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

Sulfanilamide and Sulfapyridine Therapy

Volume XI | Friday, October 27, 1939 | Number 4

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
UNIVERSITY OF MINNESOTA

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V. GOSSIP 66

Published for the General Staff Meeting each week during the school year, October to May, inclusive.

Financed by the Citizens Aid Society

William A. O'Brien, M.D.

I. LAST WEEK

Date: October 20, 1939

Place: Recreation Room
Powell Hall

Time: 12:15 to 1:30 P.M.

Program: Movie: "Great Heart"

Otogenic Meningitis
Jerome A. Hilger
Eric H. Loenholdt
R. E. Priest
Emmet W. Milhaupt

Discussion
J. A. Hilger
J. C. McKinley
T. E. Carmody
Horace Newhart
L. R. Boies

Movie: "Mastoidectomy"
L. R. Boies

Present: 146

Gertrude Gunn
Record Librarian

- - - -

II. MOVIE

Title: "Life Begins Again"

Released by: Bell Telephone Co.

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III. ANNOUNCEMENTS

1. WEDDINGS

Eleanor Mary Smith and Clarence Dennis (Surgery) - June 17, 1939.

Evelyn Shaffer (Social Service) and John Dexter Lyon - June 24, 1939.

Ruth Moulton (Psychiatric Social Service) and Dr. William Andberg (University Farm) - July, 1939.

Kathryn Buntin and Richard Jessup (Iowa) - August 19, 1939.

Adrienne Odlaug (Radiology) and Clayton Mullen - September 9, 1939.

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2. BABIES

Carl Durant Craft is receiving callers on Station 54. He arrived on October 24.

- - -

3. WARNER F. BOWERS, M.D.,Ph.D.Surg.
and
JOHN C. KENNEDY, M.D.

Announce their Association for the Continuance of the Practice of the late
Dr. C. R. Kennedy

Practice limited to General Surgery

Offices: 620 Omaha Loan and Building Association Building
Omaha, Nebraska

Phone Atlantic 6290

- - - -

4. RAY F. COCHRANE, M.D.

The Doctors of
The NICOLLET CLINIC
Minneapolis

Announce the Association of

DR. RAY F. COCHRANE

Obstetrics and
Diseases of Women

July 1, 1939

IV. SULFANILAMIDE AND SULFAPYRIDINE THERAPY

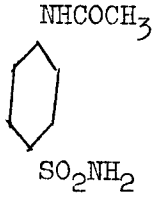
Edmund B. Flink
Wesley W. Spink

The purpose of this review is to summarize our clinical experience with sulfanilamide and sulfapyridine at the University of Minnesota Hospitals during the past two years. No attempt will be made to present a comprehensive review of the voluminous literature on this subject. For those interested, we have appended a list of the more important monographs and papers.

At the present time, there are three sulfonamide compounds used in the treatment of infectious diseases. Besides sulfanilamide and sulfapyridine, there is neoprontosil, which is a trade name for a more complex compound. We have had little experience with the latter drug. There is no reason to believe that it has any advantage over sulfanilamide. A better understanding of the action of these drugs is dependent upon knowledge of their chemical structure, and some of the changes they undergo in the body.

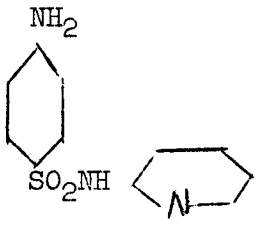
Sulfanilamide has the following structural formula:

In the body, the drug undergoes changes. Varying proportions (usually 10%) are conjugated, probably in the liver, to form acetylated sulfanilamide.

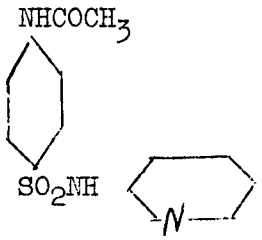


This conjugated product is inactive against organisms, and is excreted in the urine. The remainder of the compound is probably oxidized.

Sulfapyridine has the following formula:

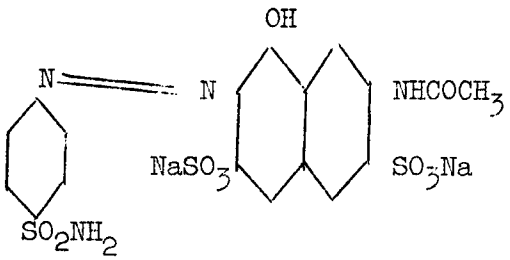


This compound is also conjugated in the body to form

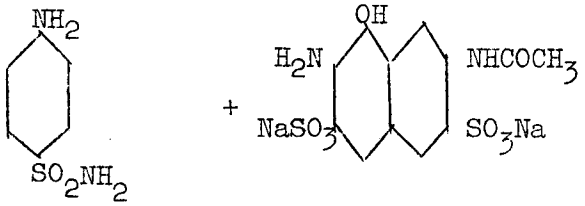


Many individuals conjugate large amounts of the absorbed drug (up to 80%) which not only is inactive, but may be precipitated in the urinary tract. The remainder of the drug is probably oxidized to form a more active compound or compounds.

Neoprontosil has the following structure:



This compound is inactive against bacteria, and in the body it is reduced to form two compounds, one of which is free sulfanilamide.



It is believed that action of neoprontosil on bacteria is dependent upon the formation of free sulfanilamide, and hence has no advantage over sulfanilamide.

SULFANILAMIDE THERAPY

During the past two years, observations have been made on 120 patients receiving sulfanilamide. Most of these patients were treated on the medical service, but cases from every service in the hospital are represented in this group.

Dose of sulfanilamide:

It is difficult to draw hard and fast rules. Our main objective has been to maintain a blood level of free sulfanilamide between 5 and 10 mgs., and in some instances 15 mgs. per 100 c.c. except for patients with urinary tract infections. The optimum blood level for the various types of bacterial infections must still be worked out.

Sulfanilamide is administered either orally in 5 grain tablet form, or subcutaneously with the purified powder dissolved in warm saline. The drug need not be, and should not be, given intravenously. Only rarely have the sulfanilamide crystals been placed directly in open wounds. Sodium bicarbonate has been administered to patients receiving sulfanilamide to prevent acidosis.

The oral administration for adults has been as follows: 3.6 grams (60 grs.) to 4.8 grams (80 grs.) were given for the initial dose, and then 0.6 grams (10 grs.) to 1.2 grams (20 grs.) every 4 hours night and day. Depending upon the clinical response, the dose has been gradually reduced, until the drug was given only in small amounts during the day. In some instances, larger doses have been necessary because of poor absorption and low sulfanilamide blood levels. On occasion, the tablets have been crushed, suspended in water, and given through a nasal tube. The fluid intake has been limited to about 3000 c.c. a day. About 10 grains of soda bicarbonate were given with each dose of sulfanilamide.

Sulfanilamide

A. By mouth (for Children)

1. Usual dose is 0.1 gm. per kg. (gr. 3/4 per lb.) per 24 hr.

2. The dose for the first day, especially as an heroic measure, may be 2 to 2.5 times this amount.

B. Subcutaneous (for Children)

1. 0.8% sulfanilamide crystals in saline, amount given calculated as above. Given in divided doses every 8 to 12 hours.

C. In urinary tract infections (for Children)

1. 0.05 gm. per kg. (gr. 3/8 per lb.) per day is usually all that is necessary.

Subcutaneous administration for adults

Sulfanilamide has been dissolved in hot physiological saline solution so that a final concentration of 0.8% of sulfanilamide has been obtained. A 1/6 molar solution of sodium lactate may be used as a solvent which will aid in the prevention of acidosis. We have found this to be an important precaution when treating diabetic patients who have an acidosis. In the initial porenteral injection from 4 to 8 grams have been given in 500 to 1000 c.c. of saline. Then every 8 hours thereafter, 1/3 of the calculated 24 hour dose has been given (usually 250 c.c. of an 0.8% sulfanilamide solution).

Correspondingly smaller doses are given to children on the basis of the calculated oral dosage.

As soon as sulfanilamide therapy has been instituted, it is necessary to watch for the appearance of toxic manifestations, and also know what level of the drug in the blood has been attained. In this connection, we have carried out, and recommend the following procedures:

1. Blood sulfanilamide determination at the end of the first 24 hours of therapy, and then one every other day during the acute stage

of the illness. As the dose is being reduced, and the patient improves, such determinations are not necessary.

2. Hemoglobin determinations and leukocyte counts should be done at least every other day as long as the patient receives the drug, and for several days thereafter. If the leukocyte drops below normal, daily differential and leukocyte counts should be done.

3. Measure the daily intake and output of fluids.

4. Toxic manifestations, and indications for stopping the administration of the drug will be discussed later.

Dose for urinary tract infections:

The recommended dose varies considerably. Fluids should be limited so that the daily output is about 1000 c.c. This allows a higher concentration of the drug in the urine. In some instances, as little as 20 grains a day in divided doses, has produced a favorable response. In most cases, we have given 3 to 5 grams a day in divided doses. The drug need not be given during the night. If a favorable clinical response is to be obtained it takes place within 4 to 5 days after therapy has been started. Failures in obtaining sterile urine cultures have been due to: the presence of organisms that resist the action of the drug; inadequate concentrations of the drug in the urine; obstruction along the urinary tract. Poor renal function has not been a contraindication for the administration of sulfanilamide, but it must be given very cautiously in small doses.

RESULTS OF SULFANILAMIDE THERAPY

1. Hemolytic streptococcus infections:

   A. Bacteremia

      Beta hemolytic streptococcal infections will be considered first. Table I shows the results with patients having a bacteremia. The accepted mortality rate for this type of infection before the introduction of sulfanilamide was approximately 70%. The mortality rate in our group treated with sulfanilamide is 36.3%.

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TABLE I

Eleven Cases of Hemolytic Streptococcus Bacteremia Treated with Sulfanilamide.

Age	Sex	Complication	Total Dose (In Grams)	Outcome
56	M	Wound Infection	12	Death
35	M	Pneumonia, Arthritis, Nephritis, Cellulitis	25	Recovery
5 Wks.	M	Pneumonia	13	Death
35	M	Cellulitis, Thrombophlebitis	27.5	Recovery
54	F	Pneumonia	11	Death
44	F	Empyema, Ca. of Cervix	36	Recovery
50	M	Gangrene of Leg	24	Death
27	F	Wound Infection. Arthritis	56	Recovery
17	F	Pneumonia	75	Recovery
53	M	Gangrene of Leg	174.6	Recovery
18	M	Mastoiditis	35.8	Recovery

B. Pneumonia and Meningitis

Only 4 patients with a hemolytic streptococcal pneumonia were treated, and no conclusions concerning the results of therapy are warranted. These patients often recover without specific therapy.

Three patients with streptococcal meningitis were given sulfanilamide. Again no conclusion can be drawn, except 2 to 3 patients recovered, which would be very unusual before the era of sulfanilamide therapy.

TABLE II

Streptococcal Pneumonia

Age	Sex	Complication	Total Dose (In Grams)	Outcome
23	F	Empyema	13	Recovery
28	F	"	40	Recovery
21	M	Empyema	33.7	Death
36	M	Empyema	8	Recovery
		Streptococcal Meningitis		
6	M	Sinusitis	51.8	Recovery
65	M	Endocarditis	12	Death
4	M	Otitis Media	30	Recovery

C. Miscellaneous hemolytic streptococcal infections. These include erythema nodosum, lymphangitis, tonsillitis, gangrene of extremity (diabetic) and scarlet fever (with antitoxin). The number of cases prevents any conclusive statement as to the therapeutic effect of sulfanilamide. All the patients recovered, and improved while the drug was being administered.

2. Gonococcal Infections

We have treated 8 patients with gonococcal complications, especially polyarthritis. We have not included in this report any results in patients having only a urethritis or cervicitis. Sulfanilamide, and possibly sulfapyridine are the best specific therapeutic agents available for gonococcal arthritis. In the treatment of gonococcal arthritis, it has been found essential to administer these drugs very early in the disease. In a few instances we have combined sulfanilamide therapy with artificially induced fever, (Kettering hypertherm), because the response with sulfanilamide alone was not wholly satisfactory. It is suggested that if at the end of one week of treatment with adequate doses of sulfanilamide (blood levels between 5 and 10 mgs. per 100 c.c.), there has been no marked improvement of the arthritis, then fever therapy should be undertaken. Table III includes patients with gonococcal infections treated at the University Hospitals. In the 7 of 8 patients with local lesions from which gonococci were recovered before treatment, cultures taken at the conclusion of therapy, were sterile for gonococci.

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TABLE III

Gonococcal Infections Treated with Sulfanilamide

Age	Sex	Lesion	Complication	Additional R_x	Dose	Result
41	F	Polyorthritis	Pelvic Inflam.		24.6	Marked Improvement
9	F	Conjunctivitis	Vaginitis		26.5	"
25	M	Polyarthritis	Urethritis	Fever (5x)	180.	"
18	F	Polyarthritis			141.	"
22	M	Polyarthritis	Urethritis	Fever (7x)	56.	"
*31	M	Polyarthritis	Urethritis	Fever (7x)	163.	"
22	F	Polyarthritis	Cervicitis		84.6	"
19	F	Polyarthritis	Cervicitis		71.	"

*Treated with Sulfapyridine, after previous attempt with Sulfanilamide.

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3. Brucellosis (Undulant Fever)

Five patients have been treated. Because of the experience of others, one patient received fever therapy in addition to sulfanilamide. It is our impression, from our small experience and a review of the literature, that the best results will be obtained in those patients treated early in the course of their disease. While no definite statement can be made at this time, it is recommended that sulfanilamide be given in adequate doses for 10 days to 2 weeks. If at the end of that time, there is little or no improvement, then combined sulfanilamide and fever therapy should be tried, providing the patient's con-

dition will allow the use of induced fever. Table IV is a resume' of patients treated.

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TABLE IV

Patients with Brucellosis
Treated with Sulfanilamide

Age	Sex	Duration of Disease	Additional R_x	Dose (In Grams)	Result
28	M	Acute (4 days)		18.	Cure
37	M	3 Yrs.	Fever (6x)	262.3	No Improvement
54	M	3 Months		72.5	Temporary Improvement
66	F	5 Months		32.	Improvement
23	M	5 Days		7.8	Improvement

4. Staphylococcal Sepsis

Because a considerable number of patients with staphylococcal sepsis seek treatment at the University Hospitals, we have given sulfanilamide to several of these patients. Dr. John Paine, of the Department of Surgery, collaborated in this study. We were mindful of the fact that most investigators state sulfanilamide is of no value in the treatment of deep seated lesions due to staphylococcus. Most people agree that the drug is useful in the treatment of urinary tract infections due to this organism. From our observations, we do not believe that sulfanilamide is of much benefit in the treatment of staphylococcal sepsis. One of us (Dr. Spink) has found that in vitro the bacteriostatic and bactericidal action of sulfanilamide is increased at higher than body temperature. Following this observation, a few patients have been treated with sulfanilamide and induced fever (Kettering hypertherm). Further clinical observations are necessary before definite conclusions can be made concerning the results of treating patients with this combined therapy. In Table V are recorded the results of treating patients with infections due to the staphylococcus aureus. Similar results were obtained in patients with sepsis due to staphylococcus albus.

TABLE V

Patients with Sepsis Due to the Staphylococcus Aureus Treated with Sulfanilamide

Age	Sex	Lesion	Complication	Additional R_x	Total Dose (In Grams)	Result
48	F	Abscess of Buttock	Reticulo-endotheliosis		24.	No Improvement
23	M	Cellulitis of Neck	" "		(91.8 (66.3	Improvement
57	M	Bacteremia	Furuncle, lung abscess	100,000 units Antitoxin	25.	Death
19	M	Acute Bact. Endocard.			20.	Death
44	M	Acute Osteo.			31.8	No Improvement
51	M	Chronic Osteo.			142.0	" "
26	M	Bacteremia	Furuncle		36.0	Recovery
18	M	Chronic Osteo.		Fever (14x)	275.0	Improvement
16	F	Chronic Osteo.		Fever (5x)	207.0	"

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v. Kidney Infections

Too few patients have been observed by us, from which to draw definite conclusions. The impression was gained, however, that sulfanilamide is of definite value in the treatment of pyelonephritis, but the drug must be administered cautiously. This is also true for cystitis.

6. Subacute Bacterial Endocarditis

We have had an unusual opportunity to treat several patients who had subacute bacterial endocarditis. While we have one patient of the series, who is apparently cured or in a remission, we do not believe that sulfanilamide is of much value in this form of sepsis. Because there is little to offer in the form of therapy for these patients, we believe at present that they should be given large amounts of the drug over a long period of time. Sulfanilamide offers a hope in the prevention of this disease. It is well known that there is often a temporary bacteremia following the extraction of teeth or tonsillectomies. If these procedures are to be carried out in patients with valvular lesions of the heart, they should receive sulfanilamide for a day before the operation, and for 2 or 3 days after. The blood level of sulfanilamide should be maintained around 5 mgs. per 100 c.c. The results of sulfanilamide therapy in patients with subacute bacterial endocarditis are tabulated in Table VI.

TABLE VI

Treatment of Subacute Bacterial Endocarditis with Sulfanilamide

Age	Sex	Lesion	Organism	Dose (In Grams)	Result
35	F	Mitral	Staph-Albus	259.5	Temporary Improvement - Death
18	F	Potent Duct. Arteriosus	Strept. vir.	191.6	? Cure
36	M	Mitral & Aortic	Strept. vir.	65.	No Improvement
25	F	Patent Interventricular Septum	Strept. vir.	53.2	"
23	F	Mitral	Strept. vir.	42.6	"
27	F	Patent Duct. Arteriosus	Strept. vir.	95.8	"
22	F	Mitral	Strept. vir.	69.9	"
66	M	Mitral	Strept. vir.	102.5	"
40	F	Patent Duct. Arteriosus	Strept. vir.	26.7	"
26	M	Mitral & Aortic	Strept. vir.	36.	"
40	M	Aortic Mitral	Strept. vir.	53.	"
29	F	Mitral	Strept. vir.	131.6	"
31	F	Aortic	Strept. vir.	64.	"
20	F	Patent Interventricular Septum	Strept. vir.	276.	"

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y. Miscellaneous Diseases

A. Pneumococcus Pneumonia

Only a few patients with pneumococcus pneumonia have been given sulfanilamide. One individual, a 52 year old male, with a type VII pneumococcus, lobar, pneumonia and bacteremia (63 colonies per cubic centimeter of blood) recovered following the administration of 58.4 grams of sulfanilamide. Another patient with a type IV pneumococcus meningitis recovered after receiving sulfanilamide and type-specific rabbit serum. It is generally accepted that sulfapyridine is much more effective in the treatment of pneumococcus infections, and we have abandoned the use of sulfanilamide.

B. Ulcerative Colitis

Two patients received sulfanilamide with no improvement.

C. Meningococcus Meningitis

One adult recovered completely following treatment with sulfanilamide.

TOXIC MANIFESTATIONS OF SULFANILAMIDE

We have observed a number of toxic signs and symptoms which may be directly attributed to the action of sulfanilamide. It should be pointed out that the number of patients with these manifestations are out of proportion to the total number of patients that we have observed. Our attention has been called to these signs of toxicity in patients on the various services, whereas many other patients receiving the drug were not seen and are not included in this general review.

1. Central Nervous System

Common manifestations encountered were headache, dizziness, mental depression, lethargy. No instances of peripheral neuritis were seen. In Table VII are tabulated a group of patients with outstanding mental aberrations. It is of interest that these developed following the administration of the drug for only a few days. All symptoms rapidly subsided following the withdrawal of sulfanilamide.

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TABLE VII

Toxic Manifestations of Central Nervous System Due to Sulfanilamide

Age	Sex	Manifestation	No. of days Drug Was Given	Total Dose (In Grams)
26	M	Psychosis	8	32.
35	M	Psychosis	2	10.6
23	M	Delirium	4	19.3
18	M	Psychosis	2	10.
30	F	Delirium	4	15.

2. Gastro-Intestinal Tract

Nausea, and occasionally vomiting occurred after the ingestion of sulfanilamide. Anorexia was another disturbing factor, especially in patients with malnutrition. We have only encountered diarrhea in one patient, which was directly related to the drug.

3. Cyanosis

This was a common finding on our patients. Studies carried out on the bloods of several of these patients by Drs. Watson, Vigness, and Spink prove that methemoglobin is the cause of the cyanosis. Rarely, sulfhemoglobin is the cause. We do not believe that this cyanosis should necessitate withdrawal of sulfanilamide. When a 1% solution of methylene blue was given intravenously to several of the patients having cyanosis, the latter promptly disappeared within 30 minutes. However, when sulfanilamide therapy was continued, the cyanosis reappeared. The per cent of circulating hemoglobin converted to methemoglobin has been quantitated by spectrocolorimetric and spectrophometric methods. In Table VIII, these values are given. Cyanosis was marked in these patients. In most of the patients, the cyanosis was moderate, and the per cent of methemoglobin was between 5 and 10%.

TABLE VIII

Per Cent of Circulating Methemoglobin in Patients Receiving Sulfanilamide

Age	Sex	Per Cent of Methemoglobin	Dose of Drug (In Grams)
31	F	31.	11. in 3 days
5 Wks.	M	23.	0.4 " 1 "
6	M	13-19	46.6 " 8 "
60	M	25-30	14. " 3 "

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4. Acidosis

The carbon dioxide combining power of the bloods of many of the patients was determined after large amounts of the drug had been given. In no instance was there any appreciable degree of acidosis due to sulfanilamide. These findings may be attributed, in part, to the fact that practically all of the patients received sodium bicarbonate.

5. Drug Fever

Four patients were observed who had a marked rise in temperature due to sulfanilamide. This manifestation usually appears after the drug has been given for several days. At times, it is difficult to determine whether the rise in temperature is due to the infection or the drug. If the temperature approaches normal following the exhibition of sulfanilamide and then after several days begins to rise, although the patient has improved clinically, one may assume that the patient has drug fever. The administration of sulfanilamide should be omitted immediately. If the drug is given again, there may be a recurrence of the drug fever. The following sequence of events was observed in a patient on the obstetrical service: A 39 year old female with fever and a urinary tract infection was given 16 grams sulfanilamide over a period of 4 days. Her temperature became normal. Nine days after the initial dose she was given a total of 4 grams over a period of 24 hours. At the end of this time, her temperature rose to 104°F. She had chilly sensations, headache, nausea, an urticarial eruption, and cyanosis. Sulfanilamide therapy was stopped, and all signs of toxicity disappeared. One week later she was given 10 grains of sulfanilamide, three times, in one day. Following this, her temperature rose to 103°, and she had a headache, nausea, vomiting, a blotchy erythema of the face, and cyanosis. These signs again abated when the drug was omitted.

6. Skin Eruptions

Seven patients had skin eruptions caused by sulfanilamide. Like drug fever, this toxic manifestation usually occurs after the compound has been given for several days. It appears abruptly and is full-blown within a few hours. The type most commonly observed by us and others was a maculo-papular eruption. We have also observed the following eruptions: scarlatiniform, purpuric, urticarial, exfoliating, vesicular, and erythematous eruptions. Intense pruritus may accompany the rash. Angioneurotic edema has also been described. Ambulatory patients receiving sulfanilamide may develop a dermatitis of those parts of the skin exposed to sunlight. Sulfanilamide therapy should be discontinued at once in any patient exhibiting an eruption. If the drug is to be given to the patient subsequently it must be used with caution, as eruptions may appear again with small doses.

7. Jaundice and Liver Dysfunction

Under Dr. C. J. Watson's direction, we have been interested in the effect of sulfanilamide upon hemoglobin metabolism and liver function. The number of cases that we have seen with derangement of liver function or increased destruction of erythrocytes is not a true indication of its frequency because of this interest on our part. Nevertheless, the results of our study permit us to conclude that these forms of toxicity are more frequent than we are led to believe from reports in the literature. Time and space do not permit us to give a detailed report of our findings.

Jaundice occurring in patients receiving sulfanilamide may be of the retention type or the regurgitation type. In several patients evidence was obtained that both were present, but in others one or the other type predominated. Laboratory evidence for the retention type occurring frequently was based on the following: decrease of the hemoglobin and erythrocyte levels (hemolysis); increase in the amount of circulating bilirubin; increase in the excretion of urobilinogen in the feces; increase in the reticulocyte levels; rise in the icteric index; indirect Van den Bergh reaction of the serum. The regurgitation type, which is due to damage to the bile capillaries, was also frequently encountered with the following findings: direct Van den Bergh reaction of the serum; increase in the excretion of urobilinogen in the urine.

Twenty patients had jaundice, which in itself is evidence of liver dysfunction. In 17 there were increased excretions of urine urobilinogen (3.5 mgs. per day is the upper limit of normal). Values up to 200 and 300 mgs. a day were not uncommon. In the majority of patients the values approached and became normal after sulfanilamide therapy was discontinued. In 2 patients, the jaundice was severe with icterus indices of 361 and 122. These individuals had peritonitis following perforation of the gastro-intestinal tract. Pure sulfanilamide crystals were placed in the peritoneal cavity at time of operation, which accounted in part for the extensive liver damage. While both patients expired, death was not due to the hepatic damage alone, as an extensive peritonitis was present in both. The plasma bilirubin levels were increased in 9 patients (1 mg. per 100 c.c. is normal).

8. Hemolytic Anemia

In practically all of our patients receiving therapeutic doses of sulfanilamide (60 grains daily) increased destruction of red blood cells occurred. In a study of several patients it was found that the anemia was of the macrocytic hypochromic type. In other words, there was not only an increased destruction of erythrocytes, but also a disturbance in hemoglobin formation. The degree of blood destruction varies; occasionally an acute hemolytic anemia occurs. We have observed this in 11 patients. If administration of the drug is discontinued and the patients are transfused, they recover. This was true in our patients. Acute hemolytic anemia usually manifests itself only after the drug has been given for several days. In Table IX we have recorded the drop in hemoglobin percentage and the doses of sulfanilamide. Others have shown that if patients developing acute hemolytic anemia are given sulfanilamide a second time, the same precipitous drop in erythrocytes will occur with very small doses.

TABLE IX

Patients with Hemolytic Anemia due to Sulfanilamide

Age	Sex	Disease	Total Dose (In Grams)	Total No. Days Before Develop. Anemia	Hemoglobin (%)	
					Before Sulfanilamide	After Sulfanilamide
35	F	Suppurative Arthritis	16.0	3	81	20
41	F	Gonococcal Arthritis	22.6	5	75	46
63	M	Pyelonephritis	13.0	5	76	49
78	M	Epididymitis	42.6	10	70	50
13	M	Erythema Nodosum	66.0	11	97	55
20	F	Mastoiditis, Meningitis	31.0	10	41	22
35	M	Hemolytic Streptococcus Bacteremia	26.2	10	71	46
23	M	Cervical Cellulitis	62.3	13	62	36
78	F	"Diabetic" gangrene	38.7	10	81	50
44	M	Chronic Osteomyelitis	31.8	7	61	32
16	F	Chronic Osteomyelitis	60.0	10	76	46

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9. Leukopenia and Neutropenia

We have observed only three patients having a marked drop in the total number of leukocytes and a neutropenia. Fortunately no patients have developed agranulocytosis at the University Hospitals. In one patient the leukocytes dropped from 19,100 to 2,000 per cu. m.m., and the polymorphonuclear neutrophiles dropped from 80% to 9% after receiving 78.6 grams of sulfanilamide; he did not develop an anemia and recovered completely. A second patient entered the hospital having 3,700 leukocytes per cu. m.m. and 27% polymorphonuclear neutrophiles after receiving only a small dose of sulfanilamide by his physician for a urinary tract infection. A third patient was given about 1,100 grains of the drug by a physician over a period of eight weeks for a streptococcal sore throat. She entered the hospital with a leukocyte count of 2,600 cells per cu.mm. and 18% polymorphonuclear neutrophiles. She was quite ill on entry; she had oral lesions due to anaerobic organisms, but she recovered.

In a few patients we have administered the compound in large doses to patients with a marked leukopenia without a further drop in the leukocyte count. We do not believe that a leukopenia is a contraindication to starting sulfanilamide therapy.

In several patients the leukocyte counts became appreciably elevated while receiving sulfanilamide.

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SULFAPYRIDINE THERAPY

A total of 75 patients have been treated with sulfapyridine. The drug has been used primarily in the treatment of patients with pneumococcus pneumonia, staphylococcal sepsis, and, in a few instances, patients with bacterial endocarditis and gonococcal infections.

Sulfapyridine has certain disadvantages as a therapeutic agent when compared to sulfanilamide. It is more insoluble, and for this reason, it is

erratically absorbed from the gastro-intestinal tract. An illustration of this erratic absorption is obtained from the following observations: two adult women of approximately the same age and weight were each given four grams of sulfapyridine by mouth and four hours later one gram. Six hours after the initial medication the level of free sulfapyridine in the blood of one was 8.5 mgs. and in the other, 51.3 mgs. per one hundred cubic centimeters of blood. Another disadvantage is that although the compound may be absorbed, the major portion may be conjugated in the body. This conjugated form is ineffective against bacteria, and may be precipitated in large quantities in the urinary tract causing hematuria, nitrogen retention, and pain. One further disadvantage is that sulfapyridine causes nausea and vomiting much more often than sulfanilamide. These symptoms are due to the action of the drug on the central nervous system. Because of the foregoing disadvantages of sulfapyridine, we believe at the present time that the compound should only be used in the treatment of patients with pneumococcus pneumonia, staphylococcus sepsis, infections due to Bacillus mucosus capsulatus (Friedlander) infections, and possibly gonococcal infections.

Dose of sulfapyridine (adult): For pneumococcus infections, it is desirable to have a level of free sulfapyridine in the blood of 4 mgs. or more per 100 cc. of blood. Because of erratic absorption intelligent therapy cannot be carried out without quantitating the amounts of free drug in the blood. At the University Hospitals the amounts of free and conjugated sulfapyridine are determined. To obtain satisfactory blood levels at the present time two grams of sulfapyridine are given in the initial dose and then one gram every four hours night and day. An equal amount of sodium bicarbonate is given to alkalanize the urine, which theoretically should prevent or lessen the precipitation of the acetylated form in the urinary tract. Within 12 to 24 hours the blood level is determined. Since sulfapyridine apparently has an antipyretic action, the administration of the drug should not be discontinued when the temperature becomes normal but continued for several more days. After 48 hours of drug therapy one gram may be given every six hours for a few days, and than one half gram three to four times a day. It is our impression that the drug has been discontinued too early in many instances.

According to Dr. I. McQuarrie of the Department of Pediatrics, the following doses of sulfapyridine are used in children:

A. For pneumonia:

1. 0.25 gm. per kg. (gr. 1-3/4 per lb.) per 24 hours for 48 hours. Then decrease the daily dose 1/3 each day for 3 days.

2. The administration of the 24-hour dose at one time is sometimes used as an alternative method.

Postoperative patients with nasal suction may be given sulfapyridine by crushing the tablets and suspending the compound in water and injecting it with a syringe through the nasal tube. The tube is then clamped off for one or two hours, and in most cases satisfactory levels in the blood are obtained.

For staphylococcus sepsis larger amounts of the drug are probably necessary. Levels of 10 mgs. or more of free sulfapyridine in the blood should be established and maintained for several days.

The effective dose for gonococcal sepsis has not been clearly established, but it appears to be less than that required for sulfanilamide.

Recently monohydrate sodium sulfapyridine has been used intravenously. This salt is more soluble than sulfapyridine. It is given intravenously only. Because of the extreme alkalinity of the solution (pH 10 - 11) great care should be exercised so that none of the

solution escapes into the tissues because of the danger of obtaining a slough. The dose is 0.06 gram per killogram of body weight. The compound is dissolved in enough warm distilled water to give a final concentration of five per cent (5%). It is then injected very slowly. From 2/3 to 1/2 of the initial dose may be given every twelve hours for a few days. It is highly desirable to give the drug orally with sodium bicarbonate after one or two intravenous injections.

RESULTS OF SULFAPYRIDINE THERAPY

1. Pneumococcus Infections

In Table X we have presented our results in the treatment of pneumococcus infections. Of these 22 patients, 8 died. Four of these fatal cases had a pneumococcal meningitis; another had an advanced form of multiple myeloma; and one had a pneumococcal peritonitis.

It is to be noted that we used specific antipneumococcal serum in addition to sulfapyridine. This combined therapy was carried out because we desired to give the patients every advantage of specific therapy. At the present time, we believe that only sulfapyridine should be given for a period of 24 to 36 hours, in the treatment of pneumococcal pneumonia. If at the end of this time, the patient has not shown satisfactory clinical improvement, therapeutic doses of specific serum should be administered. Combined serum and sulfapyridine therapy should be instituted immediately in patients with pneumococcal meningitis.

We have found sulfapyridine especially valuable, in the treatment of patients with atypical pneumococcal pneumonia. In these cases, there is only a small area of consolidation, they are not seriously ill, and a low-grade fever is present. Serum therapy in these patients is often of doubtful value, and it is expensive.

Occasionally patients are encountered who have evidence of pneumonia, but from whom a specific biological agent causing the consolidation cannot be obtained. Sulfapyridine should be given to these patients. We have done this with 11 patients, and all except one recovered. During the past winter, a number of patients were seen and treated, who had an atypical pneumonia probably caused by a filterable virus. Sulfapyridine did not appear to effect the clinical course of these patients.

TABLE X

Pneumococcus Infections Treated with Sulfapyridine

Age	Sex	Type	Lesion	Complication	Dose (Grams) in No. Days	Additional R_x (Serum)	Result
40	M	IX,VII	L.L.L.		25 - 4 days	Type VII 150,000 U.	Recovery
57	M	VIII	L.L.L.		26 - 4 days		Recovery
53	M	IX	Diffuse	Postoperative	(8 - 2 days (2.4 I.V.	Type IX 60,000	Death
43	M	I	R.V.L.	Bacteremia	4 - 1 day	Type I 160,000	Recovery
35	M	III	R.V.L. R.A.L.		13.5-3 days	Type III 140,000	Recovery
87	M	III	R.V.L.		10 - 2 days		Recovery
55	M	VI,III	R.L.L. L.L.L.	Bacteremia (III) Peritonitis Post-operative	10 - 2 days	Type VI 100,000 Type III 100,000	Death
17	F	XXII	R.L.L. L.L.L.		14 - 3 days		Recovery
19 Mos.	M	IV	L.L.L.	Pleural Effusion	10 - 5 days		Recovery
57	M	III	R.L.L.		8 - 1 day	Type III 100,000	Recovery
34	F	V	R.V.L. R.L.L.	Bacteremia	32 - 6 days	Type V 150,000	Recovery
36	M	VII,III	L.V.L.	Cardiac Failure	30 - 5 days	Type VII 100,000 Type III 120,000	Recovery
62	M	V	R.L.L.		11.5-3 days		Recovery
25	M	III	R.L.L.	Post-operative	30 - 5 days	Type III 100,000	Recovery
38	M	XXIX	R.L.L. L.L.L.	Multiple Myeloma	13 - 3 days		Death
75	F	III	R.V.L.		18 - 3 days	Type III 200,000	Death
17	M	VIII	R.L.L.	Post-operative	13 - 3 days		Recovery
37	M	XXIX	R.L.L.	Massive Collapse R.L.L.	28 - 5 days		Recovery
35	F	III	Meningitis		4 - 1 day	Type III 89,000	Death
52	M	III	Meningit.	Bacteremia	8 - 2 days	Type III 300,000	Death
6 Mos.	F	XXV	Meningit.	Bacteremia	26 - 16 days	Type XXV 25 c.c.	Death
61	M	III		Meningitis	6 - 1 day	Type III 80,000	Death

2. Staphylococcal Sepsis

We have had an unusual opportunity to treat 15 patients with this type of sepsis, due to the staphylococcus aureus. The results are shown in Table XI. Some of these were given sulfanilamide initially. It is significant that seven patients had a bacteremia, and all except one recovered. These results are quite encouraging when it is realized that the mortality rate, in general, for patients with staphylococcal bacteremia is around 75%. Sulfapyridine is of doubtful value in the treatment of patients with osteomyelitis, except those having a bacteremia. At the present time, we believe that sulfapyridine is the best single chemo-therapeutic agent in the treatment of severe staphylococcal sepsis

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TABLE XI

Patients with Staphylococcal Sepsis due to Staphylococcal Aureus Treated with Sulfapyridine and Sulfanilamide

Age	Sex	Lesion	Complication	Dose (Grams) in No. Days	Additional R_x	Result
14	F	Osteomyelitis	Bacteremia, Meningitis, Lung Abscess	35 - 10 days		Death
17	M	Perineph. Abscess		24 - 5 days		Recovery
39	F	Osteomyelitis		20 - 5 days		?Improvement
45	M	Meningitis	Post-operative	84 - 12 days	54gms.PABS	Recovery
51	M	Osteomyelitis		104 - 13 days	101.8gm."	No Change
12	M	Osteomyelitis		12 - 3 days	42 " "	No Change
12	M	Osteomyelitis	Bacteremia	21 - 7 days	6.7" "	Recovery
18	M	Osteomyelitis		25 - 6 days	292 " " Fever 14x	Improvement
42	M	Arthritis	Bacteremia	72 13 days		Recovery
15	M	Osteomyelitis	Bacteremia	76.5-10 days		Recovery
33	M	Subphrenic Abscess	Bacteremia	34 - 10 days		Recovery
61	M	Arthritis	Decubitus Ulcer	28 - 8 days		Death
35	M	Osteomyelitis		68 - 17 days		No Change
24	M	Osteomyelitis	Bacteremia	57 - 10 days	112gm.PABS	Recovery
45	M	Carbuncle	Diabetes	204 - 44 days	82 " "	Recovery

3. Bacterial Endocarditis

Three patients with sub-acute bacterial endocarditis have been treated. In two, there was no improvement, and in the third, temporary improvement. Further trial of the drug in this disease is necessary before drawing any conclusions concerning its merit.

Two patients were treated having an acute bacterial endocarditis due to the staphylococcus aureus. Both patients died, the drug having no effect on the clinical course.

TOXIC MANIFESTATIONS OF SULFAPYRIDINE

1. Central Nervous System

The outstanding signs of toxicity in patients receiving sulfapyridine are nausea and vomiting, which are of central origin, since they occur when the drug is given intravenously. About 35% of our patients had these manifestations. In several they were so severe that the drug therapy had to be discontinued. It is of considerable importance that often patients tolerated the drug poorly following the initial doses, but after it had been omitted for one or two doses, or the dose temporarily decreased, they were able to take it for several days without having nausea and vomiting.

Sulfapyridine also causes mental depression and dizziness, but no patients with psychoses were encountered.

2. Cyanosis

This is uncommon in patients receiving sulfapyridine. We have observed only one individual where the cyanosis could be attributed to sulfapyridine. Spectroscopic analysis of the blood revealed the presence of a small amount of methemoglobin.

3. Acidosis

No patients were seen who had acidosis from the drug.

4. Drug Fever or Skin Eruptions

Although we have not observed drug fever or skin eruptions in any of our patients, they have been reported by several investigators.

5. Jaundice and Liver Dysfunction

No patients developed jaundice, and no instance of liver dysfunction has been encountered. It is our impression that sulfapyridine is less toxic for the liver than sulfanilamide.

6. Hemolytic Anemia

Only one patient developed an appreciable degree of hemolysis of the erythrocytes. His hemoglobin dropped from 75% to 46% after receiving 68 grams of sulfapyridine in 17 days.

7. Leukopenia and Neutropenia

No serious decline of the total leukocyte level or of the polymorphonuclear neutrophiles was observed in any of the patients, with but one exception. In this patient, the leukocytes decreased from 9,300 to 1,450 cells per cu.mm., while the polymorphonuclear neutrophiles reached a level of 58%. She had received 168 grams of the drug for 29 days.

8. Hematuria

Only two patients had a gross hematuria, and they were given the drug intravenously. We have one patient whose kidney function has been markedly reduced following the administration of a large quantity of sulfapyridine, but he had a bilateral lesion of the kidney due to the staphylococcus aureus. In this instance, it is difficult to determine the role that the drug played in reducing the kidney function.

There have been several reports of calculi forming in the urinary tract due to precipitated acetylsulfapyridine.

In general, with the exception of the nausea and vomiting, and kidney disturbance, sulfapyridine appears to be less toxic than sulfanilamide.

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V. GOSSIP

Surgeon John R. Paine goes to Omaha to address the Omaha Midwest Clinical Society today as part of a symposium on preoperative and postoperative treatment with Ralph H. Major, John S. Lundy, Lloyd H. Mousel, Walter G. Maddock, and William L. Estes, Jr. Urologist C. Donald Creevy goes to Chicago to appear on the program of the Interstate Postgraduate meeting. Pediatrician Irvine McQuarrie goes to China, January 1, for a six-months' teaching assignment at Peiping. He will join the list of Minnesotans who have gone there for this purpose or who have come from that school to this....Everyone will be pleased to know that former head technologist, Gleva Erskine, has "gone domestic" in her new home in Grand Rapids, Minnesota. She was in the other day with a brand new baby. Her husband, Gordon Erskine, is practicing medicine there....This is "Hard of Hearing" week. Our own chief otolaryngologist, Horace Newhart, has played a very active part in promoting educational and testing programs for the hard of hearing. His work which was at first local has now assumed national proportions....This is the time of year when neurosurgeon William Thomas Peyton and his hunting cronies go to the north woods for their annual vacation. As usual, both game and stories will be brought back....An unusual course will be held at the Center for Continuation Study during the week of the federal Thanksgiving. It is being conducted as a regional offering for the central area by the Federal Security Agency of U. S. Office of Education. The title will be "Rehabilitation Training." Many of our medical men will appear on the program. These will include Asher A. White (physical diagnosis), E. T. Evans and C. C. Chatterton (orthopedic appliances), M. J. Shapiro (cardiac disabilities), Horace Newhart and H. E. Hartig (hearing aids), and E. S. Mariette and H. E. Hilleboe (rehabilitation of the tuberculous); other contributions from the University of Minnesota staff will concern themselves with Clinical Procedures and Guidance, Guidance Techniques, Vocational Adjustment for Adult Workers, Occupational Opportunities, and Case Work Methods....This is National Pharmacy Week. Dean Emeritus Wulling needed restoratives when told that his picture was being used by one of the chain drug stores as part of a window display.... Surgeon Charles B. Craft, who joined the ranks of fathers this week takes second place to none for enthusiasm. Prior to the birth of his son, he did a little practicing on the neighbors' children. The young man will be taken south in due time to inspect the land of his ancestors. The parents are receiving the congratulations of their many friends who have watched the budding family since the cavalcade to southern Minnesota a few years back....A number of Minnesota physicians will be invited to attend a special course in Premature and Newborn Care at the Center for Continuation Study in February. The conference will be sponsored by the Division of Maternal and Infant Hygiene of the State Department of Health....There is a considerable delegation from the University Hospitals seated in the back rows of the second section in the north stands of the Stadium. The distance from the field makes it difficult for the officials to hear us but we try just the same. The group was very busy last Saturday at the Ohio State game..... Neuroroentgenologists Cornelius G. Dyke, Columbia, and Merle C. Sosman of Harvard will join John D. Camp of the Mayo Foundation and Harold O. Peterson of our staff as the leaders of the faculty group for the Continuation Course in Neurologic Roentgenology at the Center for Continuation Study, November 13, 14, and 15, 1939....One of Dr. Peterson's subjects will be "Platybasia," a term known to few people? There will be a double-header at the Center, November 6 - 11 when Neurology and Cardiology will be offered in two groups at the same time....One of our guests at the Fiftieth Anniversary Celebration wrote of "our evident pride in our accomplishments" which might be taken in one of several ways.

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