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

Present Status Of Sulfonamide Therapy

Volume XII Friday, January 24, 1941 Number 13

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

Volume XII | Friday, January 24, 1941 | Number 13

INDEX

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: January 17, 1941

Place: Recreation Room
Powell Hall

Time: 12:15 - 1:10 p.m.

Program: Movie: "Home Early"

Roentgen Pelvic Morphology and Pelvimetry
A. Louis Dippel

Discussion

Present: 139

Gertrude Gunn
Record Librarian

- - -

II. MOVIE

Title: "Bone Trouble"

Released by: R-K-O

- - -

III. ANNOUNCEMENTS

1. CENTER FOR CONTINUATION STUDY

Hospital Administration -
January 27 - February 1

Uterine Bleeding -
February 3 - 5

Medical Social Service -
February 13 - 15

Dietetics -
February 20 - 22

2. ANATOMY SEMINAR

Winter Quarter, 1941.

Meetings held in room 226 Institute of Anatomy, on Saturdays at 11:30 a.m. All interested are cordially invited to attend.

Jan. 25 - Hal Downey:
The occurrence of giant lymphocytes and other immature lymphocytes in the blood in infectious diseases.

J. W. Rebuck:
Hematogenous components of the tubercle.

Feb. 1 - A. T. Rasmussen:
The tuber cinereum and hypophysis after cauterization of the infundibulum in man.

R. G. Grenell:
The corpus striatum.

Feb. 8 - L. J. Wells:
Experimental cryptorchidism in a wild rodent (Citellus).

E. S. Hegre:
Regenerative growth and endocrines.

Feb. 15 - R. F. Blount:
Function of transplanted hypophyses in respect to nerve supply.

R. A. Huseby:
Histology of the bone marrow.

Mar. 1 - C. A. Noback:
The structure of bone.

F. E. Johnson:
The blood supply of the sphincter of Oddi in the newborn.

Mar. 8 - R. L. Merrick:
The supraoptic nucleus of the dog.

T. F. Dougherty:
Studies on microglial cells.

- - -

IV. PRESENT STATUS OF SULFONAMIDE THERAPY

Wesley W. Spink
David W. Hilger

At the Staff Meeting of October 27, 1939, we reviewed the status of chemotherapy in the University Hospitals up to that time. Particular attention was given to the use of sulfanilamide, sulfapyridine, and sodium sulfapyridine. We also outlined the toxic manifestations of these compounds. During the intervening time, tremendous advances have taken place. Sulfathiazole and its sodium salt have been introduced into the therapy of certain diseases. Extensive investigations relating to the action of the sulfonamide compounds have been reported. More precise information concerning the toxicity of the drugs is available. We have revised the indications for the use of each of the compounds. We have explored the therapeutic possibilities of different methods of administration and endeavored to standardize the schedule of doses. Studies pertaining to the local use of the compounds have been extended. Finally, the development of war medicine has emphasized the prophylactic value of the drugs.

During the past three years, observations have been made in over 1000 patients treated with the various compounds at the University Hospitals. We have reviewed over a thousand papers bearing on this subject of chemotherapy. It is obvious that this mass of material cannot be incorporated within this Staff Bulletin. We shall confine ourselves to a discussion of the following: the indications for the use of each of the sulfonamide compounds; methods of administration and the doses; a comparative evaluation of the toxic manifestations; and clinical results that we have obtained in certain infectious diseases. No attempt has been made to include a review of the literature.

Although this report originates in the Division of Internal Medicine, it has been made possible only through the cooperation of all the Services in the Hospital. Many of our studies have been carried out with members of the Divisions of Surgery and Pediatrics. Since the intelligent therapeutic application of each of these compounds is dependent upon precise bacteriological data, we have been most fortunate to have had the aid of Dr. Milton Levine, Director of the Bacteriology Laboratory. Knowledge of the absorption and excretion of these drugs requires accurate determinations of the concentrations of the compounds in body fluids, and Dr. Gerald Evans and his staff have been most helpful in this respect.

We are now in a position to detail a few therapeutic principles relative to the sulfonamide compounds that are of considerable help to the clinician. They are as follows:

1. The therapeutic activity and toxic effects of the compounds are related to their chemical structures.

2. The chemicals are to a large extent specific in their anti-bacterial action. The choice of a drug for therapeutic trial will therefore depend upon the microorganism responsible for the infection.

3. The action of the compounds is primarily one of bacteriostasis. In some instances, it is bactericidal for small numbers of organisms. While the action of the drugs is independent of the immune mechanism, there is often a more efficient destruction of organisms in the presence of immune substances. Therefore, the administration of specific bacterial antibodies and antitoxins is sometimes desirable and necessary.

4. The antibacterial activity of the compounds is diminished or completely inhibited under certain circumstances. A factor or factors present in body fluids and tissues, bacterial extracts, purulent exudates, necrotic tissue, etc., are known to be inhibitory. The precise mechanism of this inhibitory action is not known, but may at times explain therapeutic failures.

5. The compounds are absorbed for the most part from the small intestine and excreted to a great extent in the urine. The maintenance of effective concentrations of the compounds in body fluids and tissues are dependent upon divided doses given day and night. The intake and output of fluids must be recorded.

6. Microorganisms may become "drug fast" or insensitive to the bacteriostatic action of the compounds and still retain their invasive and antigenic characteristics. This explains, in part, therapeutic failures.

Neoprontosil

We have had little experience with this compound at the University Hospitals. Opinion is still divided as to whether or not the antibacterial activity of neoprontosil is dependent upon the sulfanilamide that is liberated. Theoretically, a 5 per cent solution of neoprontosil would yield about 22 grains of sulfanilamide per 100 cc. Reports would indicate that even in severe infections 60 cc. of a 5 per cent solution of neoprontosil controlled the disease. In other words, only 13.2 grains of sulfanilamide would then be available. It is difficult to believe that such small quantities of sulfanilamide would be solely responsible for the clinical effect. Neoprontosil appears to be effective against the same microorganisms as sulfanilamide, particularly hemolytic streptococci. It is less toxic than sulfanilamide. Neoprontosil may be indicated in the therapy of the less severe hemolytic streptococcal infections, in low-grade urinary tract infections, ulcerative colitis, ocular infections, and in those individuals who tolerate sulfanilamide poorly. It also might be utilized in chronic diseases where it is desirable to give small doses over a long period of time. In the treatment of ulcerative colitis, Brown and his associates at the Mayo Clinic have advocated the following adult doses: 4 to 5.5 gms. divided into five equal parts are given orally in each 24 hours for 10 to 14 days. One gram is given before each meal, another at 10:00 p.m., and one gram at 3:00 a.m. After an interval of 7 to 14 days, approximately one-half the foregoing doses may be given for another 10 to 14 days. The compound has also been used in the treatment of brucellosis. In general, whenever neoprontosil is used instead of sulfanilamide, the doses should be equal to or greater than for the latter compound. Because of our limited experience with the compound, we are excluding any further discussion of it.

Sulfanilamide, Sulfapyridine and Sulfathiazole

In the material to follow, particular attention is given to our results with sulfathiazole. However, it is first necessary to review the indications for the use of the individual compounds. To facilitate this recapitulation, we have listed those diseases for which sulfanilamide has been found to be effective (Table I). In Table II, are presented the conditions for which sulfapyridine has been found to be effective, and Table III summarizes the present status of sulfathiazole. Table IV includes those diseases for which the sulfonamide compounds in general are of doubtful value. We state that they are of "doubtful value" in these conditions because in some instances conflicting reports have appeared in the literature, and in other conditions too small a number of patients have been treated from which to draw definite conclusions. In Table V are listed those diseases for which the sulfonamide compounds appear definitely ineffective.

In an attempt to clarify the indications for each of the compounds, we present in Table VI the preferential use of each drug. There may not be complete agreement in this tabulation, and no doubt it will have to be rearranged following future experience, but it reflects the results of our own experience and those of others recorded in the literature.

Doses and Methods of Administration

This phase of the subject must be dispensed with in general terms.

Sulfanilamide

In serious infections for which sulfanilamide is indicated, the blood concentration should be maintained between 5 and 10 mgs. per 100 cc., and in some instances at 15 mgs. The dose in adults necessary to sustain this level is from 10 to 15 grains given every 4 hours. From 45 to 60 grains are given as an initial dose. The doses for infants and children are roughly 3/4 to 1 grain per pound of body weight per 24 hours. From 1/3 to 1/2 this 24 hour dose may be given as an initial dose. It is generally agreed that a solution of sulfanilamide is absorbed more efficiently from the small intestine than is the tablet form. The desired blood level is attained more quickly. Therefore, the initial dose could be given as an aqueous suspension of sulfanilamide tablets or crystals, and subsequent doses administered in tablet form. Sulfanilamide may be given parenterally by the subcutaneous route using a 1 per cent aqueous solution. There is little necessity for introducing it intravenously. A solution of the compound is effectively absorbed from the rectum, and resort may be made to this avenue when necessary. We do not recommend the intrathecal administration of sulfanilamide since it passes readily into the cerebrospinal fluid from the blood. The concentrations attained in the spinal fluid are about three-fourths of that found in the blood.

In milder infections, and especially urinary tract infections, the doses may be smaller than the foregoing.

Sulfapyridine

The doses of sulfapyridine approximate those of sulfanilamide, but the drug is irregularly absorbed from the intestinal tract. In the treatment of pneumonia, it is desirable to maintain a blood level of from 3 to 5 mgs. of the free form per 100 cc. In severe cases, it may be desirable to reach levels of 10 mgs. This means that in the adult an initial dose of 2 to 4 grams is given and then 1 gram every 4 hours. The doses are then gradually reduced over a period of several days. Infants and children require about 1 grain per pound of body weight per 24 hours, with a maximum dose of 80 grains for a 24-hour period. In some conditions, as staphylococcic bacteremia and pneumococcic meningitis, the concentration should be considerably higher (10 - 15 mgs. per 100 cc). Bullowa recommends the oral use of sodium sulfapyridine. An initial dose of 4 to 5 grams is given and then 1 gram every 4 hours thereafter. In this manner the required blood concentration is reached more quickly and maintained. Apparently, the alkalinity of the compound does not act in a detrimental way on the gastrointestinal tract.

Sodium sulfapyridine, a more soluble compound, may be administered intravenously to those individuals who are unable to take the drug by mouth or to those persons seriously ill and in whom an adequate blood and tissue concentration of the compound is desired as quickly as possible. A solution of the salt may be effectively given by hyperdermoclysis. For the latter purpose, 1000 cc. of a physiological saline solution containing the drug in a concentration of 0.3 to 0.7 per cent are allowed to run in at the rate of 200 to 300 cc. per hour. This permits a satisfactory blood concentration for 24 to 36 hours. It is an effective way to treat pneumonia even though the patients are able to take the drug by mouth. From our own experience and that of others, we can conclude that the alkalinity of this concentration of sodium sulfapyridine does not irritate the subcutaneous tissue.

Although some clinicians advocate the rectal administration of sulfapyridine and its sodium salt, we do not subscribe to it. Whether or not sodium sulfapyridine should be given intrathecally is a matter of divided opinion. This will be commented upon shortly relative to the treatment of pneumococcic meningitis. While it has been recommended that sodium

bicarbonate should be prescribed along with sulfapyridine, we do not use it routinely. There is no conclusive evidence available showing that the simultaneous administration of alkalies prevents the precipitation of either the free or conjugated forms of sulfapyridine along the urinary tract of human beings.

Sulfathiazole

This compound requires essentially the same dosage schedule as advocated for sulfapyridine. In some instances we have had to use slightly larger doses because the drug is excreted more rapidly than sulfapyridine.

Sodium sulfathiazole is applicable for intravenous administration. The indications for giving the drug by this route are the same as for sulfapyridine. We have had considerable success with this form of therapy in patients with postoperative pneumonia. The incidence of nausea and vomiting is much less than has resulted with the use of sodium sulfapyridine. We have not given sodium sulfathiazole by hyperdermoclysis. In a few patients capsules containing the sodium salt have been administered orally. We are not prepared to conclude at this time that the oral use of sodium sulfathiazole has any advantage over the less soluble tablets.

Toxic Manifestations of the Sulfonamide Compounds

Due consideration must be given to the toxic effects of the sulfonamide drugs. For clinical purposes, we have outlined these effects for sulfanilamide, sulfapyridine, and sulfathiazole (Table VII) and have also indicated the conditions which demand immediate cessation of therapy. One must appreciate that sulfathiazole is more likely to result in skin eruptions with or without drug fever. Fortunately in most instances these do not appear until the compound has been given for several days and in the meantime the beneficial effects have been obtained in the therapy of pneumonia. We have treated approximately 400 patients with sulfathiazole at the University Hospitals and evidence of nerve damage has been demonstrated in only two patients. In one patient, the injury was very slight, and in the second, function eventually returned. The renal function of the patients receiving sulfathiazole must be observed very carefully. We have encountered five patients who developed oliguria as a result of sulfathiazole, and death in one patient was definitely attributable to this complication. Renal failure due to sulfathiazole is more likely to occur in elderly patients, particularly if their fluid intake is not maintained at a level so that a daily output of 800 to 1000 cc. of urine results.

Clinical Results with the Sulfonamide Compounds

Space does not permit an exhaustive analysis of our results with sulfonamide therapy at the University Hospitals. We have been particularly interested in treating patients having certain infectious diseases, and a brief review of our results to date are presented.

Brucellosis

This illness constitutes one of the most difficult diseases to diagnose correctly and is most refractory to treatment. We have now treated with sulfanilamide 13 patients in whom we felt reasonably certain that the diagnosis was accurate. The results are presented in Table VIII. In 9 individuals, there was definite improvement following the exhibition of sulfanilamide. It will be noted that patient 5 received only 5 grams of sulfanilamide because of drug sensitivity, and he then was given 6 treatments of artificially induced fever in the Kettering hypertherm. There was complete amelioration of his symptoms following this treatment, and we considered him as having recovered completely. In general, we do not believe that fever therapy, with or without sulfanilamide, is of much value for brucellosis. Two patients were better immediately after receiving sulfanilamide for several days, but then

a relapse took place. One patient failed to obtain any benefit after taking a considerable amount of sulfanilamide on two occasions, once simultaneously with artificially induced fever. Patient 13 had a most unusual brucella infection, that of subacute bacterial endocarditis. Only temporary improvement appeared to occur while he received sulfathiazole during one period, and then sulfanilamide at another time. This is the second proven case of brucella endocarditis that we have had during the past three years, and the fifth proven case that has been recorded in all the medical literature.

Our policy in treating these patients is to give enough of the drug so that a blood concentration of 5 to 10 mgs. per 100 cc. is maintained for several days. The duration of therapy depends upon the patient's response. Whether vaccines and specific serum should also be employed is a matter of conjecture in our limited experience, but they merit further trial. Sulfapyridine and sulfathiazole should also be given further consideration.

Subacute Bacterial Endocarditis

We have had the opportunity to treat a most unusual number of patients with this disease. A total of 32 individuals composes the largest group of patients on record treated in a single institution. It is because of this that we have carefully analyzed the results found in Table IX. All three compounds have been evaluated. Heparin was administered intravenously to two individuals who received sulfonamide compounds at the same time. The outcome was disastrous in both cases. Heparin was the cause of sudden death due to cerebral hemorrhage. This has occurred in other clinics, and we deprecate its further use in this disease.

The results were uniformly disappointing with the exception of one patient. Patient 2 has recovered completely, and was still well two years after treatment. When last seen she was pregnant and in good health. Although only 1 out of 32 patients has recovered, we are of the opinion that sulfonamide therapy holds out a small chance of recovery and should be offered to any patient. A review of the literature indicates that there are now several recorded recoveries. It is recommended that the compounds be given in those doses which will maintain a blood concentration of 5 to 10 mgs. per 100 cc. for long periods of time.

Staphylococcic Bacteremia

In association with Dr. John Paine of the Division of Surgery and Dr. Arild Hansen of the Division of Pediatrics, we have treated with sulfathiazole 17 patients having staphylococcemia. It is now generally accepted that sulfathiazole is the drug of choice in the treatment of this type of infection. Sulfapyridine is also an efficient therapeutic agent. The results in this series of cases are shown in Table X. Pathogenic, coagulase positive strains were isolated from the blood streams of these patients one or more times. Therapy with sulfathiazole should be aimed at maintaining a blood concentration of 5 mgs. or more of the compound per 100 cc. Some individuals were given sulfanilamide before receiving sulfathiazole. This was offered to these patients before it was learned that they were suffering from a staphylococcemia. In 2 patients sulfapyridine therapy was necessary after sulfathiazole had been given because of the appearance of skin eruptions due to the latter compound. Three patients received in addition to sulfathiazole, staphylococcus antitoxin. In using antitoxin it is necessary to administer large doses intravenously. To older children and adults, a total of 100,000 units the first day is necessary. The requirements for subsequent doses are dependent upon the condition of the patient. Another important part of therapy in this infection is the prompt surgical drainage of primary or metastatic foci. On the basis of in vitro experiments, Osgood has advocated the combined use of neoarsphenamine and sulfathiazole in the treatment of staphylococcic infections. Since the arsenical leaves the blood rapidly after being injected intravenously, he recom-

mends repeated small doses of neoarsphenamine. The suggested total daily requirements are based on the formula $\frac{\text{body weight in Kgs.}}{150}$ = grams of neoarsphenamine. This amount is divided into 3 or 4 spaced doses and given the first day. The second day's dose is three-fourths of the total first day dose given in divided amounts. This is repeated every day until the temperature is normal. He suggests that the concentration of sulfathiazole in the blood should be maintained between 8 and 10 mgs. per 100 cc. No clinical reports are available concerning the value of this combination. In patient 15 we attempted this form of therapy along with staphylococcus antitoxin. The blood stream did not become sterile, the patient died, and postmortem examination revealed an extensive pneumonia with multiple abscesses.

Sulfathiazole is of doubtful value in the treatment of well-established, localized staphylococcic lesions such as carbuncles and osteomyelitis. However, in severe cases, its administration may prevent the spread of the infection to healthy tissue or maintain a sterile blood stream.

Pneumonia

Sulfathiazole is now used almost routinely on the medical services of the University Hospitals in the treatment of pneumococcic pneumonia. We believe it to be equally as effective as sulfapyridine and it provokes less nausea and vomiting. Our results in a series of 50 patients with pneumonia have been highly satisfactory. In thirty-eight of these patients pneumococci were isolated from the sputa, while we were unable to obtain the etiologic agent in the remaining twelve. The types of pneumococci encountered are presented in Table XI. There were three patients with a pneumococcic bacteremia. All recovered. The only death in the entire group occurred in an elderly male who died three months after the onset of his pneumonia. Multiple lung abscesses had developed.

In cooperation with Dr. Carol Bellis we have analyzed the results of therapy with sulfathiazole in 22 patients having postoperative pneumonia. Sodium sulfathiazole was given intravenously to 10 of these patients. Two of the patients died, but the outcome was unrelated to the pulmonary lesions. When using sodium sulfathiazole, 2 to 3 grams are given intravenously as an initial dose, and then 1 gram every 6 to 8 hours. It is advisable to start oral therapy as soon as possible.

Pneumococcic Meningitis

During the past 3 years, 9 patients having this infection have been treated. Three patients recovered. The results for the group are presented in Table XII. Although we have treated 3 patients with sulfathiazole, it is recommended that in the future sulfapyridine should be used. At the present time, there are at least three methods of treating patients having pneumococcic meningitis.

Method I

This is the routine that we advocate and is a modification of the method of Finland and his associates at the Boston City Hospital. Sodium sulfapyridine should be given intravenously so that levels of 10 to 15 mgs. per 100 cc are attained in the cerebrospinal fluid. This means blood concentrations of 15 to 20 mgs. per 100 cc. Type-specific rabbit serum should be given intravenously to control the bacteremia. Depending upon the size of the patient, the total dose will vary from 20,000 to 300,000 units. Daily lumbar punctures should be performed during the acute stages of the illness. Foci should be drained surgically. After the initial dose of immune serum has been given, blood should be withdrawn, allowed to clot, and the serum injected intrathecally after an appropriate amount of spinal fluid has been removed. This should be repeated at daily intervals until the spinal fluid remains sterile. In this manner, fresh human complement and antibodies are introduced into the spinal canal. Sulfapyridine should be continued for several days up to two weeks after sterile cerebrospinal fluid is

obtained in order to prevent a relapse.

Method II

Flippin and Lockwood at the Philadelphia General Hospital believe that the infection can be adequately treated without introducing immune serum directly into the spinal canal. They recommend sulfapyridine intravenously and orally, maintaining a blood concentration above 8 mgs. per 100 cc. Immune serum is given intravenously.

Method III

Neal, Appelbaum and Jackson of the New York City Department of Health utilize the intrathecal administration of sodium sulfapyridine and immune serum. Their opinion is to be respected because of their extensive experience. They inject between 100,000 and 300,000 units of immune rabbit serum intravenously. Sulfapyridine is administered orally. From 10 to 15 cc. of a 2 per cent solution of sodium sulfapyridine are mixed with 10,000 to 20,000 units of immune serum and injected intrathecally each time a lumbar puncture is done. They state that this concentration of sulfapyridine does not irritate the meninges.

Urinary Tract Infections

Neoprontosil and sulfanilamide have proved to be valuable adjuncts in the therapy of infection of the urinary tract. We have found that sulfathiazole is also an effective agent. In Table XIII are presented the results in a group of patients treated in cooperation with Dr. C. D. Creevy. Treatment was successful in 13 of the 20 patients. The urine may be rendered sterile with sulfathiazole in those individuals in whom sulfanilamide therapy has been unsuccessful. It is particularly effective in the treatment of those infections due to staphylococci, B. proteus, Alpha streptococci, and E. coli. Our policy has been to administer 1 gram of sulfathiazole every 4 to 6 hours. In some instances 1 gram was given three times a day. The total dose varied between 14 and 60 grams with an average of about 30 grams. It is significant that many of the toxic reactions that follow the administration of sulfathiazole were seen in this group.

The Local Use of Sulfonamide Compounds

There is no doubt that in properly selected patients sulfanilamide and sulfathiazole are very effective when applied directly to infected tissue. Such a procedure is logical provided adequate drainage is maintained. In association with Dr. John Paine of the Division of Surgery, we have established that sulfathiazole is of considerable merit for localized staphylococcic lesions. The crystals are placed upon or in the tissue suspended in sterile water, in cod liver oil, or in a cod liver oil ointment. Recent reports from England indicate that sulfanilamide should be applied directly to amputation stumps and areas where gas gangrene has been proved to exist or is suspected.

Future Investigations

At the present time, we are investigating the merits of a new compound, sulfanilyl guanidine. Marshall and his associates at Johns Hopkins University contend that this compound may be very effective in the therapy of typhoid fever and dysentery. It reduces the bacterial flora of the intestinal tract, and there are possibilities that it will be a therapeutic aid to the surgeon for both pre- and postoperative use in patients undergoing resections of the colon and rectum. Sulfadiazine is another sulfanilamide derivative that we are prepared to investigate from a clinical viewpoint.

Table I

Diseases for which Sulfanilamide has been Found to be Effective

1. Beta hemolytic streptococcic infections (Lancefield Group A -- also B.C.G.)

   Erysipelas
   Tonsillitis
   Otitis Media
   Mastoiditis
   Septicemia
   Meningitis
   Scarlet Fever
   Pneumonia
   Empyema
   Adenitis
   Cellulitis
   Suppurative Arthritis
   Peritonitis
   Puerperal Sepsis
   Impetigo
   Osteomyelitis

2. Alpha hemolytic streptococcic infections (Strept. virid.)

   Meningitis
   Bacteremia

3. Meningococcic Infections

   Meningitis
   Bacteremia

4. Urinary tract infections (cystitis, prostatitis, pyelonephritis)

5. Gonococcal Infections

   Male and female gonorrhea and complications
   Ophthalmia
   Arthritis
   Iritis

6. Brucellosis

7. Trachoma

8. Lymphopathia venereum

9. Chancroid

10. Pneumococcic infections

11. Clostridium welchii (gas gangrene)

12. Pyelophlebitis

13. Staphylococcic infections

14. Skin infections

    Impetigo
    Pustular dermatitis
    Sycosis
    Pemphigus

15. Ulcerative colitis

Table II

Diseases for which Sulfapyridine Has Been Found to be Effective

1. Beta hemolytic streptococcal infections
2. Alpha hemolytic streptococcal infections
3. Meningococcic infections
4. Urinary tract infections
5. Gonococcal infections
6. Trachoma
7. Brucellosis
8. Lymphopathia venereum
9. Pneumococcic infections
10. Staphylococcic infections
11. Skin infections
12. Tetanus
13. Influenzal meningitis
14. Friedlander's infections
15. Chancroid

Table III

Diseases for which Sulfathiazole Has Been Found to be Effective

1. Beta hemolytic streptococcal infections
2. Alpha hemolytic streptococcal infections
3. Urinary tract infections
4. Gonococcal infections
5. Pneumococcic infections
6. Staphylococcic infections
7. Impetigo (Staph. and Strept.)

Table IV

Diseases for Which Sulfonamide Compounds Are of Doubtful Value

1. Acute Lupus erythematosus
2. Malaria
3. Tularemia
4. Fungus infections (actinomycosis)
5. Typhoid-dysentery infections
6. Plague
7. Choriomeningitis
8. Psittacosis

Table V

Diseases for Which Sulfonamide Compounds are Ineffective

1. Tuberculosis
2. Blastomycosis
3. Rocky Mountain spotted fever
4. Acute rheumatic fever
5. Atrophic or rheumatoid arthritis
6. Influenza
7. Common cold
8. Small pox (may prevent secondary infections)
9. Human equine encephalitis
10. Rabies
11. Poliomyelitis
12. Anthrax
13. Erysipelothrix
14. Syphilis
15. Trypanosomiasis
16. Diphtheria (including carriers)
17. Measles and Pertussis (may prevent secondary complication)
18. Infections mononucleosis
19. Trichinosis

Table VI

Preferential Use of Sulfonamide Compounds

Disease	Sulfanilamide	Sulfapyridine	Sulfathiazole
1. Beta hem. strept. infects. (Groups A, B, C, G)	1	3	2
2. Alpha hem. strept. infects.	2	3	1
3. Meningococcic infects.	2	1	3
4. Gonococcic infects.	3	2	1
5. Brucellosis	1	2	3
6. Trachoma	1	2	?
7. Lymphopathia venereum	1	2	?
8. Chancroid	1	2	?
9. Pneumococcic infects.			
Pneumonia	3	2	1
Bacteremia	3	2	1
Peritonitis	3	1	2
Meningitis	2	1	3
Otitis media	3	1	2
Mastoiditis	3	1	2
10. Staphylococcic infects.			
Bacteremia	3	2	1
Meningitis	2	1	3
Pneumonia	3	2	1
Tissue sepsis	3	2	1
11. Gas gangrene	1	2	?
12. Influenzal meningitis	2	1	?
13. Friedlander infects.			
Bacteremia	?	1	?
Pneumonia	?	1	?
14. Tetanus	?	1	?
15. Urinary tract infects. (cystitis, pyelonephritis,etc.)			
Staph. aur. and Albus	2	3	1
Beta hem. strept.			
Groups A, B, C, G	1	3	2
Group D	0	?	1
Alpha hem. strept.			
Strept. vir.	2	3	1
Strept. faecalis	0	?	1
E. coli	2	3	1
Proteus	2	3	1
Pyocyaneus	2	3	1
B. influenza	1	?	?
16. Skin infects.			
Impetigo			
Staph.	2	3	1
Strept.	1	3	2
Pustular dermatitis	2	3	1
Pemphigus vulgaris	?	1	?
Sycosis	1	2	?
17. Ulcerative colitis	1	?	?

Table VI (Continued)

Preferential Use of Sulfonamide Compounds

Disease	Sulfanilamide	Sulfapyridine	Sulfathiazole
18. Typhoid-dysentery infects.			
B. typhosus	2	?	1
Shigella dysenteriae	0	?	1
Shigella paradysenteriae (Flexner, Strong, Panama, etc.)	0	?	1
S. paratyphi (paratyphosus A)	2	?	1
S. Schottmuelleri (paratyphosus B)	2	?	1
S. Suipestifer (Paratyphosus C)	2	?	1
S. enteriditis (B. enteriditis gaertner)	2	?	1
19. Fungus actinomycosis	1	?	?
20. Acute lupus erythematosus	1	?	?
21. Tularemia	1	?	?
22. Psittacosis	?	1	2

Table VII

Toxic Manifestations of Sulfonamide Compounds

Manifestation	Incidence			Clinical Significance & Procedure
	Sulfanilamide	Sulfapyridine	Sulfathiazole	
Cyanosis	Common	Uncommon	Doubtful	Not serious
Nausea, vomiting	Uncommon	Common	Common	If severe, discontinue
Headache, dizziness	Common	Uncommon	Rare	Not serious
Psychoses, delerium	Uncommon	Rare	Not reported	If severe, discontinue
Acidosis	Common	Not reported	Not reported	Give sod. bicarb. or lactate sol.
Drug fever	Common	Uncommon	Common	May be serious -- discontinue
Dermatitis	Common	Uncommon	Common	May be serious -- discontinue
Hepatic damage	Common	Rare	Doubtful	Serious, discontinue
Jaundice	Common	Rare	Rare	May be serious -- discontinue
Acute hem. anemia	Occasional	Rare	Not reported	Serious, discontinue & transfuse
Moderate anemia	Common	Common	Occasional	Not serious, transfer if necessary
Leucopenia	Common	Common	Occasional	May be serious -- discontinue
Granulopenia	Occasional	Occasional	Rare	May be serious -- discontinue
Agranulocytosis	Occasional	Occasional	Not reported	Serious, discontinue
Leucocytosis	Uncommon	Rare	Not reported	Not serious alone
Hematuria	Rare	Common	Common	If macroscopic, discontinue
Oliguria & Nitrogen retention	Not reported	Occasional	Occasional	Serious - discontinue, alkalinize urine, force fluid
Arthritis	Not reported	Not reported	Occasional	May be serious -- discontinue
Conjunctivitis & Scleritis	Not reported	Not reported	Occasional	May be serious -- discontinue
Stomatitis	Not reported	Rare	Rare	May be serious -- discontinue
Neuritis	Rare	Not reported	Rare	May be serious -- discontinue
Splenomegaly	Occasional	Not reported	Occasional	Usually occurs with drug fever and dermatitis, discontinue
Hepatomegaly and Ascites	Rare	Not reported	Not reported	May be serious -- discontinue
Thrombocytopenic Purpura	Not reported	Rare	Not reported	Serious - discontinue.

Table VIII

Brucellosis Treated with Sulfanilamide

Case No.	Age Sex	Duration of Illness	Specific Diagnostic Tests	Total Dose (grams)	Comment
1	28 M	4 days	Aggls 1:1280 Skin test-pos. Bl. cult. 0	10.3	Complete recovery
2	37 M	5 yrs.	Aggls. 1:320 Skin test - pos. Bl. cult. 0	1st admission 138 2nd - 112 plus 6 fever rxs.	No improvement
3	66 F	5 mos.	Aggls. 0 Skin test - pos. Bl. cult. 0	30.6	Complete recovery
4	28 M	5 mos.	Aggls. 1:640 Skin test - pos. Bl. cult. 0	38	Complete recovery
5	37 M	6 mos.	Aggls. 1:320 Bl. cult. staph.	5. 6 fever Rxs.	Sensitive to sulfanil Complete recovery
6	30 F	5 mos.	Aggls. 1:640 Skin test - pos. Bl. cult. 0	32	Drug fever & pupura Complete recovery
7	30 M	3 wks.	Aggls. 1:1280 Skin test - pos. Bl. cult. 0	48	Complete recovery
8	54 M	4 mos.	Aggls. 1:640 Skin test - pos. Bl. cult. 0	77	Immediate improvement Recurrence 1 mo. later
9	35 M	11 days	Aggls. 0 Skin test - pos. Bl. cult. 0	75	Complete recovery
10	25 M	7 mos.	Aggls. 1:2580 Skin test - pos.	72	Marked improvement (Spondylitis)
11	23 M	1 week	Aggls. 1:1280 Skin test - pos. Bl. cult. 0	12 Triple typhoid Immune serum	Immediate improvement Recurrence 7 mos. later
12	42 F	2 mos.	Aggls. 1:320 Skin test - pos. Bl. cult. B. Abort.	53	Blood sterile Marked improvement Subsequent thyroidectomy
13	36 M	5 mos.	Aggls. 1:1280 Skin test -Neg. Bl. cult. B. Abort.	Sulfath. 39 Sulfanil. 217	Died Subacute bact. end.

Table IX

Subacute Bacterial Endocarditis

No. Age. Sex	Cardiac Lesion	Bacteriology Cols./cc.	Therapy	Comment
1-35 F.	Mitral Stenosis	S. albus 4 to 11	Sulfanil. 259.5gm.	Improvement-death*
2-18 F.	Patent duct. art.	S. vir. 30 to 200	Sulfanil. 191.6gm.	Recovery - 2 yrs.
3-20 F.	Patent intervent. Septum	S. vir. 1 to 14	Sulfanil. 276. gm.	No improvement
4-25 F.	Patent intervent. Septum	S. vir. 10	Sulfanil. 53.2 gm.	Blood sterile, temp. normal, died
5-31 F.	Bicuspid aortic valve	S. vir. 100	Sulfanil. 64 gm.	Blood sterile, temp. down, died*
6-23 F.	Mitral stenosis	S. vir. 200	Sulfanil. 42.6 gm.	No improvement,died
7-36 M.	Mitral stenosis Aortic regurgitation	S. vir. 65	Sulfanil. 87.7 gm.	No improvement,died
8-29 F.	Mitral stenosis	S. vir. 360	Sulfanil. 131.6gm.	No improvement,died*
9-66 M.	Mitral stenosis	S. vir. 150	Sulfanil. 102.5gm.	No improvement,died*
10-70 M.	Aortic regurg.	S. vir. 200	Sulfanil. 33.87gm.	Blood sterile, died
11-40 F.	Patent duct.art.	S. vir. 100	Sulfanil. 267 gm.	Blood sterile,died
12-27 F.	Patent duct.art.	S. vir. 1 to 181	Sulfanil. 95.8 gm.	No improvement,died
13-20 F.	Mitral Stenosis	S. vir.	Sulfapyr. 30 gms. Heparin	No improvement Sudden death (Heparin)*
14-16 F.	Mitral Stenosis	S. vir. - 28	Sulfathiaz. 52 gm.	No improvement,death
15-55 M.	Mitral Stenosis	S. vir.	Sulfanil. 41 gms. Sulfathiaz. 53 gm.	No improvement
16- 9 F.	Patent intervent. septum	S. vir.	Sulfapyr. 24 gms. Na para nitro benzoate 31.5gms.	No improvement
17-59 M.	Mitral stenosis Aortic stenosis & regurg.	S. vir.	Sulfanil. 36 gms.	No improvement,died*
18-22 F.	Mitral stenosis	S. vir. - 250	Sulfanil. 13	No improvement,died*
19-25 F.	Mitral Stenosis	S. vir, S.aureus Hem. strept.	Sulfapyr. 219 gm. Sulfanil. 45 gms.	Marked improvement Died*
20-36 F.	Mitral Stenosis Aortic regurg.	S. vir.	Sulfanil. 59 gm. Sulfathiaz. 46 gm. Sulfapyr. 44 gm.	Slight improvement Died*
21-27 F.	Mitral stenosis Aortic regurg.	S. vir.	Sulfanil. 110 gm. Sulfapyr. 24.5 gm.	No improvement Died*
22-26 M.	Aortic Stenosis and regurg.	S. vir.	Sulfanil. 32 gms.	No improvement, Died
23-32 M.	Aortic regurg.	Microaerophilic strept.	Sulfapyr. 69 gm. Sulfanil. 20 gm.	No improvement, Died
24-18 M.	Mitral stenosis Aortic stenosis & regurg.	S. vir. 25 Hem. strept. 30	Sulfanil. 191 gm. Sulfathiaz. 82 gm.	Blood sterile. Improvement. Died*
25-6 M.	Patent intervent. Septum	S. vir.	Sulfapyr. 90 gms.	Blood sterile, Afebrile. Improvement. Died*
26-36 M.	Mitral stenosis Aortic stenosis & regurg.	Brucella abortus	Sulfanil. 217 gms. Sulfathiaz. 39 gm.	Improvement. Blood not sterile. Died*

Table IX (Continued)

Subacute Bacterial Endocarditis

No. Age. Sex	Cardiac Lesion	Bacteriology Cols./cc	Therapy	Comment
27-50 F.	Patent intervent. Septum	S. vir. 50	Sulfathiaz. 68 gm. Sulfanil. 61 gm. Heparin	Improvement. Blood not sterile. Sudden death*
28-40 F.	Mitral stenosis Aortic stenosis regurg.	S. vir.	Sulfanil. 17 gms.	No improvement, Died*
29-40 M.	Mitral stenosis Aortic stenosis & regurg.	Microaerophilic Strept.	Sulfanil. 52 gm.	No improvement. Died*
30-17 F.	Mitral stenosis	S. vir.	Sulfapyr. 10 gm.	No improvement. Died*
31-26 M.	Mitral stenosis	S. vir.	Sulfathiaz. 45 gm. Sulfanil. 66 gm.	No improvement. Meningitis. Still being treated.
32-33 F.	Mitral stenosis	S. vir.	Sod. Sulfathiaz. 52 gms.	No improvement. Still being treated

* Autopsy

Table X

Staphylococcic Bacteremia Treated with Sulfathiazole

No. Age. Sex	Local Lesion	Blood Culture	Total Dose (grams)	Additional Treatment	Result
1-35 M.	Carbuncle	S. aureus 4x	40	91 gms. sulfapyridine, 20.5 gms. sulfanilamide	Blood sterilized - died myelogenous leukemia
2-15 M.	Osteo-arthritis	S. aureus 5x	47	Surgical drainage	Recovery
3-21 F.	Uterus	S. aureus 3x	119	Surgical drainage	Recovery
4-31 F.	Breast	S. aureus 3x	25	Mastectomy	Recovery
5-38 M.	Kidney Empyema	S. aureus 2x	37		Recovery
6-20 M.	Arthritis	S. aureus 2x	144	Aspiration hip	Recovery
7-15 M.	Osteo	S. aureus 2x	129		Recovery
8- 2week M.	Umbilicus Ears	S. aureus 1x	4.25	Sulfanilamide	Recovery
9-11 F.	Carbuncle Face	S. aureus 5x	53.5	280,000 units antitoxin, x-ray Rx	Recovery
10-17 M.	Cellulitis Chest	S. aureus 1x	144.5	x-ray Rx, 100,000 units antitoxin	Recovery
11- 9 F.	Osteo	S. aureus 4x	34.5	14.5 gms. sulfapyridine. Drainage	Recovery
12-18 M.	Ruptured appendix	S. aureus 2x	99		Recovery
13-37 F.	Osteo	S. aureus 2x	240	Drainage	Recovery
14-12 F.	Osteo	S. aureus 4x	16.25 I.V. 9 orally	37.5 gms. Sulfapyr.	Recovery
15-24 M.	Chronic	S. aureus 2x	49.5	100,000 units antitoxin, 0.9 grams neoarsphenamin	Died - autopsy
16-14 M.	Thrombophlebitis Carbuncle	S. albus 5x	13	12 gms. sulfapyrid. 6 gms. sulfanil.	Died - autopsy
17-10 F.	Osteo	S. aureus 2x	52	Drainage	Recovery

Table XI

Treatment of Pneumonia with Sulfathiazole

Pneumococcus Type	No. of Patients	Comment
I	8	1 bacteremia - serum 100,000
III	13	1 bacteremia - also sulfapyr.
III and VI	2	
V	2	
VI	1	
VII	1	Bacteremia
VIII	2	1 multiple lung abscesses - Died 3 months later
XI	2	
XVII	1	
XVIII	2	
XIX	2	
XXII	1	
XXIV	1	
Untyped	12	
Total	50	

Table XII

Pneumococcic Meningitis

No. Age. Sex	Local Lesion	Pneumo. Type	Sulfonamide Rx (gms)	Additional Rx	Comment
1-35 F.	Otitis media Mastoiditis	III	Sulfanilamide 6 Sulfapyrid. 3	Serum - Type III 20,000 - Intraspinal, 60,000 - I.V.	Bacteremia Died
2-52 M.	Mastoiditis	III	Sulfanilamide 14 Sulfapyrid. 10	Serum- Type III 280,000 I.V. Ligation int.jug.	Bacteremia Died
3-19 M.	?	IV	Sulfapyrid. 74	Serum - Type IV 360,000 Intraspinal, 60,000 I.V.	Recovered
4- 3 M.	?	XX, VII XXIV	Sulfapyrid 34.3 Massive doses at M.G.H.		Died
5- 6mos.F.	?	XXV	Sulfanil. 2.4 Sulfapyrid. 29	Serum - Type XXV 18,000 Intraspinal 40,000 I.V.	Bacteremia Died
6- 6 M.	Skull Fracture	VI	Sulfanilamide 18 Sulfapyrid. 38 Sulfapyrid. 106	Serum- Type VI 2,000 intraspinal 50,000 I.V.	Bacteremia Recovery Relapse Recovery
7-39 F.	Otitis Media Mastoiditis	III	Sulfathiaz. 108	Serum- Type III 125,000 intraspinal 175,000 I.V.	Bacteremia Peritonitis Death
8- 8 M.	Otitis Media Mastoiditis	III	Sulfathiaz. 156.5	Serum- Type III 1,000 intraspinal 136,000 I.V. Mastoidectomy	Bacteremia Recovered
9- 1 F.	Otitis Media	XVIII	Sulfathiaz. 69.5	Serum- Type XVIII 1,000 intraspinal 20,000 intramusc. 20,000 intraven.	Bacteremia Died

Table XIII

Treatment of Urinary Tract Infections with Sulfathiazole

No. Age, Sex	Lesion	Bacteriology of Urine	Total Dose (grams)	Comment
1-32 F.	Cystitis, pyelonephritis, bilateral uterosigmoidostomy	Alpha strept. E. coli	23	Urine sterile (previous failure with sulfanil.
2-56 F.	Pyelonephritis Pneumonia	Beta strept. Alpha strept. Staph. aureus E. coli	18	No effect - expired in uremia
3-32 M.	Cystitis, prostatitis	Alpha strept. Staph. albus	34	Urine temporarily sterilized
4-47 M.	Nephrostomy - Rt. renal calculus	B. proteus	14	Urine sterile 2 mos. Previous failure with sulfanilamide
5-16 M.	Tonsillitis, pyelonephritis, soft tissue abscesses	Staph. aureus Beta strept.	60	Urine sterile. Sulfapyridine given previously-severe vomiting
6-69 M.	Prostatitis Hypertrophy prostate	B. proteus	23	No effect. Previous failure with sulfanilamide
7-57 M.	Prostatitis, Urethral stricture, Suprapubic cystotomy	B. proteus	44	Urine sterile
8-41 F.	Ureteritis	E. coli Staphaureus	14	Urine sterile
9-36 M.	Left hydronephrosis Nephrectomy	B. proteus	43	Urine sterile
10-18 M.	Ureteral calculi	E. coli (blood and urine)	21	Urine sterile. Sulfanil. previously sterilized blood but not urine
11-74 M.	Cystitis, prostatitis	B. proteus	35	No effect
12-26 F.	Pyelo-ureterocystitis	E. coli	42	Urine sterile
13-63 M.	Cystitis	B. proteus	27	No effect. Previous failure with sulfapyr.
14- 7 M.	Bilateral renal calculi	B. proteus E. calculi Alpha strept. Staph.	24.25	No effect

Table XIII (Continued)

Treatment of Urinary Tract Infections with Sulfathiazole

No. Age, Sex	Lesion	Bacteriology of Urine	Total Dose (grams)	Comment
15-41 M.	Prostatitis Pyelitis	Alpha strept. Staph. aureus	38	Urine sterile
16- 9 F.	Chronicosteomyel. Pyelonephritis	Staph. aureus	56	Urine sterile
17-60 M.	Prostatic resection Cystitis	B. proteus Alpha strept. Staph.	31	No effect
18- M.	Nephrectomy Pyelonephritis	Alpha strept.	32	Urine sterile
19-49 M.	Pyelonephritis	Staph. aureus	18	Urine sterile. Previous failure with sulfanil.
20-24 F.	Pyelonephritis	Alpha strept.	28	No effect. Previous failure with sulfanil.

V. GOSSIP

The student who was so worried about his mark of "F" in Preventive Medicine actually received a "B". We made one large mistake, as he suggested..... ..The Ophthalmologists have been with us this past week at the Center for Continuation Study. They were the group that started the collection for the silver service which was eventually presented to the University by all the medical groups as an extra token of their appreciation. The memory of the late President Coffman was honored by their gift. They are buzzing with another idea which may either be a series of chimes throughout the building to call the groups to class or a record player with the start of a record collection. Other suggestions are also being received.....Next week the hospital administrators will be with us and a special feature will be Trustee Day, when the trustees will attend class. Boards of trustees play a very important role in efficient hospital management. They should occupy the same relationship to the institution that the Board of Regents does to the University. In well-run community hospitals good trustee boards never permit physicians, ministers, or undertakers to serve. In spite of their high ideals, these professional groups disqualify themselves because of their special interests. In many places, hospital troubles can be eliminated by rigidly enforcing this rule.....This is Snow Week at the University of Minnesota, and the weather is so mild that our big snow man fell down. Minnesota is developing quite a reputation for its winter program of sports, largely due to the success of the St. Paul carnival. Old timers who have not visited Minnesota for many years still talk about the ice palaces we had in the good old days. There are many skaters on our Hospital staff. Head obstetrician, John L. McKelvey, in addition to being Canada's Number One football player, was also considered an outstanding hockey player. Many a Canadian fondly remembers the occasions when they would have liked to have seen the genial gentleman depart this life. Another former hockey player is Fritz Schade, now at Worthington with the Clinic. When he played with Minnesota they had a preseasonal game with the professional Minneapolis team, the Millers. Fritz's friends turned out to see him and as he came onto the ice they gave him a loud cheer. This was too bad because it called everyone's attention to the fact that he had just tripped over a rope and fallen on his head. Another former hockey player is anesthesiologist Edward Tuohy of the Mayo Clinic. He played at Minnesota and Pennsylvania. Most American hockey players come from Minnesota, and the majority from the range district.....Speaking of ice sports, some of us less agile members of the faculty have found that skating with a chair ahead is a fairly safe way of protecting our inelastic bones. The skating twins on the other side of the campus are Comptroller Middlebrook and President's Assistant Willey. Mr. Middlebrook is limping these days from a slight accident on the ice which he insists was due to some youngster's knocking one foot out from under him as he had the other foot in the air.....The Campus Club of the University has a unique system of getting rid of its old periodicals. Instead of burning them, or selling them for waste paper, or sending them to the library, they send out a list of which ones have accumulated and the annual subscription cost. Each member is then permitted the opportunity of bidding on the current collection and the sale is made to the highest bidder....Telephone operators in hospitals have had their duties studied. They apparently include the following: paging physicians, keeping record of new, discharged, and transferred patients; answering inquiries regarding condition of patients, notifying interns of new patients, leaving switchboard to page doctors, looking up patients for the record room, calling all nearby telephones to notify relatives on account of illness or death, securing information about train arrivals or departures, sending telegrams, notifying staff of post mortems, signing for packages, acting as payment point for incidental deliveries, accepting and making room reservations, calling blood donors for transfusions, calling police dept. to establish identity of unknown persons, and many others. It is no wonder that at times the service demands seem greater than can possibly be handled. Can you help!