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The Generalized Shwartzman Phenomenon

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THE GENERALIZED SHWARTZMAN PHENOMENON: The production of typical lesions by cross transfusion and isolated renal perfusion.*

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Since the original report of Shwartzman in 1928[1] considerable attention has been directed to the changes occurring in experimental animals following the administration of various types of endotoxins and bacterial filtrates. The generalized Shwartzman phenomenon, the systemic counterpart of the localized reaction first described, is produced in the rabbit by the intravenous administration of two appropriately spaced injections of endotoxin. The first of these injections is referred to as the "preparatory" dose while the second is termed the "provoking" or "shocking" dose.[2]

Factors important in the production of the phenomenon and the "characteristic and identifying lesion" of gross bilateral renal cortical necrosis have been described in detail by Thomas and Good.[2] These investigators have shown that occlusion of the glomerular capillaries by masses of eosinophilic, homogeneous material preceded the development of gross renal cortical necrosis and hemorrhage. They suggest that this primary interference with glomerular blood flow is responsible for the fully developed lesion. Various other lesions occurring in the tissues of rabbits given two intravenous injections of endotoxin have been described by these and other authors.[2,3,4,5,6] Varying degrees of hemorrhage and necrosis in the myocardium, spleen, liver, lungs, adrenals, thymus, lymph nodes, and gastrointestinal tract have been noted.

Recently it has been demonstrated that lesions identical with those occurring in the conventional generalized Shwartzman phenomenon can be produced by a single intravenous injection of endotoxin in animals previously prepared with cortisone,[7] colloidal iron or carbon,[8] and thorotrast or trypan blue.[9] These substances are thought to act by "blocking" the reticuloendothelial system so that the second injection of endotoxin is able to exert its effect(s) unimpeded by the detoxifying activity of the cells of this system. It has been postulated[7] that the first or preparatory injection of endotoxin may act in a similar manner.

Thomas, Denny and Floyd[10] reported that an intravenous injection of meningococcal toxin in rabbits previously infected with Group A hemolytic streptococci was followed by cardiac lesions in approximately 50% of the animals, a majority of which also developed bilateral renal cortical necrosis. The cardiac lesions were characterized by the presence of "fibrinoid" beneath the endothelium of the coronary arteries and within the heart valves. Infection with pneumococci prior to the intravenous injection of meningococcal toxin has also been observed to result in similar cardiac and renal lesions.[11]

While most experimental studies have been directed toward the production of the typical changes found in the generalized Shwartzman phenomenon, Thomas and Good have been able to inhibit the reaction by the administration of nitrogen mustard[2,7] and heparin.[12] The administration of HN_2 three days prior to two successive intravenous injections of toxin prevented the development of the typical renal lesion except when the femoral bone marrow was protected against the action of the mustard by clamping the aorta at the time of its injection. It was suggested that the presence of polymorpho-nuclear leukocytes may be necessary for the production of the generalized phenomenon and that these cells are in some way involved in the production of the occlusive material

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found in the glomerular capillaries. Heparin has been observed to inhibit the production of bilateral renal cortical necrosis when given at the time of provocation in amounts required to sustain the incoaguability of the blood for at least four hours. The hypothesis was advanced that this inhibiting action of heparin was related to its anticoagulant effect and it was postulated that one of the basic disturbances in the generalized Shwartzman phenomenon concerns the blood clotting mechanism.[12]

Recent studies carried out in the Department of Pathology in collaboration with the Heart Hospital Research Laboratories have further defined the morphologic changes occurring in animals following the intravenous administration of meningococcal toxin.

Because previous reports[2,3,5,13] had been meager concerning changes produced in animals given a single intravenous injection of endotoxin, initial investigations[14] were designed to study this effect. It was found that significant changes may occur in rabbits following this procedure. Microscopically, the most consistent alterations were noted in the heart. Early changes observed in the intramural coronary arteries consisted of edema and vacuolization of the intimal and medial tunics and, at times, a fragmentation or disruption of the endothelial lining. Extensive areas of myocardial hemorrhage, necrosis, and calcification were observed and in many cases intravalvular hemorrhages were noted. In a small number (12%) of animals, in addition, a refractile homogeneous eosinophilic material was observed lying beneath the endothelium of the coronary arteries and within the heart valves. This material was morphologically and tinctorially similar to that noted by Thomas[2,10] in the glomerular capillaries of animals receiving two injections of meningococcal toxin or a single injection of toxin following infection with Group A hemolytic streptococci, and shown to satisfy the staining requirements of Altshulter and Angevine[15] for fibrinoid. Similar material was noted in the spleen (10%), liver (16%), and lungs (16%) of these animals. In only one case was bilateral renal cortical necrosis observed but in another the presence of the typical material lining the glomerular capillaries was detected.

As a result of these observations, studies were then performed to define more accurately the morphologic changes occurring in the generalized Shwartzman phenomenon. It was found that certain typical and consistent histopathologic alterations occur in the heart, spleen, liver, and lungs, as well as in the kidneys, of animals subjected to two intravenous injections of meningococcal toxin.[16] As noted previously, the renal lesion is the characteristic lesion of the generalized Shwartzman phenomenon. The extent of the gross and microscopic changes is dependent upon the interval following the second or "shocking" injection of meningococcal toxin and the death of the animal. The earliest microscopic lesions are characterized by the presence of scattered areas of interstitial hemorrhage and tubular necrosis with a variable number of occluded glomeruli. As the lesion progresses, greater areas of hemorrhage and necrosis occur, and when fully developed, the entire renal cortex and portions of the medulla are involved. At this stage virtually all the glomeruli are occluded by a dense homogeneous eosinophilic material with the tinctorial features of fibrinoid.

Alterations in the spleen are found in a greater percentage of animals than are the renal lesions, and vary in degree, as do the renal lesions, depending upon the survival time following the second injection of toxin. Microscopically the sinusoids contain a homogeneous deeply eosinophilic material morphologically and tinctorially identical to that occurring in the glomerular capillaries. Associated with the deposition of this material various degrees of congestion, hemorrhage and necrosis are observed.

Microscopic examination of the liver consistently reveals areas of focal necrosis and thrombi in the lumina or beneath the endothelium of the efferent venules. The pulmonary lesions are characterized by the presence of hemorrhage and thrombi (or emboli) within the large and small pulmonary arteries. These thrombi, as well as those in the liver, are composed of material similar to that occurring in the splenic sinusoids and glomerular capillaries.

Extensive cardiac lesions may also occur. A majority of hearts show early arterial and myocardial alterations similar to those seen following a single intravenous injection of toxin. Of greater interest, however, is the presence of fibrinoid lying beneath the endothelium or within the lumen of the coronary arteries and within the heart valves in a large percentage of cases. Less frequently gross changes are observed in other organs, always in association with the intravascular presence of the material described above.

Recently Brunson, Davis, and Thomas,[17] stimulated by the observations of Hausman and Dreyfus[18] and Walton,[19] have produced lesions identical with those described above by the administration of certain high molecular weight acidic polymers in combination with, or following, a single intravenous injection of meningococcal toxin. These polymers possess anticoagulant properties somewhat similar to heparin. Although the exact mechanism of action of these substances is unknown, part of their activity appears to be related to a combination with fibrinogen.[19,20] One of these polymers, sodium polyanethol sulfonate (Liquoid), when given alone in large quantities produced changes similar to those occurring in animals receiving a single intravenous injection of endotoxin. When given following the administration of endotoxin, or in combination with it, this activity is greatly augmented and a majority of animals develop lesions typical of the generalized Shwartzman phenomenon. Certain other alterations also occur. Subendothelial fibrinoid is occasionally found in the hepatic arteries, the capillaries of the choroid plexus, the cerebral vessels, and within the lumen and walls of the vessels of the ear.

The most striking features of the changes occurring in the generalized Shwartzman phenomenon is the presence of occlusive masses of dense refractile homogeneous eosinophilic material in the glomerular capillaries, splenic sinusoids, beneath the endothelium of the coronary arteries, and within the heart valves, as well as in the hepatic veins and pulmonary arteries. This material gives staining reactions similar to those described as being typical for fibrinoid. Kane[21] was able to demonstrate it lining the glomerular capillary basement membrane within two hours following the second injection of toxin. Studies[16] on its birefringent properties and reactivity to proteolytic enzymes suggest that it is a highly organized protein compound.

The character of the lesions, their widespread distribution, chronologic development, and inhibition by heparin, suggest that an occlusive vascular phenomenon is responsible for the ischemic necrosis observed in various organs. It would seem reasonable to assume that either some alteration in the blood accounts for the formation of this occlusive material or that it is formed in other tissues and enjoys ready access to, and circulation in, the blood stream. The present experiments were designed to test this hypothesis to see if lesions typical of the generalized Shwartzman phenomenon could be produced by the passive transfer of this material to "normal" recipient animals and organs.

Materials

138 hybrid albino rabbits of mixed sexes weighing 1 to 1.5 kilograms were used in the experiments. They were fed Purina rabbit pellets and had free access to water. Following death or sacrifice of the animals, post mortem examinations were performed and the

tissues were fixed in 10% neutral formalin. Sections were routinely taken from the kidneys, heart, spleen, liver, adrenals and lungs. Hemotoxylin and eosin were used as a routine stain and many additional sections were stained by the periodic acid-Schiff method. Selected sections from the kidneys were stained with phosphotungstic acid hemotoxylin, toluidine blue, crystal violet, and van Gieson's stain.

Meningococcal toxin was used throughout the experiments. Details of its preparation have been reported elsewhere.[2] It was diluted 1:80 or 1:1000 with sterile, pyrogen-free, isotonic saline and injected into the marginal ear vein of the animals in a volume of 2cc. Sodium polyanethol sulfonate (Liquoid) was obtained from Hoffman-LaRoche Inc. This material was dissolved in sterile isotonic saline, passed through a Seitz filter, and injected in doses of 8 or 10 mg. into the marginal ear vein. Heparin sodium (Parke-Davis) was used in certain of the experiments and was injected in various doses into the ear vein.

The polyethelene tubing was obtained in two sizes to facilitate easy connection during transfusion and perfusion. Prior to its use it was flushed with saline and clamped with rubber tipped hemostats to prevent the passage of air into the experimental animals. The "pump" used in perfusing isolated kidneys was kindly supplied by Dr. Mead Cavert of the Physiology Department. It is actually a Sterling automatic pipette manufactured by Ivan Sorvell Inc., N.Y., N.Y., and proved very satisfactory in delivering the small quantities of blood desired.

Methods

Carotid-jugular cross transfusion experiments

Donor animals were prepared by the intravenous injection of 2cc. of 1:80 meningococcal toxin. Following an interval of 18-24 hours they were given a second or shocking injection of an equal volume of the same dilution. One group of animals was given a simultaneous intravenous injection of 2 cc. of 1:1000 meningococcal toxin and 10mg. of Liquoid. As noted previously this procedure is equivalent to intravenous preparation with 2 cc. of 1:80 toxin followed 12-18 hours later by an intravenous injection of Liquoid, and identical lesions are produced as in the conventional generalized Shwartzman phenomenon utilizing two successive intravenous injections of meningococcal toxin. Control donor animals were given only a preparatory injection of toxin or were unprepared. The donor animals were then returned to their cages for periods of 2-4 hours after which they were prepared for cross transfusion. The recipient animals, with the exception of one group given a preparatory intravenous injection of 2 cc. of 1:80 meningococcal toxin, were unprepared.

Preparation for cross transfusion consisted of shaving the donor and recipient animals' necks, infiltrating with procaine HCl, and exposing the external jugular veins and internal carotid arteries of each animal. After placing ligatures about these vessels, both donor and recipient animals were given 5 mg. of heparin sodium intravenously to prevent clotting during manipulation and within the catheters. After allowing sufficient time for complete circulation of the heparin, the vessels were ligated and cannulated with polyethelene tubing. The carotid catheter of the donor animal was then inserted into the larger jugular catheter of the recipient while the recipient carotid was connected to the donor jugular in a similar fashion. The catheters were then opened with immediate transit of blood. Cross transfusion was allowed to continue for periods of 20 minutes to 1 hour as designated in table I. Following completion of transfusion, the vessels were securely ligated, the catheters removed, and the neck wound sutured. The animals survived following transfusion for periods of time varying from 2 hours or until they were killed at

24 hours. With the exception of 10 animals from the entire group of 85, all animals survived for 12-24 hours.

An additional small group of animals was used to determine if the shocking dose of toxin administered to prepared donors remained free in the circulation and was able to exert its direct effect in the recipient animal in a manner similar to a single intravenous injection of toxin. For this purpose animals were prepared by the usual method of intravenous injection of 2 cc. of 1:80 meningococcal toxin. 24 hours later one of these animals was given an intravenous injection of 0.32 cc. of undiluted toxin so that the estimated final blood dilution was 1:80 meningococcal toxin. Two hours following this procedure, blood was drawn from the shocked animal and 2 cc. of this blood was injected intravenously into the prepared animals which were then allowed to survive for 24 hours.

Isolated renal perfusion experiments.

One group of donor animals were prepared and shocked in the usual manner with 2 cc. of 1:80 meningococcal toxin. They were then allowed to "react" for average periods of 3-8 hours following shock until perfusion was begun. Another group of donor animals was given a simultaneous intravenous injection of 2 cc. of 1:1000 meningococcal toxin and 10 mg. of Liquoid. The basis for this procedure is discussed above. An average interval of 10 minutes to 6 hours was allowed to occur in this group before perfusion was started. A small group of control animals were unprepared. Recipient animals, which were to furnish "recipient kidneys" for the donors given two injections of toxin, were prepared with a single intravenous injection of 2 cc. of 1:80 meningococcal toxin 18 hours prior to perfusion. The other recipient animals used in the toxin-liquoid and control experiments were unprepared.

The donor animals were prepared for perfusion in a manner identical to those used in the carotid-jugular cross transfusion experiments. The animals which had received toxin or which were unprepared were given 5 mg. of heparin sodium intravenously immediately prior to cannulation of the neck vessels and perfusion. The animals administered toxin plus Liquoid were given no heparin because of the effective anticoagulant activity of Liquoid.

Isolation of the kidneys was carried out by administering intravenous sodium nembutal in sufficient quantities to completely relax the recipient animals. The abdomen was shaved and opened to expose the vessels in the region of the left kidney. The inferior vena cava and aorta were isolated above and below the kidney. Separate ligatures were placed about the aorta and inferior vena cava above the left renal artery and vein and below the right renal artery and vein. Ligatures were then placed about the aorta and inferior vena cava below the kidney to make cannulation possible. This procedure completely excluded the right kidney and other organs from the perfusion circuit except for the left adrenal gland. Just prior to exclusion of the left kidney from the animal's circulatory system, 5 mg. of heparin sodium was injected into the marginal ear vein of all recipient animals. Following this, the aorta and inferior vena cava above the kidney were ligated and these vessels below the kidney were separately cannulated with polyethelene catheters which were securely tied in place.

In experiments in which a "prepared" kidney was perfused with the blood of an animal which had previously received two intravenous injections of toxin, the aortic cannula was connected to the internal carotid artery cannula of the donor animal while the inferior vena cava cannula was connected to that of the external jugular vein of the donor. The cannulae were opened and the blood pressure of the donor animal utilized to effect transit of blood through the perfusion circuit. At this time the recipient animals were killed with an excess of intravenous

sodium nembutal. In the majority of experiments the isolated kidney slowly became pink in blotchy areas as fresh blood was forced into it. Usually 15 to 20 minutes following the start of the procedure the kidney was a normal reddish-pink color. In experiments in which toxin-Liquoid or unprepared donors were used the pump referred to above was utilized in an attempt to effect more rapid and complete perfusion. It was interposed in the arterial side of the circuit and calibrated to deliver between 15-20 cc. per minute. In these experiments almost immediate return of the isolated kidney to normal appearance was observed.

A variable number of donors (see tables IV,V) were used to perfuse one kidney. This was done in the attempt to insure the use of "positive reacting" donor animals. The duration of perfusion varied between 1-5 hours. Even at the upper limits of this range the kidney was observed to remain functional judging by the formation of urine from the catheterized ureter, although studies on the electrolyte content of this urine were not made.

Results

Carotid-jugular cross transfusion

The results of these experiments are summarized in table I.

Initial experiments were performed using recipient animals prepared by the intravenous administration of 2 cc. of 1:80 meningococcal toxin 18 hours prior to transfusion. Because of the previous observation[14] that a single intravenous injection of toxin resulted in considerable vascular damage, it was felt that preparation might be necessary for the deposition of fibrinoid in the highly vascular areas in which it is typically found. Tissues from the recipient animals in this group exhibited lesions which were morphologically identical to those occurring in the conventional Shwartzman phenomenon. The renal lesions which occurred in 20% of the animals were, however, not "fully developed" and were noted only after microscopic identification of the typical homogeneous, eosinophilic material occluding the glomerular capillaries. Splenic lesions, consisting of accumulations of identical material within the splenic sinusoids occurred in 60% of the recipient animals. The occurrence of this material was occasionally associated with splenic congestion and necrosis. Myocardial alterations were present in all recipient animals and consisted of areas of hemorrhage, necrosis, cellular infiltration, and occasional calcification of the muscle fibers. Intravalvular hemorrhages were also noted consistently. Cardiac fibrinoid was observed within the substance of the valves and beneath the endothelium of the intramural coronary arteries in 30% of the animals. Focal hepatic necrosis and thrombi within the lumina of the efferent venules of the liver were noted in 40%, while thrombi (or emboli) of the small pulmonary arteries were seen in 30% of the transfused animals. The material found in all of these lesions was tinctorially identical to that described previously and designated as fibrinoid.

With the exception of the low incidence of renal lesions, these results are comparable to those produced in animals given two intravenous injections of toxin. However, there was no way to definitely ascertain whether these lesions resulted because of transfer of material similar to fibrinoid, or if they were changes which occurred following the preparatory injection of toxin. For this reason, a group of unprepared recipient animals were transfused with the blood of prepared and shocked donors. None of the recipient animals of this group were observed to have renal lesions. However, splenic lesions were noted in 40%, cardiac fibrinoid in 60%, and the presence of hepatic and pulmonary fibrinoid in 20% of these animals.

With the exception of the high incidence of cardiac fibrinoid, the incidence of these lesions is comparable

TABLE I

CAROTID - JUGULAR CROSS TRANSFUSION																
Donor animals									Recipient animals							
Number of animals	Prep.	Shock	Average interval after shock	Presence of fibrinoid					Number of animals	Method	Average Duration of Transf.	Presence of fibrinoid				
				Kid.	Spleen	Heart	Liver	Lung				Kid.	Spleen	Heart	Liver	Lung
10	Toxin 1:80	Toxin 1:80	2 hrs.	5	8	1	1	6	10	Toxin 1:80	30 min.*	2	6	3	4	3
10	Toxin 1:80	Toxin 1:80	4 hrs.	7	9	6	7	4	10	No Toxin	1 hr.	0	4	6	2	2
8	Toxin 1:1000 + 10mg Liquoid	-	1 hr.	6	7	6	2	7	8	No Toxin	50 min.	0	3	5	3	4
5	Toxin 1:80	-	12 hrs. post prep	1	3	2	0	1	5	No Toxin	20 min.	0	0	1	0	0
5	No Toxin	-	-	0	0	2	0	0	5	No Toxin	30 min.	0	0	2	0	0

* Interval from preparation of recipient to transfusion 18 hrs.

All animals with the exception of the toxin-liquoid donors received 5 mg. heparin prior to perfusion.

to that following a single intravenous injection of toxin.

The possibility was then suggested that toxin administered to a prepared donor might remain unchanged and freely circulating in the blood stream for a period of time sufficiently long so that transfusion merely resulted in a situation comparable to that of administering a single intravenous injection of toxin. In the attempt to investigate this possibility, a small group of prepared animals were given an injection of 2 cc. of donor blood estimated to contain a dilution of 1:80 meningococcal toxin per cc. as outlined above under methods. The results of this procedure are summarized in table II. 14% of the kidneys from this group contained glomerular fibrinoid while 43% of the spleens, 29% of the lungs, and 14% of the livers contained this material. Cardiac fibrinoid was not observed.

In unprepared recipient animals transfused with the blood of donors prepared by the simultaneous intravenous injection of 2 cc. of 1:1000

TABLE II

INJECTION OF DONOR BLOOD INTO PREPARED RECIPIENTS									
Donor animal*		Recipient animals*							
Method	Interval after shock	Method	Number of animals	Interval after prep.	Presence of fibrinoid				
					Kid.	Spleen	Heart	Liver	Lung
0.32cc of 1:1 toxin I.V.	2 hrs.	2cc of donor blood I.V.	7	26 hrs.	1	3	0	1	2

* prepared with 2cc 1:80 toxin 24 hrs. previously

* recipients survived 24 hrs. post shock

meningococcal toxin and 10 mg. of Liquoid, no renal lesions were observed. 38% of these animals developed splenic and hepatic lesions while 63% were noted to have cardiac fibrinoid and 50% revealed fibrinoid within the small arteries of the lung.

Control groups consisting of unprepared recipient animals transfused by unprepared donors or donors receiving a single intravenous injection of toxin exhibited no renal, splenic, hepatic, or pulmonary fibrinoid. A majority of these animals, like those in the other groups, were observed to have non-specific myocardial hemorrhage and necrosis. Of unexpected and unusual interest, however, was the presence of fibrinoid within the substance of the cardiac valves in 50% of these animals. This material was morphologically and tinctorially indistinguishable from that seen in the valves of animals receiving two intravenous injections of toxin or toxin and Liquoid.

Isolated renal perfusion:

The results of these experiments are summarized in tables III and IV.

Experiments were first conducted using kidneys of recipient animals previously prepared by the intravenous injection of 2 cc. of 1:80 meningo-

TABLE III

ISOLATED RENAL PERFUSION										
Donor animals (prepared and shocked with 2cc 1:80) toxin								Recipient kidney* (prepared with 2cc 1:80 toxin)		
Number of animals	Average interval after shock	Average survival after shock	Presence of fibrinoid					Duration of perfusion	Glomerular Fibrinoid	
			Kid.	Spleen	Heart	Liver	Lung		Perfused Kidney	Non-Perfused Kidney
1	3 hrs.	9 hrs.	0	1	0	0	1	5 hrs.	-	-
2	6 hrs.	18 hrs.	1	2	0	0	1	2½ hrs.	-	-
7	8 hrs.	20 hrs.	2	5	3	3	3	4½ hrs.	-	-
5	4½ hrs.	5 hrs.	2	5	0	4	5	3½ hrs.	-	-
6	4 hrs.	8 hrs.	5	6	1	4	6	4½ hrs.	-	-

* Average interval after preparation 24 hrs.

Each animal received 5 mg. Heparin prior to perfusion.

TABLE IV

ISOLATED RENAL PERFUSION										
Donor animals (2cc 1:1000 toxin plus 10 mg Liquoid)								Recipient kidney* (no previous preparation)		
Number of animals	Average interval after shock	Average survival after shock	Presence of fibrinoid					Duration of perfusion	Glomerular Fibrinoid	
			Kid.	Spleen	Heart	Liver	Lung		Perfused kidney	Non-perfused kidney
4	6 hrs.	20 hrs.	3	3	2	2	3	3½ hrs.	+	-
2	1 hr.	11 hrs.	2	2	2	-	2	5 hrs.	+	-
2	15 min.	1 hr.	-	2	1	-	2	1½ hrs.	+	-
2	10 min.	1 hr.	-	-	-	2	1	1½ hrs.	+	-
2	1 hr	2 hrs.	1	2	-	1	2	1 hr.	+	-
5	Control animals*		0	0	0	0	0	1 hr.	5-	5-

* All control animals and all recipients received 5 mg. Heparin prior to perfusion.

coccal toxin 18 hours prior to perfusion. These kidneys were perfused with the blood of donor animals prepared and shocked with an equal amount and dilution of toxin. Both recipient and donor animals were given 5 mg. of heparin immediately prior to perfusion to prevent clotting within the cannulated vessels and polyethelene tubing. As is seen in table III, microscopic examination failed to reveal fibrinoid within the glomerular capillaries of any of these perfused kidneys nor was its presence detected in the opposite non-perfused kidney.

Heparin is known to inhibit the generalized Shwartzman phenomenon.[12] To eliminate the possibility that this material was preventing the development of the renal lesions, unprepared recipient kidneys were perfused with the blood of donor animals prepared by the simultaneous intravenous injections of 2 cc. of 1:1000 meningococcal toxin and 10 mg. of Liquoid. Because of the active anticoagulant properties of Liquoid, only the recipient animals were given 5 mg. of heparin prior to perfusion. In addition, the pump was utilized to effect more rapid and complete perfusion.

Reference to table IV shows that all of the perfused kidneys in this series were found to have fibrinoid within the glomerular capillaries on miscroscopic examination. The appearance of this material was morphologically and tinctorially identical to that found in the glomerular capillaries of the early renal lesions in the conventional generalized Shwartzman phenomenon. Typically the material appeared as a dense refractile homogeneous eosinophilic substance layered above the capillary endothelium, or completely occluding the capillary lumen, of the majority of glomeruli.

Because it was felt that the churning hemolytic action of the pump might contribute to the production of the renal lesions, a control group of unprepared recipient kidneys were perfused with the blood of unprepared donor animals. The results are summarized in table IV.

Discussion

Lesions identical to those occurring in the generalized Shwartzman phenomenon can be produced by transfusion of recipient animals with appropriately treated donors. With the exception of less frequent renal involvement, the incidence of these lesions in prepared recipient animals is similar to those observed in the generalized Shwartzman phenomenon. The decreased incidence of renal lesions suggests the possibility that these changes may occur solely as a result of the preparatory injection of toxin. However, identical lesions are produced in unprepared transfused recipients.

Of considerable interest is the complete absence of renal lesions in these animals. A number of factors may be responsible for this occurrence. During these experiments, it was often noted on sacrifice of the recipient animals, even as long as 24 hours following transfusion, that the kidneys were much smaller than normal and appeared pale and ischemic. It appears that reflex stimulation from procedures preceding and during transfusion results in marked constriction of the renal vascular bed for periods sufficiently long to prevent access of fibrinoid to the kidney and its deposition in the glomerular capillaries. Thomas also observed a markedly lessened incidence of renal lesions in animals given two successive intravenous injections of meningococcal toxin following ligation of one renal artery.[22]

One would expect a similar circumstance to prevail in donor animals subjected to the same manipulation before and during transfusion. However, the donor animals all received one or more injections of endotoxin from 1-12 hours prior to transfusion. It was also necessary to directly observe the kidneys of a considerable number of

donor animals prior to transfusion to insure the use of positive donors. As a result in many instances only those donor animals in which a renal lesion was already present were used for transfusion purposes.

In these animals the endotoxin may have effected vasodilatation of the renal vessels as observed by Smith,[23] counteracting the tendency to vasoconstriction during manipulation and transfusion.

It is also possible that the vascular damage observed to occur after a single injection of toxin is necessary for the deposition of fibrinoid within the glomerular capillaries.

Although the 5 mg. of heparin given to each animal prior to transfusion is small in comparison to the amounts found by Thomas and Good[12] to be necessary to inhibit the generalized Shwartzman phenomenon, its effect may have been an additional factor in the prevention of the renal lesions.

The presence of fibrinoid occurring following transfusion in unprepared recipient animals offers considerable evidence for its transfer by way of the blood stream. The possibility cannot be ignored, however, that sufficient quantities of freely circulating toxin may be present in the blood of prepared donor animals 2-4 hours following its injection. The transfer of this toxin may then act in a manner similar to a single intravenous injection of meningococcal toxin. The results of experiments in which prepared recipient animals were injected with 2 cc. of donor blood containing an estimated dilution of 1:80 meningococcal toxin, do not exclude the possibility that this may occur. However, the incidence of these lesions is more nearly comparable to those occurring in animals following a single intravenous injection of toxin. It is also difficult to imagine that a prepared animal is able to detoxify such an abnormally large amount of toxin in 2 hours time. Studies are in progress to evaluate this problem more carefully.

The presence of fibrinoid within the cardiac valves of transfused animals which received no previous treatment is of considerable interest. The possibility that this material is not identical to that found in the valves of animals given two intravenous injections of toxin is unlikely when one considers its characteristic position and morphologic and tinctorial similarity to fibrinoid. There is, of course, the possibility that the material found in the valves of animals in the generalized Shwartzman phenomenon is not the same substance as that found in other sites, even though it is indistinguishable from this material. However, previous experiments strongly suggest that this material is the same. Bilateral nephrectomy prior to two intravenous injections of toxin greatly increases the incidence of fibrinoid within the heart valves and beneath the endothelium of the coronary arteries. Splenectomy prior to a single intravenous injection of toxin has also been noted to markedly increase the incidence of cardiac fibrinoid.[24]

A possible explanation for the presence of fibrinoid within the valves of transfused normal animals may be found in the recent work of Thomas, Smith and Von Korff.[25] These investigators have demonstrated the presence of a "heparin precipitable protein" in the plasma of animals given a previous intravenous injection of endotoxin. The plasma of 20% of normal animals was also noted to contain a small amount of this material which appears to be related to or closely associated with fibrinogen. It is suggested that the heparin precipitable protein may be a precursor for the occlusive "fibrinoid-like material" found in the generalized Shwartzman phenomenon. Since small amounts of heparin were used in the control transfusion experiment, it is possible that the valvular fibrinoid represents the deposition of this material beneath the endothelium and

within the substance of valves damaged during transfusion. That considerable hemodynamic alterations and damage to the fragile heart valves may occur, is suggested by the frequent observation of intravalvular hemorrhages and extensive myocardial alterations which occur in both experimental and control animals subjected to carotid-jugular cross transfusion.

Renal lesions identical to those occurring in the generalized Shwartzman phenomenon were produced only in the group of animals in which unprepared recipient kidneys were perfused with the blood of donors given a simultaneous intravenous injection of meningococcal toxin and Liquoid. The absence of renal lesions in the group in which donor animals were given two injections of toxin seems to be due to the inhibitory action of heparin given prior to perfusion. A majority of donor animals were explored prior to perfusion in the attempt to use only "positive reactors" as revealed by direct observation of early renal lesions. It seems reasonable to assume that the administration of heparin may have prevented the further development of circulating fibrinoid (or its precursor) and passage into and deposition in the recipient kidney.

That the use of Liquoid in renal perfusion experiments does not introduce an "artifact" into the production of these lesions is shown by the fact that the intravenous injection of this material in association with meningococcal toxin results in lesions identical to those occurring in the conventional generalized phenomenon.

Summary

The methods of production and the characteristic histopathologic features of the generalized Shwartzman phenomenon have been briefly reviewed. Experiments designed to show the production of lesions typical of this phenomenon by passive means have been described.

By carotid-jugular cross transfusion, using donor animals given meningococcal toxin or meningococcal toxin and Liquoid, fibrinoid lesions of the kidney, spleen, liver, lungs and heart were observed in the recipient animals. The incidence of the renal lesions, however, was much less than that observed in the conventional generalized phenomenon. Control donor and recipient animals given no toxin or Liquoid developed cardiac fibrinoid lesions in a high percentage of cases, but no other lesions were demonstrated.

By isolated renal perfusion using donor animals prepared with meningococcal toxin and Liquoid the renal lesion typical of the generalized Shwartzman phenomenon was produced in all recipient kidneys.

The similarity between these lesions and those of the generalized phenomenon, and the variation in the incidence of certain lesions is discussed. A series of photomicrographs illustrating the various lesions is presented.

REFERENCES

1. Shwartzman, Gregory.
Studies on bacillus typhosus toxic substances. I. Phenomenon of local skin reactivity to B. Typhosus culture filtrate.
J. Exp. Med. 1928, 48:247-268.

2. Thomas, Lewis and Good, Robert A.
Studies on the generalized Shwartzman reaction. I. General observations concerning the phenomenon.
J. Exp. Med. 1952, 96:605-624.

3. Apitz, K.
A study of the generalized Shwartzman phenomenon.
J. Immunology 1935, 29:255-266.

4. Shwartzman G., Klemperer, P., and Gerber I. E.

The Phenomenon of local tissue reactivity to bacterial filtrates. (The role of altered vascular responses in certain human diseases) J. A. M. A. 1936, 107: 1946-1951.

5. Gerber, I.
The Shwartzman phenomenon in the kidneys of rabbits. Observations on the effects of intravenous administration of bacterial filtrates.
Arch. Path. 1936, 21:776-796.

6. Black-Schaffer, R., Hiebert, T. G., and Kerby, G. P.
Experimental study of purpuric meningococcemia in relation to the Shwartzman phenomenon.
Arch. Path. 1947, 43:28-54.

7. Thomas, Lewis and Good, Robert A.
The effect of cortisone on the Shwartzman reaction. The production of lesions resembling the dermal and generalized Shwartzman reactions by a single injection of bacterial toxin on cortisone treated rabbits.
J. Exp. Med. 1952, 95:409-428.

8. Smith, Richard T., Thomas, Lewis and Good, Robert A.
Generalized Shwartzman reaction. V. Effect of intravenous injection of colloidal iron or carbon on response of rabbits to meningococcal toxin.
Proc. Soc. Exp. Biol. and Med. 1953, 82:712-715.

9. Good, Robert A., and Thomas, Lewis.
Studies on the generalized Shwartzman reaction. II. Production of the phenomenon in rabbits with thorotrast or trypan blue.
J. Exp. Med. 1953, 96: 625-641.

10. Thomas, Lewis, Denny, Floyd W., and Floyd, Jean.
Studies on the generalized Shwartzman reaction. Lesions of the myocardium and coronary arteries accompanying the reaction in rabbits prepared by infection with group A streptococci.
J. Exp. Med. 1953, 97: 751-766.

11. Good, R. A., Thomas, Lewis, and Smith, R. T.
Unpublished observations.

12. Good, R. A., and Thomas, Lewis.
Studies on the generalized Shwartzman reaction. IV. Prevention of the local and generalized Shwartzman reactions with heparin.
J. Exp. Med. 1953, 97:871-888.

13. Morgan, Herbert R.
Pathologic changes produced in rabbits by a toxic somatic antigen derived from Eberthella Typhosa.
Am. J. Path. 1943, 19:135-145.

14. Brunson, Joel G., Gamble, Charles N. and Thomas, Lewis.
Morphologic changes in rabbits following the intravenous administration of meningococcal toxin. I. Effects produced in young and in mature animals by a single injection.
Am. J. Path. To be published.

15. Altshulter, C. H. and Angevine, D. M.
Histochemical studies on the pathogenesis of fibrinoid.
Am. J. Path. 1949, 25:1061-1077.

16. Brunson, Joel G., Thomas, Lewis, and Gamble, Charles N.
Morphologic changes in rabbits following the intravenous administration of meningococcal toxin. II. Two appropriately spaced injections; the role of fibrinoid in the generalized Shwartzman phenomenon.
Am. J. Path. To be published.

17. Brunson, Joel G., Davis, Richard L., and Thomas, Lewis.
Morphologic changes in rabbits following the intravenous administration of meningococcal toxin. III. The effects produced by endotoxin in association with certain high molecular weight acidic polymers.
Am. J. Path. To be published.

18. Hausman, Robert, and Dreyfus, Pierre M.
Intracapillary precipitates produced in rabbits by means of sodium polyanetholsulfonate.
Arch. Path. 1953 56:597-606.

19. Walton, K. W.
Investigation of the toxicity of a series of Dextran sulfates of varying molecular weight.
Brit. J. Pharm. and Chemo. 1954 9:1-14.

20. Compendium, Roche: herausgegeben von der Firma Hoffman-LaRoche and Cie.
A. B. Basel, 1948, p. 168 u. 223.

21. Kane, D. J., Good, R. A., and Thomas, L.
Histologic studies of the renal lesion in the generalized Shwartzman phenomenon.
Anat. Rec. 1952, 112:349 (abstract).

22. Thomas, Lewis.
Personal communication.

23. Smith, H. W.
Harvey Lecture Series 1939-40, 35:166.

24. Brunson, Joel G. and Gamble, C.N.
Unpublished observations.

25. Thomas, L., Smith, R. T., and Von Korff, R.
Cold-Precipitation by heparin of a protein in rabbit and human plasma.
Proc. Soc. Exp. Biol. and Med. 1954, 86:813-818.

II. MEDICAL SCHOOL NEWS

Coming Events

Jan. 31 - Feb. 2	Continuation Course in Ophthalmology for Specialists
February 3	Special Lecture; "The Cell and Its Parts; Genetic Re-Combination Mechanism;" Dr. Joshua Lederberg, University of Wisconsin; 8:00 p.m.
February 3 - 5	Continuation Course in Otolaryngology for Specialists
February 7 - 12	Continuation Course in Neurology for General Physicians and Specialists
February 9	J. B. Johnston Lectureship; "Cerebral Circulation and Oxygen Consumption;" Dr. Seymour S. Kety, National Institute of Neurological Diseases and Blindness; National Institute of Health, U. S. Public Health Service, Bethesda, Maryland; Mayo Auditorium; 8:15 p.m.
February 14 - 16	Continuation Course in Internal Medicine for Internists
February 17 - 19	Continuation Course in Cancer Detection for General Physicians

* * *

Dr. John Anderson Returns to Faculty as New Head of Pediatrics

A distinguished alumnus of the Medical School, Dr. John A. Anderson, has returned to his alma mater as Professor and Head of the Department of Pediatrics. Dr. Anderson, a native of Sioux Falls, South Dakota, graduated in 1933 and served his internship at the University of Minnesota Hospitals. After further training and research work in pediatrics in Denver, Colorado, he returned to Minnesota in 1937 where he was a member of the faculty of the Department of Pediatrics until 1943. From 1943 to 1949 he headed the Pediatrics Department at the University of Utah Medical School and since 1949 he has held a similar position at Stanford University Medical School.

Dr. Anderson succeeds as head of the Department of Pediatrics Dr. Irvine McQuarrie who requested that he be relieved of administrative duties in order to devote his remaining five years on the faculty to research and writing. Dr. McQuarrie was recently honored for his 25 years of outstanding service to the University.

All members of the faculty join in welcoming Dr. Anderson and extending to him our very best wishes. We are sure that Dr. McQuarrie in particular is pleased that his former pupil has been selected to succeed him and to carry on the tradition of scholarship that has marked the Pediatrics Department for so many years.

* * *

School of Public Health Offers New Course

Dr. Gaylord Anderson, Mayo Professor and Director, School of Public Health, has announced that the School of Public Health is giving a new elective course at the graduate level entitled Public Health Aspects of Cardiovascular Disease. The course will consider the epidemiology of cardiovascular disease and some of the public health problems associated with attempts to reduce the toll from these conditions.

The course will be given from 2:30 to 4:00 p.m. on Tuesdays and Thursdays in the Conference Room of the Laboratory of Physiological Hygiene.

Continuation Courses

Continuation Courses in Ophthalmology and Otolaryngology for Specialists in those fields will be held at the Center for Continuation Study during the week of January 31 to February 5, 1955. The course in Ophthalmology will be held from January 31 to February 2, that in Otolaryngology from February 3 to 5. Physicians may register for one or both courses. Guest speakers in ophthalmology will be Dr. P. J. Leinfelder, Professor of Ophthalmology, Iowa State University, Iowa City, Iowa, and Dr. Frank W. Newell, Associate Professor of Ophthalmology, Northwestern University Medical School, Chicago. This course will be presented under the direction of Dr. Erling W. Hansen, Clinical Professor and Head, Department of Ophthalmology, University of Minnesota Medical School. Guests in otolaryngology include Dr. Howard House, Associate Professor of Otolaryngology, University of Southern California, Los Angeles; and Dr. Peter Pastore, Professor of Otolaryngology, Rhinology, and Laryngology, University of Virginia Medical College, Richmond, and Dr. L. R. Boies, Professor and Head, the Department of Otolaryngology, University of Minnesota Medical School, will direct this course.

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Faculty News

Dr. Arnold Lazarow, Professor and Head, Department of Anatomy, delivered the Annual Robert J. Terry Lecture of the St. Louis Medical Society on December 7. His subject was "Studies in Experimental Diabetes."

Dr. Harold O. Peterson, Clinical Professor of Radiology, gave a series of daily lectures on neuro-radiology to the Colombian Radiological Society of Bogota from November 22 through December 3. He also gave a Refresher Course at the Radiological Society of North America Meeting on myelography, December 10, at Los Angeles.

An exhibit, "Deficiency of Intestinal Gas in Infants" by Doctors Frances P. Conklin, Alexander R. Margulis, and Charles M. Nice, Jr., was awarded the second prize in the clinical section at the Radiological Society of North American Meeting in Los Angeles.

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Publications of the Medical School Faculty

Benjamin, H. G.: Gastric Sarcoma. Minn. Med., 37: 218, 1954.

Hyde, J., Riggle, C. M., and Gellhorn, E.: The Dependence of Unit Discharges on Frequency and Intensity of Stimulation of the Motor Cortex in the Macaque. J. Cellular & Comparative Physiol., 43: 293, 1954.

Gellhorn, E., Riggle, C. M., and Ballin, H. M.: Summation, Inhibition, and Proprioceptive Reinforcement under Conditions of Stimulation of the Motor Cortex and Their Influence on the Activity of Single Motor Units, J. Cellular & Comparative Physiol., 43: 405, 1954.

Gellhorn, E., Koella, W. P., and Ballin, H. M.: The Influence of Hypothalamic Stimulation of Evoked Cortical Potentials. J. Psychol., 39: 77, 1955.

Gellhorn, E.: Blood Sugar and Autonomic Nervous System. Acta Neurovegetative, Bd., 9: 74, 1954.

III.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

January 10 - 15, 1955

Monday, January 10

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.

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

12:30 - 1:30 Physiology Seminar; Chemical and Histochemical Studies on Carbohydrates of Secretions and Connective Tissue; Ronald E. Glegg; 214 Millard Hall.

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; Room 100, Mayo Memorial.

4:30 - Public Health Seminar; Public Health Problems of Agriculture; Dean Harold Macy; 15 Owre Hall.

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 Pediatrics 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 Ward Rounds; Begin Floor E4.

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

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

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.

Monday, January 10 (Cont.)

Minneapolis General Hospital

9:30 - Pediatric Rounds; Richard Raile; Station K.

10:30 - 12:00 Medicine Rounds; Thomas Lowry; Station F.

11:00 - Orthopedic and Fracture Rounds; Drs. John Moe and Arthur Zierold; Station B.

11:00 - Pediatric Seminar; Erling Platou; Classroom, Station M.

12:30 - Surgery Grand Rounds; Dr. Zierold, Station E.

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

2:00 - Pediatric Rounds; Stations I and J.

Veterans Administration Hospital

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

1:30 - Cardiac Conference; Drs. Smith, Berman, Roseth, Simonson, Tamlyn, and Farquhar; Conference Room, Bldg. I. ; Rounds immediately following conference.

Tuesday, January 11

Medical School and University Hospitals

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

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

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

12:30 - Bacteriology and Immunology Seminar; 1050 Mayo Memorial.

12:30 - Anatomy Seminar; Myelinated Fibre Diameters in Peripheral Nerves; Andrew Quilliam; 226 Jackson Hall.

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

3:30 - Pediatric Seminar; 1450 Mayo Memorial.

4:00 - 5:00 Pediatric Rounds on Wards; Irvine McQuarrie 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.

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

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.

Tuesday, January 11 (Cont.)

Ancker Hospital (Cont.)

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; Station J.

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

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

11:00 - 12:00 Medicine-Surgery Conference; Classroom, Station M.

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

12:30 - ECG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

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

3:30 - Pediatric-Psychiatry Rounds; Jack Wallinga; Station I.

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 Pathology, Pulmonary Tuberculosis; Conference Room, Bldg. I.

1:30 - 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.

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

Wednesday, January 12

Medical School and University Hospitals

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Paul Lober and L. G. Rigler, Todd Amphitheater, U. H.

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

12:30 - Physiology Seminar 212; Selected Topics in Respiration: Respiratory and Circulatory Effects of Hypothermia; E. B. Brown; 129 Millard Hall.

12:30 - 1:20 Radio-Isotope Seminar; Betatron Room in Cobalt Underground Section, U.H.

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

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

Wednesday, January 12 (Cont.)

Medical School and University Hospitals (Cont.)

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 Residents Lectures; Todd Amphitheater, U. H.

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

5:10 - 6:10 Endocrine Seminar; Periodicity in Pituitary Control of the Ovary; Marthella Frantz; 271 Lyon Laboratories.

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.

3:00 - 5:00 Infectious Disease Rounds; Auditorium.

Minneapolis General Hospital

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

9:30 - Pediatric Rounds; Henry Staub; Station 1.

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

12:15 - Pediatrics Staff Meeting; Classroom, Station I.

1:30 - Pediatric House Staff Seminar; Erling Platou; Station I.

1:30 - Pediatric Rounds; Erling Platou; Classroom, Station I.

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, Swenson, Nesbitt, and Sadoff.

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 Room, Bldg. I.

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

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, January 13

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, A. Kremen, and B. Zimmermann; Todd Amphitheater, U. H.

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; Report of Meeting of Radiological Society of North America; 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.

Ancker Hospital

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 Medicine Resident Rounds; W. F. Mazzitello.

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

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

Minneapolis General Hospital

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

9:30 - Pediatric Contagion Rounds; R. B. Raile; Station K.

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

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. Zierold and Moe; Classroom.

1:00 - House Staff Conference; Station I.

Veterans Administration Hospital

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

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

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.)

Friday, January 14

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.

10:30 - 1:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, 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; Some Experimental Observations on the Contractile Proteins of Failing Myocardium; Ellis S. Benson, Esther F. Freier, Ben E. Hallaway, Joseph L. Sprafka, Ivan D. Baronofsky; Powell Hall Amphitheater.

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

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 - 5:00 Physiology Seminar 213; Selected Topics in Advanced Neurophysiology: Role of the Vestibular Apparatus and the Cerebellum in the Extrapyramidal Motor Activity; Werner Koella; 129 Millard Hall.

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

5:00 - Urological Seminar and X-ray Conference; A503, Mayo Memorial.

Ancker Hospital

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

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

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

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

9:30 - Pediatric Rounds; Elizabeth Lowry; Station J.

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

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

Friday, January 14 (Cont.)

Minneapolis General Hospital (Cont.)

1:00 - 3:00 Clinical-Medical Conference; Thomas Lowry; Classroom, Station M.

1:30 - Pediatric Contagion Rounds; L. Wannamaker; Station K.

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 - Pathology Slide Conference; E. T. Bell; Conference Room, Bldg. I.

Saturday, January 15

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; L. G. Rigler, J. Friedman, Owen H. Wangensteen and Staff; Todd Amphitheater, U. H.

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

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

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 H.

9:30 - Pediatric 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.