THE SULFONAMIDES

AN HISTORICAL PHARMACOLOGICAL AND CLINICAL REVIEW OF SULFANILAMIDE SULFAPYRIDINE AND SULFATHIAZOLE

By

Jack Edward Clifford

A Thesis Submitted for the Degree of Doctor of Medicine

University of Wisconsin

1941

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CONTENTS

CHAPTER I

HISTORICAL ASPECTS

In 1908, Gelmo,[1] a research chemist for the I. G. Farbenindustrie Dye Works, Germany, synthesized the compound p- amino-benzene sulfonamide. He knew nothing of its therapeutic potentialities and saw in it only an intermediary in the composition of organic dyes with certain features in stability and fastness. According to Maher[1] the following year, 1909, a preliminary investigation by Harlein, Dressel and Koethe demonstrates that a related compound - No. 8 on the chart, - possessed the ability to combat experimental streptococci infection. However, Long and Bliss,[2] in their book, make no reference to the aforementioned experimental work but state that Harlein, Dressel and Koethe prepared azo dyes with sulfonamide only for textile purposes. In the next few years Eisenberg[1] attempted to cure experimental infections with certain azo dyes of the chrysoidine type. In 1917 Jacobs and Herdelberger,[2] following the method of Gelmo prepared para amino-benzene sulfonamide hydrocupriene. They wrote, "many of the substance described in this paper were highly bacteriocidal in vitro, a property which will be described in the appropriate place by our colleague, Dr. Martha Wallstein." Unfortunately for all there is no evidence that these preliminary observations were ever extended. In 1920 the basic formula for Prontosil was patented by the Farbenindustrie Dye Works. This patent No. 149,428 was not fully described in the English literature until 1935. This patent was issued to Doctors Fritz Meitzsch and Joseph Klarer of the I.G.

In 1932 Meitzsch and Klarer[1] added the sulfamido group to the original chrysoidine of Eisenberg and demonstrated that the compound possessed value against experimental streptococcal infection.

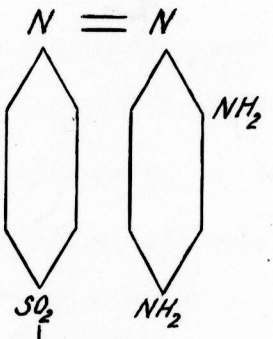
In May, 1933, at a meeting of the Dusseldorf dermatogical Society Dr. Foerster of Dusseldorf reported on the treatment of a staphylococcal infection with the compound streptozon (prontosil). This work stimulated a concentrated program of research which resulted in the production of voluminous poorly organized literature which is accumulating more rapidly than it can be absorbed.

The credit[3] for making the most remarkable recent advances in modern therapeutics - namely, the discovery of the anti-streptococcal activity of an azo dye containing the sulfonamide group belongs entirely to Domagk and his assistants, Meitzsch and Klarer of the I. G. Farbenindustrie at Elberfield. The[1] first systematic reports of experimental data relating to the sulfonamides were all contained in the history making contributions of Gerhard Domagk in 1935 and 1936. His results were ideal - all of his infected non-treated animals died and all his infected treated animals lived.

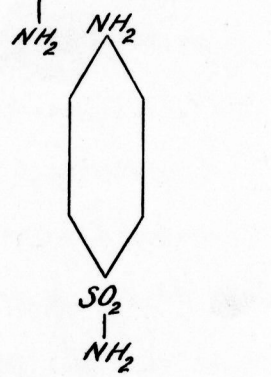
French works, not to be outdone by the Germans, became active in 1935 led by Professor Constantin Levaditi.[1] In the same year Trefouels, Nitti and Bovet of the Pasteur institute, reported that the p-amino-benzene sulfonamide portion of the German prontosil was the really active part of the Prontosil molecule. This view was accepted by Domagk in 1936 and since that time most of the laboratory investigations have used this nucleus as the fundamental compound for study and comparison. This

work brought to the limelight the work of synthesis of p-amino-benzene sulfonamide by Gelmo in 1908 - 28 years previously.

The French broke down german Prontosil, a patented chemotherapeutic drug, retained the active nucleus and presented to the world a cheap non-patented drug called prontylin or in this country Sulfanilamide.



German Prontosil



French Prontylin or Sulfanilamide

In June, 1936, Colebrook and Kenny[4] and Buttle, Gray, and Stephenson[5] contributed masterly papers confirming the work of Domagk and Trefouel. They also observed that p- amino-benzene sulfonamide was effective against meningococci, staphylococci and pneumococci types 1 and 2.

The first reference[1] to the sulfonamides in American literature

appeared as an abstract of a German article, in the J. A. M. A. of June 13, 1936. The first use of prontosil in the United States if attributed to Dr. Ashley Weech in New York City, July, 1935.

Since 1936, the search has been for new derivatives of the sulfanilamide nucleus, capable of exerting activity with less danger of toxicity and for compounds possessing a higher efficiency against some of the bacterial offenders which are relatively immune to the action of sulfanilamide.

One of the outstanding compounds in the group was given to the world by Lionel Whitby,[3-6] assistant pathologist of the Middlesex Hospital, London, who reported in the May 28, 1938, issue of Lancet, that two sulfanilyl-aminopyridine (sulfapyridine) was very effective in protecting mice against 10,000 lethal doses of pneumococcus type I and to afford considerable protection against 10,000 lethal doses of other pneumococci types II, III, V, VII, and VIII. Sulfapyridine was one of the many compound synthesized by Dr. A. J. Ervins and Mr. M. A. Philips in the chemical research laboratories of May and Baker, Ltd. at Dagenham, England. This drug was first patented and marketed in Great Britain by May and Baker under the non-descriptive name of "M and B. 693" and later was given the name of "Dagenan."

The drug was first introduced in this country by Merck and Co., Inc. who obtained the patent rights from May and Baker. Merck and Co. immediately distributed sufficient quantities of this drug to clinics during the winter of 1938 and 1939. Eighteen thousand cases of pneumonia were treated as a result.

Evans and Gaisford[7] were the first to report on the value of sulfapyridine in the treatment of lobar pneumonia.

In August, 1939, Fosbinder and Walter[8] reported the preparation of 2 sulfanilamido - 4-methylthiazole and thiazole compounds. These compounds were studied for their chemotherapeutic activity against infections in mice. They compared favorably in efficiency to sulfanilamide and sulfapyridine. Similarly Lott and Bergeim[9] synthesized two of these compounds namely sulfathiazole (2 p- amino-benzene) thiazole and sulfamethylthiazole 2(p- amino-benzene sulfanimido) 4-methyle thiazole. Long[10] in a report for the Council on Pharmacy and Chemistry credits Fosbinder and Walter with the first synthesis of the Sulfanilamido derivatives of heterocylic amines. Maher[1] states that Lawrence has shown that sulfathiazole, sulfamethylthiazole and sulfaphenylthiazole are superior to sulfanilamide and sulfapyridine in their inhibitory action against several types of pneumonia and against Group A Beta hemolytic streptococci. The methyl and phenyl derivatives were especially active against cultures of staphylacoccus aureus. In the fall of 1939 Gross, Cooper and Lewis[12] published the first experimental work done with the thiazoles.

At the recent meetings of the American chemical society of Cincinnati, a new compound of sulfanilamide - pyrimidine was reported by Drs. Roblin, Williams, Winnek, and English of the American Cynamide Co. This compound was called sulfadiazine to eliminate confusion with sulfapyridine. Feinstone[11] in December, 1940, reported on the toxicity, absorption and chemotherapeutic activity of this drug and it will be taken

up later in this report.

The search for new chemotherapeutic agents in the sulfonamide group continues but it will only be after vigorous study in the fields of chemistry, pharmacology and clinical medicine that the true value of these drugs will be known.

CHAPTER II

NOMENCLATURE

The multiplicity of trade marked names attached to the various chemotherapeutic compounds based on sulfanilamide has created a great deal of confusion for practicing physicians, teachers, and students alike. It will be the purpose of this chapter to clarify, if possible, the existing confusion by taking the general names outlined in Chapter III and listing their trade names.

The dye substance Prontosil and Neo-prontosil[16] have continually been confused because of changes in their names and because different names have been used for the same substance in different countries.

"Prontosil" was the name eventually given to the original effective dye substance. It has not been marketed in the United States or Canada, but can be obtained as far as we know throughout the rest of the world. The substance called "Neo-prontosil" at the present time in the U.S.A., Canada, and England was formerly known as "Prontosil solution" or "Prontosil Soluble." It is still known by the latter name upon the continent. It differs chemically from prontosil (Chapter III) and is marketed as a solution, or in tablet form.

The following trade names of sulfanilamide and derivatives have been taken from E. A. Northley's[17] article in Chemical Reviews August, 1940:

<u>Sulfanilamide:</u>

1. Colsulanyde

2. Despetyl
3. Estreptocida
4. 1162 F
5. Lysococcine
6. Prontosil album
7. Prontylin
8. Sanamide
9. Septoplex
10. Stramide
11. Streptrol
12. Streptamide
13. Streptocide
14. Streptocide album
15. Sulfamidyl
16. Sulphanamide P.

Prontosil:

1. Prontosil plavum
2. Streptozon

Neo Prontosil:

1. Prontosil soluble
2. Streptocid rubrum
3. Streptozon S
4. Azosulfamide

Sulfopyridine

1. Coccoclase
2. Dagenan
3. Eubasinum
4. Eubasin
5. M & B 693
6. Pyriamide

Sulfathiazole

The thiazoles' have no trade name and are known as such.

CHAPTER III

CHEMICAL DESCRIPTIONS

Sulfanilamide

Sulfanilamide[13] is a white crystalline powder possessing a slightly bitter taste which disappears promptly leaving a somewhat more lingering sweetish aftertaste. It is relatively insoluble in H_2O, a little less than 1 part in 100 passing into a solution at a room temperature of 22° C. For parenteral use it is customary and advisable to employ an 0.8 per cent aqueous solution. Such a solution may be sterilized and is relatively stable. The aqueous solution is colorless and neutral to litmus. No satisfactory solvent has as yet been found which enables one to give it clinically in concentrated form.[16] Melting point is from 165 to 166.5° C. Sulfanilamide is an official preparation (See U.S.P. Second Supplement, 1939).

Sulfapyridine

Sulfapyridine[14] is a white crystalline powder, melting at 190.5°C. It is soluble in H_2O to the extent of 28 mg. in 100 cc. at 27.5° C. This is almost 30 times less than the solubility of sulfanilamide, but the solubilities of both substances increase rapidly with rising temperatures.

Sulfapyridine[14] sodium monohydrate is a white crystalline powder which decomposes on heating at 300° C. It dissolves in H_2O at room temperature to the extent of 54 gm. per 100 cc. which is equivalent to 40 gm. per 100 cc. of solution or 35 gm. per 100 gm. of solution. It

has a pH of 10-11. It is suitable for parenteral therapy. These drugs are not official drugs but are accepted by the Council for inclusion in the N. N. R.[18]

Sulfathiazole

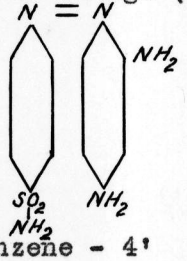
Sulfathiazole[15-18] is a white crystalline powder which is poorly soluble in H_2O. At 28° C only 90 mgm. dissolves in 100 cc. of H_2O (.09% concentration). A saturated aqueous solution has a pH of 6.0. Sodium Sulfathiazole, in contrast, is soluble in H_2O to approximately 5%, the solution being alkaline to pH of 10.5. Sulfathiazole and its sodium salt are not official drugs and are not described in N. N. R. However, the Council (1940) has adopted sulfathiazole as a nonproprietary name.

Comparison of structural formulae[13]

A. Sulfanilamide of Gelmo (considered the parent substance)

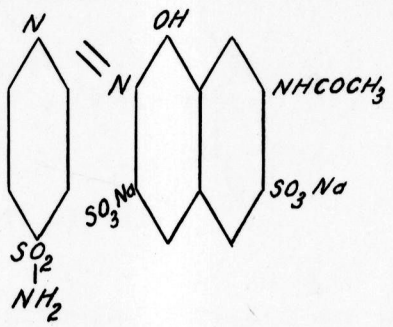
Para amino-benzene sulfonamide

B. Original Prontosil of Domagk (not marketed in the country)



2,4 - Diaminoazobenzene - 4' - sulfonamide

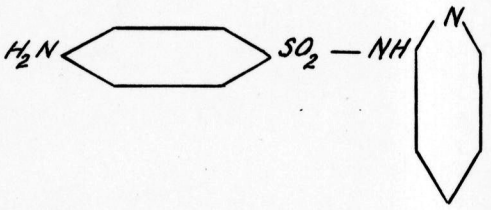
C. Prontosil soluble of Domagk (in this country known as Neo-Prontosil)



This substance is about 4% soluble in H_2O.

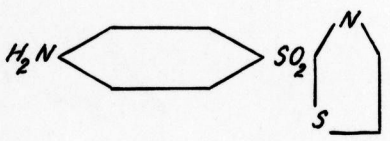
Disodium 4 sulfamidophenyl - 2 - azo - 7 acelylamino - 1 - hydroxy-naphthalene - 3,6 - disulfinate

D. Sulfapyridine



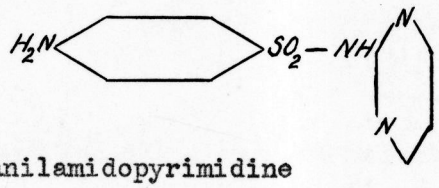
2 - Sulfanilamido pyridine

E. Sulfathiazole



2 - sulfanilamido thiazole

F. Sulfadiazine



2 - sulfanilamidopyrimidine

Upon inspection of the preceding formulae one can readily see why sulfanilamide is called the "parent substance." In each the benzene ring on the left contains the same substituent which is always in the para position.

CHAPTER IV

MODE OF ACTION

Sulfanilamide[18] and its congeners differ from all other antiseptics in that they represent the first chemotherapeutic agents capable of being taken orally which are not only effective against serious bacterial infections but which also exhibit very little toxicity for the host. The mechanism of action of these compounds has therefore received considerable attention. The importance of elucidating the mechanism of action lies in the fact that a more intelligent development of new compounds and a more rational use of sulfanilamide and its allied drugs will then be possible. Numerous theories, many un-substantiated by facts, have been advanced to explain the mechanism of the anti-bacterial action of the sulfanilamide chemicals. The problem of major importance is whether the drug acts directly on the bacteria or whether the defense forces of the host are involved. Because the mode of action of this drug is by no means settled an attempt will be made to present the various theories on the subject.

Bliss and Long[19] in their earlier studies concluded that sulfanilamides effect in the treatment of experimental streptococci infections in mice was primarily one of slowing down the rate of multiplication of the streptococci, thus permitting the phagocytes to dispose of them. There was little evidence to show that the chemical exerted a bactericidal effect "in vivo." They also stated that bacteriostasis is the only factor demonstrable in the control of clostridium Welchii infection

in mice.

Osgood[20-21] working with bone marrow cultures of beta hemolytic streptococcus to which were added various concentrations of sulfanilamide, states that the major action of sulfanilamide on the hemolytic streptococcus seems to be the neutralization of toxins with no direct effect on phagocytosis.

Long, Bliss, and Feinstone,[22] in a later report on further observation on the mode of action of sulfanilamide, both in vitro and in vivo substantiate their earlier observations that the drug decreases the rate of multiplication of susceptible bacteria. They were unable to confirm certain of Osgood's[20-21] observations regarding the antitoxic action of sulfanilamide.

Bigler, Clifton, and Werner[23] in an extensive report on the leukocytic response to sulfanilamide considered that mode of action of the drug seems to be independent of the leukocytes in that it does not produce an increase in the total leukocytes or in the proportion of the polymorphonuclear cells. However, Long and Bliss[20] noted that phagocytosis was increased in the peritonial exudates of mice infected with beta hemocytic streptococci, but they state it was impossible to decide whether this effect is primarily on the streptococci or on the phagocytes.

Working with experimental hemolytic streptococcic meningitis in rats Adolph and Lockwood[24] conclude that sulfanilamide seems to act, not by promoting phagocytosis, but rather by restricting the multiplication of the cocci and preventing invasion of the tissues and the blood stream.

Lockwood and Lynch[25] studying the bacteriostatic action of sulfanilamide and sulfapyridine on various organisms draw the following conclusions:

1. Sulfanilamide has a bacteriostatic and limited bacteriocidal action in vitro on hemolytic streptococci, staphylococci, pneumococci, and the colon bacillus. The magnitude of the effect is dependent principally on

   a. The concentration of the drug

   b. The concentration of "peptone" in the culture medium (peptone connotates any product of protein digestion whether artificially prepared in vitro or by natural enzymatic processes in vivo.

2. That sulfanilamide acts by interfering with the nutritional requirements of susceptible bacteria and that bacteria can die out in a phagocyte free environment through starvation and autolysis.

3. The addition of peptone to medium such as serum, which are deficient in nitrogen easily assimilable by bacteria, supplies such an excess of nitrogenous material that the bacteriostatic action of the drug is to a large degree inhibited.

Colebrook and his associates[26] in an early report in December, 1936, showed that the action of para amino-benzene sulfonamide was both bacteriostatic and bacteriocidal on the broth cultures of hemolytic streptococci and that following the administration to man and animals, their blood is bacteriocidal to hemolytic streptococci.

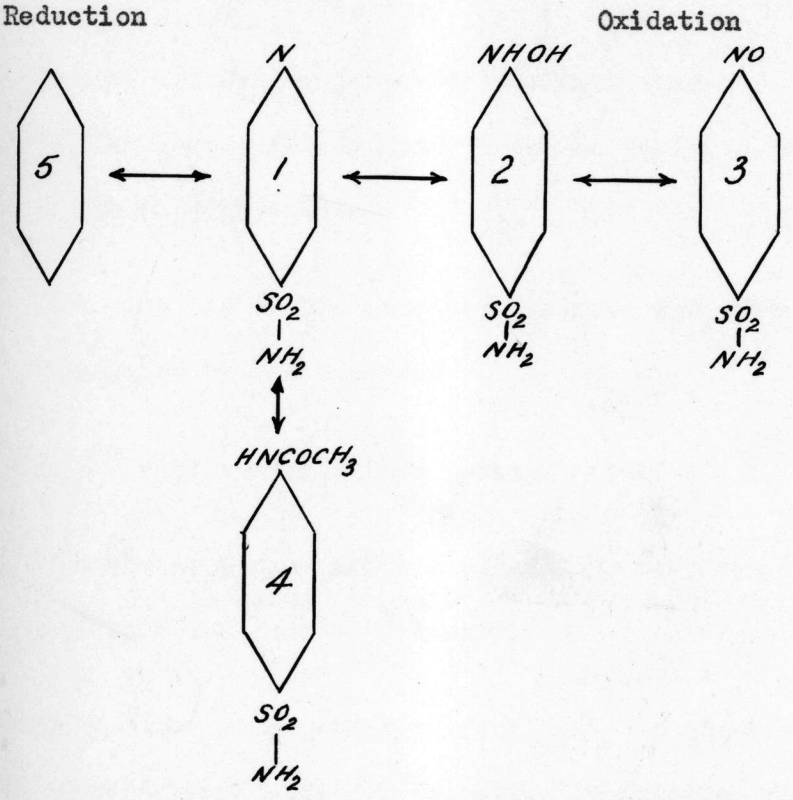
In a paper following Whitby's original report, he and McIntosh[27]

showed that the drug stimulated neither leukocytosis or phagocytosis and that the speed of formation of natural immunity was not interfered with in any way. They also observed that the drug was for a time inactive, as a lag period of from 4 to 7 hours during which the organism multiplied at a normal rate, both in the vivo and vitro experiments. This lag period was explained by the time necessary for the absorption of the drug by the bacteria.

Fleming[28] states that sulfapyridine retards the growth in human blood of pneumococci and hemolytic streptococci in concentrations which it is reasonable to suppose can be obtained therapeutically but that in the above concentrations it has no bacteriocidal effect. He further added that if the blood is rendered "immune" by the addition of some specific immune serum, the apparent effect of the chemical is enhanced.

Chandler and Janeway[29] observed that in high concentration of 1 to 10,000 sulfanilamide had no demonstrable effect on phagocytosis but in more dilute solutions (1-40,000 to 1-80,000) phagocytosis was increased markedly. They concluded that the high concentrations of the drug were toxic to the leukocytes and organisms, but that in more dilute solutions it affected only the organism.

In December, 1940, Mellon[30] following the work of Shinn, Main, and Mellon,[31] published an interesting report on the mode of action of the sulfonamides in which he described the "Oxidation theory."



The above chart illustrates the oxidation - reduction potentialities of sulfanilamide.

1. Sulfanilamide
2. Hydroxylamine derivative which is an anti-catalase or the active bacteriostatic agent
3. Nitroso derivative which is capable of oxidizing hemoglobin to mithemoglobin and which appears to be closely related to the oxidation responsible cyanosis developed by use of sulfanilamide.
4. Acetyl derivative or inactive form of sulfanilamide which is formed in the liver. This reason for its inactivity is because the NH_2 group is blockaded and oxidation cannot take

place.

The theory the Mellon proposes is simply this:

1. Sulfanilamide is oxidized by the bacteria to the hydracylamine derivative.

2. Normally the enzyme catalase destroys H_2O_2 which is liberated by the bacteria.

3. Hydroxylamine derivative poisons catalase.

4. Therefore, H_2O_2 is allowed to accumulate which in turn inhibits the growth of bacteria.

Mellon further states that sulfanilamide is inactive toward highly virulent bacteria until it is partially oxidized to stages whose chemical properties make for inactivation of the germs enzymes thereby interfering with their food supply. An accompanying effect of this starvation process is to permit the accumulation of their own excretory products of which H_2O_2 is one. Thus, they may be said "to stew in their own juice." He also concludes that although sulfathiazole has the ability to cure dramatically the highly fulminating forms of infection it lacks the ability to cure localized purulent infection caused by the same germ. This is due to the fact that local conditions are anaerobic and block effectively any oxidative change in the molecule. However Maher[33] feels that the levels of peroxide in the body fluids are not capable of exerting any influence on the bacteria and that furthermore there is no good evidence to show that the necessary amount of decom-

position of the drug occurs in the body.

Keefer[32] feels that there are at least two essential conditions necessary for therapeutic effectiveness.

1. It is necessary to subject the organisms to a concentration of the chemical that will produce maximum bacteriostasis (7-10 mg. % in blood)

2. It is also necessary for the body to be able to phagocytize organisms and destroy them.

He therefore ascribes to the theory that sulfanilamide is only bacteriostatic and that the defense mechanisms of the body exert the final destruction of the organisms.

By examining the preceding pages one can readily see that the mode of action of the sulfonamides is not clearly understood. Numerous studies on the action of these drugs in vitro and in vivo have been published. Various organisms and different experimental animals have been used but as yet the work is far from complete.

Following is a summary of the theories that have been offered relative to the action of the solfonamides.

1. Bacteriostatic
2. Neutralizes bacterial toxins
3. Stimulates phagocytosis
4. Bacteriocidal
5. Alters the organism so that phagocytosis can take place
6. Interference with the nutritional requirements of the

bacteria

7. Oxidation to a hydroylamine which acts as an anti-catalase and prevents the destruction of H_2O_2 in and around the bacteria.

CHAPTER V

ABSORPTION, DISTRIBUTION AND EXCRETION

Sulfanilamide is rapidly and completely absorbed by the gastro-intestinal tract of the human and circulates in the blood and tissues as such.[34] This absorption occurs largely in the duodenum and upper jejunem.[33] The onset of vomiting which usually accompanies too large a dose will obviously decrease the absorption of the drug. Sulfanilamide is more rapidly absorbed than sulfapyridine and sulfathiazole according to Blake.[37]

After absorption it is distributed throughout the fluid medium of the body. According to Maher[36] the drug follows the distribution of H_2O in almost the same general sense as does alcohol and has even been proposed as a means of studying the distribution of H_2O. Marshall[38] states that the drug seems to be present in a little higher concentration in the plasma than in whole blood; in the saliva, pancreatic juice and cerebral spinal fluid its concentration is a little lower than that existing in the blood. Long[39] states that sulfanilamide exists in the tissues (with the exception of bone, fat, and nervous tissue) - (which according to Marshall[38] contain much lower amounts) in about the same concentration as the blood. It passes over readily into all transudates and exudates in which it exists in a concentration of about 3/4 of that noted in the blood. Marshall[40] found that after oral administration of sulfanilamide the drug was found to exist in a somewhat lower concentration in the spinal fluid than in the blood.

Soon after sulfanilamide[39] is absorbed in the body tissues a certain proportion of it is changed (mainly in the liver) to acetylated or "conjugated" sulfanilamide. This form of the drug has no therapeutic activity. Generally from 10-20% is converted to the inactive form. Hence in determining the sulfanilamide content of the body fluids results are expressed in mg. % of "free" and total sulfanilamide.

Marshall[40] states that after the ingestion of a single dose the concentration in the blood depends on

1. The dose per unit of body weight
2. The rate and completeness of absorption from the intestinal tract.
3. The distribution ratio of the drug in the body
4. Efficiency of the kidneys in excreting the drug
5. The amount of inactive, conjugated form in the body

Marshall uses an initial dose of 60 gr. The level of the drug rises to a peak in the blood in 3 to 4 hours - to equilibrium with the tissue fluid - and then passes back out from the tissues through the blood and out in the urine. Such a single dose is almost completely eliminated in 24 - 36 hours. If, according to Marshall,[40] the drug is given in divided doses it takes from 2 to 3 days to establish an equilibrium between the amount injected and the amount excreted and after equilibrium is established it takes about the same time to free the body of the drug. When the body is in equilibrium one can frequently account for almost 100% of the daily dose ingested by the total excretion of

the sulfonamide in free and conjugated form. By this method the blood concentration can be maintained fairly constant for a long time. If the blood concentrations are maintained at a level of from 11 to 16 mg. % about .07 to .12 gm. per kilo should be excreted. It is important to remember that the peak of concentration in the blood is reached within 3 to 4 hours after the initial dose and that it then falls off rapidly. For this reason the drug should be given at 4 hour intervals so that the blood concentration of sulfanilamide be kept at a constant level.

Sulfanilamide is almost entirely excreted by the kidney. However small amounts[36] leave the body by way of the feces and perspiration. The excretion is similar to that of urea[41] but reabsorption by the tubules occurs to a greater extent. One can recover as high as 90% of an injected single dose in the urine.[36] Sulfanilamide is excreted very rapidly by the kidney (24 hours for a single dose) and consists of both the free and acetylated form. Long[39] states that 50% or more is in the inactive-acetylated form. Since sulfanilamide[40] is so rapidly excreted by the kidney one might expect with impaired renal function that smaller doses would suffice to raise the blood concentration to any given level and that after stopping the drug it would take longer to clear the body of the substance. Marshall[40] found that in patients with impaired renal function the sulfanilamide appeared to be excreted more slowly.

Studies by Long[39] on Neoprontosil show that

1. By the oral route it is readily absorbed by the G.I. tract
2. Reduced in the body to sulfanilamide probably in the G.I.

tract rather than the tissues.

3. It is excreted readily by the kidney and 90 to 92% can be recovered as free and acetyl forms of sulfanilamide.
4. If Neoprontosil is administered by the parenteral route much more is recovered in the urine as neoprontosil, and much less is reduced to sulfanilamide.

Sulfapyridine

An extensive study was made by Kinsman[36] et al on the absorption, concentration in the blood and excretion of sulfapyridine with the following results.

1. Oral administration of the drug: an initial dose of 2 gm. followed by 1 gm. every four hours; an initial dose of 4 gm. followed 4 hours later by 1 gm. every 4 hours and an initial dose of 4 gm. followed 8 hours later by 1 gm. every 4 hours.

2. Absorption is very erratic; the height of the absorption curve being unpredictable from identical doses and from patient to patient and there being no correlation between the size of the dose and the height of the blood concentration. In general, the blood concentration is higher following a dose of 2 gm. than of 4 gm.

3. Acetylation or conjugation of the drug occurs very

rapidly after it enters the blood stream - so that 35% of it is conjugated within the first hour. The degree of acetylation varies tremendously, the average being about 33% but variants from 0 to 100% were noted. During elimination the "free" form of the drug leaves the blood stream more rapidly than the "conjugated" form so that during this phase the actelytated form is much greater than at any other time.

4. After the withdrawal of the drug by mouth its elimination occurs rapidly at first, then more slowly, so that as long as 5 days later appreciable quantities can still be found in the blood and urine. The drug disappears from the urine at about the same time that it does from the blood. From 21 to 56% of drug taken by mouth can be recovered in the urine.

Long[39] has made some interesting comparisons with sulfapyridine:

1. Levels of sulfapyridine rise more slowly in the blood, do not reach the same concentration, are maintained over a longer period than would be expected of sulfanilamide.

2. Sulfapyridine is distributed in the body the same as sulfanilamide.

3. It is not as well absorbed as sulfanilamide or neo-

prontosil.

4. A higher degree is conjugated to the acetylated form which from a therapeutic standpoint is a waste.

5. Only a little more than half can be accounted for in the urine which substantiates No. 3.

Because of the slow rise sulfapyridine concentration in the blood it has been suggested by Blake[37] that the initial dose should be given intravenously so that adequate blood concentrations can be established rapidly.

Sulfathiazole

Sulfathiazole[42] is rapidly absorbed from the gastro-intestinal tract but very slowly absorbed from the rectum. The drug[43] disappears from the blood very rapidly. In some cases this may be an advantage (e.g., ease of removal in presence of toxic reactions) and in others may be a disadvantage (e.g., differently in maintaining an adequate blood concentration). Following oral administration, the percent of acetyl-sulfathiazole in the blood is greater than the percent of sulfapyridine under similar circumstances. It is distributed in the tissue, transudates and exudates in same manner as sulfanilamide. However, the amount present in the specific body fluids and tissues is inconstant. Penetration of the spinal fluid is poor and sulfathiazole is not recommended in meningeal infections. Sulfathiazole is excreted almost

entirely through the kidney and at a very rapid rate. Because of the rapid excretion of the drug, it is difficult to maintain an adequate blood level of sulfathiazole even with adequate administration.

It has been noted that after 24 hours of therapy concentrations of sulfathiazole in the blood are often much lower than would be expected. This is attributed to the rapid absorption and excretion. It is therefore important to adjust the dosage and schedule of administration to maintain adequate concentration in the blood.

CHAPTER VI

ROUTES OF ADMINISTRATION

Sulfanilamide

1. Oral[44]

This is the easiest, safest, and cheapest method of giving the drug. It may be ingested in the form of tablets or capsules. The tablets can be pulverized and given in a half glass of H_2O which considerably facilitates absorption. The drug can be given in the formula of infants and to older children in jelly and cereal.

2. Subcutaneous Administration[44]

This method offers no advantages except in patients who may be unable to take medication because of vomiting, coma or uncooperativeness, or in whom a satisfactory blood concentration has not been obtained by the oral route. Absorption is more rapid from the subcutaneous tissue than from the intestinal tract.

The disadvantages of subcutaneous infection are, expense, pain, and difficulty of maintaining a constant blood level especially when infusions are given every six to eight hours. The preparation of a sterile solution of sulfanilamide is as follows: 0.9% solution of

NaCl is sterilized by boiling in a pyrex flask for several minutes. The solution is permitted to cool until bubbling has ceased and then 1.0 gm. of sulfanilamide (not tablets) is added for each 100 cc (1% sol.), the flask being gently shaken until all the drug has dissolved. When the solution has cooled to 37° C it is ready to inject by any hypodermoclysis method. Fresh solution should be made every day, and should be kept at room temperature. Solutions which have a slight yellow discoloration are decomposed and must not be used.

3. Intrathecal Injection

In streptococcal, meningococcal and pneumococcal meningitis the drug has been injected intrathecally as an adjuvant to, but not as a substitute for, oral or subcutaneous therapy. When introduced in the subarchnoid space (prepared by method in 2) high concentrations are obtained but fall quickly because of the direction of the diffusion gradient. It must be kept in mind that sulfanilamide enters the spinal fluid rapidly, after absorption, and in concentrations only slightly below that of the blood. Therefore intrathecal injection offers no distinct advantage over methods 1 and 2 and may cause considerable discomfort for the patient.

4. Other Routes of Administration

a. Intravenous

Unnecessary and contra-indicated

b. Rectal

Little quantitative information available.

Large bowel absorbs sulfanilamide more slowly.

Sulfapyridine

1. Oral[44]

Sulfapyridine should be given by this route, whenever possible, in capsule or tablet form. Tablets may be crushed and suspended in several ounces of H_2O, milk, or fruit juice which probably facilitates absorption. The drug may be administered into the duodenum by means of a nasal catheter if nausea and vomiting occur.

2. Subcutaneous administration[44]

The necessity of parenteral administration of the drug arises more frequently than sulfanilamide because of poor intestinal absorption and because of more frequent occurences of severe grades of nausea and vomiting. Blake and Haviland[45] have devised a method by which 2 gms. of sulfapyridine is dissolved in 1500 cc of 0.9% of NaCl or in 1000 cc of 5% glucose solution or in 500 cc

of each. The technique is same as described under sulfanilamide. This solution may be given intravenously also. Two hypodermoclysis daily at 12 hour intervals are usually given for maintenance of adequate blood levels. Sulfapyridine given in the aforementioned solutions has the advantage over Na sulfapyridine in that it can be given both by vein and subcutaneously and that they do not cause tissue injury and they supply water and electrolytes to febrile patients.

3. Intravenous Administration[44]

Sodium sulfapyridine is given by the intravenous method when sulfapyridine by the oral route is inadequate or nausea and vomiting ensues. Long[47] has described its preparation. A 5% solution of Na sulfapyridine (5 gm. in 100 cc) is prepared by dissolving the required amount in distilled H_2O (5% solution is almost isotonic). This drug is unstable to heat and hence such solutions cannot be sterilized. However, a 5% solution has a pH of 10.7 to 10.8 and therefore is somewhat bacteriocidal. The drug should always be administered by the intravenous route and should not be mixed with any other types of parenteral solutions. This drug will produce painful induration and sloughing if allowed to get into the tissues so one should be sure that the needle is well in the vein

before starting. The solution is allowed to run in at a rate of 5 cc per minute for from 10 to 15 minutes. Dose is 1 cc. of 5% solution per kilogram of body weight.

Sulfathiazole[44]

Sulfathiazole is usually administered by mouth. This is practical because of rapid absorption and because of absence of severe nausea and vomiting. If parenteral administration is necessary Na sulfathiazole may be given intravenously in a 5% solution by the same technique as for Na sulfapyridine. The same precautions also apply as outlined in part 3 under sulfapyridine.

CHAPTER VII

DOSAGE

Sulfanilamide

The dose of sulfanilamide[52] depends upon many factors, including especially:

1. The age of patient
2. Type and severity of infection
3. Route of administration
4. Functional capacity of the kidneys
5. The success with which the desired level of blood sulfanilamide is attained.

Thus, children and adults tolerate sulfanilamide better than do older individuals. Severe infections necessitate heavier medication than mild ones; larger amounts of the drug must be given when the subcutaneous route is employed than when oral administration is used; great care must be exercised in the dosage administered to persons with impaired renal function. The best method of regulation is by determining the blood level of the drug. With severe infections[47-48] due to streptococcus, meningococcus or Welch bacillus it is important to attain an effective level in the blood as soon as possible. A large initial dose is therefore advised in order to bring about the desired level of 10 mg. percent as quickly as possible and that this level be maintained and increases by doses of the drug given at 4 hour intervals both day

and night. The maintenance dose should be given until a marked clinical improvement in the condition of the patient is noted. It should then be decreased slowly day by day but should not be discontinued until patient is ready to be up and about. It is important to remember that the administration of sulfanilamide should be discontinued only under the most exceptional circumstances when there is a severe infection. Charts 1 and 2, worked out by Long[47-48] on the basis of therapeutic blood levels, measured by Marshall's method[50] show the amounts of the drug necessary to establish levels of from 10 - 15 mg. percent (in severe infections) and from 5 - 10 mg. percent (in mild or moderately severe infections) in which sulfanilamide is indicated. The charts are self explanatory. J. A. Kolmer,[51] Professor of Medicine at Temple University differs with Long[47-48] concerning the dosage of sulfanilamide. In general Kolmer uses higher initial doses with the maintenance dose about the same. The following charts[51] are taken from Kolmer's article.

Chart III - For severe infections

Blood level of 10 - 15 mg. percent

Chart IV - For moderately severe infections

Blood level 5 - 10 mg. percent

Chart V - For mild infections

Blood level determinations not required

Chart VI - For severe infections and in treatment of patients who cannot swallow or if vomiting interferes with

oral administration, parenteral administration of sulfanilamide and neoprontosil is required.

Chart VII - At times it is frequently advisable to give the drug orally and parentally especially in treatment of severe infections.

TABLE I[47-48]

THE AMOUNTS OF SULFANILAMIDE NECESSARY TO ESTABLISH THERAPEUTICALLY EFFECTIVE BLOOD LEVELS (10 TO 15 MGMS.%) QUICKLY IN PATIENTS ILL WITH SEVERE HEMOLYTIC STREPTOCOCCAL, MENINGOCOCCAL, GONOCOCCAL, PNEUMOCOCCAL, OR WELCH BACILLARY INFECTIONS

Weight of Patient		Initial Dose Per Os		Maintenance Dose Per Os Q 4 Hours (day and night)		Total Dose First 24 Hrs.		Total Daily Dose Bicarbonate of Soda	
Kilos	Pounds	Grams	Grains	Grams	Grains	Grams per Kilo	Grains per Pound	Grams	Grains
70	150	4.8	80	1.2	20	0.15	1.2	3.6	60
60	125	4.2	70	0.9	15	0.15	1.2	3.0	50
45	100	3.6	60	0.9	15	0.18	1.3	3.0	50
35	75	3.6	60	0.9	15	0.23	1.8	3.0	50
23	50	3.0	50	0.6	10	0.26	2.0	1.8	30
11	25	1.8	30	0.3	5	0.3	2.2	0.9	15

TABLE II[47-48]

THE AMOUNTS OF SULFANILAMIDE NECESSARY TO ESTABLISH THERAPEAUTICALLY EFFECTIVE BLOOD LEVELS (5 TO 10 MGMS.%) IN PATIENTS ILL WITH MILD OR MODERATELY SEVERE INFECTIONS IN WHICH SULFANILAMIDE THERAPY IS INDICATED

Weight of Patient		Calculated Daily Doses				Dose per OS Q 4 Hours (day and night)		Total Daily Dose Bicarbonate of Soda	
Kilos	Pounds	Grams	Grams per Kilo	Grains	Grains per Lb.	Grams	Grains	Grams	Grains
70	150	5.4	.07	90	0.6	0.9	15	3.6	60
60	125	5.4	.09	90	0.7	0.9	15	3.6	60
45	100	5.4	.12	90	0.9	0.9	15	3.6	60
35	75	4.2	.12	70	0.9	1. of 1.2* 5 of 0.6	1 of 20 5 of 10	2.4	40
23	50	3.6	.16	60	1.1	0.6	10	1.8	30
11	25	1.8	.16	30	1.2	0.3	5	1.2	20

* 1 dose of 1.2 grams followed by 5 of 0.6 grams

TABLE III[51]

DOSAGE OF SULFANILAMIDE FOR THE TREATMENT OF SEVERE INFECTIONS

Weight		First Dose		Every Four Hours*		Total, First Twenty-four Hours		Daily Maintenance Dose**	
Pounds	Kilograms	Grains	Grams	Grains	Grams	Grains	Grams	Grains	Grams
25	11.3	30	1.9	5	0.3	55	3.5	30	1.9
50	22.7	50	3.2	10	0.65	100	6.5	60	3.9
75	34 to 45.4	60	3.9	15	1.0	135	8.7	90	5.8
125	56.7	70	4.5	15	1.0	145	9.4	90	5.8
150	68.0	80	5.2	20	1.3	200	13.0	120	7.8

1. These doses are usually required for establishing a level of 10 to 15 mg. per hundred cubic centimeters of blood.
2. Calculate dosage according to body weight.
3. Give large initial dose, followed by maintenance dose every four hours.
4. The total daily dose is approximately 1 grain per pound (0.13 Gm. per kilogram) of body weight.
5. Give ½ grain (0.03 Gm.) of sodium bicarbonate with each grain (0.06 Gm.) of sulfanilamide orally.

* Day and night
** Usually for two to six days; reduce when improvement occurs.

TABLE IV[51]

DOSAGE OF SULFANILAMIDE FOR THE TREATMENT OF MODERATELY SEVERE INFECTIONS

Weight		Orally, Every Four Hours*		Total, Twenty-Four Hours**	
Pounds	Kilograms	Grains	Grams	Grains	Grams
25	11.3	5	0.3	30	1.9
50	22.7	10	0.65	60	3.9
75 to 100	34.0 to 45.5	10	0.65	60	3.9
125	56.7	15	1.0	90	5.8
150	68.0	15	1.0	90	5.8

1. These does are usually required for establishing a level of 5 to 10 mg. per hundred cubic centimeters of blood.

2. Calculate total amount required per day; divide into six parts and give does every four hours.

3. The total daily dose is approximately ½ grain per pound (0.066 Gm. per kilogram) of body weight.

4. Give ½ grain (0.03 Gm.) of sodium bicarbonate with each grain (0.06 Gm.) of sulfanilamide orally.

* Day and night.

** Usually for two to four days; reduce when improvement occurs.

TABLE V[51]

DOSAGE OF SULFANILAMIDE FOR THE TREATMENT OF MILD INFECTIONS

Weight		Orally, Every Four to Six Hours*		Total, Twenty-Four Hours	
Pounds	Kilograms	Grains	Grams	Grains	Grams
25	11.3	2½	0.16	15	1.0
50	22.7	5	0.3	15	1.0
75 to 100	34.0 to 45.4	5	0.3	30	1.9
125	56.7	10	0.65	30	1.9
150	68.00	10	0.65	45	2.9

1. Calculate total amount required per day; give dose every four hours for several days and then every six hours.
2. Give ½ grain (0.03 Gm.) of sodium bicarbonate with each grain (0.06 Gm.) of sulfanilamide orally.

* Preferably day and night.

TABLE VI[51]

DOSAGE OF SULFANILAMIDE AND NEOPRONTOSIL FOR PARENTERAL ADMINISTRATION

	1% Solution of Sulfanilamide			5% Solution of Neoprontosil		
Infection	Per Lb.*	Total in 24 Hrs. per Lb.	Equivalent per 150 Lbs. in 24 Hrs.	Per Lb.*	Total in 24 Hrs. per Lb.	Equivalent per 150 lbs. in 24 Hrs.
Very severe.....	1 cc.	4 cc.	600 cc. (6 Gm.)	0.2 cc.	0.8 cc.	120 cc. (6 Gm.)
Moderately severe...	0.6 cc.	2.5 cc.	400 cc. (4 Gm.)	0.1 cc.	0.5 cc.	80 cc. (4 Gm.)

1. This method of administration is to be used in case of vomiting or inability to swallow (comatose state).

2. A 1 per cent solution of sulfanilamide may be used (subcutaneously or intravenously) or a 5 per cent solution of neoprontosil (subcutaneously or intramuscularly).

*Every six hours.

TABLE VII[51]

DOSAGE OF SULFANILAMIDE AND NEOPRONTOSIL FOR COMBINED ORAL AND PARENTERAL ADMINISTRATION

Infection	Total Dose per 20 Lbs. in 24 Hrs.	Oral Dose per 20 Lbs. Every 4 Hrs.	Parenteral Dose per 20 Lbs. Every 12 Hrs.	
			1 per Cent Sulfanilamide	5 per Cent Neoprontosil
Very severe.....	1.2 Gm. (20 gr.)	0.1 Gm.	20 cc. or	6 cc.
Moderately severe.....	0.8 Gm. (12 gr.)	0.1 Gm.	10 cc. or	2 cc.

1. This method is always advisable for the first two to six days in severe infections.

2. It may be continued until convalescence is established if full dose cannot be given orally.

3. Give oral doses every four hours and parenteral doses every twelve hours.

TABLE IX[71]

TOXIC MANIFESTATIONS

Manifestations		
Dizziness; depression; disorientation	Common	Requires caution in ambulatory patients
Anorexia and nausea.....	Common	Seldom requires stopping treatment
Vomiting*; acidosis.....	2 to 5%	Usually prevented by administration of alkalis; may require parenteral administration
Cyanosis.....	Common	Of little clinical significance
Drug Fever.....	3 to 9%	May be forerunner of hemolytic anemia or agranulocytosis; stop treatment
Dermatitis.....	1 to 3%	Best to stop treatment temporarily if not urgently required
Milk hemolytic anemia.....	Common	Not dangerous; watch carefully; treatment may continue
Severe hemolytic anemia.....	2 to 4% adults 8 to 10% children	Dangerous; stop treatment or continue with transfusions
Transient neutropenia.....	40 to 50%	Treatment may continue; but watch carefully
Agranulocytosis.....	Uncommon	Very dangerous; over 80% mortality rate; stop treatment
Toxic hepatitis.....	Rare	Stop treatment
Hematuria and uroliths*.....	Infrequent	Stop to reduce treatment; cautious dosage in cases of nephritis
Porphyrinuria.....	Infrequent	Caution in dosage
Peripheral neuritis**.....	Uncommon	Stop treatment
Inhibition of spermatogenesis...	Doubtful	No significance

* Particularly likely to occur after the use of sulfapyridine

** Particularly likely to occur after the use of sulfanilyldimethylsulfanilamide.

TABLE VIII[51]

DOSAGE OF SULFAPYRIDINE FOR THE TREATMENT OF PNEUMONIA

Patients	Dosage
Children	Orally: 1 to 1½ gr. per pound (0.13 to 0.2 Gm. per Kilogram) of body weight each twenty-four hours; divided into six doses
Adults	Initial dose, orally: 2 Gm. (31 gr.); then 1 Grm. (15 gr.) every four hours for a total of 25 Gm.*
	Intravenously:** 1 Gm. of sodium sulfapyridine dissolved in 25 cc. of saline solution every four to six hours
	Intramuscularly:** 1 Gm. of sodium sulfapyridine dissolved in 3 cc. of water every four to six hours

* Except when treatment is started on or after fifth day (total 15 Gm.).
** For children: Less according to age and weight. Especially advisable in the treatment of patients with pneumococcic meningitis.

If sulfanilamide be given by hypodermoclysis, either subcutaneously or intravenously, the dose of a 1 percent solution (prepared as in the previous chapter) is as follows:

The calculated dose[49] is the same as in the oral method. At initial hypodermoclysis half of calculated first day dose should be given; subsequent clysis should be given at 8 hour intervals with one-third of calculated first days dose being given.

Neoprontosil[49]

The oral dose of neoprontosil is the same as for sulfanilamide.

For prontosil solution given by subcutaneous route doses are:

40 pounds or under - - 1.5 cc per pound per day

50 to 120 pounds or over - - 1 cc. per pound per day.

This is given in divided doses at six hour intervals.

Sylfapyridine

There are no hard and fast rules regarding the total amount of this drug to be administered because of irregular and poor absorption from the gastro-intestinal tract. The blood level depends on many factors (see under sulfanilamide dosage) the most important being the degree of absorption. Long[47] has outlined the dose of sulfapyridine in severe infections including lobar pneumonia as follows:

Children

40 pounds or under - 1 gr. per pound body weight for initial dose

40 pounds or over - 7 gr. per pound for initial dose.

Then

1/4 initial dose four times daily for next four days

Then

1/2 the above four times daily for five days or until the temperature is normal.

1/4 level teaspoon of $NaHCO_3$ two times daily is given to combat acidosis.

In Adults

Initial dose - 4 gms. or 60 gr.

Then

1 gm. or 15 gr. every four hours until temperature has been normal for 48 hours

Then

1 gr. at 8 A.M., 12 - 4 - 10 P.M. for four days

Then

.5 gm. four times a day until patient is ready to leave his bed

1/2 level teaspoon $NaHCO_3$ is given three times per day.

Determinations of the blood levels of free and total sulfapyridine are essential for safe and adequate therapy and should range from 6 - 10 mg. percent in severe infections.

Chart VIII from Kolmer's[51] article deals with dosage of sulfapyridine in treatment of pneumonia.

(All charts are self-explanatory)

Dosage of Na sulfapyridine was taken up under the route of administration of this drug.

Sulfathiazole[53]

Sulfathiazole is poorly soluble and hence must be administered by the oral route. In the treatment of pneumococcic pneumonia in adults (patients over 14 years of age) the initial dose of sulfathiazole should be 4.0 gm., to be followed by 1.0 gm. every 4 hours day and night until the patient's temperature has been normal for 72 hours. Then discontinue the drug. In children ill with pneumococcic pneumonia the initial dose should be based on 0.15 gm. per kilogram (up to 25 kilograms body weight) and the total daily dose is calculated on the same basis. The total daily dose should be divided into 4 equal parts and administered at 6 hours intervals, until the temperature has been normal for 36 hours. Then stop the drug. Sulfathiazole should not be used in the therapy of any type of meningitis because the drug does not pass over readily into the spinal fluid.

The drug should not be used in the treatment of minor staphylococcic infections such as localized boils and small carbuncles or in mild furunculosis. In large boils or carbuncles, the initial dose for adults should be 4.0 gm., followed by 1.0 gm. every 4 hours, day and night, for from 5 to 7 days. In diffuse staphylococcic cellulitis, lymphangitis, or acute osteomyelitis, 4.0 gms. should be given as an initial dose, to be followed by doses of 1.5 gms. every 4 hours day and night as long as evidence of a spreading infection continues. Then reduce the dose to

1.0 gm. every 4 hours day and night and continue as indicated. In staphylococcic bacteremia the initial dose for adults should be 4.0 gms. followed by 1.5 gms. every 4 hours day and night until the temperature has been normal for 48 hours. The dose may then be reduced to 1.0 gm. to be given every 4 hours day and night for 14 days, at which time the dose may be reduced to 0.5 gm. every 4 hours day and night to be continued for a minimum of 14 days. In severe staphylococcic infections in children, the initial dose should be calculated on the basis of 0.2 gm. per kilogram of body weight (up to 20 kilograms of weight). The total daily dose is calculated on the same basis, and should be divided into six parts, given at 4 hour intervals day and night until the temperature has been normal for 48 hours. Then each dose may be cut by one-third and treatment should be continued at this level of dosage for 14 days, at which time the current dose may be reduced by one-half. In staphylococcic bacteremia there is a great possibility that a relapse may occur unless prolonged treatment with the drug is employed. In chronic staphylococcic infections, such as osteomyelitis, not enough information is available to warrant definite instructions as to the use of the drug.

It is to be remembered that surgical measures, both supportive and operative must be used in the treatment of staphylococcic infections in conjunction with sulfathiazole whenever indicated. Surgical drainage of purulent foci must be effected, because while the druf may halt the invasive manifestations of staphylococcic infection, it will not by itself cure areas of localized infections, and a flare-up of the infection from such areas is likely to occur if they are not properly drained.

Na sulfathiazole may be given intravenously by the same technique as for Na sulfapyridine. A 5% aqueous solution is employed and injected slowly.

CHAPTER VIII

CLINICAL TOXICOLOGY

Therapeutic doses of the sulfonamides[54] produces a wide variety of toxic manifestations, most of which are mild and of no consequence, but a few of which are serious and occasionally fatal. It is important to recognize these toxic responses, and to differentiate them from the illness for which sulfanilamide has been given. Despite the amount of publicity given to the toxic manifestations of these drugs it is possible to administer the drug widely and with relative impunity.

Anorexia, Nausea and Vomiting

Anorexia and nausea is a very common toxic manifestation. Vomiting occurs in about three to eight percent of patients being treated with sulfanilamide, however, vomiting constitutes a real problem when using sulfapyridine because of its frequency. Kinsman[55] offers two explanations for the cause of vomiting:

1. A local irritating action of the drug on the stomach
2. A central action on the vomiting center

However, Na sulfapyridine given intravenously causes vomiting which is strongly evidenced in favor of 2.

If vomiting is severe[56] the drug should be given by the parenteral route. The fluid intake should be kept up and NaCl should be administered to prevent dehydration and a hypochloremia from developing. Henshaw[58] administers sulfapyridine in milk and 100 percent oxygen is given

by inhalation to relieve nausea.

Nervous System

Dizziness, tinnitus, malaise, and headaches[54] are mild symptoms referable to the nervous system which are common and of no real clinical importance. Dizziness is more common with sulfanilamide therapy than with either sulfapyridine and sulfathiazole. The recognition of dizziness is important especially in people who drive cars, airplanes or other vehicles. Patients should be warned of this toxic manifestation.

True toxic psychosis[56] are very rare, fortunately, but if present they may take any form. If maniacal in type the drug should be stopped and the patient watched very carefully.

Neuritis either peripheral or central is also very rare but if present the drug should be stopped.

Cyanosis

Cyanosis occurs in 90 to 100 percent of patients receiving full doses of sulfanilamide.[56] It is less frequent and less intense after administration of sulfapyridine or sulfathiazole. The oxygen carrying capacity of the blood is not seriously impaired[54] and therefore cyanosis is not considered a serious problem. However in emphysema, any type of cardiac disease, anemia, pneumonia or when operative procedures are contemplated the necessity of relieving the cyanosis especially when due to methemoglobin arises. Cyanosis is then treated with methylene blue after the method of Wendel[62] and Hartman.[54] As to the method of production of the cyanosis there is considerable dispute.

Vigness and Spink,[57] Campbell,[63] Posner,[64] ascribed to the theory that cyanosis is due to the production of sulf-hemoglobin and methemoglobin. If this is true the oxygen carrying power of the blood would be decreased and at times seriously impaired and would produce an anemic anoxia. Dyspnea would then be a prominent feature accompanying the cyanosis. Therefore, it can be said that the production of cyanosis in any patient showing mild oxygen want from any cause (see Best and Taylor) should be considered a serious toxic manifestation and treated immediately.

However, Marshall and Waltz[59] and many others have failed to demonstrate any appreciable amounts of methemoglobin in the blood of patients treated with sulfanilamide and so concluded that a black pigment, an oxidation product of sulfanilamide is formed in the body and stains the red blood corpuscles without altering the oxygen carrying power of the blood. Archer and Discombe[60] advanced the theory that sulfanilamide served as a catalyst in the combination of H_2S and hemoglobin to form sulfhemoglobin. They therefore state that sulfates as cathartics were contraindicated with sulfanilamide therapy. However, the chief cause of the color is still in dispute.

Drug Fever

Drug fever is fairly common (3 - 11%) in sulfanilamide and sulfathiazole therapy but is relatively uncommon after use of sulfapyridine. It most commonly occurs between the 5th and 9th day but may occur anywhere from 1st to 13th day. There are three factors which differentiate

from the fever produced by the infection;[54]

1. Occurs most commonly from 5th to 9th day. Fever from infection is usually normal after 3rd day.

2. A secondary rise in fever after patient has shown clinical improvement suggests drug fever.

3. Onset of drug fever is usually accompanied by other mild toxic drug symptoms such as headache, dizziness, nausea, etc.

It is best to stop the drug and force fluids for 24 to 48 hours. This should be adequate to restore the temperature to normal.

Sulfonamide Dermatitis

Various rashes may occur and are usually preceded by fever and malaise. They are more frequent with sulfanilamide and sulfathiazole therapy but do not occur very often when sulfapyridine is being used. Rashes[56] may occur anywhere from 1st to 13th day, more common[54-56] from 5th to 9th. The rashes may be urticarial, angioneurotic edematous, erysipeloid, morbelliform, scarletiniform, petechical or purpuric and the lesion may progress to a exfoliating dermatitis. Usually[55] almost the entire body is affected, but in some instances the rash is limited to the buttocks or legs or is confined to palms of hands or soles of feet. There usually is no itching or discomfort.

In a certain[56] number of individuals photosensitization of the skin seem to play a role in the production of the rash. For this

reason patients receiving the sulfonamides should stay out of the sun until 3 days after cessation of the drug. Treatments other than expectant and symptomatic is unnecessary. It appears wisest to stop the drug unless the patients life depends on continuance. (For an excellent article on the application of these drugs to dermatology see (64).)

Disturbances in Acid-Base Equilibrium

During the administration of full clinical doses of sulfanilamide[54] an increase in the pH of urine due to renal excretion of Na and K accompanied by a decrease in the CO_2 combining power of the plasma is noted. These changes are usually not very serious and do not constitute a reason for discontinuance of the drug. Acidosis of any type has not been reported in sulfapyridine or sulfathiazole therapy. The nature of the changes noted is a matter of dispute as is the treatment. There are two schools of thought:

1. Primary alkali-deficit type of compensated acidosis.
   In this type there is renal loss of Na and K due to the fact that the renal tubules partially lose their ability to reabsorb fixed base, or a mobilization[65] of the basic ions in the blood with excretion in the urine. Long and Bliss[56] therefore recommend the simultaneous administration of $NaHCO_3$ with each dose of sulfanilamide.

2. Primary CO_2 deficit type of compensated alkalosis.
   Hartman[66] the chief proponent of this view states

that a CO_2 deficit alkalosi is produced by over-ventilation. The increased urinary excretion of basic carbonates is then merely a mechanism whereby the body tries to compensate for this alkalosis and therefore the administration of more alkali in the form of bicarbonate is considered irrational. As soon as enough base has been excreted in the urine to compensate for the CO_2 deficit the urine will shift to the acid side. Then if an alkaline urine is desired Ringer's lactate solution may be given; this would make a chloride deficit unlikely.

Because of this dispute the treatment of the condition is not settled. Three types of treatment are now in use:

1. $NaHCO_3$ with each dose (widely used)
2. Ringer's lactate solution
3. NaCl - advanced by Goodman and Gilman[54]

Toxic effects on the Red Cells

A. Mild Anemia[54]

This type of toxic manifestation is common in sulfanilamide therapy, rare with sulfapyridine and has not been reported with sulfathiazole. The anemia is macrocytic and hypochronic and hemolytic in character. The bone marrow[67] shows moderate normoblastic hyperplasia. If the hemoglobin drops to 60% the drug must be discontinued or a blood transfusion given along with ferrous sulfate 0.6 gm. daily.

B. Acute Hemolytic Anemia

This may occur with sulfanilamide or sulfapyridine but has not been reported with sulfathiazole. In practically all instances it makes its appearance in the first five days of therapy. The essential clinical and laboratory features are;[54]

Clinical	Laboratory
Nausea	Leukocytosis (up to 90,000)
Vertigo	Reticulocytosis
Fever	Hyperbilirubinemia
Pallor	Hemoglobinuria
Jaundice	Urobilinuria
Heptatic swelling	RBC - 1 - 4 million
	Hemoglobin reduced

The treatment[54-56] of this condition consists of

1. Discontinuance of the drug
2. Force fluids
3. Blood transfusion P.R.N.
4. Administration of iron salts
5. Frequent laboratory and clinical examination

Toxic Effects on White Blood Cells

Mild to severe forms of neutropenia or agranulcytosis occur early or late in the course of therapy with sulfanilamide and sulfapyridine. One case has been reported with sulfathiazole.[75] This type of toxic manifestation is not very common but one must always be on the lookout

for it. It is important to check the white blood cell count[56] daily on and after the 12th day of treatment up to the 25th day. If the count drops and the poly's are decreased it probably means the beginning of an acute agranulocytosis. The method of production is unknown but is probably due to a personal idiosyncrasy.

Treatment[54] of this condition consists of:

1. Immediate cessation of the drug
2. Force fluids to hasten elimination
3. 3 cc of pentnucleotide two times daily OR
4. Adenine sulfate 1 to 2 gms. daily
5. Blood transfusions - small and frequent

Hepatic Effects

Acute toxic hepatitis characterized by jaundice without anemia has occurred following sulfanilamide and sulfapyridine therapy, but not following sulfathiazole therapy (at least not reported). It occurs early or late and is usually accompanied by an exfoliative dermatitis. There is evidence of liver dysfunction[68] such as urobilinogenuria, elevation of serum bilirubin and the occurence of a direct Van de Bergh reaction.

Treatment consists of:

1. Immediate cessation of drug
2. Force fluids
3. Increase CHO in diet
4. Restriction of fats in diet

5. Intravenous glucose 5%

6. General symptomatic therapy

Hematuria and Anuria

Hematuria[56] has not been reported in the course of therapy with sulfanilamide but is quite frequently present when sulfapyridine and sulfathiazole are being used. This is due[69] to the formation and deposition of sulfapyridine and sulfathiazole crystals and concretions in the kidneys and ureters. If injury to the tubules, pelvis and ureters is serious enough anuria with concurrent azotemia may ensue.

Treatment consists of:

1. Stopping the drug

2. Forcing fluids

3. If vomiting is present NaCl must be given parenterally

Miscellaneous Toxic Effects[56]

1. Hyperleukocytosis up to 90,000

   Accompanies acute hemolytic anemia

2. Purpura hemorrhagica

   Occurs with sulfanilamide and sulfapyridine. Drug should be stopped.

3. Injection of Sclera and Conjunctiva

   Occurs frequently with sulfathiazole between 5th and 9th day.

4. Stomatitis

Very rare - occurs with sulfanilamide

5. Painful joints

Accompanies sulfathiazole and sulfanilamide therapy - rare.

6. Visual and Auditory disturbances

Reported with all three drugs - only rarely seen

Generally speaking sulfanilamide, sulfapyridine, and sulfathiazole are capable of producing about the same number of toxic manifestations but in varying degrees. However,[54] experimental studies in animals and clinical observations[73] indicate the sulfapyridine is more toxic than sulfanilamide and that sulfathiazole[74] is the least toxic of the three. A comparison of the toxicity is well shown in Chart XI while the toxicity of sulfanilamide is shown in Charts IX and X.

TABLE X[71]

THE TOXIC MANIFESTATIONS OF SULFANILAMIDE NOTED IN THE TREATMENT O
307 ADULT PATIENTS AND 101 CHILDREN

Type of infections, adult group
Streptococcic infections.....107
Other infections.....200

Type of infections, children
Streptococcic infections.....
Other infections.....

Toxic Manifestation	Frequency, Adults	Frequency, Children	Comment
Dizziness, anorexia nausea, vomiting	Anorexia common	Anorexia common	Rarely severe enoug discontinuing use o
Cyanosis	90 to 100%	90 to 100%	Of little clinical
Simple Fever	9%	3%	Very important warn stop use of sulfani
Dermatitis	1.6%	3%	Best to stop use of
Acidosis	3.6%	2%	Can be prevented is is given as a routi
Renal irritation	0%	0%	If renal function i is not excreted wel
Jaundice (without anemia)	0.6%	0%	Stop use of sulfani
Mild hemolytic anemia	Common	Common	Not dangerous: cont and observe patient
Acute hemolytic anemia	2.9%	8.9%	In general stop use drug may be given wi transfusions
Agranulocytic angina	0.3%	0%	Stop use of sulfani

* These 408 patients were kept in bed and under close observation during the major portion of their treatment with sulfanilamide.

TABLE X[71]

ANIFESTATIONS OF SULFANILAMIDE NOTED IN THE TREATMENT OF
307 ADULT PATIENTS AND 101 CHILDREN

t group
ns.....107
.....200

Type of infections, children
Streptococcic infections.....58
Other infections.....43

Frequency, Adults	Frequency, Children	Comment
Anorexia common	Anorexia common	Rarely severe enough to warrant discontinuing use of sulfanilamide
90 to 100%	90 to 100%	Of little clinical importance
9%	3%	Very important warning sign; always stop use of sulfanilamide
1.6%	3%	Best to stop use of sulfanilamide
3.6%	2%	Can be prevented is sodium bicarbonate is given as a routine
0%	0%	If renal function is low, sulfanilamide is not excreted well
0.6%	0%	Stop use of sulfanilamide
Common	Common	Not dangerous: continue use of drug and observe patient carefully
2.9%	8.9%	In general stop use of sulfanilamide: drug may be given with multiple transfusions
0.3%	0%	Stop use of sulfanilamide

ents were kept in bed and under close observation
or portion of their treatment with sulfanilamide.

TABLE XI[72]

THE CLINICAL TOXIC MANIFESTATIONS OF SULFANILAMIDE, ENOPRONTOSIL, SULFAPYRIDINE OR THE SULFATHIAZOLES WITH THEIR TIME OF APPEARANCE IN THE COURSE OF THERAPY

Toxic Manifestation	Sulfanilamide	Neoprontosil	Sulfapyridine
Nausea and Vomiting	Uncommon occurs early	Rare	Very frequent
Dizziness	Common occurs early	Rare	Common occurs early
Psychoses*	Rare occurs early 0.6%	Not reported	Reported 0.3%
Neuritis*	Rare generally early	Not reported	Not reported
Cyanosis	Very common occurs early and late	Rare	Faint, common, occurs early
Acidosis	Common if soda is not given, occurs at any time 1.9%	Not reported	Not reported
Fever*	Common, generally 5th to 9th day, may occur from 1st to 21st day 10%	Rare	Uncommon, generally 5th to 9th day may occur from 1st to 30th day 4%
Rash*	Common, may take almost any form, generally 5th to 9th day, may occur from 1st to 21st day 1.9%	Rare	Not very common, generally 5th to 9th day. May occur from 1st to 30th day 2%
Hepatitis**	Rare Early or late 6%	Not reported	Rare Early or late
Hematuria**	Not reported	Not reported	Common, generally 1st to 10th day 8%
Anuria with Azotemia **	Not reported	Not reported	Not uncommon, 2nd to 14th day. Blood pressure normal. Fundi normal .3%
Acute leukopenia** with Granulocytopenia	Not uncommon, 1st to 10th day 0.3%	Rare	Common, especially in children. 1st to 10th day 0.6%
Agranulocytic Angina**	Uncommon, generally between 17th and 25th day. May occur from 14th to 40th day 0.1%	Rare	Uncommon, generally between 17th and 25th day. May occur from 14th to 40th day 0.3%
Hyperleukocytosis*	In presence of acute hemolytic anemia	Not reported	In presence of acute hemolytic anemia
Mild Hemolytic Anemia	Very common early and late 3%	Rare	Common, early and late
Acute Hemolytic Anemia	Common, especially in negroes - generally 1st to 5th day 1.8%	Rare	Uncommon, generally 1st to 5th day .6%

TABLE XI[72]

ICAL TOXIC MANIFESTATIONS OF SULFANILAMIDE, ENOPRONTOSIL, SULFA- OR THE SULFATHIAZOLES WITH THEIR TIME OF APPEARANCE IN THE COURSE OF THERAPY

Sulfanilamide	Neoprontosil	Sulfapyridine	Sulfathiazole
Uncommon occurs early	Rare	Very frequent	Rare
Common occurs early	Rare	Common occurs early	Uncommon
Rare occurs early 0.6%	Not reported	Reported 0.3%	Not reported as yet
Rare generally early	Not reported	Not reported	Not reported as yet
Very common occurs early and late	Rare	Faint, common, occurs early	Uncommon, occurs early
Common if soda is not given, occurs at any time 1.9%	Not reported	Not reported	Not reported as yet
Common, generally 5th to 9th day, may occur from 1st to 21st day 10%	Rare	Uncommon, generally 5th to 9th day may occur from 1st to 30th day 4%	Common, 5th to 9th day 10%
Common, may take almost any form, generally 5th to 9th day, may occur from 1st to 21st day 1.9%	Rare	Not very common, generally 5th to 9th day. May occur from 1st to 30th day 2%	Very common, generally 5th to 9th day 5%
Rare Early or late 6%	Not reported	Rare Early or late	Not reported as yet
Not reported	Not reported	Common, generally 1st to 10th day 8%	Common, 1st to 10th day 2.5%
Not reported	Not reported	Not uncommon, 2nd to 14th day. Blood pressure normal. Fundi normal .3%	Reported 7th day 0.7%
Not uncommon, 1st to 10th day 0.3%	Rare	Common, especially in children. 1st to 10th day 0.6%	Reported as occurring 3rd to 10th day 1.6%
Uncommon, generally between 17th and 25th day. May occur from 14th to 40th day 0.1%	Rare	Uncommon, generally between 17th and 25th day. May occur from 14th to 40th day 0.3%	Not reported as yet
In presence of acute hemolytic anemia	Not reported	In presence of acute hemolytic anemia	Not reported as yet
Very common early and late 3%	Rare	Common, early and late	Not reported as yet
Common, especially in negroes - generally 1st to 5th day 1.8%	Rare	Uncommon, generally 1st to 5th day .6%	Not reported as yet
Rare	Not reported	Rare	Not reported

Acidosis	Common if soda is not given, occurs at any time 1.9%	Not reported	Not reported
Fever*	Common, generally 5th to 9th day, may occur from 1st to 21st day 10%	Rare	Uncommon, generally 5th to 9th day may occur from 1st to 30th day 4%
Rash*	Common, may take almost any form, generally 5th to 9th day, may occur from 1st to 21st day 1.9%	Rare	Not very common, generally 5th to 9th day. May occur from 1st to 30th day 2%
Hepatitis**	Rare Early or late 6%	Not reported	Rare Early or late
Hematuria**	Not reported	Not reported	Common, generally 1st to 10th day 8%
Anuria with Azotemia **	Not reported	Not reported	Not uncommon, 2nd to 14th day. Blood pressure normal. Fundi normal .3%
Acute leukopenia** with Granulocytopenia	Not uncommon, 1st to 10th day 0.3%	Rare	Common, especially in children. 1st to 10th day 0.6%
Agranulocytic Angina**	Uncommon, generally between 17th and 25th day. May occur from 14th to 40th day 0.1%	Rare	Uncommon, generally between 17th and 25th day. May occur from 14th to 40th day 0.3%
Hyperleukocytosis*	In presence of acute hemolytic anemia	Not reported	In presence of acute hemolytic anemia
Mild Hemolytic Anemia	Very common early and late 3%	Rare	Common, early and late
Acute Hemolytic Anemia	Common, especially in negroes - generally 1st to 5th day 1.8%	Rare	Uncommon, generally 1st to 5th day .6%
Purpura Hemorrhagia	Rare	Not reported	Rare
Injection of Sclerae* and Conjunctivae	Not reported	Not reported	Not reported
Visual Disturbances	Rare	Not reported	Rare
Jaundice**	With hepatitis or acute hemolytic anemia	Not reported	With hepatitis or acute hemolytic anemia
Painful joints*	Reported	Not reported	Not reported
Stomatitis	Rare	Not reported	Not reported
Gastro-intestinal Tract	Bleeding rare, diarrhoea uncommon	Not reported	Bleeding reported

* Best to stop drug and force fluids
** Imperative to stop drug and force fluids
\# Corrected for percentages -- J. A. M. A., February 8, 1941, page

ommon if soda is not ven, occurs at any me 1.9%	Not reported	Not reported	Not reported as yet
ommon, generally 5th 9th day, may occur om 1st to 21st day 0%	Rare	Uncommon, generally 5th to 9th day may occur from 1st to 30th day 4%	Common, 5th to 9th day 10%
ommon, may take al- ost any form, gen- rally 5th to 9th ay, may occur from st to 21st day 1.9%	Rare	Not very common, generally 5th to 9th day. May occur from 1st to 30th day 2%	Very common, generally 5th to 9th day 5%
are arly or late 6%	Not reported	Rare Early or late	Not reported as yet
ot reported	Not reported	Common, generally 1st to 10th day 8%	Common, 1st to 10th day 2.5%
ot reported	Not reported	Not uncommon, 2nd to 14th day. Blood pressure normal. Fundi normal .3%	Reported 7th day 0.7%
ot uncommon, 1st to 10th day 0.3%	Rare	Common, especially in children. 1st to 10th day 0.6%	Reported as occurring 3rd to 10th day 1.6%
ncommon, generally etween 17th and 25th ay. May occur from 4th to 40th day 0.1%	Rare	Uncommon, generally between 17th and 25th day. May occur from 14th to 40th day 0.3%	Not reported as yet
n presence of acute emolytic anemia	Not reported	In presence of acute hemolytic anemia	Not reported as yet
ery common arly and late 3%	Rare	Common, early and late	Not reported as yet
ommon, especially n negroes - general- y 1st to 5th day 1.8%	Rare	Uncommon, generally 1st to 5th day .6%	Not reported as yet
are	Not reported	Rare	Not reported as yet
ot reported	Not reported	Not reported	Common, especially in conjunction with rash & fever. 5th to 9th day 4%
are	Not reported	Rare	Not reported as yet
ith hepatitis or cute hemolytic nemia	Not reported	With hepatitis or acute hemolytic anemia	Not reported as yet
eported	Not reported	Not reported	Reported with rash etc.
are	Not reported	Not reported	Not reported
leeding rare, iarrhoea uncommon	Not reported	Bleeding reported	Not reported

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rected for percentages -- J. A. M. A., February 8, 1941, page 514.

CHAPTER IX

THERAPEUTIC USES OF THE SULFONAMIDES

It is of greatest importance[76] in the treatment of infection that the correct etiological diagnosis be made. Hence, it is a good plan to have the infective agent identified by bacteriological cultural methods. However, one should never hesitate to employ these drugs if one feels that upon the basis of clinical diagnosis, the existence of an infection known to respond to one of these agents has been proved. Chart 12, taken from Long[76] is an attempt to evaluate the comparative clinical value of orally administered sulfanilamide, sulfapyridine and sulfathiazole. In estimating the value of these drugs, Long has considered the following:

1. Controlled experimental data regarding the efficiency of the right drug in the particular type of infection under consideration.

2. Clinical knowledge concerning the efficacy of the drug.

3. Ease with which the drug is absorbed and excreted.

4. The toxic manifestation which may arise.

Before considering[1] the specific indications for sulfonamide therapy, it might be well to discuss briefly the precautions and contra-

indications which allow for the safe and rational use of these drugs.

Precautions - Sulfanilamide

1. Administer only to patients who are suffering from infections in which the drug is expected to be of value.

2. If possible, always establish a bacteriological diagnosis before starting the drug.

3. The patient should be seen at least once daily. If the patient is ambulatory he should be instructed in the early detection of toxic symptoms.

4. Individuals who are hospitalized should have their pulse, temperature, and respiratory rate recorded at four hour intervals.

5. Chills, fever, vomiting, jaundice, headache, deep or rapid breathing, weakness or sore throat constitute warning signals.

6. The hemoglobin and total white count should be determined at least every day because of the possibility of acute hemolytic anemia or agranulocytosis.

7. The blood level must be determined as often as possible to insure optimal concentrations.

8. The patients renal function must be known and factors inhibiting absorption should be closely observed.

Contraindication to Sulfanilamide

1. History of previous serious toxic reactions such as agranulocytosis, acute anemia, purpura hemorrhagica, drug fever, jaundice, etc.

Precuations and Contraindications with Sulfapyridine

1. The only absolute contraindication to this drug is the previous occurence of serious toxic manifestations as under sulfanilamide.

2. If renal function is impaired proceed with caution because of the formation of concretions in the kidney with this drug.

3. The evidence of toxic effect from this drug is greater so that extreme caution should be observed.

4. Those listed under sulfanilamide also apply here.

The contraindications and precautions to be observed in the therapeutic administration of sulfathiazole are similar to those previously outlined in detail for sulfanilamide and sulfapyridine.

Streptococcal Infections

Sulfanilamide is considered the drug of choice in the treatment

of Beta hemolytic streptococci infections by Long,[76] Goodman and Gilman,[54] Brown,[77] Kolmer,[70] and many others. Dramatic results are rarely seen when the invading organism belongs to Lancerfield Group B C or G. Patients ill with streptococcus viridans[54] septicemia respond well to sulfanilamide but this drug is relatively ineffective in infections caused by anaerobic streptococci.

Fortunately most serious streptococcal infections in man are due to Lancerfield G-A hemolytic streptococcus (Beta hemolytic streptococcus).

Included in this group are:

1. Acute otitis media
2. Acute hemolytic septicemia
3. Acute tonsillitis or pharyngitis
4. Acute laryngitis
5. Erysipelas
6. Purpueral sepsis
7. Streptococcal meningitis
8. Streptococcal peritonitis
9. Streptococcal pneumonia
10. Enpyema
11. Septicemia
12. Osteomyelitis
13. Cellulitis
14. Ludwigs angina

The committee on chemotherapeutic agents of the National Research

Council headed by Perrin H. Long[78] has recommended that sulfanilamide be used in the treatment of hemolytic streptococci infections - as follows:

A. Severe hemolytic streptococcus infections such as meningitis, septicemia, severe cellulitis, acute osteomyelitis, and acute mastoiditis.

1. Drug of choice - Sulfanilamide
2. Dosage - initial dose 6 gm. oral; 1 gm. every four hours until temperature is normal for 7 days. Then .5 gm. four times daily for at least 10 days after a clinical cure has been effected.

B. Mild or moderate severe hemolytic streptococcus infections such as Erysipelas, mild cellulitis, and tonsillitis.

1. Drug - Sulfanilamide
2. Dosage - Initial dose - 2 gm. Then 1 gm. every four hours until temperature normal for 5 days.

C. Otitis media

This condition is generally caused by hemolytic streptococcus but may be caused by pneumococci or other organisms. Treatment should be started as under B. If an bacteriological analysis the infecting organism turns out the pneumococcus or

staphylococcus sulfathiazole should be substituted, the dose being 1 gm. every four hours until temperature is normal for 5 days, then .5 gm. four times daily for at least ten days after a clinical cure.

Pneumonia

Evans and Gaisford[79] were the first to report a series of cases treated with M. and B. 693. Their results showed a mortality of 8% as compared with 27% in a control series. Since that time the literature has been flooded with reports on the treatment of pneumonia by chemotherapeutic agents. "Pepper et al"[79] reporting on 400 cases showed a gross mortality of 7% on all types of pneumonia using sulfapyridine. (Long[81] reported a mortality of 7.2% and concluded that sulfapyridine is far superior to sulfanilamide in treatment of this disease).

Following the introduction of sulfathiazole many reports have appeared confirming the efficacy of sulfapyridine and sulfathiazole in the treatment of pneumococcal pneumonia. Wagoner and Hunting[82] reporting on a study of 101 patients concluded that sulfathiazole is as effective as sulfapyridine in the treatment of pneumonia, only one death was reported in this series. Volini, Levitt and O'Neill[83] made a comparative study in 169 patients. Their results showed that sulfathiazole was as effective an agent as sulfapyridine in the treatment of pneumonia due to pneumococcus. They also concluded that sulfapyridine was more effective in type I and III while sulfathiazole proved better in types II and VII. Peters[84] studying 8,134 cases collected from the

literature showed a mortality of 18.5% for serum treatment cases; 7.9% for sulfapyridine treated cases. In a recent analysis of 3000 cases[85] under the pneumonia control program of the State of Illinois the mortality of serum treatment alone in 170 patients was 14.7%, with sulfapyridine in 1167 patients mortality only 3.8% while in 1464 cases of combined drug and serum the mortality was 10.9.

Blake[105] in treating 109 cases of pneumococcal lobar pneumonia with sulfapyridine alone, 41 with sulfapyridine and anti-pneumococcis serum and 100 with sulfathiazole concluded that chemotherapy alone is adequate in bringing about prompt recovery in most patients under forty and in the later decades of life it is often remarkably efficient except in people suffering from severe chronic disease. Blake also concluded that sulfathiazole was the drug of choice.

The relation of specific sera to sulfapyridine in the treatment of pneumonia has been set forth by Dr. O. Robertson,[85] professor of medicine of the University of Chicago.

A. Advantages of specific sera and sulfapyridine therapy

	Serum	Sulfapyridine
1. Termination of disease in early cases	6-12 hours	2-5 days
2. Physician time required for administration	2-4 hours	-0-

	Serum	Sulfapyridine
3. Discomfort of patient during treatment	very little	may be marked
4. Toxic reaction	slight	may be marked
5. Fatalities from treatment	0	rare
6. Serum sickness	15%	0
7. Occurrence of complications	rare	?
8. Period of hospitalization	10 days	10 days
9. Results on Mortality	5-8%	5-8%

B. Limitations of specific sera and sulfapyridine therapy

Specific sera	Sulfapyridine
1. Serum sensitiveness	1. Patients with damaged kidney
2. Asthmatics	2. Patients with liver disease
3. Small children	3. History of previous sulfonamide toxicity
4. Severe cardio vascular disease	4. Diversity of toxic reactions
5. Type III pneumococcus infections	

6. Types for which serum not
available immediately

7. Pneumococci which do not
fall in one of 32 types

The committee on chemotherapeutic agents[78] of the National Research Council has recently published a report representing the combined efforts of the best known men in the chemotherapeutic field. The treatment of pneumonia in this report is as follows:

Classification of Pneumonia

A. Primary caused by:

1. pneumococcus principally
2. beta hemolytic streptococcus
3. Friedlander's bacillus
4. Staphylococcus

B. Secondary - complicating other diseases such as influenza, measles, etc., caused usually by:

1. higher types of pneumococci
2. betahemolytic strepococcus
3. haemophillus influenzal
4. staphylococcus
5. gram negative micrococci
6. streptococcus viridans

Treatment

A. Primary Pneumonia

1. Pneumococcal pneumonia

Chemotherapy is recommended in all cases because:

a. highly effective except in the aged with chronic disease

b. effective against all types of pneumococci

c. may be given at once without waiting for type determination

d. administration technique is simple and inexpensive

e. applicable to treatment of most bacterial pneumonia other than pneumococci

Sulfathiazole is recommended as the drug of choice because:

a. greatly superior to sulfanilamide in scope and effectiveness of therapeutic actions

b. at least equivalent to sulfapyridine in scope and effectiveness of therapeutic action

c. causes much less nausea, vomiting and mental disturbances than sulfapyridine

d. other untoward reactions are less frequent and less severe than sulfapyridine

e. the problem of excessive acetylation is not encountered to same degree as it is with sulfapyridine.

Administration of sulfathiazole should be started at once - etiological diagnosis being carried out at the same time. Initial dose (oral) 4 gm. - then 1 gm. every four hours until temperature has been normal for 72 hours. If patient unable to take the drug orally or the infection very severe sodium-sulfathiazole (5% solution) may be given intravenous in a dose of .06 gm. per kilogram of body weight. An initial dose of 4 gm. followed by 2 gm. every six hours should be given.

Serum therapy is recommended in addition to sulfathiazole for

1. Patients with early stages of the disease (72 hours after onset) only when they have failed to show satisfactory response to 48 hours of chemotherapy.

2. Patients with late stages of the disease (72 hours after onset) who have a bacteremia or who have failed to respond to chemotherapy alone.

The dosage is 200,000 units of anti-pneumococcal rabbit serum intravenous to patients with early stage and 300,000 in a severe form or late stages. If these prove insufficient 100,000 units may be given every 8 hours.

2. Primary Pneumococcia due to Hemolytic streptococcus, Friedlander's bacillus and staphylococcus

Sulfathiazole is recommended in all cases. Method of treatment is same as for primary pneumococci pneumonia.

B. Secondary Pneumonia

Sulfathiazole is recommended in all cases in which pneumococci, hemolytic streptococci, staphylococci, or Friedlanders bascilli are found and believed to be of etiologic significance. The method and dosage are same as in cases of primary pneumonia. Chemotherapy with the sulfonamides is of no demonstrated value for many patients with broncho-pneumonia of indeterminate (visur) etiology, with streptococcus viridans or haemophilus influenzae.

Meningitis

In meningitis due to hemolytic streptococci excellent results have been obtained with sulfanilamide therapy. Silverthorne and Brown[86] compared the mortality rate before and after 1937 and found a mortality rate of 95 to 100% before the advent of chemotherapy. This rate has been reduced to 22 to 30% since the use of sulfanilamide. Neal and Applebaum[87] Long and Bliss,[2] and many others have confirmed Silverthorne's and Brown's observations.

In the treatment of meningococcal meningitis Banks[88] reported a mortality of 16.9% in patients treated with combined serum and sulfanilamide while a rate of 6.6% with sulfanilamide and sulfapyridine treatment alone.

Perry[89] reported on 900 cases of meningitis treatment with sulfapyridine with a mortality rate of 6 to 7% - no serum was used in this series.

Specific treatment meningococcus meningitis[78]

1. Serum - not generally recommended
2. Chemotherapy - sulfanilamide is recommended as the drug choice. Initial oral dose is 6 gm. followed by 1 gm. every 4 hours until temperature has been normal for 7 days. The intrathecal administration is not indicated.

Purulent Meningitis - treatment of[78]

In case the cause of a purulent meningitis is not promptly established chemotherapy should be instituted with sulfapyridine at once. Initial dose is 4 gm. followed by 1 gm. every 4 hours until temperature is normal for 7 days.

In streptococcal meningitis the treatment is the same as for meningococcus meningitis. It should be stressed that sulfathiazole should not be used in any form of meningitis.

Staphylococcal Infections

The clinical efficacy of sulfathiazole in the treatment of staphylococcal infections is well established. It is the only one of the sulfonamides, which is of any real value in this type of an infection and should be the drug of choice in all cases.

Treatment is as follows[78]

A. Localized Boils and Carbuncles

1. Small furuncles

a. Apply hot wet dressings

b. Incise and drain when definite fluctuation develops

c. Chemotherapy not indicated

2. Large boils and carbuncles

Sulfathiazole as drug of choice: initial dose of 4 gm. and 1 gm. every four hours. Hot packs and drainage must accompany the drug.

B. Diffuse cellulitis, Lymphangitis and acute osteomyelitis

1. Immoblize and elevate the infected part

2. Apply warm wet saline dressings

3. Give sulfathiazole - 4 gm. then 1.5 gm. every 4 hours until spreading of disease stops. Then 1 gm. every 4 hours for at least 7 days.

4. Employ surgical treatment for any areas of localized suppuration.

C. Staphylococcal Bacteremia

1. Give sulfathiazole - initial dose 4 gm. followed by 1.5 gm. every 4 hours until patients temperature has been normal for 48 hours then 1 gm. every 4 hours for 14 days.

2. Identify foci and drain.

D. Chronic Staphylococcal Suppuration (as in chronic osteomyelitis)

1. Maintain drainage by packing with petrolatum gauze to the depths of the wound until sequestration of necrotic bone and tissue has occurred and wound is covered with clean granulations.

2. Oral administration of sulfathiazole is not much value. Local application of powdered sulfathiazole may be helpful.
Boggs,[90] however, has had good results with the use of sulfathiazole in treatment of osteomyelitis.

Gas Bacillus Infections

Sulfanilamide[54] has revolutionized the therapy of infections caused by clostridium Welchii with the consequent saving of life and limb. A review of the literature on this subject by Kolmer[51] clearly shows the effectiveness of this drug on Clostridium Welchii infection in both vivo and vitro studies. The author is familiar with a case reported by Cosgrove and Barry[91] in which remarkable success was attained by the combined use of gas-bacillus anti-toxin and sulfanilamide.

Specific treatment of Clostridium Welchii infections[78]

All rational surgical procedures, such as debridement, should be

carried out as soon as possible and all necessary supportive treatment be administered.

A. Serum therapy

1. Prophylactic Dose

polyvalent-tetanus gas gangreen antitoxin 5,500 units

2. Therapeutic Dose

20,000 to 40,000 units given intravenously - repeat in 12 - 24 hours if necessary.

B. Chemotherapy

1. Prophylaxis

Sulfanilamide - drug of choice - Initial dose 6 gm. followed by 1 gm. every 4 hours for 7 days.

2. Treatment

Initial dose of sulfanilamide is 6 gm. Subsequent doses of 1 gm. every 4 hours until temperature is normal for 48 hours - then 0.5 gm. every 4 hours until complete recovery. Crystalline sulfanilamide may be used locally with 0.1 gm. per sq. inch of surface treated.

Virus Disease

Among the disease which are caused by filterable viruses, the only clear evidence of therapeutic activity of these drugs is in lymphogranuloma venerum in which both sulfanilamide and sulfapyridine seem to

be about equally valuable. In other virus disease such as the common cold, influenze, poliomyelitis and smallpox, therapy with these drugs has been useless. Torpin et al,[92] Earle,[52] Hamilton,[94] and Marino et al,[93] have reported the value of sulfanilamide therapy in the treatment of lymphogranuloma inguinale. There is considerable dispute at present as to whether the drug acts directly on the virus or whether it influences only the secondary invaders. However, it is generally admitted that regardless of where the action of the drug is exerted it causes a marked symptomatic improvement with the closing of fistulas and the alleviation of complicating rectal strictures.

Urinary Infections

The results of sulfanilamide[54] therapy in the treatment of urinary tract infection are most satisfactory. More than 90% of uncomplicated bacillurias can be entirely cured. Generally speaking sulfanilamide is highly effective against[70] B. coli, bacillus proteus, hemolytic streptococcus and staphylococci. It is ineffective[54] in streptococcus fecalis and non hemolytic green and hemolytic enterococci. Rammel Kamp and Stoneburner[95] using sulfathiazole in treatment of urinary tract infection due to escherichia coli, bacillus proteus and staphylococcus aureus concluded that this drug was highly effective. Comparison studies in vitro by these men showed that sulfathiazole was the most effective bacteriocidal, and bacteriostatic sulfonamide against E coli, B proteus and staphylococcus aureus. Mandelic acid should be used when the causative agent of the urinary tract infection is either streptococcus fecalis,

enterococci (hemolytic or non hemolytic) and Group D hemolytic streptococci because the sulfonamides are ineffective against these organisms. It should also be remembered that mandelic acid acts only in an acid urine and should not be used in infections with B proteus because this organism splits urea and consequently renders the urine alkaline.

Undulant Fever

Menefee and Poston[97] tested the action of sulfanilamide in vitro on brucella organisms of the caprine, bovine, and porcine types. They found that this drug exerts a marked bacteriostatic action on these organisms but they were unable to demonstrate any marked bacteriocidal effect. Clinically the drugs hasten recovery with early alleviations of fever and other symptoms but according to Schroeder[96] relapses are frequent so that according to Kolmer[70] the continuous administration of either sulfanilamide of sulfapyridine in decreasing dose for at least two months following a clinical cure is indicated.

Chancroid

Previous to the advent of the sulfonamides[70] all drugs employed have proved ineffective in the management of this tedious disease which has no mortality and causes no chronic invalidism but is ranked as the highest type of a nuisance. Greenblatt and Sanderson[98] treated 113 cases of chancroid with sulfanilamide giving 400 to 500 gr. over a period of 1 - 2 weeks. The result was so good that they consider the drug a specific for this disease. Hutchison[99] treated 35 cases of chancroid by 3 different methods for the purpose of comparisons. Here are the results:

	Hospital Stay
1. Heat locally - antiseptic applied to ulcers	46.2 days
2. Ducrey Baccilis vaccine	46.7 days
3. Sulfanilamide	15.5 days

Gonoccal Infections

Sulfanilamide and sulfapyridine have been employed successfully in the treatment of gonococcal infections including urethritis, prostatitis, epididymitis, salpingitis, cervicitis, vulvovaginitis, opthalmitis, orchitis, endocarditis, meningitis, and peritonitis[58] Silver and Elliott[100] report cures of 58.5% in less than a month in treatment of 200 cases. In 1425 patients 47% were cured in less than a month and the duration of attendance at the clinic was reduced from an 83 day average in 2000 patients in 1936 before sulfanilamide was used to 31 days with sulfanilamide therapy. Prebble[101] in a series of 246 patients with gonorrhea using sulfapyridine effected a cure in 66% of his patients, 24% were apparently cured and 9.7% were failures or had relapses. Dees and Young[102] analyzing 2,727 cases of gonorrheal urethritis treated with sulfanilamide found that 68% were cured. In 669 cases local treatment was also given with 58% cures. The dosage recommended by them is 80 gr. daily for 2 days; 60 gr. daily for 3 days; and 40 gr. daily for 5 - 8 days. Many believe that[54] sulfapyridine is definitely superior to sulfanilamide and should be preferred to it in the treatment of gonococcal infections (for dosage see Chapter VII).

Batchelor et al[103] treated 939 cases of gonorrhea with either sulfanilamide or sulfapyridine. He found the sulfapyridine was much easier to use and recommended the following doses:

> First to fourth day, 4 gm. daily; fifth to eighth day 3 gms. daily, ninth to fourteenth day, 2 gms. daily; making a total of 40 gms. Irrigation and antiseptic treatment should not be employed during the first week but may be added thereafter, if the healing is incomplete. Mahoney, Wolcott, and Van Slyke[104] report their experiences in the treatment of gonorrheal infections with sulfathiazole. 106 patients were treated with sulfathiazole and the cure rate was 91% showing that sulfathiazole is an infective addition to the therapy of gonorrhea.

Rheumatic Fever

It has been the general belief that the sulfonamides are not only without curative effect but their use is contraindicated in the treatment of rheumatic fever. However, in the February 15, 1941, issue of J.A.M.A., Thomas et al[106] report some very interesting results with the use of sulfanilamide in preventing recurrences of acute rheumatic fever. They gave the drug continuously, from November to June, in doses of 1.2 gm. daily, to a group of 55 patients who had a recent history of acute rheumatic fever. Sixty-seven patients with a similar history were given no prophylactic treatment with sulfanilamide. None of the patients who received sulfanilamide had a major attack of acute rheumatic fever or

an acute beta hemolytic streptococcus infection while 15 of the patients receiving no treatment developed recurrent acute rheumatic fever during the control period. Their results definitely prove that sulfanilamide has a place in the prophylactic treatment of reoccurrences of rheumatic fever.

Scarlet Fever

The committee on chemotherapy of the National Research Council[78] recommend the following treatment for scarlet fever:

1. Active Immunization with Toxin - This procedure is not recommended for the following reasons:
   a. High percentage of immune subjects among adults
   b. Five or more injections of toxin are usually required to produce immunity.

Exception: Active immunization should be used for nurses with positive reactions to Dick tests and for orderlies assigned to care for patients with scarlet fever.

2. Simple Toxic Scarlet Fever (Exanthematous Stage)

   Specific treatment:

   a. Antitoxin: Recommended in all cases in which the disease is moderately severe to extremely severe and the patient is not hypersensitive to horse serum. The antitoxin should be given in one dose as soon as the diagnosis is made, intramuscularly if the disease is moderately severe and intravenously

if it is severe to extremely severe, according to the following schedule: moderately severe, 18,000 units; severe, 27,000 to 36,000 units, and very severe, 45,000 units.

b. Sulfanilamide: No therapeutic effect on the toxic stage. It should be used for prophylaxis of septic complications in the dosage of 0.5 gms. four times daily for the period of the quarantine.

3. Toxic and Septic Scarlet Fever (Exanthematous Stage)

Specific treatment:

a. Antitoxin (globulin concentrated): Recommended as stipulated in the foregoing section. Patients with early septic lesions (purulent rhinopharyngitis, sinusitis, otitis media, mastoiditis, or marked lymphadentis, and so on) in general are actually or potentially more toxic than patients with simple toxic (uncomplicated) scarlet fever. The doses used should be larger, according to the following schedule: if the disease is moderately severe, 27,000 units; if severe, 45,000 units, and if very severe, 63,000 units.

b. Sulfanilamide: Recommended in addition to antitoxin for its chemotherapeutic effect on septic lesions. Initial dose: 6 gm. Subsequent doses: 1 gm. every

four hours, day and night, until the temperature has been normal for five days; then 0.5 gm. four times daily for the period of quarantine.

4. Late Septic Complications (Postexanthematous Stage)

Specific treatment:

a. Antitoxin: of no value; not recommended.

b. Sulfanilamide: Recommended; dosage and duration of treatment as given in the foregoing section.

5. Precautions:

a. Antitoxin: The usual precautions employed in giving horse serum should always be used. Serum disease may be expected in approximately 25 per cent of cases.

b. Sulfanilamide: Symptoms and signs of acute hemolytic anemia, neutropenia, drug fever, dermatitis and hepatitis should be watched for carefully and sulfanilamide stopped at once if they appear.

In the previous discussions on the therapeutic uses of the sulfonamides an attempt was made to present conditions in which the use of these drugs has proved of definite value. However there are numerous other diseases in which the true value has not yet been established. For a detailed estimate of the comparative clinical value of these drugs Chart XII should be consulted. There are certain infections[54] known

to be uninfluenced by sulfonamide therapy including syphilis, tuberculosis, malaria, typhoid fever and virus disease. They can be used if secondary infections complicate these diseases.

TABLE XII

An ESTIMATE OF THE COMPARATIVE CLINICAL VALUE OF ORALLY ADMINISTERED SULFANILAMIDE, NEOPRONTOSIL, SULFAPYRIDINE OR THE SULFATHIAZOLES IN THE TREATMENT OF INFECTIONS

Disease	Sulfanilamide	Neoprontosil	Sulfapyridine	Sulfathiazoles
OLYTIC STREPTOCOCCAL INFECTIONS				
Tonsillitis	++++	++++	++	
Pharyngitis				
Peritonsillar Abscess	++++		++	
Ludwig's Angina	++++		++	
Acute Sinusitis	++++		++	
Otitis Media	++++	+	++	
Mastoiditis	++++	+	++	
Meningitis	++++	0	++	
Erysipelas	++++	++++	++	
Scarlet Fever	++++		++	
Adenitis	++++	++	++	
Cellulitis	++++		++	
Pneumonia	++++		++	
Empyema	++++		++	
Peritonitis	++++		++	
Puerperal Sepsis	++++		++	
Septicemia	++++		++	
Osteomyelitis	++++		++	
Ulcers	++++	++	++	
Impetigo				
Miscellaneous	++++		++	
VIRIDANS STREPTOCOCCAL INFECTIONS				
Abscess	++		++	
Osteomyelitis	++		++	
Tooth Sockets	++++			
Endocarditis	+		+	
Meningitis	++++		++++	
Septicemia	++++			
NON-HEMOLYTIC STREPTOCOCCAL INFECTIONS				
ANAEROBIC STREPTOCOCCAL INFECTIONS	0		0	
PNEUMOCOCCAL INFECTIONS				
Pneumonia	+	0	++++	++
Meningitis	+	0	++++	
Peritonitis	+		++++	
Otitis Media	++	0	++++	++
Mastoiditis	++	0	++++	
Sinusitis	++	0	++++	
MENINGOCOCCAL INFECTIONS	++++		++	
BRUCELLA INFECTIONS	++		++	
GONOCOCCAL INFECTIONS				
Male Gonorrhea	++++		++++	
Female Gonorrhea	++++	+	++++	
Vulvo-vaginitis	+		+	
Arthritis	++++		++++	

Vulvo-vaginitis	+		+
Arthritis	++++		++++
Endocarditis	++++		++++
Ophthalmia	++++		++++
STAPHYLOCOCCAL INFECTIONS			
Sepsis	+		++
Pneumonia	+		++++
Carbuncle	+		++
Meningitis	+		++
Endocarditis	+		
Osteomyelitis			++
E. COLI TISSUE INFECTIONS	++		++
CHANROID	++++		++
TYPHOID FEVER	0		0
PARATYPHOID FEVER	0		0
GAS GANGRENE	++++		++
TULAREMIA	0		0
TUBERCULOSIS	0		0
INFLUENZAL MENINGITIS	+		++
FRIEDLANDER'S INFECTIONS	+		++++
URINARY TRACT INFECTIONS			
E. coli	++++		++
A. aerogenes	++		++
B. pyocyaneus	+		+
Proteus	++++		
Enterococcal	0	0	0
Staphylococcal	++		++
Group B Hem. Strept.	++		++
ACTINOMYCOSIS	++		
TRACHOMA	++++		++
ULCERATIVE COLITIS	+	++	
MALARIA	+	+	+
ROCKY MOUNTAIN SPOTTED FEVER	0		
TRICHOMONAS	0		
LUPUS ERYTHEMATOSUS	+		
PHEMPHIGUS	+		+
VIRUS DISEASES			
Lymphogranuloma Venereum	++++		++++
Common Colds	0	0	0
Influenza	0	0	0
Poliomyelitis	0		0
Small Pox	0		0
RHEUMATIC FEVER	0	0	0

++++ = Preferred Drug
++ = Active
+ = Slight Activity
0 = Should not be used
Blank = Insufficient Data for Evaluation

TABLE XII

An ESTIMATE OF THE COMPARATIVE CLINICAL VALUE OF ORALLY ADMINISTERED SULFANILAMIDE, NEOPRONTOSIL, SULFAPYRIDINE OR THE SULFATHIAZOLES IN THE TREATMENT OF INFECTIONS

	Sulfanilamide	Neoprontosil	Sulfapyridine	Sulfathiazoles
	++++	++++	++	
bscess	++++		++	
	++++		++	
	++++		++	
	++++	+	++	
	++++	+	++	
	++++	0	++	
	++++	++++	++	
	++++		++	
	++++	++	++	
	++++		++	
	++++		++	
	++++		++	
	++++		++	
s	++++		++	
	++++		++	
	++++		++	
	++++	++	++	
	++++		++	
AL				
	++		++	
	++		++	
	++++			
	+		+	
	++++		++++	
	++++			
OCOCCAL				
CAL				
	0		0	
IONS				
	+	0	++++	++
	+	0	++++	
	+		++++	
	++	0	++++	++
	++	0	++++	
	++	0	++++	
TIONS	++++		++	
	++		++	
NS				
	++++		++++	
ea	++++	+	++++	
s	+		+	
	++++		++++	

TIONS	++		++	
TECTIONS				
orrhea	++++		++++	
onorrhea	++++	+	++++	
ginitis	+		+	
s	++++		++++	
itis	++++		++++	
ia	++++		++++	
INFECTIONS				
	+		++	++++
	+		++++	
	+		++	++++
	+		++	
	+			
tis			++	++
INFECTIONS	++		++	++
	++++		++	
	0		0	
ER	0		0	
	++++		++	
	0		0	
	0		0	
NGITIS	+		++	
NFECTIONS	+		++++	
NFECTIONS				
	++++		++	
es	++		++	
eus	+		+	
	++++			
al	0	0	0	0
ccal	++		++	++
m. Strept.	++		++	
	++			
	++++		++	
TIS	+	++		
	+	+	+	
SPOTTED FEVER	0			
	0			
TOSUS	+			
	+		+	
nuloma				
reum	++++		++++	
lds	0	0	0	0
	0	0	0	0
itis	0		0	
	0		0	
R	0	0	0	

= Preferred Drug
Active
Slight Activity
Should not be used
k = Insufficient Data for Evaluation

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