# Staff Meeting Bulletin
# Hospitals of the » » »
# University of Minnesota




# Renal Damage Due to Sulfonamides

Volume XVI | Friday, November 10, 1944 | Number 5

STAFF MEETING BULLETIN
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INDEX



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I.

# UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
## CALENDAR OF EVENTS

No. 46

November 13 to November 18

Visitors Welcome

Monday, November 13

9:00 - 10:00 Roentgenology-Medicine Conference; L. G. Rigler; C. J. Watson and Staff, Todd Amphitheater, U. H.

9:00 - 11:00 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff, Interns Quarters, U. H.

12:30 - 1:30 Pathology Seminar; Factors Influencing Induction of Leukemia in Mammary Cancer in Mice; E. T. Bell, 104 I. A.

Tuesday, November 14

9:00 - 10:00 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff, Eustis Amphitheater, U. H.

11:00 - 12:00 Urology Conference; C. D. Creevy and Staff, Main 515, U. H.

12:30 - 1:30 Pathology Conference; Autopsies; Pathology Staff, 104 I. A.

12:30 - 1:30 Physiology-Pharmacology Seminar; The Intestinal Absorption of Water and Electrolytes; Intestinal Absorption of Electrolytes Studied by Isotopic Tracers; V. Lorber; 214 M. H.

4:30 - 5:30 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Station 54, U. H.

4:00 - 5:00 Pediatrics Grand Rounds; I. McQuarrie and Staff, W-205 U. H.

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

5:00 - 6:00 Roentgen Diagnosis Conference; A. T. Stenstrom, L. P. Anderson; 515-M, U. H.

Wednesday, November 15

9:00 - 11:00 Neuropsychiatry Seminar; J. C. McKinley and Staff, Station 60, Lounge, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Carcinoma of Body of Pancreas, C. J. Watson, O. H. Wangensteen and Staff, Todd Amphitheater, U. H.

12:30 - 1:30 Pediatrics Seminar; The Maintenance of Nitrogen Balance by the Intravenous Administration of Plasma Proteins and Protein Hydrolysates; F. Adams, W-205 U. H.

12:30 - 1:30 Physiological Chemistry Literature Review; Staff, 116 M. H.

4:30 - 5:30 Neurophysiology Seminar; Application of the Adrian Bronk Law to Optical Receptors; Mr. Grant Dahlstrom; 214 M. H.

Thursday, November 16

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff, Todd Amphitheater, U. H.

12:30 - 1:20 Physiological Chemistry Seminar; Spectropholometeric Studies of Fats; Analysis by Conjugation and Tracer Studies; Norman Kretchmer; Direct Analysis and Studies of Rancidity; Leah Cohodas; 116 M. H.

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

5:00 - 6:00 Roentgenology Seminar; Strangulated Intestinal Obstruction; R. Beiswanger; M-515, U. H.

Friday, November 17

9:00 - 10:00 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; East 214 U. H.

10:30 - 12:30 Otolaryngology Case Studies; L. R. Boies and Staff, Out-Patient Otolaryngology Dept.

11:45 - 1:15 University of Minnesota Hospitals General Staff Meeting; Diverticulosis and Diverticulitis; W. A. Fansler, Powell Hall Recreation Room.

1:30 - 2:30 Medicine Case Presentation; C. J. Watson and Staff, Eustis Amphitheater, U. H.

1:00 - 2:30 Dermatology and Syphilology; Presentation of selected cases of the week; Henry E. Michelson and Staff; W-306 U. H.

1:30 - 3:00 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton and Staff, Todd Amphitheater, U. H.

Saturday, November 18

8:00 - 9:00 Surgery Journal Club; O. H. Wangensteen and Staff, Main 515, U. H.

9:00 - 10:00 Pediatrics Grand Rounds; I. McQuarrie and Staff, W-205, U. H.

9:15 - 10:30 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler and Staff, Todd Amphitheater, U. H.

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff, Main 515 U. H.

10:00 - 12:00 Medicine Case Presentation; C. J. Watson and Staff, Main 515 U. H.

11:30 - 12:30 Anatomy Seminar; Alloxan Diabetes in Mice and Rats; C. H. Morningstar; Relationship of the Teeth to the Maxillary Sinus, I. A. 226.

## II. RENAL DAMAGE DUE TO SULFONAMIDES

Wendell H. Hall
Wesley W. Spink

While penicillin has replaced the sulfonamides to some extent in the treatment of infections, the sulfonamides continue to be of importance because of their lesser cost, greater ease of administration and greater effectiveness in most infections due to gram-negative organisms. One of the most urgent problems since the development of the newer derivatives of sulfanilamide has been the high incidence of renal damage resulting from their use in the treatment of infection. Enough is known about the pathologic physiology of sulfonamide renal damage at present to make it worthwhile to review the problem.

The chief route of excretion of the sulfonamides is through the kidneys. These drugs are in part bound to the plasma proteins and therefore are not entirely filterable through the glomeruli.[1] Davis has found that at plasma concentration of 10 mg. per 100 c.c. the degree of plasma binding is 20% for sulfanilamide, sulfapyridine 40%, sulfadiazine 55%, and sulfathiazole 75%.[2] The slow rate of excretion of sulfamerazine appears to be due in part to the relatively high (84%) proportion which is bound to plasma proteins.[3] The sulfonamides are bound to the plasma proteins to a greater extent when acetylated than when in their free form.[4] Since they are bound chiefly to the plasma albumin, only the unbound fraction is filterable through the glomeruli.

Recent renal clearance studies of sulfonamides carried out with inulin and creatinine have indicated that there are considerable differences between the derivatives of sulfanilamide in regard to their tubular secretion and reabsorption. Sulfanilamide is apparently excreted by glomerular filtration with a considerable degree of tubular reabsorption.[5] Sulfapyridine, sulfadiazine and sulfamerazine are reabsorbed to a marked extent in the renal tubules but sulfathiazole appears to be excreted almost exclusively by glomerular filtration.[6] There is less tubular reabsorption of the conjugated compounds than of the free sulfonamides.[7]

Preliminary acute and chronic toxicity experiments in laboratory animals with sulfanilamide and its derivatives may forecast the renal complications which may be anticipated following administration of these drugs to man. Crystals and precipitated granules have been observed in the renal convoluted tubules of rats, rabbits, and dogs given sulfanilamide.[8] However, this association has not been noted with sulfanilamide in man. With the advent of sulfapyridine, the findings of urinary concretions and crystals of the acetylated drug was much more common and extensive.[9,10,11,12] In many instances the renal pelves and ureters were filled with acetyl sulfapyridine crystals. Sulfathiazole showed a similar tendency to precipitate out in the form of acetyl crystals with perhaps greater damage to the renal tubules.[13] Similar renal lesions have been produced in laboratory animals with sulfadiazine, but only with larger doses.[14,15,16] Sulfamerazine concretions occurred only at high blood levels in dogs and monkeys.[17] In experiments with the sodium salts of sulfanilamide derivatives, renal complications have been more easily produced than with the acids, and the precipitate has often consisted of the free drug rather than its acetylated derivative.[13]

In man the kidney complications associated with sulfonamide therapy have resembled those produced in experimental animals. Renal manifestations constitute the most frequently encountered of the serious complications caused by the sulfonamides, with the exception of sulfanilamide. In various reports the incidence of this complication has varied from 1% to 10%. It is by far the most common fatal toxic complication of sulfonamide therapy.[18]

Several factors have been mentioned in the literature in relation to the production of renal complications in man. The age of the patient has not appeared to be important; the incidence of kidney damage has been no greater in infants and children than in adults. Kawaichi and Barnes[19] reported that the incidence of sulfathiazole and sulfapyridine concretions was higher in Orientals than in Caucasians.

The incidence of renal damage has varied considerably among the various sulfanilamides. The incidence due to sulfanilamide has been very low. Because of its great solubility, sulfanilamide rarely causes crystalluria. Most of the renal complications, which have been reported as being due to sulfanilamide have been associated with acute hemolytic anemia and precipitation of hemoglobin casts in the renal tubules.[20] Sulfapyridine, on the other hand, causes frequent renal complications. During sulfapyridine therapy, microscopic hematuria has been reported as occurring in 40% of adult patients.[21] Sulfathiazole has also been a frequent cause of renal damage. In a large series of patients, Dowling and Lepper[22] reported the incidence of renal calculus (pain, gross hematuria, anuria, or oliguria) following sulfathiazole therapy was 2.8% as against 1.6% for sulfapyridine and 1.5% for sulfadiazine. With ordinary doses the incidence of renal calculus with sulfadiazine was only 0.9%. The incidence of renal calculus with sulfadiazine in other reports has varied from 0.9% to 2.9%.[23,24,25] Although it was thought that sulfamerazine would produce less renal damage than sulfadiazine, this hope has not been realized.[26-29]

Sulfonamide kidney complications usually do not appear until the third or fourth day of treatment and often later. When the sodium salts are given intravenously renal symptoms and signs may appear within 24 hours.[25] It seems to be generally agreed that renal complications due to obstruction by precipitated drug is much more common with daily doses of 6 gm. or more than with doses of 4 gm. or less per day.[22,25] Such complications are also more common in patients given the sodium salts of the sulfonamides. Crystalluria has been reported to follow the ingestion of as little as 10 grains of sulfathiazole.[30] Renal damage not associated with obstruction by sulfonamide crystals may develop after only a few grams of the sulfonamide has been taken.[30,31] Obstructive renal complications during sulfadiazine therapy are very uncommon with maximum blood levels (free) of 5 mg. per 100 c.c. or less but are very common if the blood level is maintained at more than 10 mg. per 100 c.c.[25] Renal damage on a toxic basis often occurs in the absence of high blood concentrations.[30] Since urinary sulfonamide concretions are almost always made up of acetylated sulfonamide crystals it has been postulated that patients who acetylate a particularly high percentage of the drug would be expected to be unusually vulnerable to renal damage.[32] It must be remembered however that sulfathiazole causes urinary tract obstruction just as often as sulfapyridine although much less of the sulfathiazole is excreted in the acetylated form.

The sulfonamides are weak acids which ionize and form soluble salts in alkaline solutions.[33] As the pH of the surrounding media increases the degree of ionization and hence the solubility of sulfonamides and their acetylated derivatives increases. Thus if the pH of urine is increased from 6.5 to 7.5 the solubility of free sulfathiazole and the less soluble acetyl sulfathiazole is increased 200-300%.[34,35,36] An equivalent increase in alkalinity increases the solubility of the free and conjugated forms of sulfadiazine 600-800% and of sulfamerazine 400-500%.[17,37,38] The solubility of sulfapyridine and acetyl sulfapyridine do not change appreciably within the physiologic pH range of human urine.[39,41] It is of interest to note that although sulfadiazine is the least soluble of the sulfonamides in general use it has not produced a higher proportion of renal obstruction. Although free sulfadiazine is less soluble than acetyl sulfadiazine renal concretions are almost always composed of acetyl sulfadiazine. During therapy with sulfathiazole and sulfadiazine it has been noted that the incidence of crystalluria is significantly lower in alkaline urine than in acid urine.[35,37,42-44] The pH of the urine has been found to be acid in many cases of renal blockage due to sulfathiazole, sulfadiazine and sulfamerazine.[19,27] On the contrary sulfapyridine has frequently formed urinary concretions while alkalies have been given and in the presence of an alkaline urine.[45,46]

Curtis and Sobin[39,47] found that the solubility of acetyl sulfapyridine in urine increased as the specific gravity of the urine increased and that this increase in solubility was due to urea. They also reported that the administration of urea prevented the formation of acetyl sulfapyridine stones in rats. Barnes and Kawaichi[48] demonstrated that the solubility of sulfathiazole and sulfadiazine increases greatly as the temperature of urine is increased from 98°F. to 105°F. They also presented six instances of anuria due to sulfapyridine which appeared to follow an abrupt fall in body temperature.

It is generally agreed that a low fluid intake is one of the most common causes of renal obstruction during sulfonamide therapy. This is especially true when high blood levels are maintained. Nausea and vomiting frequently precede the onset of a sulfonamide renal complication.[27,49] It is particularly dangerous to inject the sodium salts of the sulfonamides intravenously into a dehydrated patient.[49]

Inspection of solubility tables indicates that there is a discrepancy between the solubilities of the parent sulfonamides and their acetylated derivatives in the urine and the total amount of sulfonamide excreted in the urine. The difference is made up in part by "free" sulfonamide which is diazotizable but which has been conjugated in the liver with glucuronic acid and is very soluble in urine. Scudi and his associates[51,52] have shown that if liver damage is produced in rats with phosphorus and they are subsequently given sulfapyridine less of the water soluble glucuronate is excreted in the urine and more insoluble acetyl sulfapyridine is excreted. The incidence of renal concretions increased from 10% to 60%.

Both experimental and clinical evidence has appeared which indicates that renal insufficiency and urinary obstruction with stasis may contribute to the pathogenesis of renal damage due to sulfonamides.[49] Thus among six patients with fatal anuria due to sulfathiazole observed in this hospital, three were found to have only one kidney functioning prior to sulfathiazole therapy.[53]

Evidence which is available at present strongly indicates that the sulfonamides produce renal damage through several different mechanisms. By far the most common form of kidney complication is the precipitation of crystals within the urinary tract forming concretions and even uroliths which obstruct urine flow. Such precipitation may occur in the ureters and renal pelves, as is frequently the case with acetyl sulfapyridine, or the crystals may form and lodge in the renal tubules, a frequent site of acetyl-sulfathiazole and acetylsulfadiazine concretions. Sulfanilamide does not cause urinary obstruction by formation of drug crystals but may lead to tubular blocking with precipitated hemoglobin products in cases where it produces an acute hemolytic anemia. Either intra- or extra-nephritic obstruction produces tubular dilatation and atrophy but does not damage the glomeruli. Numerous animal studies have indicated that sulfonamide deposits in the form of crystals and amorphous masses laid down in the renal tubules, pelves, ureters and bladder may not only be injurious mechanically but are toxic to tissue as well. The crystalline deposits are often surrounded by evidences of acute inflammation and tissue necrosis.

The collecting tubules and, to a lesser extent, the convoluted tubules of the kidney are particularly damaged. They may be denuded of their lining epithelial cells and in other portions their epithelium may simply appear swollen and vacuolated. Protein and blood elements appear within the tubules and Bowman's capsular spaces. The crystals often penetrate the tubular walls and come to lie in the interstitial tissue of the kidney. They are surrounded by a cellular infiltrate which is usually chiefly mononuclear. Actual granulomas may be seen which are made up of necrotic tissue, fibroblasts, collagen, epithelioid cells, and multinucleated giant cells. Perivascular leucocytic exudate is found about both the arteries and veins, particularly in the peripelvic region. Thrombi form in the small renal veins and if the vessel is occluded a small area of hemorrhage may result.[13,16,54-57] Evidence that the renal tubular damage is toxic in nature is the fact that many of the fatal cases have shown focal areas of necrosis in the liver, spleen, lymph nodes and bone marrow as well.

There have been several reports of toxic renal damage due to sulfonamides in which obstruction by concretions has apparently been lacking.[18,30,31,66-71] Tubular necrosis has been the principal finding at autopsy. Clinically these cases have been characterized by oluguria, anuria, moderate, albuminuria, uremia and usually a fatal outcome without any episode of pain, hematuria or crystalluria. At autopsy focal necrosis in the liver, spleen, heart, lungs, brain, lymph nodes and bone marrow have been reported as accompanying a wide-spread tubular necrosis. The renal glomeruli are usually intact, and crystals and other drug deposits are not found. One must be certain however that microscopic sections have been prepared by the frozen section technique and examined under a polarizing microscope with the Nicol prisms crossed since sulfonamide crystals are dissolved out of tissues by the usual fixatives and stains.[72,73] It is possible that in some cases the toxic nephritis is on the basis of a drug idiosyncrasy or hypersensitivity since it has been reported as following repeated courses of sulfathiazole and after only small doses have been given.[30,66,69] Severe tubular injury has also been observed after acute hemolytic anemia induced by sulfanilamide.[74] Anuria has been reported as following the development of a rash; this is most likely due to a drug idiosyncrasy.[31]

The recent work of Rich[75,76,77] has indicated that if sulfonamide therapy is continued in the presence of drug fever or a rash vascular lesions may be produced which are identical with those of periarteritis nodosa. Similar lesions can also be produced with horse serum. Besides the vascular lesions widespread focal, inflammatory and necrotic lesions are found in the kidneys and other viscera. A very interesting case report by Dotta and Delporte[78] confirms the idea that sulfonamides can cause renal damage by an allergic mechanism. In this instance sulfanilamide was administered. After 5 doses of 2 gm. each the patient developed generalized urticaria, profound oliguria, hypotension, albuminuria and azotemia. Crystals were never found in the urine and there was no hematuria or anemia. The patient recovered completely but had a recurrence of his urticaria without oliguria when sulfanilamide powder was placed in an abscess. A patch test with sulfanilamide was negative.

There have been a few reports of acute glomerulonephritis developing during sulfonamide therapy.[16,30,77,79] However the relationship has not been well established; furthermore patients with acute glomerulonephritis have been found to improve during sulfonamide therapy.[43] If renal pain, hematuria, oliguria or anuria appears in a patient being treated with a sulfonamide it is most likely that the renal findings are due to the sulfonamide. However a careful differential diagnosis should be made. In the great majority of obstructive sulfonamide nephropathies crystals and red blood cells will be found in the sediment of the fresh urine. It should be recalled that the finding of crystals in urine which has cooled to room temperature has no particular significance. A flat X-ray film of the abdomen showing nothing significant may be of help since sulfonamide urinary concretions are not radio-opaque. Intravenous and retrograde pyelography may be necessary to make the diagnosis in a few cases. Oliguria and anuria with uremia may be due to ureteral obstruction by stones, tumor, etc. Pyelonephritis and heart failure with passive congestion of the kidneys must be ruled out. Recently a patient was observed in this hospital in whom anuria and uremia developed after the ingestion of 12 gm. of sulfadiazine. Autopsy revealed thrombosis of both renal arteries with bilateral renal infarction. In postoperative patients one must also consider the possibility of shock and reflex mechanisms which may lead to anuria. Bywaters'[80] publications on crush injury have indicated that anuria may develop after ischemic muscle necrosis. During the past year a patient was seen on the surgical service in whom the right femoral vein was ligated because of thrombophlebitis. He was given sulfadiazine. Shortly after the venous ligation multiple incisions were made in his leg because of massive swelling with impairment of its circulation. It was then noted that his urine output was much reduced, and his blood urea nitrogen rose steadily. He also became jaundiced. No crystals and only a few red blood cells were found in his urine. The patient recovered after a protracted illness. It was difficult to decide in this case whether the renal and hepatic complications were due to the sulfadiazine or muscle necrosis. In patients with jaundice and anuria one must also consider the possibilities of a hemolytic blood transfusion reaction and the so-called "hepato-renal" syndrome; in the latter condition the renal damage is thought to be secondary to hepatic damage.[81] The sulfonamides, and particularly sulfanilamide, have been known to produce liver damage; but in clinical practice it is difficult to assess the relative roles of infection and the sulfonamides in cases exhibiting the hepato-renal syndrome.

During the last three years 20 patients have been observed in the University of Minnesota Hospitals in whom renal complications have developed during sulfonamide therapy. During this period sulfathiazole and sulfadiazine have been the drugs used most often. During the past 18 months sulfamerazine has also been used extensively. Sulfapyridine is not used in this hospital because more recently developed sulfonamides are more effective therapeutically and are tolerated better. The age of the 20 patients varied from 3 years to 84 years (average 32.6 years). Males predominated in a ration of 3:2 over females. Sulfadiazine alone was incriminated in 11 patients whereas sulfathiazole was the sole cause of the renal complication in only 2 patients. It should be pointed out that sulfadiazine has been used in full doses much more frequently than sulfathiazole in this hospital. Sulfamerazine was used alone in 6 of the patients with renal damage. It has been apparent that sulfamerazine causes renal damage just as often as sulfadiazine. In one patient renal complications arose with each of the 3 drugs--sulfamerazine, sulfathiazole, and sulfadiazine.

One of the patients with a renal reaction due to sulfathiazole received 19 gm. of the drug before the onset of the complication; in the other the dose was unknown. The dose of sulfadiazine received before the onset of kidney complications varied from 8 gm. to 91 gm. (average 33.2 gm.). Two of these patients had been given massive doses of sodium sulfadiazine (25 gm. in 2 hours), intravenously for the treatment of subacute bacterial endocarditis. The dose of sulfamerazine given before the appearance of renal complications varied from 10 gm. to 35 gm. (average 19.7 gm.). One of these patients had been given 25 gm. of sodium sulfamerazine intravenously because of subacute bacterial endocarditis; another had been given 4 gm. of sodium sulfamerazine intravenously every 8 hours for 3 doses for the treatment of meningitis.

As is well known the blood sulfonamide concentration rises quickly to a high level when the sodium salts are injected intravenously. Six of the 20 patients in this series had been given the sodium salt of one of the sulfonamides intravenously. In 15 of the patients the concentration of free sulfonamide in the blood had been determined at the time of the onset of the renal irritation. In one instance of oliguria due to sulfathiazole the blood level (free) was only 2.5 mg. per 100 c.c. In 8 patients with sulfadiazine reactions the values for free sulfadiazine in the blood ranged from a trace to 107.6 mg.% (average 36.2 mg. %). However, if one disregards the two instances of hematuria following 25 gm. of sodium sulfadiazine given intravenously the average blood concentration was only 9.0 mg. %. The finding of two instances of urinary obstruction and hematuria with blood concentrations of only 1.0 mg. per 100 c.c. and a trace of free sulfadiazine respectively in the blood suggests that excessive acetylation may have been a factor in these cases although the total blood concentration was not determined. In 6 patients with renal damage due to sulfamerazine the blood concentration varied from 5.0 mg. per 100 c.c. to 33.8 mg. per 100 c.c. (average 17.2 mg. per 100 c.c.). These high concentrations probably are the explanation for the unexpectedly frequent renal complications with sulfamerazine therapy.

In the majority of instances where the pH of the urine was tested at the onset of the renal complication it was found to be acid. The urine pH in 15 patients varied from 4.0 to 8.0. In one patient receiving sulfathiazole the urine pH was 4. In 7 patients given sulfadiazine the urine pH ranged from 5.5 to 8.0 (average 6.9); in two instances the pH was 8.0. One of the latter patients had been given 25 gm. of sodium sulfadiazine intravenously plus sodium bicarbonate and large amounts of fluid. Her blood concentration of free drug reached 107.6 mg. per 100 c.c. and she had a short episode of gross hematuria but she never had crystalluria or oliguria. It seems likely that in this patient crystals formed temporarily in the proximal renal tubules where the pH of the urine is lower. In 7 patients with urinary concretions due to sulfamerazine the urine pH at the onset varied from 4.0 to 7.0 (average 6.0). One of these patients had been given ammonium chloride (5 grains every 4 hours) along with sulfamerazine (1 gm. every 4 hours) because of an acute bronchitis. She developed gross hematuria and bilateral ureteral obstruction due to crystalline masses after only 16 gm. of sulfamerazine. The pH of the urine obtained by catheter from the left renal pelvis during cystoscopy was 4.8.

The specific gravity of the urine was tested at the onset in 7 patients and varied from 1.003 to 1.023 (average 1.014).

Dehydration was almost as important a factor as the urine reaction in the production of urinary complications in this series. There were 4 patients in whom the average daily fluid intake was less than 2500 c.c. before the onset of renal irritation. The average fluid intake on the day before the onset of urinary symptoms was 2820 c.c. and on the day of onset was 3070 cc. The average urine output on these days was 1150 c.c. and 940 c.c. respectively. It should be noted that 10 of the 20 patients were known to have excreted less than 1500 c.c. of urine during the 24 hours prior to the onset of urinary complications. Also 14 patients complained of nausea and vomiting at some time preceding their urinary difficulties. One patient who developed anuria after taking only 8 gm. of sulfadiazine had vomited repeatedly during the two days that she took the drug.

Pre-existing renal disease may have contributed to the urinary sulfonamide complication in two of the patients. One of them had bilateral chronic pyelonephritis with progressive renal insufficiency ending in death. Autopsy revealed numerous small concretions in each renal pelvis with extensive and severe pyelonephritis. The other patient was a 23 year old male who had recurrent left renal pain for many years and had been given an unknown amount of sulfathiazole by his local physician. Within a few days he complained of vomiting, abdominal pain and hematuria. On the following day he was unable to void any urine. He was admitted to this hospital after 48 hours of complete anuria, and at this time he was delirious. He was tender in both flanks and had a flaccid paralysis of his arms and legs. Urine: specific gravity 1.010, sugar 0, albumin 2+, RBC 4+, WRC 2+, casts 0, crystals 0. His blood urea nitrogen was 315 mg. per 100 c.c. He was given 1000 c.c. of saline solution intravenously, but he died 24 hours after his admission to the hospital, Autopsy revealed a small left kidney weighing 115 gm. Its pelvis contained a large staghorn calculus, and there was extreme hydronephrosis. The right kidney weighed 180 gm., had a granular surface and cut sections contained yellow crystalline material, especially in the medullary pyramids. No crystals were found in the pelves, ureters or bladder but a small calculus was found in the right renal pelvis. Microscopic sections revealed sulfathiazole crystals in the tubules of the right kidney. There was marked destruction and dilatation of the tubules of the right kidney, and almost complete atrophy of the tubules of the left kidney.

Other complications which might have been due to the sulfonamides given to these patients were noted as follows: fever 5, headache 4, chill 2, morbilliform rash 2, hiccough 2, abdominal distention 1, diarrhea 1, and anemia 1.

A 19 year old girl was given 1 gm. of sulfadiazine every 4 hours for 12 doses. She then developed urinary frequency, pain in the back and over the bladder, dulled sensorium, gross hematuria and complete anuria for 21 hours. Her blood urea nitrogen was 40 mg. per 100 c.c. and her blood $CO_2$ combining power was 36 vol. per 100 c.c. No crystals were found in her urine in 6 specimens examined. Her urine was alkalinized by giving large doses of sodium bicarbonate intravenously. She was also given glucose solution intravenously. After 21 hours of complete anuria she was cystoscoped under local anesthesia. The bladder was inflamed and contained 95 c.c. of grossly bloody urine. The left ureteral orifice was normal and spurts of clear urine were seen coming from it. No urine was seen coming from the right ureter. Ureteral catheters were easily introduced up to both renal pelves. No crystals were found. The renal pelves were lavaged with hot water every hour and the catheters were removed after several hours. On that day 30 c.c. of urine was collected from the right ureteral catheter, 49 c.c. from the left and 385 c.c. from the indwelling catheter in the bladder. The ureteral catheters were re-inserted on the following day and the renal pelves again lavaged hourly with sterile warm water. The catheters were removed 2 days later. The patient made an uneventful recovery. When discharged her urine was entirely normal and and her B.U.N. was 20 mg. per 100 c.c. However, it was found that her hemoglobin had fallen from 15.2 gm. to 9.9 gm. per 100 c.c. (final RBC 3,996,000).

In the 20 patients in this series the most frequent urinary symptom was pain. Pain was present in 15 patients--usually it was present in the lumbar or flank areas but occasionally was present also in the lower quadrants of the abdomen. Urinary frequency occurred in 3 patients and dysuria in 4 patients. Oliguria was observed in 16 patients, and in 5 patients this progressed to total anuria lasting from 6½ hours to several days. Hematuria occurred in 17 patients and in 8 was severe enough to be grossly visible. Crystalluria occurred in 7 of the 20 patients at some time during their clinical course. Four patients with microscopic hematuria and 4 patients with gross hematuria were never observed to have crystalluria. In some of these patients it is likely that deposition of sulfonamide crystals was confined to the renal tubules. In two patients who had hematuria without recorded crystalluria, sulfonamide crystals were observed in the renal tubules at autopsy in one and in the ureters during cystoscopy in the other. It should be emphasized that urine should be centrifuged before the sediment is examined for sulfonamide crystals.

Flank tenderness was elicited in 8 patients, and psoas spasm and generalized edema were observed in 1 patient. Albuminuria (trace to 3+) occurred in 7 patients and granular casts were seen in the urinary sediment of 1 patient. A strongly positive reaction with Ehrlich's reagent was observed in the urine of two of the patients; the exact etiology of the urobilinogenuria was not determined. It was of short duration and there was no other evidence of liver dysfunction. The blood urea nitrogen concentration became elevated in 6 of the patients; in one fatal case it rose to 315 mg. per 100 c.c. Two of the patients with uremia also had a mild acidosis.

It is of interest to review the prophylactic measures that had been taken in these 20 patients. Eleven patients had been instructed to drink 2500 c.c. or more of liquids daily. A few had been taking as much as 4 and 5 liters of fluid daily, but these patients had also been given huge doses of sulfonamides (25 gm. of sodium salt intravenously). Nine of the patients had been given sodium bicarbonate in doses varying from 4 to 16 gm. per day (average 11 gm.). The urine pH at the onset of symptoms in these cases varied from 6.0 to 8.0 (average 7.1); in only one of these patients was the urine alkaline in all specimens tested. The latter patient had been given massive dose chemotherapy for subacute bacterial endocarditis.

Active therapy after the appearance of the urinary complication consisted of conservative measures in 13 of the 20 patients. The sulfonamide drug was discontinued and fluids were forced in all of the patients. Eight of the patients were given sodium bicarbonate in order to alkalinize their urine. None of these patients had complete anuria except one patient with hydronephrosis whose case history has been given. His was the only fatal outcome in this group. The great majority of these patients recovered quickly. However, one patient continued to have ureteral colic for several months; careful urologic study failed to reveal any organic basis for the pain. Seven patients were cystoscoped because of complete anuria. Ureteral catheters were passed upward to the renal pelves, tied in place and irrigated every hour for several hours with warm sterile water or 2½% sodium bicarbonate solution. In 6 instances definite ureteral obstruction by sulfonamide concretions were observed, and in one patient no obstruction was found. Six of these patients recovered quickly, and one patient died after several weeks because of chronic pyelonephritis. In several cases the concretions were very difficult to remove and success was attained only after spinal anesthesia and considerable manipulation.

## Prevention of Sulfonamide Renal Damage

There are several definite measures which can be taken to prevent kidney complications during sulfonamide therapy.

1. The dose of the sulfonamide should not be any greater than necessary. Thus it is well known that not more than 2 to 3 gm. daily of the sulfonamides in common use is necessary in the treatment of most urinary tract infections. Dowling and his associates[82] reported that in a series of 160 cases of pneumococcic pneumonia treated with sulfadiazine doses of 0.5 gm. every 4 hours seemed just as effective in the average patient as doses of 1 gm. every 4 hours. No renal complications were observed in the 81 patients receiving 3 gm. daily. The concentration of the sulfonamide in the blood should be determined at least every third day. It is unnecessary in the great majority of infections to maintain a blood concentration of more than 8 to 10 mg. per 100 c.c. Such concentrations can be maintained in most patients with 4 to 5 gm. of sulfadiazine daily and 2 to 3 gm. of sulfamerazine daily. The sodium salts of the sulfonamides should not be given by rapid intravenous injection except when absolutely necessary.

2. In any patient in whom drug fever is suspected or in whom a rash or other manifestation of drug idiosyncrasy occurs the sulfonamide should be immediately discontinued. If other sulfonamides are given subsequently, the first test doses should be small.

3. The volume of fluid ingested and urine excreted should be measured accurately even though the patient may be ambulatory. The amount of fluid ingested should be sufficient so that at least 1000 c.c. and preferably 1500 c.c. of urine is excreted per 24 hours. Schemm[83] has suggested that fluids may even be given safely in large amounts to patients with cardiac failure if their sodium intake is maintained at a low level. In patients with nausea and vomiting particular attention should be

paid to the fluid balance when sulfonamides are given.

4. The drug should be discontinued if gross hematuria appears. Microscopic hematuria may be related to the infection which has indicated the use of a sulfonamide, and not due to the drug. Nevertheless, it is a presumptive sign in many instances of renal irritation due to the sulfonamide, and one must proceed cautiously when it appears. Likewise, renal pain and persistent oliguria are sufficient indication to discontinue sulfonamide therapy.

5. The pH of the urine should be maintained at 7.5 or higher by the administration of alkalies. The alkali used most commonly for this purpose is sodium bicarbonate. There is abundant experimental and clinical evidence that this method of prevention is effective.[27,35,42,85-87] The dose of sodium bicarbonate must be sufficient to keep the urine continuously alkaline. As little as 4 gm. (1 tsp.) of sodium bicarbonate may render the urine alkaline.[88,89] However, the effect lasts only a few hours. In order to keep the urine alkaline throughout the day it is recommended that 15 to 20 gm. of sodium bicarbonate be given daily in divided doses. As has been well known for many years it is often difficult to keep the urine continuously alkaline; in some patients as much as 45 gm. of sodium bicarbonate may be necessary.[90,91] The reaction of a fresh specimen of urine should be tested each morning so as to be sure enough alkali is being given. If this urine is acid the dose of alkali should be increased.

The danger of alkalosis is not great. The $CO_2$ combining power of the blood will rise, and as shown by Palmer and Van Slyke,[92] the rise can be calculated if it is assumed that the absorbed sodium bicarbonate is uniformly distributed throughout an amount of fluid equal to 70% of the body weight. One must be particularly careful to watch for the possibility of alkalosis in any patient with dehydration, hypochloremia or reduced renal function. There is very little evidence that alkalis damage the kidneys except in the presence of alkalosis.

It should be noted that sodium bicarbonate has some secondary effects. In normal individuals it causes a moderate diuresis of water. In patients taking sulfadiazine, sodium bicarbonate causes increased gastro-intestinal absorption but also increased excretion of the sulfadiazine.[50,93] Hence the blood sulfadiazine level may fall slightly when sodium bicarbonate is given.

If the alkali must be given parenterally the sodium bicarbonate may be given as a 3 to 5% solution in sterile distilled water or physiological saline intravenously. In such patients one can also use sixth-molar sodium lactate. Gilligan and her associates[95] have found that 500-1500 c.c. will alkalinize the urine, and 1100 c.c. given daily in divided doses every 12 hours will maintain the urine alkaline.

The use of sodium bicarbonate and sodium lactate is contra-indicated in patients with cardiac failure since sodium salts tend to increase edema. It has been suggested recently that potassium bicarbonate be used in these patients. Ohnsty and Wolfson[96] treated 9 patients who had cardiac failure and pneumonia with sulfadiazine and 2 gm. of potassium bicarbonate every 4 hours. They were able to maintain an alkaline urine, and none of their patients developed evidence of potassium poisoning. There has been considerable hesitancy in the use of potassium bicarbonate in cardiac patients with renal disease since it is known that an elevation of the serum potassium may be associated with cardiac irregularities and even cardiac arrest.[97] However, Winkler, Hoff and Smith[98] have pointed out that it is unlikely that fatal potassium poisoning by oral administration can occur in the presence of nephritis as long as urine is being excreted. Potassium salts should not be used in the presence of uremia.

Treatment of Sulfonamide Kidney Complications

1. As mentioned previously the sulfonamide should be discontinued at the first sign of renal irritation or obstruction of urine flow.

2. Fluids should be urged. If the patient is unable to take fluids well by mouth, parenteral fluids should be given. Peterson, Goodwin and Finland[50] have shown that 5 or 10% glucose in distilled water will reduce the concentration of sulfadiazine in urine more rapidly than physiological saline.

3. The urine should be kept alkaline. However, Peterson etal[50] also found that sodium bicarbonate causes more diuresis of sulfadiazine than of water; hence the concentration of the sulfadiazine in the urine rises. Also Lehr[99] has reported that in experimental urinary obstruction due to sulfadiazine in rats 3.33% saline solution or a mixture of 1.67% ammonium chloride and 3.33% sodium bicarbonate in water were more effective in relieving the obstruction than either water or sodium bicarbonate solution. The former solutions lead to an acud urine, but Lehr believes their beneficial effect may be due to the diuresis produced.

4. Local heat and nitrites may be tried but are not very helpful. In the presence of anuria due to a toxic nephritis diathermy treatments may lead to a diuresis by producing an increased blood flow through the kidneys.[100]

5. In any patient with anuria if a diuresis does not result after 12 hours cystoscopy and ureteral catheterization should be carried out. Spinal anesthesia may be necessary for this procedure. If the catheters can be introduced into the renal pelves they should be tied in place and irrigated every hour with warm 5% sodium bicarbonate solution until the return solutions are clear and a diuresis has been established. The catheters may usually be removed after several hours. This procedure is effective in the great majority of cases of anuria due to extra-renal obstruction and in some cases of tubular obstruction.

6. In some small children and in adults in very poor condition cystoscopy and ureteral catheterization may be impossible. A few such patients have been treated successfully by uretero-pyelostomy.[46,101,102] Renal decapsulation has been performed in a number of such patients and a flow of urine re-established.[46,60,65,102-104] However, the procedure seems to offer little to recommend it.

Summary

1. The most frequent serious toxic complication of sulfonamide therapy is renal damage. The most common form of renal damage is that due to precipitation of sulfonamide crystals within the urinary tract. There is evidence that toxic kidney damage and nephritis secondary to drug sensitivity may follow sulfonamide treatment.

2. Twenty cases of sulfonamide renal damage observed at the University of Minnesota Hospitals in the last 3 years are reviewed.

3. Urinary obstruction by sulfonamides is preventable. Effective methods of prevention include careful regulation of drug dosage, adequate fluid intake and maintenance of an alkaline urine.

4. The treatment of sulfonamide kidney complications is reviewed. In patients with anuria, cystoscopy and ureteral catheterization should be performed within 12 hours if conservative measures fail to establish a diuresis.

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III. GOSSIP

James Drummond was a hospital visitor this week. Jim hails from Rochester where for many years he has been head of Worrall Hospital, and incidentally, one of America's outstanding carilloneurs. Rochester's winters have been growing longer and colder for him, so Jim decided to move to Santa Fe, New Mexico for a change of scenery. Just before he left for the Twin Cities to visit his friends, officials from St. Mary's Hospital asked him to become their credit manager, so back to Rochester he has gone. We are glad that he has decided to stay.....In Duluth I visited with Frank Hirschboeck and Russell Moe, and Jim McGee of Superior. Our friends in Duluth and Superior are as busy as ever. Their hospitals have always been rated the outstanding interne services in the country. Every staff man takes an interest in teaching and the services in laboratory, x-ray, and records are tops. In the anticipated demand for places for training for the post-war period these institutions should be utilized.....To Glencoe to celebrate the 25th anniversary of the founding of the McLeod County Public Health Association. Again I am impressed with the fine work which the public health nurses are doing. In this county of 20,000 persons, one nurse attempts to carry the load when they need four. The 150 lay persons who attended the meeting are efficient helpers of the nurse. The physicians and dentists turned out in force. I was interested to find that they are conducting a tuberculosis case finding survey in which the physicians are donating their time and services, and the county commissioners are paying for the cost of film. This is one county in which everyone puts service ahead of professional privilege. They are proud of the fact that their children are protected against contagious disease, and do not quarrel as to the way in which it should be done. It was in this county that their oldest physician told me that the medical profession made a mistake when it charged for smallpox vaccination. He believed that with vaccine supplied by the state, that physicians should have made their contribution to the cause of public health in the form of service without fee. The high esteem in which the physicians in this county are held by their people is the old story of "bread cast upon the waters."....The steam shovel is busy east of the present nurses' home getting ready for the new building which will be erected there to take care of the increased nurse enrolment. Many of the nurse instruction units now located in the Hospitals will be moved there, and the new classrooms will also be located there. As one goes around the building the impression gained is one of extreme crowding. In the post-war period we hope to have the Mayo Memorial Building to take care of "the school of clinical medicine." It is proposed to erect a tower in the area now occupied by flower beds and parking space in front of the building. It will be connected to the hospital proper by wings, and on both sides there will be a underground parking garage. The unit will also house a full-sized auditorium for all-medical school assemblies. In addition, it will contain administrative offices, laboratories, and seminar rooms. Other proposed additions include the new School of Public Health building which will be located opposite the present Health Service. Further additions to our buildings are necessary if the anticipated post-war expansion occurs. We need a new library, more out-patient space, more clinical bed space, and more teaching rooms. Returns from the men overseas indicate that the majority want postgraduate and/or graduate training before returning to practice. The Minnesota State Medical Association and the American Medical Association have sent questionnaires asking for specific details of the men's post-war plans. Colonel P. Long, in a recent issue of the Journal of the American Medical Association, points out that a man who has been out of practice for a year requires from three to six months of indoctrination before he can be of value clinically. Many of our men have been away for four years on administrative and field assignment and will need our assistance. If we prepare for all we must also take care of our nurses, technicians, and other medical associates. Many places now occupied by student nurses in Powell Hall will be given over to graduate nurses taking specialty training.