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The Generalized Shwartzman Phenomenon in Rats

John A. Gronvall and Joel G. Brunson, M.D.

Lesions of the generalized Shwartzman reaction are regularly produced in rabbits by two properly spaced intravenous injections of gram-negative bacterial endotoxin. The characteristic and identifying change is bilateral renal cortical necrosis, due to blockage of glomerular capillaries by a hyaline substance with the morphologic and staining properties of fibrinoid. Similar lesions are caused by intravenous doses of certain acidic polymers with high molecular weights, such as Liquoid (sodium polyanethol sulfonate), given either with endotoxin or alone in sufficiently large amounts.

Data reported by several investigators strongly suggest that fibrinogen is involved in formation of fibrinoid; for example, the fact that fibrinogen is altered in rabbits given endotoxin. Moreover, the renal lesion is prevented by large doses of heparin.

These reports, however, have dealt exclusively with changes in rabbits. Endotoxins have produced hemorrhagic skin reactions in mice, but resistance of rats is often mentioned. Piel and associates, describing renal lesions produced in rats by heterologous hyperimmune antiserum, noted occasional renal changes like those of the generalized Shwartzman phenomenon, but it was emphasized that this response had never been regularly evoked in the rat.

Because of the apparent limitation of this phenomenon to the rabbit, which is notoriously hyperreactive in many ways, the possible relation of the Shwartzman response to human disease has been questioned.

We, therefore, investigated the effects of gram-negative bacterial endotoxins and Liquoid in rats.

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*This is an abstract of a report given at the Staff Meeting of the University of Minnesota Hospitals on March 23, 1956. A copy of the complete report, including tables and references, may be obtained by writing to the Editor, UNIVERSITY OF MINNESOTA MEDICAL BULLETIN, 1342 Mayo Memorial, Minneapolis 14, Minn.

1 Senior Medical Student.

2 Instructor, Department of Pathology.

† These studies were aided by grants from the Minnesota Heart Association and the American Heart Association.

‡ Part of this work was done while Mr. Gronvall held a National Science Foundation Research Fellowship.
The generalized Shwartzman phenomenon was produced in a high percentage of animals by intraperitoneal injection of endotoxin with Liquoid or of Liquoid alone, in large quantities. Lesions resembled those observed in rabbits but developed more slowly, and the incidence in various organs varied from that in rabbits. The route of injection apparently accounted for these differences.

Morphologic similarity of the lesions in rats and rabbits, modification of the reaction by heparin, and changes in the heparin-precipitable protein fraction of plasma as lesions develop imply that similar basic mechanisms underlie the phenomenon in both animals.

**Materials and Methods**

Subjects were 298 albino rats of the Sprague-Dawley strain of both sexes and varying weights.

Meningococcal endotoxin was prepared as described by Thomas and Good. *Escherichia coli* toxin, prepared by a modified Boivin technic, was obtained from Dr. R. T. Smith. Liquoid was furnished by Hoffmann-LaRoche, Inc. These materials were dissolved in isotonic saline in such concentrations that 1 cc. was injected at each dosage. From 5 to 20 mg. of Liquoid and from 0.025 to 0.1 cc. of toxin were administered in single injections.

Heparin was supplied by the Upjohn Company. The heparin-precipitable protein fraction in plasma was determined by adding 0.1 cc. (1 mg.) of heparin to 5 cc. of blood. This was centrifuged at 1,800 r.p.m. for 20 minutes, and the plasma was drawn off and refrigerated at 4°C for two hours.

All injections were given intraperitoneally.

The animals died or were killed 24 to 48 hours after the last injection. Postmortem examination was done, and tissue sections were prepared. In addition to routine staining with hematoxylin and eosin, certain specimens were processed with Mallory’s phosphotungstic acid hematoxylin, toluidine blue, and the periodic acid-Schiff method.

**Results: Morphologic Changes**

More animals died within 24 hours after simultaneous injection of toxin and Liquoid than after a single dose of either substance alone. Pathologic changes in each group of animals were similar, but incidence of the different lesions varied somewhat from group to group. The kidneys, liver, and adrenals were most often involved. No lesions were found in the brain, pancreas, and testes.

About 20% of all subjects had gross bilateral renal cortical necrosis. It was not seen after a dose of endotoxin alone but occurred in
60% of those given 20 mg. of Liquoid alone and in 40 to 50% of those given toxin and Liquoid together in the largest dosage used. The liver was grossly congested and enlarged; microscopically, focal hemorrhage and necrosis were often noted. At times, the whole adrenal appeared hemorrhagic.

**Influence of Heparin on Lesions**

Because large amounts of heparin prevent development of fibrinoid lesions in rabbits given only two injections of endotoxin and/or Liquoid, three intraperitoneal injections of heparin in doses of 5 or 10 mg. each were given to rats. The first was administered an hour before injection of toxin and Liquoid, the second at the same time as these agents, and the third an hour later.

The animals receiving 10 mg. of heparin at each injection had fewer glomerular lesions than those given 5 mg. of heparin or none. Neither of the two groups protected by heparin had gross renal cortical necrosis.

The lethal effects of toxin and Liquoid were not counteracted by heparin. In 16 of 20 rats, however, considerable blood was found in the peritoneal cavity, indicating that hemorrhage may have contributed to death.

In the kidneys of nine rats given heparin, small amounts of fibrinoid were seen in the glomerular capillaries, and in six it was associated with increased cellularity, rather like that of acute proliferative glomerulonephritis.

**Heparin-Precipitable Fraction and Development of Lesions**

In a final test, the relation of the heparin-precipitable fraction (HPF) in plasma to the appearance of fibrinoid lesions was observed. This protein fraction was found in slightly varied quantities in each of 30 normal control rats. Cold precipitability and heat lability were similar to those of HPF occurring in rabbits after intravenous injection of endotoxin.

Then, three groups of rats were given intraperitoneal endotoxin and Liquoid and were killed four, eight, and twelve hours later. As the period before death lengthened, the number of animals having this precipitable plasma fraction gradually declined, and the drop correlated with increasing deposition of fibrinoid material in renal glomerular capillaries. Of the eight rats killed after 12 hours, only one had HPF but six had typical fibrinoid in glomeruli.
Discussion

Results of the experiments indicate that rats and rabbits react in much the same way to Liquoid and gram-negative bacterial endotoxin. Although the rat tends to resist large doses of endotoxin alone, addition of Liquoid greatly enhances the lethal effects and the rate of morphologic changes. Comparable synergistic action has been observed in rabbits.

Renal lesions of the generalized Shwartzman phenomenon are produced in rabbits by two intravenous injections of gram-negative endotoxin, by endotoxin with small amounts of Liquoid, or by large doses of Liquoid.

We have demonstrated that a similar kidney lesion is caused in rats by intraperitoneal endotoxin and Liquoid combined or by large quantities of Liquoid alone. With appropriate dosage, lesions are equally numerous in the two animals. In rats, however, kidney changes apparently develop more slowly; the earliest detectable fibrinoid deposits are seldom noted until six to eight hours after administration of toxin and Liquoid. In some rats, moreover, fibrinoid material is deposited in large renal arteries, an effect not observed in rabbits.

Cardiac, pulmonary, and splenic fibrinoid lesions are decidedly fewer in rats than in rabbits, but the incidence of hepatic fibrinoid and necrosis is appreciably higher. These differences may be explained by methods of injection, since the intraperitoneal route may allow more gradual absorption and direct access to the liver.

Prevention or modification of the renal lesion by heparin is further evidence of parallel reactions and also indicates that some change in the blood-clotting mechanism may influence the development of fibrinoid or its precursors.

Glomerular cellular proliferation with minimal fibrinoid deposits in rats given heparin with toxin and Liquoid is of interest, in view of Piel's statement that occasional rats receiving heterologous hyperimmune serum had renal lesions of the Shwartzman type. These findings suggest that minimal or controlled deposition of fibrinoid in the glomeruli, acting over a longer time, may be associated with a proliferative cellular reaction, in contrast to the capillary occlusion and necrosis produced by large uncontrolled fibrinoid deposits in animals not given heparin.

The cold-precipitable protein fraction is not normally found in plasma of healthy rabbits but is present after one injection of endo-
toxin. After injection of Liquoid, it disappears rapidly from the plasma, and its fall corresponds with the occurrence of diffuse fibrinoid lesions.

In contrast to the behavior of this fraction in rabbits, the substance was found to occur naturally in rats. Though disappearance after toxin and Liquoid injection is slower than in rabbits, it agrees with the slower development of fibrinoid compound in rats. These studies suggest that the heparin-precipitable fraction of plasma is involved in the formation of fibrinoid in both rats and rabbits.
The Effect of Hyaluronidase on Experimental Urinary Lithiasis

Kenneth S. Helenbolt, M.D.,1 and C. D. Creevy, M.D.2

No urologic disease offers a more varied pattern of interest than lithiasis. It is accepted that calculi result from an imbalance of crystalloids and colloids formed naturally or abnormally in the urinary tract. Crystalloids are bound together in the stone by a colloidal matrix. The literature abounds with information concerning crystalloids, but the relative lack of data on urinary colloids is noteworthy.

Not until 1861 was the foundation laid for colloidal chemistry. Later, the ultramicroscope showed brownian movement of colloidal solutions, or sols. The protective action of urinary colloids was demonstrated in 1919, and organic components of calculi were found to be colloidal in 1945.

Because colloid particles are between microscopic and molecular systems, with size less than the wave length of visible light, they must be viewed by reflected light. To date, colloids obtained from normal urine are mucin, nucleic acid, chondroitin-sulfuric acid, glycogen, and a complex carbohydrate containing nitrogen.

Urinary colloids are influential in keeping insoluble compounds in a hypersaturated solution. Therefore, at least two early investigators attempted to augment natural constituents. Goldberg (1932-34) found that intramuscular injections of chondroitic sulfuric acid were effective, despite reactions at the injection site. In human subjects with phosphaturia, Snapper (1936) cleared urine in two days, without change of urinary pH, by giving 2 gm. of sodium benzoate three times a day plus dietary supplements of glycocoll.

In 1950, Butt championed urinary protective colloids. Renal lithiasis appeared to be less common in Negroes than in the white

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1Medical Fellow, Division of Urology.
2Professor and Director, Division of Urology.
†Wydase used in this investigation was supplied by Wyeth Laboratories, Inc., Philadelphia.

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race, in females than in males, and in gestating than in nonpregnant women. Among 680 Pacific Theater natives observed during World War II, the incidence of stone was almost inversely proportional to the amount of protective colloid in the urine.

Butt, Hauser, and Seifter determined urinary colloids by several methods: (1) ultramicroscopic gradation of colloidal activity, first with the darkfield attachment and later with the Leitz Ultropak microscope; (2) electrophoretic studies of noncentrifuged urine, on the principle that lyophilic colloids prevent crystalloid deposition; (3) determination of surface tension on ultracentrifuged urine by the pendant-drop technic, the criterion being that tension is inversely proportional to the quantity of beneficial colloid; and (4) photo-ultramicrographic recordings.

Subsequently, Butt attempted to increase protective colloids with hyaluronidase because of its spreading properties. He noted that 150 turbidity-reducing units in 1 cc. of isotonic sodium chloride solution, injected subcutaneously, often cleared urinary clouding and sediment. Results were manifest in 30 minutes and lasted 24 to 48 hours.

Hyaluronidase is a lyophilic enzyme with an estimated molecular weight of 60,000 to 70,000. Its substrate, hyaluronic acid, is a strongly peptizing polymer with a weight of 200,000 to 2,000,000, and it is a viscous mucopolysaccharide with units of acetylglucosamine and glucuronic acid.

Hyaluronidase depolymerizes hyaluronic acid in the skin and subcutaneous tissues. After this action dissipates locally, the acid reconstitutes itself, and part of the excess formed is excreted in the urine as glucuronides.

Except for righting some metabolic disorders, previous measures against renal lithiasis had been unsatisfactory. These have included improving causative states, reducing stone-forming urinary crystalloids, increasing their solubility through changes in pH, preventing absorption of dietary phosphorus, and preventing aggregation of crystalline particles in the urine.

Of 30 patients with recurrent calculi, 28 were treated successfully by hyaluronidase alone; 150 to 300 units were given every one to three days for six to fourteen months. Stones did not grow nor did new ones form.

In 1954, Butt stated that therapeutic effects are best observed with uncentrifuged aseptic urine allowed to settle for an hour at
room temperature. Another dose is indicated when turbidity increases in successive four-hour samples.

As an alternative, one may note comparative deposition on glass tips attached to indwelling catheters. When pretreatment urine is free of turbidity and sediment, measurements of surface tension are useful; values should drop 8 to 14 dynes per centimeter one-half hour to two hours after injection. Finally, long-term results are best shown by serial radiography every 60 to 90 days.

For subcutaneous injection, 5 to 10 cc. of isotonic saline solution is added to 1,500 units of hyaluronidase, which remains stable for two weeks without refrigeration. Dosage is regulated to keep the urine clear for 16 to 24 hours after injection. From 300 to 600 units is required daily in 80% of cases, but up to 2,400 units per day may be needed with infections.

Contraindications to hyaluronidase are (1) renal dysfunction, (2) rare hypersensitivity to the drug, (3) sensitization reactions from inadequate dosage, (4) lack of urinary clearing six to eight hours after reception of 1,800 units, (5) relative inefficiency against vesical stones, and (6) excessive cost. Retail prices are currently $1.25 per 150 units and $3.30 for 1,500 units.

In contrast to earlier reports, hyaluronidase is now provided as an adjunct to all customary measures for renal lithiasis.

From 311 patients, 36 aged 13 months to 78 years were chosen for therapy because of a strong tendency toward rapidly growing concretions. Certain subjects had many small stones, and the rest harbored large calculi with or without small ones.

During and after publication of Butt's work, hyaluronidase was enthusiastically employed in clinics and laboratories. Ravich, using the new Urotensiometer (Clay-Adams Co.) which gives direct readings of urinary surface tension, stated in 1954 that hyaluronidase lowered values but not to normal levels.

Smiddy used a Stalagmometer, which readily shows surface tension by a drop-weight method. Data indicated that surface tension may vary in a given individual, that tension and specific gravity are inversely related, and that subcutaneous doses do not affect urinary surface tension.

Dingley and Badenoch, after giving 1,000 units every day or two for three to ten months in eight cases, concluded that the results scarcely justified prolonged treatment.
Prien noted a possible sensitization reaction in a man taking 150 units daily for ten days, then 15 units every other day for two months with sodium bicarbonate to keep urine alkaline.

Flocks noted in 1955 that hyaluronidase did not protect urinary calcium salts, as measured by the calcium precipitability method.

In laboratories, three investigations of hyaluronidase and bladder stones in rats showed little or no value in therapy.

However, Puntriano, who employed Butt's technic in sheep and cattle, advocated implantation of hyaluronidase pellets in these animals in autumn to avoid economic loss from urinary stones.

In this institution, lyophilized hyaluronidase (Wydase) was tried on guinea pigs, whose dietary requirement of vitamin C makes their metabolism comparable to that of man.

An open suprapubic cystotomy was performed under pentobarbital anesthesia, and a coil of copper wire was anchored to the bladder dome with nylon thread. The incision was closed with absorbable suture, and each animal was given a prophylactic dose of penicillin.

Beginning on the seventh postoperative day, 0.2 cc. of saline solution containing 30 turbidity-reducing units of Wydase was injected subcutaneously. This is comparable to 2,400 units in human adults, the maximum used by Butt. The controls received similar doses of boiled hyaluronidase.

Animals were either killed or died of peritonitis or obstruction of the bladder neck by wire. Weight of the dried calculus found about the foreign body was determined in 31 experimental animals and 15 controls. In many cases, urine cultures were taken, oven-dried slides of urinary film were graded for colloidal activity using a medical microscope, and pH of urine was determined. All analyzed stones contained calcium and magnesium phosphates, as well as calcium carbonates and oxalates.

Apparently, size of the induced calculus and infected and/or alkaline urine were positively correlated. No relation was noted between the size of stone and colloidal activity twenty-four hours after hyaluronidase injection. Finally, weights of calculi in experimental and control animals were compared. Apparently, stone was less likely to develop in the experimental group.

Other lines of investigation being pursued in this country are (1) suppression of urinary calcium and magnesium excretion by oral doses of sodium phytate, (2) studies on the mechanism of biologic calcification and interpretation of urinary biocolloids, and (3) greater ex-
cretion of urinary glucuronides which secondarily increase solubility of calcium phosphate in urine; for this purpose, salicylamide and acetylsalicylic acid therapy have been suggested.

Obviously, no definite conclusions can be drawn from our paper. However, as experimental and clinical data accumulate, our material may be of value in defining the true place of hyaluronidase in treatment of urinary lithiasis.
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Lewis J. Weller  
Arthur H. Wells  
W. B. Wells  
Stanley P. Wesolowska  
Robert K. West  
M. Westby  
M. L. Whalen
Annual Members (continued)

Joseph L. Whelan
Richard A. Whitney
Francis M. Whittaker
John J. Wild
B. H. Williams
J. A. Williams
M. R. Williams
W. Lane Williams

Harold A. Williamson
Louis Winer
Winona Clinic
A. Cabot Wohlrabe
Donald E. Wohlrabe
Earl H. Wood
Thomas D. Wright
Merrill B. Yeomans

Lauritz S. Ylvisaker
Milo A. Ypuel
C. B. Young
Nelson A. Young
S. F. Yugend
H. B. Zimmermann
Thomas Ziskin
Postgraduate Education

Proctology for General Physicians

The University of Minnesota announces a continuation course in Proctology for General Physicians which will be held at the Center for Continuation Study from May 14 to 19, 1956. All aspects of rectal and colonic disorders will be taken up during the week long session. Guest speaker will be Dr. Hyrum R. Reichman, Head of the Proctologic Clinic at the University of Utah Medical School. The program will be presented under the direction of Dr. Walter A. Fansler, Clinical Professor and Director, Division of Proctology.

Surgery for General Surgeons

The University of Minnesota, in cooperation with the American College of Surgeons, is offering a continuation course in Surgery for General Surgeons from May 24 to 26, 1956. Half-day sessions will be devoted to preoperative and postoperative care, cardiovascular surgery, and abdominal surgery including ulcer and gallbladder surgery. One session will be devoted to informal case presentations and a surgical pathological conference. Registrants will also have an opportunity to attend operative clinics or, alternatively, to attend a session devoted to advances in surgical research. This year’s guest speaker will be Dr. Robert M. Zollinger, Professor and Chairman, Department of Surgery, Ohio State University College of Medicine, who in addition to participating in the course will also deliver the Annual E. Starr Judd Lecture on Thursday evening, May 24, to which all course registrants will be invited. The course will be presented under the direction of Dr. Owen H. Wangensteen, Professor and Chairman, Department of Surgery.

Notice

All continuation courses presented by the University of Minnesota are approved for formal postgraduate credit by the American Academy of General Practice. Attendance certificates will be furnished on request.

Further information concerning the above programs or others to be presented may be obtained by writing to Dr. Robert B. Howard, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14.
Coming Events

April 26 . . . . Student-Faculty Coffee Hour; Foyer, Mayo Auditorium; 3:30 to 5:30 P.M.

May 7-12 . . . . Continuation Course in Electrocardiography for General Physicians

May 10 . . . . Student-Faculty Coffee Hour; Foyer, Mayo Auditorium; 3:30 to 5:30 P.M.

May 14-19 . . . . Continuation Course in Proctology for General Physicians

May 15 . . . . DULUTH CLINIC LECTURE; “Experimental Hepatic Injury in its Relation to Hepatic Disease in Man”; Dr. Paul Gyorgy, Professor, Department of Pediatrics, Hospital of the University of Pennsylvania, Philadelphia; Mayo Memorial Auditorium; 8:00 P.M.

May 22 . . . . MINNESOTA MEDICAL FOUNDATION LECTURE; “The Patient Who Won’t Get Well”; Dr. Donald W. Hastings, Professor and Director, Division of Psychiatry, University of Minnesota Medical School; 4:30 P.M. (During 103rd Annual Meeting, Minnesota State Medical Association, Rochester, Minnesota)

May 24 . . . . E. STARR JUDD LECTURE; “Clinical and Experimental Observations on the Pancreas”; Dr. Robert M. Zollinger, Professor and Chairman, Department of Surgery, Ohio State University College of Medicine; Mayo Memorial Auditorium; 8:00 P.M.

May 24 . . . . Student-Faculty Coffee Hour; Foyer, Mayo Auditorium; 3:30 to 5:30 P.M.

May 24-26 . . . . Continuation Course in Surgery for Surgeons


WEEKLY CONFERENCES OF GENERAL INTEREST

Physicians Welcome

Monday, 9:00 to 10:50 A.M. Obstetrics and Gynecology
Old Nursery, Station 57
University Hospitals

12:30 to 1:30 P.M. Physiology-
Physiological Chemistry
214 Millard Hall

4:00 to 6:00 P.M. Anesthesiology
Todd Amphitheater,
University Hospitals

Tuesday, 12:30 to 1:20 P.M. Pathology
104 Jackson Hall

Friday, 8:00 to 10:00 A.M. Neurology
Station 50, University Hospitals

9:00 to 10:00 A.M. Medicine
Todd Amphitheater,
University Hospitals

1:30 to 2:30 P.M. Dermatology
Eustis Amphitheater,
University Hospitals

Saturday, 7:45 to 9:00 A.M. Orthopedics
Powell Hall Amphitheater

9:15 to 11:30 A.M. Surgery
Todd Amphitheater,
University Hospitals

For detailed information concerning all conferences, seminars and ward rounds at University Hospitals, Ancker Hospital, Minneapolis General Hospital and the Minneapolis Veterans Administration Hospital, write to the Editor of the BULLETIN, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14.