mazzitello.

2:00 - 3:00 Routine ECG Interpretation; Ben Sommers; Medical Record Library.

Minneapolis General Hospital

9:30 - Neurology Rounds; Heinz Bruhl; Station 4.

10:00 - Psychiatry Grand Rounds; R. W. Anderson and Staff; Station 3.

Thursday, April 28 (Cont.)

Minneapolis General Hospital (Cont.)

11:30 - 12:30 Clinical Pathological Conference; John I. Coe; Classroom.

12:30 - 2:30 Dermatology Rounds and Clinic; Carl W. Laymon and Staff.

1:00 - Fracture X-ray Conference; Drs. Campbell and Moe; Classroom.

Veterans Administration Hospital

8:00 - Experimental Surgery Laboratory Meeting; Conference Room, Bldg. I.

8:30 - Hematology Rounds; Drs. Hagen and Duryea.

9:00 - Surgery Grand Rounds; Conference Room, Bldg. I.

9:00 - Surgery Ward Rounds; D. Ferguson and Staff; Ward 11.

11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.

1:00 - Infectious Disease Conference; Conference Room, Bldg. I. (Rounds immediately following conference).

4:00 - 5:00 Seminar on Radioisotopes in Medicine; Methods and Principles of Radiation Measurement; Conference Room, Bldg. I.

Friday, April 29

Medical School and University Hospitals

8:00 - 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.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

11:00 - 12:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Eustis Amphitheater, U. H.

11:45 - 12:50 University of Minnesota Hospitals Medical Staff Meeting; Forty Years of Social Service at University Hospitals 1915-1955; Annie Laurie Baker; Powell Hall Amphitheater.

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

1:00 - 2:00 Physiology Seminar 212; Selected Topics in Respiration: Respiratory and Circulatory Effects of Hypothermia; E. B. Brown; 214 Millard Hall.

1:30 - 2:30 Dermatology Grand Rounds; Presentation of Cases from Grouped Hospitals (University, Ancker, General and Veterans) and Private Offices; H. E. Michelson and Staff; Eustis Amphitheater, U. H.

2:30 - 4:00 Dermatology Hospital Rounds; H. E. Michelson and Staff; Begin at Dermatological Histopathology Room, C-394 Mayo Memorial.

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

3:30 - 4:30 Dermatology-Physiology Seminar; 3rd Floor Conference Room, Heart Hospital.

4:00 - 5:30 Chest X-ray Conference; Chest Staff and Charles Nice; Todd Amphitheater, U. H.

Friday, April 29 (Cont.)

Medical School and University Hospitals (Cont.)

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

5:00 - Urological Seminar and X-ray Conference; A-503, Mayo Memorial.

Ancker Hospital

8:00 - 9:00 Pediatric Rounds; Charles Steinberg; Contagion 1.

10:30 - 11:30 Pediatric Contagion Rounds; Richard Smith; Contagion 1.

11:00 - 12:00 Contagion Rounds; Harry Orme; Contagion 5.

2:00 - 3:00 Routine EKG Interpretation; Resident Staff.

3:00 - 4:00 Medical-Surgical-Pathological Conference; Auditorium.

4:00 - 5:00 Medical Journal Club; Conference Room, E5.

4:00 - 5:00 X-ray Surgery Conference; Auditorium.

Minneapolis General Hospital

10:00 - Otolaryngology Conference; Robert A. Priest, Large Classroom.

10:30 - Pediatric Surgical Conference; Tague Chisholm and B. Spencer; Classroom, Station 4.

12:00 - Surgery-Pathology Conference; Drs. Campbell and Coe; Classroom.

1:00 - 2:00 ECG Conference: Boyd Thomes and Staff; Classroom, Station 4.

2:00 - 4:00 Clinical-Medical Conference; Thomas Lowry; Classroom, Station 8.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

11:00 - 12:30 Psychiatry Case Conference; Werner Simon; Psychiatry Department, VA Hospital Annex.

12:30 - Urology X-ray Conference; X-ray Department.

1:00 - Autopsy Conference; E. T. Bell; Conference Room, Bldg. I.

2:00 - Chest Pathology Follow-Up Conference; E. T. Bell; Conference Room, Bldg. I.

Saturday, April 30

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.

9:00 - 9:30 Pediatric Grand Rounds; Eustis Amphitheater, U. H.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

9:15 - 10:00 Surgery-Roentgenology Conference; Alexander R. Margulis, Owen H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

Saturday, April 30 (Cont.)

Medical School and University Hospitals (Cont.)

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

10:00 - 12:00 Otolaryngology Seminar on Current Literature; L. R. Boies and Staff; Todd Memorial Room, A-675 Mayo Memorial.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

9:30 - 11:00 Medicine Grand Ward Rounds; W. F. Mazzitello.

11:00 - 12:00 Medical Clerk Case Conference; W. F. Mazzitello.

Minneapolis General Hospital

8:00 - Urology Staff Conference; T. H. Sweetser; Main Classroom.

9:00 - Psychiatry Grand Rounds; R. W. Anderson; Station 3.

9:30 - Pediatrics Rounds on all Stations; R. B. Raile.

11:00 - 12:00 Medical X-ray Conference; O. Lipschultz, Thomas Lowry and Staff; Main Classroom.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - Medical X-ray Conference; Conference Room, Bldg. I.

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* Indicates special meeting. All other meetings occur regularly each week at the same time on the same day. Meeting place may vary from week to week for some conferences.