5-1-1940

Effects of sulfanilamide

Robert Hillyer
University of Nebraska Medical Center

EFFECTS of SULFANILAMIDE

By

Robert Hillyer

SENIOR THESIS

PRESENTED TO THE COLLEGE OF MEDICINE

UNIVERSITY of NEBRASKA

OMAHA, 1940

EFFECTS of SULFANILAMIDE

THE EFFECTS OF SULFANILAMIDE

Para-amino-benzene-sulfonamide (now officially sulfanilamide) (1) still crests the wave of popularity. Its level of therapeutic value may be ultimately found at the crest of that wave, for the drug has withstood severest criticism from the time of practical revelation. Born in an age in which medical science is dominated by therapeutic nihilists, promoted in the face of world cognizance of its attributes and sandy foundation, and existing while these pitfalls were illustrated and explained, no nemesis has yet been indicated. The only way in which sulfanilamide has completed its undulation-- fallen from its crest-- has only been apparent, for we are rising to a level at which therapeutic value has always remained, more or less the same, with those who have followed closely the rules set forth long ago for safe usage. These rules collectively only require intelligent supervision during administration, as will further be shown.

Probably the main factor in keeping general impression of therapeutic value from undulating was the affair with Massengill Company of Bristol, Tennessee. A drug known as "Elixir Sulfanilamide" was manufactured by this concern. The following proportions were used in this "elixir" (2):

Sulfanilamide	58½ pounds
Elixir flavor	1 gallon
Raspberry extract	1 pint
Saccharin soluble	1 pound
Amaranth solution 1/16	1½ pints
Caramel	2 fluidounces
Diethylene glycol	60 gallons
Water q.s.	80 gallons

This solution was tested for flavor, according to the Food and Drugs Act, but not for effect on human life. Consequently at least 73 persons died as a direct result of taking this drug. Twenty others took the "elixir" but the exact cause of death could not be determined.

World-wide publicity accompanied the confiscation of this drug during the months of September and October in 1937. The company sent at least a thousand telegrams the first day, stubborn salesmen and physicians had to be dealt with by law, and a drag-net had to be set from coast to coast in a heightening drama that drew the scrutiny of all who would be interested.

Congress required a report from the Secretary of Agriculture, and it was seen that the diethylene glycol caused the fatalities.

Reverting from this parody in personal impression, the history of sulfanilamide is seen to be brief (3) (4). In 1908 a chemist by the name of Gelmo (5) was working on the azo dyes with an industrial interest. He first

mentioned the paraaminosulfonamide compounds. There was no clinical application of the azo dye stuffs until years later when many compounds of these dyes with sulfonamide were made. Eisenberg (6) first conceived their bactericidal powers. From these investigations sprang scarlet red, included in "New and Non-official Remedies" by the American Medical Association in 1912 as a valuable drug in the treatment of chronic ulcers and wounds. At the Dusseldorf Dermatological Society on May 17, 1933, (2) it was reported by Foerster that a red dye called Prontosil had had a remarkable effect in a child suffering from a staphylococcal pyaemia. Subsequently there were many reports on the effects of the dye chiefly in hemolytic streptococcal infections. Domagk (7) however, was the first to offer experimental proof. He pointed out the antistreptococcic action of certain azo dyes in artificially infected animals. Soon after this some French investigators (8) showed that the active factor in this red dye Prontosil was para-amino-benzene-sulfonamide, later re-named sulfanilamide. Many other workers varified this work (9-11). The azo dye was seen to be not the essential component. It was proved that the p-aminobenzenesulfonamide group is set free by the reduction of the prontosils in the body. In vitro also the prontosils must be

reduced before they become bacteriostatic. Mietzsch and Klarer (12)(1935) made a new compound from the original prontosil by adding an azonaphthalene ring to the sulfonamide group. This compound was the red dye which has been known and used as prontosil soluble and as prontosil and now is to be called neoprontosil. Domagk's work with the original prontosil in mice gave the impetus to the tremendous strides now being made in chemotherapy.

My purpose in writing this paper is to summarize the literature on this subject, attempting to procure, to my own satisfaction, a working plan for use of the drug, avoiding toxic manifestations. A recent case of toxic hepatitis in Omaha will be analized, and anything that may be in common with the toxic manifestations will be observed. The use of this drug in relation to the "practice of medicine" as well as to the "science of medicine" will be discussed from the influence of the reading.

It must be here stated that, since well over two thousand articles have been published in the last three years and several good books written on the subject (13, 14), this paper, in its brevity, can not pretend to be unbiased in its conclusions.

The effects of sulfanilamide and allied compounds are well, though not completely, studied. It is interesting to know that sulfanilamide was introduced as a specific chemotherapeutic agent for hemolytic streptococcic infections. In such a capacity it promised to rival salvarsan in chemotherapeutic advancements, but it has broken from this specificity, for further experimental and clinical trials showed that it had a wide, but peculiarly selective, effectiveness. Certain organisms are influenced by it while closely related organisms, for reasons which at present cannot be appreciated, are entirely unaffected.

Before the time when sulfanilamide was put to practical use clinically, there were many experiments carried on in attempts to understand the action of these compounds in vivo as in contrast to the action in vitro. Various organisms and many different experimental animals have been used. Many conclusions have been put forth that warrant acknowledgement. These suggestions have been well summarized as follows (15):

Sulfanilamide--

(1) acts mainly as a bacteriostatic agent;
(2) stimulates phagocytosis;
(3) neutralizes bacterial toxins;
(4) is bactericidal under certain conditions;
(5) delays the growth of organisms until mononuclear phagocytes accumulate;
(6) alters the organisms so that phagocytosis can take place.

The methods used have been quite variable and may account for many of the differences of opinion. The action may also be different with different organisms. The action of the drug as a bacteriostatic agent is most emphasized in the literature (11, 16-22). The very history of the drug implies that it has this effect, as has been briefly reviewed.

The point in question in study of effects here is whether sulfanilamide inhibits the growth of the bacteria, enhances the natural body defenses so that it can throw off the organism, or a combination of the two. The literature seems to show that the first of these is most obvious, but that the body defenses are bolstered as well, and now still further attributes are seen for the drug. There seems to really be three great groups of effects: (1) Those concerned with bacteriostasis, (2) those concerned with stimulating the natural body defenses, and (3) those concerned with destroying the harmful effects of the micro-organism, altering it in a way to spead the resolution of the infective process, or destroy it directly.

In the early periods of sulfanilamide history, when the bacteriostaticaction of sulfanilamide was many times shown by inhibition of the growth of streptococci

in cultures, and Colebrook, Buttle, and O'Meara (20) even exerted a belief that there was a bactericidal effect in the presence of whole blood, it was immediately thought that a similar effect in vivo might be the source of the therapeutic activity of the compounds. However, those workers who did find evidence of an inhibitory effect (23) felt that it was too slight to account for the remarkable qualities of the drug.

Many differences in technique vary the results. Long and Bliss (13) state, "We were unable to test, satisfactorily, strains of hemolytic streptococci belonging to Group F, owing to the fact that with these minute organisms large inocula are required to start growth even in drug-free broth. When sufficiently large inocula were used no bacteriostasis was found. The same was true for the minute members of Group G, although the regular streptococci in this group were highly sensitive to sulfanilamide." Thus the size of the inoculum is very important. In the same way these men have shown that the age of the culture, the virulence of the culture, difference in the medium, dilution of the medium, and other factors, make it impossible to draw any definite conclusions, but the fact that some benificial findings are almost omnipresent is an unimpeachable fact.

Mellon, Gross, and Cooper (14) bring up the question of possibility of a shock effect of sulfanilamide. They bring up the point that there is always a possibility that the infection of a foreign substance intravenously may in certain patients bring about a reaction. No more material is apparent in this point since their writing.

In connection with the idea that sulfonamide compounds aid in phagocytosis Levaditi and Vaisman (23) advanced the theory that these compounds in some way interfere with the development of the capsules of growing streptococci and thus deprive them of their virulence. This would be of special interest in study of action on pneumococci. The many works of these authors (23) do not lead to any definite conclusions regarding relation to phagocytosis, and they are one of the most dominant teams working on the question. In May, 1935 these men state that phagocytosis was only vigorous in the control mice of their experiments; Levaditi later claimed that an "intraleukocytic culture" was responsible for this confusion and stated that phagocytosis was enhanced; in June, 1935 they decided that it was more probable that the defenses of the germ were lessened; two years later their conclusions were

still not definite. Other writers seem to offer the same indefinite results.

It is of note that the leukocyte pattern of the blood is not changed in any way by administration of sulfanilamide or allied compounds (24, 25). The blood elements found in the tissues are also unchanged (26). Moreover, the sulfonamide derivatives have been found by a number of observers to be harmless to various kinds of tissue cells in cultures when applied in the concentrations used therapeutically (23, 29). Further, it has been shown that no chemotropic effect upon polymorphonuclear leukocytes is exerted (28).

The effect of sulfonamide compounds on the toxins of various micro-organisms or on the toxic affects of these infectious elements is a pressing question. This carries still deaper into detailed pathologic study. The effects of the compounds on various toxins have been studied by many men. Osgood and Brownlee (29) claim that sulfanilamide neutralized the hemotoxin of streptococci after the manner of an antitoxin.

By complicated study of the metabolism of micro-organisms which have been subjected to therapeutic concentration of sulfonamide compounds, it has been suggested by many works that, since this metabolism

is in many instances altered, there may be a direct bactericidal affect in some conditions (30-33).

The most recent work to be published is that of Lockwood and Lynch (34). If this work is varified it will incite a different attitude toward the mechanism of action of sulfanilamide than is now generally believed. These workers observed that amounts of peptone of only 1 mg% in culture medium had a definite effect on the population curve, with or without sulfanilamide, emphasizing the practical inaccuracy of most of the experimental work on the bactericidal action of blood and serum. Certain bacterial strains (apparently most of them) require these products of protein catabolism to obtain nitrogen for their own metabolism. They seem unable to utilize the more complicated combinations. Thus, normal human serum, without sulfanilamide, is not a good medium for propagation of even relatively invasive strains of hemolytic streptococci. On the other hand, the addition of peptone made the serum favorable for even the less virulent strains. The effect of sulfanilamide in vitro is, therefore, only maximal when even small traces of peptone are eecluded from the serum. Hence, it is likely that under these circumstances the serum medium

is deficient in the readily assimilable nitrogen necessary for biologic activity.

Lockwood and Lynch worked on the hypothesis that sulfanilamide interfered with the ability of hemolytic streptococci to utilize protein-split products in serum and that the presence of peptone provided assimilable nitrogen in such excess that sulfanilamide could no longer act with optimal effectiveness. They state, "The precise mechanism by which peptone interferes with the action of sulfanilamide is, we believe, necessary for any fundamental understanding of the action of sulfanilamide in vivo."

Working with freshly drawn human blood serum, defibrinated with glass beads, and an inoculum of young hemolytic streptococci, they prepared a series of tubes to incubate. In these were various concentrations of peptone and sulfanilamide together and separate. The same procedure was used with Bacillus coli in urine, and in a similar way the action of sulfanilamide on pneumococci and staphylococci, in human serum, was studied.

The population curves of the various concentrations show that by decreasing the concentration of sulfanilamide or increasing the concentration of pep-

tone the proliferation of the micro-organisms is enhanced by some direct or indirect fashion. The addition of peptone to sulfanilamide-free control serums produced a marked increase in the rapidity of outgrowth. A concentration of a hundred times as much sulfanilamide as peptone is necessary to produce bacteriostasis that is as great as in peptone-free serum containing sulfanilamide.

In the same work, Lockwood and Lynch experimented with urine and soon saw that in the presence of peptone sulfanilamide no longer had the power to reduce the population curve of the colon bacillus. They point out the fact that in the course of tissue breakdown peptone is present in plentiful amounts, and that this could account for the favorable action of sulfanilamide in the more generalized infections as contrasted to its failure to get response in more localized morbidity, in most instances and reports. Ballenger and his associates (35) show that conditions in the urinary tract which might lead to an increased production of products of tissue breakdown may account for failures of sulfanilamide therapy. Coincidently this seems highly feasible.

The same relations between concentration of peptone and sulfanilamide are shown with Staphylococcus

aureus are shown, and the effects of peptone on the actions of sulfanilamide and sulfapyridine on streptococci and the pneumococcus type III are studied. In the latter the action of sulfapyridine seems superior.

It is of special note that the presence of from 0.01 to 0.1 mg of peptone to a large extent overcomes the bacteriostatic effect of even 1 mg per cubic centimeter of sulfanilamide (See later-- local implantation).

With reference to the possibility that sulfanilamide may act as an anti-catalase, these writers point out that it acts on Bacillus coli which is generally considered to be highly resistant to the lethal effects of hydrogen peroxide.

Lockwood and Lynch offer amazing comment: "Normal human serum does contain minute quantities of free amino acids and other derivatives of protein catabolism. Since the organisms that are known to be susceptible to sulfanilamide are not in general actively proteolytic, it is reasonable to suppose that when they are inoculated into blood serum they depend at least in part on obtaining assimilable nitrogen for protein metabolism from previously hydrolyzed protein. Since the concentration of such free amino nitrogen is rarely high it is obvious that the addition of very small

traces of peptone may markedly alter the amount of assimilable nitrogen and thus significantly improve the status of the serum as a culture medium for non-proteolytic organisms, such as the hemolytic streptococcus. The fact that effective sulfanilamide action depends on the exclusion of added peptone suggests immediately that the drug must act in some way through interference with the ability of thebacteria to utilize the traces of assimilable nitrogen in whole blood, serum, urine or other body fluids.

"It is possible that sulfanilamide combines in some way with the free amino nitrogen of protein degradation products and renders them unsuitable for bacterial utilization. This particular point is still under investigation, but other possible explanations of the precise mechanism involved are also being studied. Such a concept would appear to explain why the sulfanilamide compounds are active only against certain organisms and in certain specialized mediums.

"Furthermore, it would explain the failure of sulfanilamide to destroy hemolytic streptococci in localized areas of tissue proteolysis, such as abscesses or heavily traumatized wounds. It would account for the failure of these drugs to act on the localized

suppurative lesions of staphylococcic origin and the successful results which have at times attended its use in diffuse staphylococcic cellulitis and bacteremia. This hypothesis is consistent with the spectacular effects of sulfapyridine in pneumococcic infections, because of the minimal tissue injury in the lung in pneumococcic pneumonia."

There will probably be much work similar to this, and its relations to the now prevailing concepts of the action of the sulfonamide compounds seem obvious. This summary of the article will be later referred to.

As previously shown, sulfanilamide was first thought of as a specific for hemolytic streptococcic infections. This concept has waned. The following outline (36) summarizes well the morbid conditions upon which the drug has a satisfactory, therapeutic effect. This is here presented as a foundation for discussion because it seems most representative of the literature.

CASES IN WHICH SULFANILAMIDE IS CERTAINLY USEFUL

Acute hemolytic Streptococcus Infections.
- Streptococcus Meningitis.
- Primary Streptococcus Peritonitis.
- Erysipelas.
- Streptococcus Septicemia from any source.
- Puerperal Infections.

Colon Bacillus Infections-- particularly of the Urinary Tract.

Meningococcus Meningitis and Meningococcemia.
Gonococcus Infections.
Undulant Fever (Brucellosis).
Chancroid (Ducrey's Bacillus).

CASES IN WHICH CLINICAL RESULTS ARE LESS CERTAIN BUT IN WHICH THE DRUG MAY BE OF VALUE

Acute Streptococcus Infections.

Tonsillitis	Bronchopneumonia
Otitis	Empyema
Mastoiditis	Cellulitis
Sinusitis	Adenitis
Scarlet Fever	Cholecystitis

Pneumococcus Infections.
Urinary Infections with B. Proteus, B. Typhosus, Staphylococcus aureus, and possibly other organisms.
Gas Bacillus Gangrene.
Ludwig's Angina.
Nonspecific Colitis.
Malaria.
Trachoma.

CASES IN WHICH SULFANILAMIDE IS OF DOUBTFUL OR NO VALUE

Most forms of Infectious Arthritis (lately successful).
Rheumatic Fever.
Staphylococcus General Infections (lately successful).
Influenza Bacillus Meningitis.
Friedlander Bacillus Infections.
Putrid Lung Abscess.
Urinary Infections With Streptococcus Fecalis.
Subacute Bacterial Endocarditis.

The earliest experiments, as shown in the introduction, were with peritonitis in eeperimental animals. It is essential that chemotherapy be started early, before the peritoneum is much damaged. Meningococcus and gonococcusinfections are remarkably held for resolution by sulfanilamide.

In cases of streptococcic meningitis the use of

sulfanilamide has been found to bring amazing results. The disease was formerly thought to be practically always fatal. It was only a chance of one in a hundred that recovery would be reached. Gray (37) found only 65 cases with recovery in the medical literature, and most hospitals have few records of recovery prior to use of sulfanilamide. In Johns Hopkins hospital (38) all patients admitted with this disease died, prior to institution of chemotherapy with sulfanilamide. Schwentker, et al (38), first reported the complete recovery of a patient suffering from such an infection in which the recovery was without a doubt due to administration of the drug. This marked the beginning of a new series of vital statistics as far as the disease was concerned. Arnold (39), and Smith and Coon (40) also reported recoveries in the same year, and since that time there have been numerous reports of the successful use of sulfanilamide in the treatment of hemolytic streptococcal meningitis (41-43). Neal (44) used a combination of neoprontosil and sulfanilamide. Long and Bliss (13) point out, however, that there is quite definite proof that Neoprontosil does not pass over into the spinal fluid, so there is little evidence which warrants the belief that the combined use of the drugs in hemolytic streptococcal meningitis is more effective

than is that of sulfanilamide alone. They state (page 169 in #13), "The available evidence tends to show that sulfanilamide has reduced the case fatality rate in hemolytic streptococcal meningitis from 97 per cent to about 35 per cent. This latter figure can be made lower if the disease is recognized in its inception and then intensively treated with sulfanilamide."

It is surprising that the literature offers so few references to streptococcus peritonitis. Most are associated with puerperal infections. Colebrook and Kenny (24) reported a series of cases of puerperal sepsis treated with prontosil. Of the ten patients, there were four with generalized peritonitis and six in which there were indications of a beginning generalized peritonitis. In this group of ten, there was one fatality. Foulis and Barr (45) reported four cases of generalized peritonitis with three recoveries. Long and Bliss (11) report one case with complete recovery. A recent article gives some good results with use of sulfanilamide in treatment of peritonitis associated with appendicitis. It is to be noted, however, that this series is not of specific infection, (46). With reference to their series of peritonitis cases in general, they state, "The mortality in a series of 809 consecutive cases of acute appendicitis has been reduced from 1.5% in the first 552 cases to 0.4% in

the last 257 cases. This improvement is, we believe, the result of the employment of sulfanilamide in all severe cases in the latter group." In relation to feasability they state, "Sulfanilamide readily diffuses into the peritoneal fluid in the experimental animal. All the available material indicates that the peritoneum is a favorable site for the action of sulfanilamide."

If means could be used to diagnose cases of primary streptococcus peritonitis, it is most probable that the mortality and course of infection could be reduced amazingly by employment of sulfanilamide.

There can be little doubt that the introduction of the sulfonamide compounds in chemotherapy has considerably reduced the mortality of erysipelas. Toomey (47) reported 1907 cases. In the 1313 untreated cases the mortality was 15.5%, in those in which antitoxin was used (520) it was 13%, and in 74 cases in which sulfanilamide was used the mortality was 4%. Snodgrass and his associates (48, 49) have shown that the mortality from the disease in the Ruchill Hospital in Glasgow, Scotland, has been reduced from 7.9% to 2.3%. These workers all show that the clinical course of the disease is shortened as well as its danger to

life lessened. The disease has always claimed more people in the aged and young groups. These groups seem to be especially aided by the drug. If any abscess formation occurs, surgical drainage should be instituted to hasten recovery. Dosage for the infection is quite as is used in other cases, however, some feel that it is especially important to have a high blood-concentration of the drug here.

Most of the cases of septicemia, as with the peritonitis cases, are in relation to puerperal infection or local infection or such, where the diagnosis is inferred. Colebrook and his associates (20, 24) in 1936 reported 12 cases of hemolytic streptococcal bacteremia among their puerperal sepsis cases. Of these, eight were uncomplicated by coexisting peritonitis. These patients were treated with prontosil. In one of these cases the blood culture showed 5,000 colonies on the first two days of treatment, 3,000 colonies on the third day, and on the fourth day of treatment the blood culture was sterile. The patient was discharged on the twenty-first day. In another case, sulfanilamide therapy for four days resulted in normal temperature and pulse, and in sterility of the blood which had previously yielded positive cultures.

In a third case the blood culture became sterile on the third day of treatment, metastatic abscesses associated with the bacteremia rapidly resolved, and the patient's general condition rapidly improved. In a fourth case, there was a spectacular remission of the signs and symptoms in twenty-four hours after the beginning of treatment, followed by a steady improvement of the patient's condition. There were three fatalities in this group of 12 patients. Foulis and Barr (45) encountered only one fatality in their series of cases of puerperal sepsis among which eight, including the fatality were septicemic. Robinson (50) presented a case of hemolytic bacteremia with bronchopneumonia following tonsillar enlargement and purulent cellulitis in the neck. Incision and drainage in the neck region was instituted and antiscarlatinal serum and sulfanilamide were used and the patient recovered. Scal (51) presented a case which followed a sinusitis and had concomittent joint involvement and recovered after administration of the drug. McCarthy (52) reported a case of postscarlatinal hemolytic streptococcal septicemia which was cured after use of neoprontosil and sulfanilamide. Whitby (53) reports four out of five favorable results. In all these reports it seems to

be essential that chemotherapy be maintained until complete recovery is obtained.

Other forms of septicemia have been reported as responding favorably to administration of the drug. Dyke (54) has reported that the administration of sulfapyridine brought about a prompt recovery in a patient who was ill with a pneumococcal septicemia occurring after a lobar pneumonia which was accompanied by empyema. O'Brien and McCarthy (55) noted the recovery of a patient who had been ill for sixteen days with a staphylococcal septicemia. Quite recently (56) two cases of bacteremia with Staphylococcus aureus hemolyticus were treated by administration of sulfanilamide with good results.

Colebrook and his associates in 1936 (24) showed that there were such remarkable results from the use of the sulfonamide compounds in puerperal sepsis that the fatality of the infection could be astonishingly reduced. Their work is so clear that it leaves no room for doubt. The clinical reports of publications since that time have not been able to enlarge upon the point to any considerable extent. Further reports seem only to substantiate the more early work. Colebrook et al (57, 58), used the Prontosils in their treatment

and these drugs are still used in this disease. It was this early work which led to the more or less general use of the prontosils in cases where the infecting agent is a hemolytic streptococcus. There doesn't seem to be much indication that they are effective in puerperal sepsis due to the anaerobic group of streptococci. Colebrook and Kenny (57) reported that from 1931 through 1935 the mortality in puerperal infections in Queen Charlotte's Hospital that were due to hemolytic streptococci varied from 16.6 to 31.6 per cent per year, while the number of deaths from streptococcal peritonitis varied from 15 to 23 per year during the same period. Prontosil therapy was started in January, 1936, and from then until August, 1936, 64 patients ill with hemolytic streptococcal puerperal sepsis were treated, with a case fatality rate of 4.7 per cent and one death from peritonitis. It was further noted in the treated patients that no pelvic masses developed after treatment had been commenced. A prompt fall in the temperature within twenty-four to seventy-two hours was noted in the majority of the patients treated with the Prontosils. Rarely were recurrences of the fever encountered. Twelve of the 64 patients had blood cultures positive for beta

hemolytic streptococci when therapy was begun, and of these, nine made a prompt recovery. It was brought to Colebrook's attention that the case fatality rate of the patients ill with streptococcal puerperal fever admitted to the Northwestern Fever Hospital in London had declined from 22 per cent in 1933 to 5.26 per cent for the first half of 1936, while no such decline had been noted in the fatality rates recorded in puerperal sepsis in Queen Charlotte's Hospital during the same period. Thus there was the question of a decline in virulence of the hemolytic streptococcus rather than the effects of Prontosil therapy which was causing the changed fatality rate. However, it was observed that, whereas the rates dropped at Northwestern Fever Hospital, it was only after the institution of Prontosil therapy that the death rate dropped at Queen Charlotte's Hospital. Also it was concluded that twenty or thirty of the more severe cases surely must have responded to the drug, for the recovery was phenomenal.

Coming to the urinary tract in the originally accepted outline for this therapeutic discussion it has this month, since the work of Lockwood and Lynch (34), become advisable to dissertate: Mellon and fellow

workers (32, 59) presented the "Phenomenon of Potentiation". In explaining this phenomenon they carried out lengthy experiments. These men had a case of meningitis which recovered with great rapidity after the administration of sulfanilamide. They used the bacteria from this case for in vitro experiments since they assumed sulfanilamide should undoubtedly have remarkable effect on this strain. They made their dilutions using a broth as a diluting menstruum, and found that the bacteriostatic effect of the sulfanilamide was completely lost in 24 hours, and was not as appreciable, as it surely was in their patient. They then proceded to use various dilutions of serum and combinations of serum and broth, and found the bacteriostatic action of the sulfanilamide still not sufficient to account for the remarkable effect in vivo. Next they made their dilutions in an 0.85 per cent solution of sodium chloride and found that the number of colonies was less with and without the sulfanilamide. They here pointed out that this solution of sodium chloride itself had a bacteriostatic effect. The bacteriostatic effect was then studied when serum and salt were used in various dilutions, and then they carried out the dilutions with serum, salt and sul-

fanilamide. Here they found that instead of a summating bacteriostatic effect of the salt and the sulfanilamide an even far greater static effect was noted. Therefore, they concluded that there was a "potentiating" effect of the salt so that the effect of the sulfanilamide approached that assumed to have taken place in the body of the patient with the remarkable recovery.

Besides showing the probability of many mistakes being made in such work, they also brought up many new questions relative to the effects of sulfanilamide. Many of these were directed to therapy in urinary tract infections. "Does the urine potentiate sulfanilamide's action in infections of the genito-urinary tract?" they ask. They point out that in cases of cystitis, pyelitis, and such it seems most possible that the in vitro bacteriostatic effect of the sodium chloride could be transferred.

Kenny, et al (60) have shown remarkably rapid sterilization of the urine in 46 cases of pyelitis due to Bacillus coli after administration of sulfanilamide. The urine often contained as many as 125 million organisms per cubic centimeter in advance of treatment.

In attempting to find the answer to their query

concerning urinary tract infections Mellon, et al prepared a series of dilutions, seeded with a micro-organism obtained from a cystitis case. The dilutions were made, respectively, in broth alone, urine and broth and urine alone, so that all possibilities of combinations of culture medium, diluent, test medium and concentrations of sulfanilamide were used. From this work they had wonderful evidence to conclude that "a critical bacteriostatic effect of sulfanilamide can only be obtained in vitro under conditions where the organisms are not only tested in urine, but diluted in urine as well. If they are diluted in broth, even though the tests are made in urine, the effect of the sulfanilamide is negligible."

Thus it was shown that the sulfanilamide worked so marvelously in urine because urine was the only medium present. The urine, they theorized, had the "potentiating effect" that they had previously attributed to a solution of normal saline. They also pointed out that when there was any tissue destruction present in cases of pyelitis or cystitis the sulfanilamide no longer was as effective. This, they argued, was due to the changes in the chemical make-up of the urine in the presence of the protein catabolism, and was quite

similar to their in vitro experiments where they diluted their seeded urine with broth or used the broth as a test medium.

Now this work must be correlated with the recent work of Lockwood and Lynch (34), previously described. It will be remembered that they concluded that sulfanilamide acted only in the presence of a limited amount of peptone, and thus they explained the fact that the drug could combat an acute, generalized infection, whereas, it could not cope with a situation in which there was tissue destruction, because of the presence of an overwhelming amount of peptone from protein catabolism.

In projecting Lockwood and Lynch's work on that of Mellon, et al, we can see that the reason sulfanilamide acts in the urine dilutions and not in the broth dilutions, in the saline dilutions and not in the broth or broth-serum dilutions, is that there is plenty available nitrogen in the form of break-down products of protein in the broth, which are obviously not present in the salt, or appreciably so in the urine. However, as pointed out, the drug did not work in the face of tissue destruction. Here again it could be that this is because of the presence of peptones. This seems a logical explaination of a great work.

The urinary tract infections, as above described, are much nearer in vitro experiments than anything worked with heretofor. Once more it seems that the urologists have the oportunity to do thourough work, with a profound understanding, because they can see what they are doing. On the other hand, if this work holds up, the action of sulfanilamide throughout the body can now be better visualized.

Working in this body system, and with these theories, another major point is brought to view. That point is the complete lack of specificity of the sulfonamide compounds. It is now more than ever seen that it is not the genus or species of the micro-organism that is concerned so much as the manner in which it manifests itself in its morbid activity in the body. Many micro-organisms seem to have no susceptability to the therapeutic action of sulfanilamide whatsoever, but the most of them have shown some weakness. In the body, however, many of these infectious agents manifest themselves in such a manner that it is improbable that they will ever be satisfactorily combated by these known methods of chemotherapy.

In a recent article (36) some cases of urinary tract infections were analyzed according to the or-

ganisms in the following chart:

URINARY TRACT INFECTIONS ACCORDING TO ORGANISMS

	Cases	Cured
B. Coli	29	22
B. Proteus	12	2
B. Friedlander	2	0
B. Pyocyaneus	2	1
Staphylococcus aureus	2	1
Nonhemolytic Streptococcus	2	2
Enterococcus combined with B. Coli	3	1
	52	29

A great many different micro-organisms have been experimented with and tried in clinical combat. It is sufficient to say here that most have some response reported, so the drug may be tried, at least.

It is important to beware of kidney damage in administration of sulfanilamide. After several days of chemotherapy there will be a considerable heaping up of blood concentration of sulfanilamide if it is not properly excreted. Another important thing to remember in dealing with the urinary tract is that about half of the drug is in the urine in its inactive conjugate form. This is the acetyl derivative that is also found in the blood stream. There is a considerably greater amount of this form found with the administration of sulfapyridine, but this drug is superior in action in many instances. Because of the greater amount of the conjugate form, crystals often bring

havoc as will later be shown in the discussion of ill effects.

Schwentker, Gelman, and Long (61) withheld specific meningococcal antiserum in ten cases of meningococcal meningitis in 1937. Instead, they administered sulfanilamide subcutaneously and intraspinally, and all but one of these patients recovered. The one fatality was very ill on admission and was considered lost anyway. There were signs of encephalitic involvement in this case, and concomittent pneumonia was met on the fifth day. The spinal fluid of this patient had been sterile for three days and there was a marked reduction in the spinal fluid cell count to 158 cells on the day of death as a result of sulfanilamide therapy. All patients responded with a reduction in the spinal fluid cell count which occurred progressively beginning with the institution of the therapy in some cases and precipitously, after several days, in others. The spinal fluid and the blood during this time became sterile. In addition, a child that had meningococcal septicemia without meningitis, was also cured in the same manner.

Harvey and Janeway (62) mentioned the case of a ten-month-old baby manifesting meningococcal meningitis that was recovering as a result of sulfanilamide therapy,

but developed hemolytic anemia which necessitated a number of blood transfusions. The patient recovered. Among the more extensive confirmatory papers are those of Banks (63) and Waghelstein (64). These and many more reports show this to be one of the astounding uses of the sulfonamide compounds. There are many points to consider in therapy here, the details of which cannot be discussed. There are differences in which the sulfonamide compounds diffuse into the spinal fluid. The prontosils seem to diffuse most poorly. There is a lag in the concentration in the spinal fluid as contrasted to the blood concentration. The use of intraspinal administration has been less prominent in late reports, but it may have its place. Combinations with antiserum are used also.

Long and Bliss (13, page 188) report excellent curative results after intensive therapy with the drug in five patients suffering from acute meningococcemia, without signs of meningitis.

One of the most important developments in the administration of sulfanilamide was the introduction of treatment of gonorrhea by this method. The first significant reports with favorable results were by Dees and Colston (65) and Herrold(66). Since that time a great deal of literature is to be found. Among

the few who found unsatisfactory response are Anwyl-Davies (67), and Brunet, Reinhardt and Shaw (68). There is no unanimity of opinion as yet, regarding the optimum time for beginning treatment, the amounts of the drug that should be used, the duration of therapy, or the auxiliary measures which should be instituted in the course of treatment. It seems, from a review of the various opinions upon the subject, that the later therapy is started in the course of the disease the more successful are the ultimate results. In Dees and Colston's original paper (65), it was noted that while failures in treatment occurred in only 7.5 per cent of fresh cases, 11.5 per cent of the patients previously treated by other methods did not respond to sulfanilamide. Herrold, however, reported that only four of 14 patients ill with acute gonorrhea made a quick response to sulfanilamide therapy. He also advanced the possibility that better results would be obtained in new infections if the patient had previously had gonorrhea than in those individuals suffering from their first attack.

Many of the early reports on the use of the sulfonamide compounds were dissappointing because the wrong drug was used. Prontosil therapy is now known

to be unsatisfactory. As before brought out in this paper, in view of the present knowledge of drug action, the effects in the urinary tract are quite similar to the in vitro reactions, and the prontosils must be reduced to an active form in vivo before they will have a bacteriostatic effect. There is no reducing agent in the urine of sufficient power to do the work of the magnesium powder in vitro.

With reference to the previously made statement that it seems that therapy is best started after the disease has been active for a few days or more, Alyea and his co-workers (69) concluded from their studies that the patient who starts treatment a week after the onset of his discharge has an equal chance of being cured with one who begins treatment earlier. Breakey and Harrold (70) however, reported that the average duration of infection was twenty-one days in their acutely ill patients, and fory-five in the chronic cases when treated with sulfanilamide. This is to be contrasted with an average duration of infection of one hundred and four days in 50 of their patients treated previous to the introduction of sulfanilamide. Colston and his associates (71) divided their patients into those who had anterior urethritis, anterior and post-

erior urethritis, and anterior and posterior urethritis with complications. The average duration of the disease in these three groups was twenty-seven, twenty-eight, and thirty-three days respectively.

In the last year there have been reports, too voluminous to describe in this paper, of the use of other sulfonamide compounds in the treatment of gonorrhea. Many men are now using sulfapyridine for chemotherapy here. Since this drug acts in a fashion similar to sulfanilamide, and in many instances show greater action, it is probable that the success claimed for it is well founded. It must be remembered that well over half of this drug is in the acetyl derivative. This product is inactive and is to produce harmful crystal deposits in the urinary tract. Consequently, the drug must be used with care, and the fluid balance of the patient as well as his acid base balance must be well watched. These dangers will be discussed later.

Roth (72) reported a series of cases of specific urethritis, for which he used Disulon, a brand of sulfanilyl-sulfanilamide, for chemotherapy. In a group of 44 cases of acute gonorrhea treated with sulfanilamide he obtained a 47% fraction of complete cures in two weeks. In a series of 22 cases that were

treated with sulfanilyl-sulfanilamide he obtained 73% cures in this same length of time. In a series of his private cases, at the same time, he reported 71% of 42 cases resulted in two-week cures when treated with potassium permanganate irrigations and sulfanilamide. With the same irrigations but with Disulon as a chemotherapeutic agent he obtained 92% cures in two weeks. There were also 12 cases which did not respond to sulfanilamide that did respond to Disulon.

In the face of such reports as this for other derivatives, it surely is advisable to try sulfapyridine or sulfanilyl-sulfanilamide if good results cannot be obtained with sulfanilamide.

That sulfanilamide is extremely beneficial therapeutically in cases of uncomplicated gonorrhea has been shown by many workers (65,66,73-76) however, there are still other attributes offered for the drug in infections where the gonococcus is the infectious agent. Coggeshall (77) et al report a series of cases of arthritis from the gonococcus. They showed that in cases of gonorrheal arthritis the sedimentation rates fell very rapidly upon administration of the drug, showing striking and immediate relief. The sedimentation rates remained the same for a similar series of

cases suffering from rheumatoid arthritis where no change of the clinical course was observed. They showed how the largest percentage of clinical cures can be obtained in patients with gonorrheal arthritis if sulfanilamide in doses sufficient to maintain a blood-sulfanilamide level of 10 mg% or higher is maintained for a week or longer, and it is administered early.

There is a recent report (46) of a series of 100 patients with gonorrhea who were treated with sulfanilamide alone resulting in 45% cures in two weeks. The writers suggested that giving vitamin C with the drug would improve the figures. They also used it with gonococcic vaccine and obtained 81% two-week cures.

Without a doubt, the use of sulfanilamide in treatment of gonorrhea will do a great deal in helping to rid the populace of disease, and to relieve them in suffering.

Brucella infections have attracted much interest of workers with sulfanilamide. There is a good deal of work done with these micro-organisms to try and determine whether or not the drug has any effect on antibody formation. Welch, Wentworth and Vaisman (78) did much work on this subject and finally concluded, "In Brucella infections sulfanilamide appears to act

through stimulation of the defense mechanism of infected animals by increasing the production of specific opsonins, thus effecting neutralization of the endotoxin or aggressin-like substances, with resulting phagocytosis."

Kato and Lane (79) reported the case of a six-year-old girl suffering from undulant fever who was treated with sulfanilamide. Two relapses occurred, each of which was also similarly treated. No conclusions were drawn nor was any statement made of the effect of the drug on the clinical course of the disease.

Heretofore, chancroid has been a stubborn affliction to handle. Therefore, the medical field is pleased with the marvelous results obtained with sulfanilamide therapy. Many workers have reported good response (80-84).

Hutchison (81) has observed that formerly it required an average hospital attendance of forty-six days before a chancroid with or without bubo was cured, and incision of the bubo had to be performed in five out of six cases. Since the introduction of sulfanilamide therapy in this disease he had not performed an incision and the average hospital attendance had been reduced to fifteen days.

A great deal of the illness found among patients in a general practice is due to tonsillitis, pharyngitis, and sinusitis. Since the introduction of sulfanilamide it has carried the reputation of being a more or less specific drug for streptococci. Consequently in many cases of pharyngitis it has been immediately administered because of the impression that most of such infections are due to the streptococcus. Even when this is the infectious agent, it must again be emphasized that the material on the effects of the drug, more and more show that it is not the infecting micro-organism that is entirely responsible for whether response will be had or not. The way in which that infecting agent manifests itself in the morbid condition must also be considered.

In agreement with many men recently before them, Rhoads and Afremow (85) report a series of sore throats from which hemolytic streptococci were cultured. Half were treated with sulfanilamide and half were not. Some cases had to be dropped from the series because of toxic reactions which necessitated the discontinuance of the drug after a few days usage. They found the drug not to reduce the severity of the symptoms, shorten the period of incapacity or reduce the incidence

of complications. The carrier state was also seen not to be shortened because the cultures were positive for a longer time in the treated group. The treated group, probably coincidentally, was hospitalized longer than the control group. Careful study of the reports presents the impression that if the two columns were not labeled one could not tell one from the other. The only differences in the courses of the two columns is that toxic manifestations of the drug other than the usual cyanosis occurred in one half of the cases in which sulfanilamide was administered. In some instances these reactions even brought serious concern. These writers conclude, "It is not wise to make sweeping generalizations on the base of one series of controlled cases. Sulfanilamide is a drug of proved value in severe infections of deep structures due to the hemolytic streptococcus. However, in the average uncomplicated case of tonsillitis orpharyngitis due to hemolytic streptococci the advisability of its routine use is questionable. Certainly no physician should be censured for withholding the drug in these conditions unless complications such as severe cervical adenitis, paranasal sinusitis, otitis media, mastoiditis or meningitis supervene."

Long and Bliss noted that sulfanilamide therapy radically altered the course of acute streptococcal otitis media (30). Since that time many other observers (86,42) have varified their reports. Hageman and Blake (86) reported that all of 11 patients suffering from otitis media recovered from their disease, without complications, following sulfanilamide therapy.

The problem of whether it is a wise procedure to treat a simple acute streptococcal mastoiditis with sulfanilamide alone is a difficult one. Hageman and Blake (86) have reported that only two of 11 patients who were treated with sulfanilamide for acute streptococcal mastoiditis required mastoidectomy after sulfanilamide was started. In nine instances the disease subsided without surgical intervention. These men also recommended the use of sulfanilamide in treatment of acute mastoiditis following mastoidectomy. These men reported, as well, that only one of nine cases of purulent hemolytic streptococcal sinusitis required surgical treatment after sulfanilamide had been started, and in this one patient a mixed bacterial infection was present. Other observers (87,88) have stated that they noted favorable effects following the therapeutic use ofthe drug in acute sinusitis. These men also

noted remarkable response of chronic otitis media and mastoiditis.

Long and Bliss (13) state that they have had excellent results in treatment of cellulitis with sulfanilamide. They show that the use of wet soaks or packs, as is customary, is unnecessary as an adjunct to the treatment, andit may do harm because it leads to abscess formation. They state that the drug should be continued until at least two days of normal temperature have elapsed and there is a marked regression of the local lesion. Thereafter it should be continued in lessened doses until recovery is complete. If an abscess is incised, the drug should be continued in small amounts until the wound has healed.

Hageman and Blake (86), and McIntosh and Wilcox (87) have shown fine results from sulfanilamide therapy for lymphadenitis from hemolytic streptococcic infection. They give lower blood concentrations of the drug than is usually held for other infections. It may be promptly discontinued when the lymphadenopathy has receded. Here again the soaks seem unnecessary.

Hageman and Blake (86) and Fleming (89) first have shown good results in chemotherapy for hemolytic streptococcal pleurisy. Surgical intervention should

be used only if absolutely necessary, they insist.

There is a good deal of conflict of opinion regarding the effectiveness of sulfanilamide against scarlet fever. Paul N. Morrow of the University of Nebraska College of Medicine tells of a very large series he followed on pediatrics at The Philadelphia Hospital for Contagious Diseases. The final observations were so confusing that the variations could all be from imperfect statistical methods. There was no tangible improvement under this therapy, either in course of disease or number of complications.

Mellon (14) discusses scarlet fever at great length in setting forth criteria of therapeutic efficiency, with reference to sulfanilamide. He reminds the reader of the mistaken impression that once prevailed concerning the similarity of streptococci. Workers then thought that if a serum should be effective against erysipelas it should also be effective against scarlet fever. However, it was soon found that the serum used for one not only would not work on the other, but the serum for the erysipelas of adults would not combat that of the infant, in which the mortality from the disease ranges from 80 to 90 per cent! He (14) describes sulfanilamide as a "non-specific serum", going

on to discuss the variation in age of the patients suffering with erysipelas who respond to therapy. Here again the error is seen in thinking that sulfanilamide is a specific chemotherapeutic agent for streptococcic infections. Once more it must be stressed that the ability of the drug to act seems to depend not only on the micro-organism concerned with, but also on the manner in which that micro-organism manifests itself in the morbid process in the body.

Observing this fine variation in strains of streptococci it is no wonder that reports vary so much on effect of the drug on scarlet fever. The writings are so voluminous on this subject that they cannot be completely covered here. It may be stated, however, that for every attribute found for sulfanilamide in this instance there is a contrary one. Sako and his associates (90) conclude, after study of an extensive series, that the drug should be used at the onset of the disease, and, although it does not alter the course of the fever period, it considerably cuts down on the number of complications. On the other hand, Toomey (91) concludes, after a similar study, that the drug does not cut down on the number of complications at all, but should be used if these

complications arise. Now, when we can realize that the drug has no action against most infections where there is a local problem at hand, we wonder if it can be of any benefit for these complications, since they are of such a nature in most instances. Surely, the tissue destruction in a pharyngeal abscess would prevent any local action of sulfanilamide, and it has been previously shown that only part of the cases of otitis media are of a nature that will alow action of the drug. Still, at the same time it was shown that, in view of occasional benefits, it should be tried in most cases.

In cases of scarlet fever, surely, if signs of toxic reaction are met, the drug should no longer be administered, for there is no indication that sulfanilamide is a very important therapeutic agent.

The introduction of sulfapyridine has brought many favorable reports concerning its use in combating pneumococcus pneumonia. Prior to this development the benefits derived from the sulfonamide compounds in treatment of lobar pneumonia were scant and in no way comparable to the results achieved with antiserum. Heintzelman, et al (92), offered one of the earliest works in this line. Nineteen cases of pneumococcus

pneumonia were reported by them. Nine were treated and ten were used as controls. The pneumonia was of Type III. Seven of the nine treated cases recovered, and two dies, in contrast to the ten untreated cases, among which two patients recovered and eight died. They found that if the drug was given early in the disease the chances of benefit from it was better. A few other workers (93,94) also gave favorable reports of the use of sulfanilamide in the treatment of lobar pneumonia. However, there seemed to be no evidence that broncho-pneumonia would respond. Evans and Gaisford (95) were the first men to report the fine response of pneumococcus pneumonia to sulfapyridine. A hundred patients who were suffering with the disease were treated with the drug and a hundred others were given only symptomatic treatment. There was no apparent difference in ages of the two groups or in variance of the types of pneumococci discovered. The cases were all received at the same season of the year and from the same locality. Only 44 of the 200 patients were successfuly typed. The fatality rate in the treated series was eight per cent, whereas in the other group the rate was 27 per cent. Of those patients who recovered, 44 had a normal temperature by the sixth

day in the treated group, while only 20 in the untreated series had normal temperatures on the sixth day. If the treatment was discontinued too soon in the course of the disease, secondary fevers associated with recurrences or a spread of the pneumonia were noted.

Following this impressive report, there was much study of chemotherapy for this disease (96-100). These papers were not only confirmatory in nature, but they also became increasingly more demonstrative of success, until now it is frequently a decision to be made-- to use the drug or the serum. The journals of the year 1939 carry too much material to describe in the space here alotted. Suffice to say that results are about as good in cases treated with sulfapyridine as in cases treated with antiserum (101). Most writers emphasize the fact that patients should still be typed because of occasionally finding one who does not respond satisfactorily to drug administration. Some recommend use of both the antiserum and the sulfapyridine. This use of sulfapyridine is far superior to similar use of other sulfonamide compounds that have as yet been tried. (101,102)

As this paper is today written work is being done with sulfapyridine in treatment of pneumonia. The

Omaha World Herald (Tuesday, March 19, 1940) carries the following Associated Press dispatch: "New York, March 18-- A display showing a drop of 40 thousand in pneumonia deaths in the United States in the last year will be one of the new exhibits at the New York world's fair this summer.

"Sulfapyridine, the new medicine for pneumonia, will be shown as playing an important part in this great saving. Whether the surprising drop from 130 thousand deaths in 1938 to 91 thousand in 1939, was all due to the new remedy is not yet known.

"Medical reports have pointed to the possibility some of the decrease in 1939 might have been because of milder types of pneumonia that year.

"However, the exhibit will contain evidence that sulfapyridine last year cured nine out of every 10 persons to whom it was administered."

It is interesting to note that in the same edition there is evidence, through the International News Service, that two persons, one in Chicago and one in San Francisco, were showing wonderful response to sulfanilamide administration for staphylococcic septicemia. The pace these drugs are setting is phenomenal!

One of the most talked of uses of sulfanilamide the last few months is its local implantation. The amount of talk, and probably the amount of use of this nature seems to far surpass the literature on the subject. An obstetrical term ago Jensen, Johnsrud and Nelson (103) reported local implantation of the drug in compound fractures with favorable results. These men treated 39 compound fractures with this local implantation of the drug and as a result found no single primary wound infection. Of 94 cases treated in as nearly exact fashion as possible except for the local implantation, 27 per cent resulted in primary wound infection.

These men pointed out the following factors to be concerned with here: Sulfanilamide crystals in a wound dissolve slowly. The last of the drug leaves the body in about 60 hours. Marshall, et al (104), showed that after one single large dose of sulfanilamide, the last of it was excreted by 24 hours. Therefore, Jensen, et al concluded that there must be still some of the sulfanilamide at the wound site for at least 18 hours. These latter men go on to state that the highest blood level of the drug in their patients so treated was found in 18 hours. These latter men go on to show that since the solubility of sulfanilamide is 0.8

per cent at body temperature, this concentration of the drug is probable at the wound site. Thus a concentration of 800 mg% is maintained for a considerable length of time, whereas only 10 to 20 mg% can safely be maintained by administration per os. From these facts it can be seen that a concentration of 80 times the magnitude is theoretically obtained. These men conclude that this manner of treatment uses a bactericidal effect of the sulfanilamide for organisms more susceptible to the drug and a bacteriostatic effect for others.

Jensen, et al did some experimenting with guinea pigs in the following manner. They used seventeen animals. Seven were used as controls. In the controls they fractured a rib with scissors through a wide incision, and in the other ten 0.5 gm of sulfanilamide was implanted in similarly produced compound fractures. Five out of the seven controls had primary wound infection, while seven out of the 10 of the others healed uneventfully. Of the ten treated animals it is of note that one of the three which suffered infection was not closed tightly, to observe the effects if the drug could fall from the wound, and another of those infected had had blood drawn from its heart at frequent intervals.

Jensen, et al conclude from their fine study that, "The local use of sulfanilamide has opened the way for more effective treatment of contaminated wounds. The amount to be used in each specific wound depends upon the extent of trauma and contamination." They recommend 5-20 gm (no more), and show the necessity of painstaking debridement. They believe the drug only bacteriostatic against staphylococci, even in concentrations approaching one per cent.

Since the work of Lockwood and Lynch (34) with peptone broth it will be interesting to see further work in this line. Lockwood and Lynch show that a concentration of sulfanilamide must be about 100 times that of the products of protein catabolism before there is therapeutic effectiveness. Work is therefore warranted in these higher concentrations. The concentration of peptone in the tissue fluids at a wound site could easily be 10 mg%, and if this concentration were reached the concentration of 800 mg% of sulfanilamide would be insufficient.

This would encourage complete debridement as recommended by Jensen, et al (103). On the other hand, it seems there has been evidence (before presented) that certain instances where there is a small degree

of tissue damage as in otitis media, certain cases of cellulitis, and such, there has been a favorable response to sulfanilamide. This brings out the point that a line must be drawn somewhere showing the degree of tissue destruction that is necessary before any beneficial response is possible. It also shows that the drawing of this line, as with the drawing of similar lines in medicine, is practically impossible. Since the wound infections are here non-specific, the non-specificity of our drug is again seen!

The attributes of local implantation are highly feasible. Study of effects for guidance of use are inadequate. Since a wound is easily seen for study, it is not believed ostentatious to think that this pharmacologic study is necessary. Since sulfanilamide is taken up by the body tissues without apparent damage to them, is it possible that here is a satisfactory antiseptic? The action is above stated by Jensen, et al to be bacteriocidal!

Clostridium welchii infections have also brought considerable comment in the last year. Early in the history of sulfanilamide, Bohlman (105) reported three cases of gas gangrene which responded wonderfully to sulfanilamide administration within 24 hours.

This finding was apparently confirmed by Kennedy (106).

Sadusk and Manahon (107) report two cases of postabortal Clostridium welchii infection with positive blood cultures in which the blood stream was rapidly sterilized by the use of sulfanilamide and the patients recovered. They also carried out some experiments and adequately showed the bacteriostatic action of sulfanilamide on Clostridium welchii in vitro. Such action, they showed, was inversely proportional to the number of organisms used as the inoculum.

We are taught that patients who succumb to gas gangrene in the first week are overcome with the great toxicity of the organism. However, it is seen that in the second week the fatalities are from septicemia arising from secondary infection. Whether the Clostridium welchii, which is seldom the etiologic factor, per se of the septicemia, is in the blood stream or some other organism, it is undoubtedly a most ideal occasion for use of the drug, for more each day it is shown that sulfanilamide takes care of a multiplicity of septicemias. What could be more ideal for administration of the drug than a generalized infection too acute for tissue destruction, no matter what the etiologic factor, within certain limits!

In reviewing the therapeutic effects of sulfanilamide as just related, the inadequacy of thetreatise is seen. New developments are constantly appearing. Those now coming to the foreground seem to be dominantly of treatment of different infections than heretofore attacked. Staphylococcus infections, bacillus infections, subacute-bacterial-endocarditis, and even the tubercle bacillus are now being approached. In its entirity we are again reminded of the extreme nonspecificity of the sulfonamide compounds and of their confusing action. The manner in which these therapeutic effects hook up with cellular metabolism and catabolism in the body and the metabolism of the bacterial invader, must not be forgotten in this mad scramble for blind cure, lest physiology suffer in the wake.

TOXIC EFFECTS

Any one who gives sulfanilamide should be acquainted with the toxic effects of the drug and the severity to which each individual toxic reaction can extend. For this reason these effects will be classified according to severity. This method of classification has been used by many writers for reason of its practical-

ness (36,108). Generally these effects are put in two groups, one group of those which are common and seldom severe enough to cause alarm; and another of those which are rare but dangerous and contraindicate continuance of treatment. This is a fine way of thinking of these reactions, however, the grouping is still more adequate if a third group is inserted. The composite picture might result in the following outline:

SYMPTOMS OF MILD TOXICITY (Frequently seen, but usually do not require discontinuance of the drug.)
Moderate cyanosis.
Anorexia, nausea.
Dizziness, headaches, tinnitus, slight mental confusion.
Weakness, fatigue.

SYMPTOMS OF MODERATE TOXICITY (Call for close observation, but do not call for the discontinuation of the drug when it is very much needed.)
Vomiting, sense of oppression.
Cyanosis or mild dyspnea.
Mild, slowly developing anemia.
Diarrhea and abdominal pain.
Mild rash or itching.
Paresthesia, diplopia.
Acidosis.
Slight fever.

SYMPTOMS OF SEVERE TOXICITY (Call for the immediate discontinuation of the drug and corrective measures.)
Drug fever.
Tachycardia.
Leukopenia.
Jaundice.
Acute anemia.
Dermatitis.
Psychosis, or disorientation.
Albuminuria, hematuria.
Diplopia.

This outline will not always be a true guide to severity of a toxic reaction. People who have taken the drug may often say that the nausea with the administration can be of an intolerable nature.

Patients taking the sulfonamide compounds should undoubtedly be in bed during the course of treatment, not take other medicine unless absolutely necessary, and should probably not enter any high altitude unless required (?).

Cyanosis is so often seen in the course of therapy that it is generally disregarded. It is an erroneous belief that it should be present before therapeutic effect can be found! Long and Bliss (13) state, "In our experience, cyanosis has not been an alarming toxic manifestation and can generally be disregarded. We have noted its appearance following the administration of 0.6 of a gram of sulfanilamide, and, on the other hand, we have seen patients who were receiving large doses of the drug in whom cyanosis was minimal." By large doses it would be assumed that Long and Bliss meant large doses, for they have done superior work with the drugs from all angles and insist upon high blood levels! They go on to describe the "black" or "brown" color that either arterial or venous blood assumes. When this blood is shaken or bubbled with

oxygen it does not regain its normal color. When sulfanilamide therapy is stopped, however, the darkness disappears and the normal color of the blood is assumed.

The only writers who agree on the origin of the cyanosis are those who attribute it to about three factors. (109,110) These men state that both sulfhemoglobinemia and methemoglobinemia result as well as the formation of an unknown pigment. They both agree that the methemoglobinemia is dominant. Some workers have attributed the cyanosis to the formation of sulfhemoglobin predominantly (24, 110-113), some attribute it more to formation of methemoglobin (110, 111,114-117), and some attribute it to an unknown cause, possibly by a discoloration of the red blood cells by a pigment formed in the course of sulfanilamide therapy (115) or to reduced hemoglobin (118).

Chesley (117) concludes after his study that he had successfully ruled out the formation of sulfhemoglobin and methemoglobin in eight cases showing extreme cyanosis. Bigler and Werner (119) conclude that the "cause is still not clear. -- -- -- Only in some instances has spectroscopic examination of the blood revealed presence of sulfhemoglobin and methemoglobin bands. -- -- -- Also the cyanosis does not seem to

depend on oxygen saturation of the arterial blood." These men also agree with Long and Bliss (13) in that the cyanosis does not seem to depend on the age of the patient, daily dosage or the length of time the drug is administered.

Colebrook and Kenny (24) attributed a great deal of the cyanosis to concurrent use of magnesium sulfate as a cathartic during prontosil administration and advised its immediate sessation. They did not recommend cutting down on sulfur-containing foods or drugs, but did encourage diets that would produce a minimum of hydrogen sulfide in the lower powel.

Archer and Discombe (120) believe that the cyanosis is a sign of approaching danger and insist that regular blood examinations should be made of all who are cyanotic. It will be shown below, however, that this should be done in all treated patients.

The use of methylene-blue in combating the cyanosis was originally suggested by Houschild (cited by 121), advocated by Wendell, and favored by Hartmann, et al (122). Campbell and Morgan conclude (121): "(3) In methaemoglobinaemia, whether produced by 2 p-aminobenzenesulphonamideopyridine or by sodium nitrite, methylene-blue is effective in causing the rapid disappear-

ance of the cyanosis by converting methaemoglobin to hemoglobin.

"(4) The dye is active when given intravenously, intramuscularly or by mouth.

"(5) It is suggested that routine employment of methylene-blue in conditions calling for the prolonged administration of sulfapyridine may be a useful measure preventing cyanosis.

"(6) Methylene-blue has no effect in preventing or modifying cyanosis of sulphaemoglobinaemia."

Treatment of the cyanosis truly would rest the patient from possible anoxemia. Although methylene-blue seems good its scope in prevention and treatment is limited. The various abnormalities of the blood pigment produced by sulfonamides is not fully understood. One to two mg per kg of body wt IV or one to two gr (65-130 mg) per os, given every four hours is quick to bring and maintain response from methemoglobinemia.

Cyanosis deserved special early treatment, for it is the standard upon which so many toxic manifestations of the administration of the drug are based. Many of these unfavorable reactions may be correctly paralleled to the color of the patient, so to speak, but many

of these findings indicate possible further severity along similar lines. As in cases of congenital anomalies, where one is present always beware of another. A mild dermatitis may be indication of approaching jaundice or agranulocytosis for often these manifestations are multiple. In the same fashion one who has had mild toxic reaction during one course of therapy may be the victim of a more severe episode during a later course.

A good example of this multiplicity of similar reactions is seen in the nervous system. Those who frequently administer the drug are familiar with the nausea, dizziness, headaches, tinnitus, and even slight mental confusion that frequently accompany early days of therapy. Some, on the other hand, offer reports of rather severe cases of toxic peripheral neuritis (123,124). It is of note that these reports deal especially with some of the newer derivatives. Perhaps this effect is more peculiar to one of these newer compounds than it is of the more established drugs. Mild mental disturbances are not uncommon in patients who are receiving sulfanilamide. Many individuals complain of feeling depressed, although occasionally the drug causes elation. Frequently, the ability to concentrate upon a given problem is disturbed.

Frank disorientation is uncommon, although mild confusion is often seen. Hallucinations, both auditory and visual, have been noted. Mania is rare but occasionally occurs. Hogan and McNamara (125) have described a toxic psychosis which developed in a patient during treatment with the drug. Following the removal of the drug the patient showed a steady improvement. Danziger (126) observed a patient who twice had a toxic reaction, characterized by cyanosis, confusion, and negativism, which occurred in each instance four days after sulfanilamide therapy had been stopped. The mechanism of this reaction was considered to be unknown. It is obvious that in certain instances it is very difficult to distinguish between the abnormal mental reactions frequently noted in the course of severe acute febrile infections, and those due to sulfanilamide therapy.

Early in the history of the drug several specific cases of neuritis were observed. A rather severe toxic optic neuritis was reported in 1937 (127).

Recently two cases of encephalomyelitis following the administration of sulfanilamide were described, one of which ended fatally (129). The total doses taken were small (14 gm and 18 gm) and if the drug was responsible the patients must have been more than or-

dinarily susceptible to it. Vascular changes were seen in some of these cases of encephalomyelitis and their relation to the demyelinating lesions was discussed. These men offered evidence that patients suffering from certain illnesses, including acute rheumatic fever and lupus erythematosus, are especially liable to develop toxic manifestations aftertaking sulfanilamide.

Tachycardia is sometimes observed, and not infrequently only apparent because of the obvious cyanosis which is so often present. Also the tachycardia may be blamed upon the changes in the blood stream by methemoglobin and sulfhemoglobin formation. Dozzi (128) presents a case which might establish the likelihood of cardiac damage resulting from the use of sulfanilamide. In this case there was a transient nodal rhythm following use of the drug.

Long and Bliss (130), and Dees and Colston (131) offer undisputable evidence that a febrile reaction frequently occurs during administration of sulfanilamide. Since these works many more reports of a febrile reaction have been offered (32,133). These men all impress the reader with the confusion that may arise in diagnosis when this foreign fever occurs. Hageman and Blake (132) noted the frequent occurrence of a fever

reaction along with a toxic dermatitis. Gallagher (133) analyzes the fevers which he observed and concluded that this reaction was probably based on idiosyncracy similar to that seen by other observers in other toxic manifestations of the drug therapy.

An interesting case of severe drug-fever was recently presented in the literature (133). The patient underwent a 12-day course of sulfanilamide therapy in 1937. During this course the patient developed a morbiliform rash and general malaise. In 1939 there was again reason to administer an extensive regieme with the drug. The patient was to have four 20 gr doses on the first day. After the second dose general malaise, headache, cyanosis, chilliness and fever were evident. The drug was stopped immediately, but the temperature of the patient continued to rise. Fluids were forced. On the second day, although the drug was no longer administered, a rash became prominent. It was of a morbilliform nature as it had been in the previous course. The temperature reached 104 degrees by the end of the second day, and the white blood count dropped from 17,000 to 9,000 in this short interval. On the fourth day the patient was again comfortable and afebrile. The rash gradually faded.

Long and Bliss (13, page 275) state, "Our experience with this toxic manifestation (fever) of sulfanilamide therapy has been essentially that of Hageman and Blake. We have noted drug fever occurring as early as two hours andas late as twenty-one days after the institution of sulfanilamide, although the usual time of appearance of drug fever is between the fifth and tenth days of treatment. In our experience 9 per cent of adults and 3 per cent of children develop drug fever in the course of sulfanilamide therapy. We have also noted that fever may be the initial sign when a serious toxic manifestation such as hepatitis, acute hemolytic anemia, or agranulocytosis is developing. Because of such observations we have come to the conclusion that fever constitutes one of the most important warning signs in the course of sulfanilamide therapy, and feel that the physician must "stop, look, and listen" when drug fever develops."

Foreign writers (13) have done much in the study of the effects of sulfanilamide on spermatogenesis. There seems to be no conclusive evidence that it is in any way damaged.

The dermatitis that has been so frequently re-

ported as a toxic manifestation of sulfanilamide administration, is peculiar. Early in the use of the drug it was noted that patients exposed to sunlight were especially affected. Since the great majority of patients who were ambulatory and most frequently exposed to sunlight were those suffering from gonorrhea, it was at first thought that there was some connection between this disease and the drug administration. However, this has been discredited. The literature on this phase of toxic effects is voluminous (134-142). The rash has been described as exfoliative (139), purpuric (141), morbilliform (134), varioliform (135), and urticarial (136). Some workers have noted a peculiar stomatitis concomittent with the exanthem (136,138). They described these oral lesions as being similar to mucous patches of secondary syphilis. This would be good to remember in diagnostic examination.

Schwentker and Gelman (144) first described the rash. They stated, "It is distinctly morbilliform in character, made up of maculopapular lesions slightly raised from the surrounding unaffected skin and brownish-red in colour; although it does not fade completely when pressure is applied, the blanching of the rash is considerably more marked than that seen with a typical

measles eruption. Usually almost the entire surface of the body is affected, but in some cases the rash has been limited to the buttocks or the legs. In some of our patients the eruption was seen on the palms of the hands and the soles of the feet while the mucous membranes were apparently unaffected. There was no itching or other abnormal sensation at the site of the lesion.

"The rash usually develops rapidly without any prodromal symptoms, the entire evolution occupying only about 12 hours. Fever, and general malaise have always been present and have sometimes preceded the eruption by several hours. The temperature rises suddenly, usually ranging between 101 and 103 F., and then drops to normal gradually over a period of 2 to 4 days. The malaise disappears with the fever. No other symptoms have been observed. The blood count shows no significant alteration.

"With discontinuance of sulfanilamide therapy the eruption fades rapidly and may disappear completely. If the sulfanilamide treatment is not discontinued the time of appearance of the primary rash, the eruption fades and disappears completely in about seventy-two hours."

Schlesinger and Mitchell (134) offer a good summary of dermatitis which we are here concerned with. They also described many cases, among which were ten in children. They state that the eruption usually is first seen in five to seventeen days after original administration with continuation. In their series it was generally preceded by a leukopenia. An interesting "natural history" of the eruption was given: First a prodromal period was noted with a fever and transient leukopenia, and following this the rash appeared, often with splenomegaly. A few days after the drug was stopped the rash started to gradually fade in most every incident. Schonberg (141) points out the manner in which the rash can easily be confused with that of scarlet fever.

An interesting case of delayed photosensitization has been recently presented (140). In this Paper it is stated that photosensitization of the skin due to sulfanilamide is a relatively rare occurrence, but should be carefully guarded against because of the increased use of the drug. The case reported is unusual because it illustrates delayed photosensitivity of the skin brought on many months after therapy was started and discontinued, due to exposure to sunlight

and artificial sunlight. These photosensitized areas were large deep, dark brown patches, apparently fixed in the skin, with a sharp line of demarcation, occurring after withdrawal of the sulfanilamide. Some of these areas broke down and caused troublesome ulcers. It was emphasized that patients taking sulfanilamide should be strictly warned against exposing themselves to sunlight or artificial sunlight during or after the taking of sulfanilamide.

From this multiplicity of manifestations in the skin, it is seen that no definite dermatitis can be watched for. If one does occur, however, one should be certain of its origin, and should watch for other toxic reactions. When confronted with such reactions the drug should be discontinued only if it is not an essential part of the therapeutic regime, but if continued, daily blood counts should be made and other key-signs watched for!

With the use of sulfapyridine increasing every day, and our satisfactory understanding of the precipitation of acetyl-sulfapyridine in the kidney (145), an oportunity for dramatic action is occasionally offered the alert urologist. This is beautifully exemplified by Carroll, et al (146). These men had a

case of complete anuria following the administration of sulfapyridine and, wisely, they did a cystoscopy, lavaged the ureters with warm water, and the patient rapidly recovered. The first of their conclusions well summarize the story and its lessons: "1. The supersaturation of acetylsulfapyridine crystals during the administration of sulfapyridine is sufficient at times to cause a complete obstruction in the urinary tract.

"2. This condition can be promptly and satisfactorily relieved by cystoscopically inserting catheters in the ureters andpelves, and lavage with warm physiologic solution of sodium chloride or sterile water.

"3. These crystals, even in large amounts, which cause obstruction, are not opaque to the x-rays; therefore a flat roentgenogram is of no value. The symptoms of kidney colic and/or hematuria should make one suspicious of crystalline concretions in the urinary tract and should not be mistaken for gastric upsets.

"4. The hematuria noted clinically is probably the result of minute traumatism of the mucous membranes by the crystals rather than damage to the renal parenchyma and therefore is of no grave consequence.

"5. The forcing of fluids in conjunction with sulfapyridine therapy is probably appropriate, since

it will relieve the supersaturation of the urine to some extent."

To be sure, the inert salt of sulfanilamide is also precipitated in the urinary tract if the concentration is great enough, however, this is unlikely since the inert form is not nearly so dominant in the blood stream or in the urinary tract as it is with sulfapyridine (147).

Much experimenting has been done with porphyrinuria in rats, both with sulfanilamide and with related compounds (148,149). Oakley, and Bensley and Wilen have well emphasized the dangers in administration of the drug in the face of renal damage (150,151). Bensley and Wilen showed the gravity in delayed sulfanilamide excretion in a case of pneumonia with renal failure. Ravel and Curtis (152) emphasize the seriousness of hematuria and abdominal pain associated with sulfapyridine administration. Many other workers have been concerned with the formation of urinary calculi here (153,154).

Concern will next be directed to the apparently most grave toxic manifestations of sulfanilamide, namely acute hemolytic anemia, agranulocytic angina and hepatitis. The fatalities accredited to the drug are

practically always in this category except for a stray case of anuria or such now and then.

Harvey and Janeway (62) offer the first report of acute hemolytic anemias, characterized by a sudden onset with a marked drop in hemoglobin and red cells, jaundice, disturbed liver function, urobilinuria, or in severe cases, hemoglobinemia and hemoglobinuria, marked reticulocytosis, and leukocytosis. They described three cases, all showing these similarities. In each incidence the extreme anemia seemed to develop in less than 48 hours. Later in the same quarter Kohn (155) gave similar evidence. Since that time there have been numerous similar reports (156-158). Wood (158) reported 21 cases of acute anemia which developed in patients who had received sulfanilamide in the johns hopkins Hospital. He noted an incidence of acute anemia of 8.3 per cent in 144 children and 2.4 per cent in 378 adults. No predisposing factors were noted in the analysis that Wood made of these patients, but he did find that all of the patients who developed acute anemia had fever at some time during the period of sulfanilamide therapy. No relationship to dosage, concentration of the drug in the blood, or acidosis was observed. In all of the 21 cases the fall in hemoglobin was shown to

begin between twenty-four and seventy-two hours after treatment was started. The time of maximum anemia occurred between the third and seventh days, with the greatest number of patients (nine) developing maximum anemia on the fifth day. Nausea and dizziness were found to be the earliest symptoms of an approaching anemia, while fever and an increased urobilinuria were the earliest signs of the toxic reaction. One or more transfusions were needed to combat the anemia in 13 of the 21 reported cases. None of the patients died. Free hemoglobin was demonstrated in the serum of at least one of Wood's patients. Four of the 21 patients were subsequently given sulfanilamide for therapeutic purposes and three of them developed acute hemolytic anemia. The patients were subsequently given sulfanilamide for therapeutic purposes and three of them developed acute hemolytic anemia. The patient who escaped anemia did not have fever at the time of the second course of the drug.

Several workers have found that there is an increased reticulocyte count accompanied by a moderate decrease in the hemoglobin and red blood cells in patients who were being treated with sulfanilamide (159,160).

Long and Bliss state (13), "Our own experience leads us to believe that sulfanilamide produces a mild

hemolytic anemia in many individuals. This is especially true if treatment with the drug is prolonged over a period of several weeks. These anemias are characterized by a slow, but progressive, drop in the hemoglobin and red blood cells, a moderate reticulocytosis, and often a mild urobilinuria. Anemia of this type is not to be feared and does not constitute a contraindication to further therapy. If the hemoglobin drops below 60 per cent and further treatment with the drug is needed, a transfusion is indicated. However, if at this point the drug can be stopped without fear of a recurrence of the infection, the blood rapidly regenerates."

Agranulocytosis in its apparently limited variations is undoubtedly the most serious of the toxic manifestations. A very pathetic picture is painted by the literature of this quite sudden death, suffering with severe angina in most instances. This manifestation has been attributed to Prontosil, Neoprontosil, sulfanilamide, benzyl sulfanilamide, sulfanilyl dimethyl sulfanilamide, and sulfapyridine (161-177).

The general effects of sulfanilamide upon the white blood cells in general have been studied at great length. Bigler et al (119) attempted to show that there

was generally a marked depression of the number of white cells. In some instances, these men state, the depression hinges upon being a leukopenia. However, they found the lower limits of their white blood counts to be about 5,000 per cubic millimeter, and they admitted that part of the decrease was apparent since the white cells were not fewer in comparison to other cellular blood elements. Campbell (159) did not find any effect of sulfanilamide upon the white blood cells. Hedid extensive studying on the subject, which is not yet closed by any means.

Agranulocytosis has been known to occur in intoxication with various other drugs. Dinitrophenol, amidopyrine, allonal, and novaldin have been known to produce a similar picture, although the severity seldom approaches that of the reported cases with sulfanilamide intoxication (162). No correlation between these drugs has been seen.

Jennings andSouthwell-Sander (160) present a very interesting case in which there was both agranulocytosis and a profound anemia. Dolgopol and Hobart (175) suggest that blood counts only be done twice a week. They point out that in most of the fatalities reported, no blood count was done in the interval of development

and that if such was watched twice a week regularly, the development would no doubt be seen. Most men, however, agree with Borst (165), in his early article, where he emphasizes that to avoid these fatalities daily blood counts and observation of throat is necessary. Not only granulocytopenia but also hyperleucocytosis has been attributed to sulfanilamide and allied compounds (177).

Borst (165) reported one of the earliest cases of fatal outcome. He attributed this death to the administration of not more than 1.8 gm of prontosil daily, although the patient's previous history may have indicated some predisposing disease of the bone marrow. This investigator decided, in view of the number of severe toxic reactions concomitant with his use of prontosil, to treat subsequent patients with sulfanilamide. Since that time, the number of severe toxic reactions concomitant with the use of other derivatives of sulfanilamide and sulfanilamide itself have been quite well balanced.

Young (178) reported another of the early cases of agranulocytosis with fatal termination. His was in a case of acute rheumatism which, following the failure of salicylate therapy, had been treated with 3 gm of

sulfanilamide daily for 18 days. Treatment was discontinued at this time because the clinical condition of the patient was frankly worse. A blood specimen taken four days later showed complete agranulocytosis and positive culture for hemolytic Staphylococcus aureus and Streptococcus viridans, although a negative blood culture had been reported three weeks earlier. Death occurred on the following day. One the day prior to death the blood showed 1,880 lymphocytes and no leukocytes. The author believed the agranulocytosis to be either of the idiopathic type of unknown etiology or to be due to sulfanilamide therapy. Other cases, reported in the opening paragraph of discussion of this toxic effect, are quite similar to these two. The dosage varies within certain limits, being quite small in some cases. The onset of the depression of the white cells is also not always spaced the same from the day of onset of therapy, but in general, the depression starts in from two to five days. Young's case, above described, is an exception in that it apparently took over two weeks for the agranulocytosis to develop.

Relations to bone marrow disease and septicemia as above shown in two cases, brings up the question

of whether or not to use sulfanilamide and its derivatives in the control of sepsis with secondary agranulocytosis or in sepsis following granulocytopenia that is induced by other drugs such as before mentioned. Again Long and Bliss (13) may be turned to for supreme opinion. They state, "We think that in patients suffering from agranulocytosis and streptococcal sepsis, therapy with these drugs is not only indicated, but may be life-saving." They also advise, for other cases of agranulocytosis from sulfanilamide, "The first step to be taken when agranulocytosis develops is to provide for the rapid elimination of the drug. Fluids should be forced vigorously by the peroral and, if necessary, by the intravenous route. The diet is unimportant, except that it should have a high vitamin content, especially of vitamin C. This may be reinforced by the daily intravenous injection of 500 milligrams of cevitamic acid. If angina is a prominent symptom, the throat should be treated by the topical application of sodium perborate or neoarsphenamine, there being no indication that the use of either of these drugs is dangerous in this condition. We are inclined to think that the less a patient suffering from agranulocytosis is disturbed by misguided attempts at palliation, the

better. There is scant evidence that nucleotide preparations are of value in this condition and we never advise their use. Transfusions also should be avoided unless the hemoglobin drops below 60 per cent, since transfused blood is of questionable therapeutic value in the absence of a definite hemoglobin deficit."

Hageman andBlake (130) and Long and Bliss (132) were early to report jaundice as one of the toxic manifestations of sulfanilamide therapy. Theydescribed this as being of a mild nature and did not attach much significance to it, except that it represented some sort of liver damage, the extent of which was not understood. Long and Bliss associated this jaundice with marked decrease in liver function in some instances. They also noted that there was no acute hemolytic anemia in the patients observed, for as before stated a jaundice is found in those cases quite often. Other workers were quick to varify these reports (49, 179-182). These men also reported cases of extreme hepatitis with fatalities.

The case presented by Cline (181) is different from the others in that it was an acute yellow atrophy in the course of sulfanilamide therapy. The patient

had been given the drug over a period of two months, and at the termination of theperiod it was found that he had been taking it far in excess of thephysician's orders. The case gave many diagnostic troubles. It was at first thought to be a catarrhal jaundice. There was no rash present as found in some other reported cases. The illness from the drug covered a period of ten days and ended fatally. The signs of liver insufficiency gradually progressed during this period. An autopsy was done, and the typical findings of acute yellow atrophy were recorded.

Bannick and his associates (179) have reported two instances of fatal jaundice in the course of sulfanilamide therapy. They, however, attributed only one of the deaths directly to the drug. Saphirstein (180) described an exfoliating dermatitis and acute hepatitis in a patient who received sulfanilamide over a period of seventeen days. The dermatitis and hepatitis cleared within two weeks. Garvin (182) has observed five patients who developed a toxic hepatitis in the course of, or subsequent to, sulfanilamide therapy. In four of these, the hepatitis was considered definitely to be a toxic reaction to the drug. Two of the patients developed jaundice and hepatitis while receiv-

ing the drug. In the other three sulfanilamide had been stopped four, seven and thirty-five days before evidence of liver injury became apparent. An exfoliating dermatitis was associated with the hepatitis in three patients, one of whom died. There was no reason to suspect the existence of previous liver damage in any of these patients. One patient had previously suffered from a toxic reaction to sulfanilamide. Other reports have been published of fatal toxic hepatitis from drug administration (183,184).

Charles P. Baker, M. A., M. D., of the University of Nebraska College of Medicine, offers the following case for analysis. The patient was admitted to the Methodist hospital, Omaha, Nebraska, on August 16, 1939.

History: Caesarian section for full term baby 2-20-39. past 15 years "colitis" which consisted of gas pains and belching. This was relieved during the pregnancy. Two weeks ago joint pains with swollen joints. Patient treated with sulfanilamide. Following this noted nausea, dizziness, faintness and confusion. Four days ago first noted yellow tinge to skin. Has had no abdominal pain but says upper abdomen has been tender. Following the jaundice joint pains have been relieved.

Physical examination: Skin markedly yellow. Tenderness in right upper quadrant.

Laboratory: Hemoglobin 84%, WBC 8,000. Urine-- bile present. Stools very light with bile present in small amounts occasionally. Van den Bergh immediate direct reaction. Serum bilirubin 18 mg%.

Course: 8-21-- Hb 75%, RBC 3,750,000. Stools slight

test for bile. Serum bilirubin 15 mg%. Edema present. Given transfusions.
8-23-- roentgen studies. No calculi found. Liver not enlarged.
9-14-- serum bilirubin 31 mg%. Considerable ascites found. Total serum protein 4.5 mg%.
9-20-- serum bilirubin 15 mg%.
9-27-- paracentesis.
9-30-- serum bilirubin 14 mg%.
10-2-- irrational.
10-3-- dd.

An autopsy permit was obtained. The liver was found to weigh only 750 gm. The ducts were entirely open. The organ was firm, and nodular in appearance. In microscopic section some post mortem change was noted in the liver. The connective tissue was greatly increased in amount, in some regions being the only tissue present except for compressed bile ducts. Most all of the parenchymal tissue was more or less completely degenerate. However, in one area there was fine evidence of attempted regeneration. Here the cords of cells were fresh in appearance, and they were arranged in irregular formation about central veins which were not well centered. No other significant finding was apparent.

In considering this case it is noted that the toxicity had overwhelmed the restorative powers of the liver. No doubt the liver of one person is different in its regenerative powers than that of another. The

great predominance of degeneration over regeneration in this specimen shows the failure of this restorative power here. Sections of the bile ducts were taken at many levels to be assured that no obstruction had been present. Previous liver damage is not in evidence in the story. The fact that the patient had had previous toxic reaction to sulfanilamide showed the apparent idiosyncracy to the drug which here seemed to be present.

The edema of this patient was no doubt due to two great factors: Through the intimate relationship of the liver with the protein metabolism of the body the protein level of the blood was considerably reduced as shown by the periodic laboratory studies. With the great contraction of the liver which was evident at autopsy it is easy to understand that considerable portal obstruction must have been present.

No other drugs are known to have been administered to the patient in this case, and apparently only the usual dosage was taken over a period of about ten days.

The difficulty in diagnosis here emphasizes the fact that many of these cases could easily go unreported. The intimate hook up with protein metabolism is here again suggested by the liver reaction in the nature of an idiosyncracy.

SUMMARY

In the statement of purpose of this paper it was said that an attempt would be made to find something in common with the effects of sulfanilamide and allied compounds, as interpreted from the literature on the subject. It is felt that an important generality can now be, not made, but only emphasized. This generality concerns not only the therapeutic effects, but also the toxic manifestations of drug administration as well. This gross impression is seen in most all of the late literature, and can easily be found between the lines of the earliest. This one fact-- that in deciding where to use the drug, why, and when, what to watch for in the giving, how to watch for it, why, and when, and if it comes, in many more relatives-- it is not the micro-organism that is concerned, the concomitant morbidity that may be present or the fear of reaction that is to control and guide therapy-- it is the manner in which these micro-organisms manifest themselves in the body, the ability of the body to standany mild therapeutic measures, and the response to those measures as interpreted by a fair knowledge of what to expect.

During the affair with Massengill and Company, before mentioned, a layman, or even many students of medical science, might have said, "That is sad-- so

many people meeting death because of this new drug, but it is a wonderful discovery. We must give the men credit for that." Few even realize that the early history of the drug was not even American! In the same misinterpretation, that has followed the development of our collective knowledge of the drug, it is noted that the first report of therapeutic action of the compound was as acting against a staphylococcus infection in man (septicemia). Still, this was not heeded because the first proof of therapeutic activity was in experiments with streptococci-- experiments that, incidently, don't work in the laboratory with the staphylococcus. However, the professional world was quick to assume that the drug was a specific for streptococci. It is only now coming to light that a multiplicity of micro-organisms are affected. Staphylococcus septicemias can be treated quite as well as streptococcus ones if they are attacked at a similar stage in the disease process where there is parallel tissue destruction. In the same way, through the few years of active history of the sulfonamide compounds, we turn from the remarkable work of one man to that of another, forgetting to retain that of the first. The literature has been too profuse and voluminous for general study, but soon each practicing person will have read at least one of the frequently appearing short summaries

that are now seen, and a more representative impression will be almost universal.

Dangers are seen in the mistaken impression that the drug is more or less a specific for streptococci. General use in sore throats is seen to be harmful as before shown, and at the same time an important opportunity to save a life may be missed by harboring this belief. These opportunities may arise in the face of concomitant morbidity which may have to be bucked, but a thourough understanding of what is being bucked to affect must be realized.

Intimacy with a recent case of toxic hepatitis has been interesting in this report. The analysis of the morbid process involves many physiological considerations as before shown. If signs of hepatic insufficiency are met, the administration of the drug should be stopped at once and palliative measures resorted to. These signs appear early enough to be adequate danger signals if daily vigilance is possible.

Physicians in general practice and in most of the special practices of medicine and surgery have no choice about using these drugs. Some have hesitated because of the occasional toxic reactions. Others have been overly zealous without due regard for them.

The extreme value of these drugs demands that the physician use them; the possibility of toxic reactions demands that he use them intelligently.

The precautionary measures needed in using these drugs are not difficult. So much laboratory work may be found an inconvenience but these drugs are often life-saving measures and deserve the full attention of the attending physician.

CONCLUSIONS

1. It is not the micro-organism so much as the manner in which that micro-organism manifests itself in the morbid process in the body, that is concerned with in determining the therapeutic effects of sulfonamide compounds.

2. The toxic effects of sulfonamide compounds need not be feared if daily vigil is kept during administration.

BIBLIOGRAPHY

(1) Report of the Council on Pharmacy and Chemistry: Sulfanilamide, J.A.M.A., 108:1340, April 17, 1937.
(2) Report of Secretary of Agriculture-- Submitted in response to House Resolution 352 of Nov. 18, 1937, and Senate Resolution 194 of Nov 16, 1937: Deaths due to elixir of sulfanilamide-- Massengill, J.A.M.A., 109: 1985-1988, Dec. 11, 1937.
(3) Report of the Council on Pharmacy and Chemistry: Sulfanilamide, J.A.M.A., 108:1888, May 29, 1937.
(4) Long, P. H., and Bliss, E. A.: Clinical use of sulfanilamide and its derivatives in the treatment of infectious diseases, Ann. Int. Med., 11:575, 1937.
(5) Gelmo, P.: Ueber Sulfamide der p-amidobengolsulfonsaure, J. f. prakt. Chem., 77:369, 1908.
cited from-- Bigler, J. A., and Haralambie, J. Q.: Sulfanilamide and related compounds., Am. J. Dis. Child., 57:1110, May 1939.
(6) Eisenberg, P.:
cited from-- Long, Perrin H., and Bliss, Eleanor A.; "The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds," page 2, New York, MacMillan Company, 1939.
(7) Domagk, G.:
cited by #6, page 3.
(8) Trefouel, J., Nitti, F., and Bovet, D.:
cited by Mellon, R. R., Gross, P., and Cooper, F. B.; "Sulfanilamide Therapy of Bacterial Infections," page 7, Baltimore, Charles C. Thomas 1938.
(9) Buttle, G. A. H., Gray, W. H., and Stephenson, D.: Protection of mice against streptococcal and other infections by p-aminobenzenesulphonamide and related substances, Lancet 1:1286, 1936.
(10) Fuller, A. T.: Is p-aminobenzenesulphonamide the active agent in Prontosil therapy?, Lancet 1:194, 1937.
(11) Long, P. H., and Bliss, E. A.: (a) Para-aminobenzene-sulfonamide and its derivatives: Experimental and Clinical observations on their use in the treatment of Beta-hemolytic streptococcic infection, J.A.M.A., 108:32, Jan 2, 1937.
(12) cited by Hoerlein, H.: New class of chemotherapeutic agents against streptococci, with special reference to prontosil and prontylin, M. Rec., 146:11, 1937.
(13) Long, Perrin Hamilton, and Bliss, Eleanor A.: "The Clinical and Experimental use of sulfanilamide, sulfapyridine and allied compounds", New York, McMillan Company, 1939.

(14) Mellon, Ralph Robertson; Gross, P., and Cooper, F. B., "Sulfanilamide Therapy of Bacterial Infections", Baltimore, Charles C. Thomas 1938.
(15) Keefer, E. S., and Rantz, L. A.: Studies of hemolytic streptococcal infection. IV The mode of action of sulfanilamide on hemolytic streptococci in vitro, Arch. Int. Med., 62:109, July, 1938.
(16) Keefer, C. S.: Sulfanilamide: Its mode of action and use in the treatment of various infections, New Eng. J. M., 219:562, Oct 13, 1938.
(17) Bliss, E. A., and Long, P. H.: Observations on the mode of action of sulfanilamide, J.A.M.A., 109: 1524-1528, 1937.
(18) McKinney, R. A., and Mellon, R. R.: Sulfanilamide and macrophage response to hemolytic streptococcal peritonitis in mice., Proc. Soc. Exper. Biol. and Med., 37:333-336, 1937.
(19) Gay, F. P., and Clark, A. R.: On the mode of action of sulfanilamide in experimental streptococcus empyema., J. Exper. Med., 66:535-548, 1937.
(20) Colebrook, L., Buttle, G. A. H., and O'Meara, R. A. Q.: The mode of action of p-aminobenzenesulphonamide and Prontosil in hemolytic streptococcic infections, Lancet 2:1323-1326, 1936.
(21) Hoare, E. D.: Bactericidal changes induced in human blood, Lancet 1:655-659, 1938.
(22) Osgood, E. E., and Brownlee, I. E.: Culture of human marrow; studies on the mode of action of sulfanilamide, J.A.M.A., 110:349-356, 1938.
(23) Levaditi, C., and Vaisman, A., Compt rend. Soc. de biol., 119:946,1935. cited by #14.
Other works by these Frenchmen cited by #13 and #14.
(24) Colebrook, L., and Kenny, M.: Treatment of Human Puerperal infections and of experimental infections in mice with prontosil, Lancet 1:1279, 1936 (June 6).
(25) Rosenthal, S. M.: Studies in chemotherapy; effect of p-aminobenzene sulphonamide on pneumococci in vitro, Public Health Report 52:192, Febr 12, 1937.
(26) McMahon, B. J.: Influence of sulfanilamide on infected sinuses of rabbits; chemical and microscopic studies, Arch. Otolaryng., 28:233, August 1938.
(27) Same as #22.
(28) Coman, D. R.: Effect of prontosil-- related compounds upon chemotropism of leukocytes, Am. J. M. Sc., 196:273, 1938 (Aug).
(29) Same as #22.
(30) Long, P. H., and Bliss, E. A.: Para-aminobenzenesulfonamide and its derivatives; clinical observations on their use and treatment of infections due to beta hemolytic streptococci, Arch. Surg., 34:351, Febr 1937.

(31) Long, P. H., and Bliss, E. A.: Use of para amino benzene sulphonamide or its derivatives in treatment of infections due to beta hemolytic streptococci, pneumococci and meningococci, South M. J., 30:479, May 1937.
(32) Mellon, R. R., and Bambas, L. L.: Bacteriostatic effect of sulfanilamide in spinal fluid of convalescent cases of streptococcal meningitis, Proc. Soc. Exper. Biol. and Med., 36:682, June 1937.
(33) Barron, E. S. G., and Jacobs, H. R.: Effect of prontosil and prontylin on metabolism of bacteria, Proc. Soc Exper. Biol. and Med., 37:10, Oct 1937.
(34) Lockwood, John S. and Lynch, Helen M.: Mechanism of action of sulfanilamide, J.A.M.A., 114:936, March 16, 1940.
(35) Ballenger, E. G., Elder, O. F., McDonald, H. P., and Coleman, R. C.: Failures in the treatment of urinary tract infections with sulfanilamide, J.A.M.A., 112:1569, April 22, 1939.
(36) Reuben, O.: Clinical experiences with sulfanilamide therapy, N. Y. State M. J., 39:418, March 1, 1939.
(37) Gray, H. J.: Streptococcic meningitis, J.A.M.A., 105:92, 1935.
(38) Schwentker, F. F., Clason, F. P., Morgan, W. A., Lindsay, J. W., and Long, P. H.: Use of para-amino-benzene-sulphonamide or its derivatives in treatment of beta haemolytic streptococcal meningitis, Bull. Johns Hopkins Hosp., 60:297, 1937 (april).
(39) Arnold, J. G., Jr.: Treatment of hemolytic streptococcic meningitis with para-amino-benzene-sulfonamide; report of case, with recovery, Ann. Int. Med., 10:1198, Febr 1937.
(40) Smith, H. B., and Coon, E. H.: Meningitis due to hemolytic streptococcus; report of 2 cases with recovery after use of prontosil and sulfanilamide, Arch. Otolaryng., 26:56, July 1937.
(41) Mitchell, A. G., and Trachsler, W. B.: Report on use of sulfanilamide and its derivatives at Children's Hospital of Cincinnati, J. Pediat., 11:183, Aug 1937.
(42) Horan, V. G., and French, S. G.: Sulphonamide in treatment of acute mastoiditis, Brit. M. J., 2: 942, 1938 (nov 5).
(43) Carey, B. W., Jr.: Use of para aminobenzenesulfonamide and its derivatives in treatment of infections due to B Streptococcus hemolyticus, meningococcus, and gonococcus; report of 38 cases, J. Pediat., 11:202, August, 1937.

(44) Neal, J. B., and Appelbaum, E.: Experience with sulphanilamide in meningitis, Am. J. M. Sc., 195: 175, Febr 1938.
(45) Foulis, M. A., and Barr, J. B.; Prontosil album in puerperal sepsis, Brit. M. J., 1:445, 1937 (febr 27).
(46) Jacoby, Adolph: Sulfanilamide in the treatment of gonorrhea, New. Eng. M. J., 221:102, July 20, 1939.
(47) Toomey, J. A.: Prognosis and treatment of erysipelas, Ann. Int. Med., 12:166, Aug. 1938.
(48) Snodgrass, W. R., and Anderson, T.: Prontosil in treatment of erysipelas; controlled series of 312 cases, Brit.Med. J., 2:101, July 17, 1937.
(49) Snodgrass, W. R., Anderson T., and Rennie, J. L.: Sulphamido-chrysoidine, sulphanilamide, and benzyl-sulphanilamide in treatment of erysipelas; controlled series of 242 cases, Brit. M. J., 2:399, Aug 20, 1938.
(50) Robinson, G. L.; case of streptococcal septicaemia treated with prontosil, Lancet, 1:509, Febr 27, 1937.
(51) Scal, J. C.; septicemia following acute sinusitis treated with sulfonamide compounds, New York State J. Med., 37:1147, June 15, 1937.
(52) McCarthy, J. D.: Prontosil and Prontylin--case report, Nebraska M. J., 22:186, May 1937.
(53) Whitby, Lionel, E. H.: Experimental assessment of therapeutic efficiency of amino compounds with special reference to p-benzylaminobenzenesulphonamide, Lancet, 1:1517, 1937 (June 26).
(54) Dyke, S. C.: Pneumococcal septicaemia treated with M&B693, Lancet 2:621, Sept 10 1938.
(55) O'Brien, E. J. and McCarthy, C. J.: Staphylococcal septicaemia treated with M&B 693, Lancet 2: 1232, Nov 26, 1938.
(56) Goldberg, S. L., and Sachs, A.: Sulfapyridine in the treatment of staphylococcus aureus bacteremia, J.A.M.A., 113:1639, Oct 28, 1939.
(57) Colebrook, L. and Kenny, M.: Treatment with prontosil of puerperal infections due to haemolytic streptococci, Lancet 2:1319, Dec. 5, 1936.
(58) Colebrook, L. and Purdie, A. W.: Treatment of 106 cases of puerperal fever by sulphanilamide (streptocide), Lancet 2:1237, Nov 27, 1937.
(59) Mellon, R. R., and Shinn, L. E.: Potentiating influence of urine on sulfanilamide's bacteriostatic effect on E. coli in vitro, Proc. Soc. Exper. Biol. and Med., 37:331, Nov, 1937.
(60) Kenny, M., Johnson, P. D., and von Haebler, T.: p-aminobenzenesulphonamide in treatment of Bacterium coli infections of urinary tract with note on 2 plate bacterial count, Lancet, 2:119, July 17, 1937.

(61) Schwentker, F. F., and Gelman, S., and Long, P. H.: Treatment of meningococcic meningitis with sulfanilamide, J.Am.M.A., 108:1407, April 24, 1937.
(62) Harvey, A. M., and Janeway, C. A.: Development of acute hemolytic anemia during administration, J.A.M.A, 109:12-16, July 3, 1937.
(63)Banks, H. S.: Serum and sulphanilamide in acute meningococcal meningitis; preliminary survey based in 113 cases, Lancet, 2:7, July 2, 1938.
(64) Waghelstein, J. M.: Sulfanilamide in treatment of 106 patients which meningococcic infections, J.A.M.A., 111:2172, Dec. 10, 1938.
(65) Dees, J. E., and Colstrom, J. A. C.: Use of sulfanilamide in gonococcic infections; preliminary report, J.Am.M.A., 108:1855, May 29, 1937.
(66) Herrold, R. D.: Treatment of gonorrhea and other infections in urinary tract with sulfanilamide, Urol. and Cutan. Rev., 41:468, July 1937.
(67) Anwyl-Davies, T.: Treatment of gonorrhea with specific antitoxin, Brit. M. J., 2:553, Febr 13, 1937.
(68) Brunet, W. M., Reinhardt, C. H., and Shaw, N. D.: Use of sulfanilamide in gonorrhea in male; preliminary report and a warning, New Eng. J. Med., 218:287, Febr 1938.
(69) Alyea, E. P., Daniel, W. E., and Harris, J. E.: Sulfanilamide therapy in gonorrhea and its complications, South. M. J., 31:395, April, 1938.
(70) Breakey, R. S., and Harrold, J. F.: Sulfanilamide in urologic infections, J. Mich. State Med. Soc., 37: 425, May 1938.
(71) Colston, J. A. C., Dees, J. E., and Harrill, H. C.: Treatment of gonococcicinfections with sulfanilamide, South. M. J., 30:1165, December 1937.
(72) Roth, Louis F.: Sulfanilyl-sulfanilamide (Disulon) Vs. sulfanilamide in treatment of acute gonorrhea in the male, Journal of Urology 43:483, March 1940.
(73) Crean, T. F.: The use of prontosil in the treatment of gonorrhea, Lancet 2:895, Oct 16, 1937.
(74) Cokkinis, A. J.: Treatment of gonorrhea with oral sulfanilamide, Brit. M. J., 2:905, Nov 6, 1937.
(75) Marvin, H. P., and Wilkinson, W. E.: Gonococcic meningitis-- treatment with sulfanilamide, J.A.M.A., 110:800-802, Mar 12, 1938.
(76) Farrell, J. I., Lyman, Y., and Youman, G. P.: The rationale of sulfanilamide in gonococcic urethritis, J.A.M.A., 110:1176, 1938.
(77) Coggeshall, H. C., and Bauer, W.: Treatment of gonorrheal and rheumatoid arthritis, New Eng. J. M. 220:85, Jan. 12, 1939.

(78) Welch, H., Wentworth, J. A., and Mickle, F. L.: The use of sulfanilamide in the diagnosis and treatment of Brucellosis, J.A.M.A., 111:226, July 16, 1938.
(79) Kato, E. and Lane, C. R.: Brucella abortus infection, Lancet 2:77-79, July 10, 1937.
(80) Hanschell, H. M.: Sulphanilamide in treatment of chancroid, Lancet 1:886, April 16, 1938.
(81) Hutchison, A.: Treatment of bubo with sulphanilamide, Lancet 1:1047, May 7, 1938.
(82) Chargrin, L.: Sulfanilamide dermatitis, Arch. Dermat. and Syph., 38:476, 1938.
(83) Kornblith, B. A., Jacoby, A., and Wishengrad, M.: Treatment of chancroid with sulfanilamide, J.A.M.A., 111:523, Aug 6, 1938.
(84) Fields, R. J., and Weinstein, J. J.: Use of sulfanilamide powder locally in treatment of chancroid, Urol. and Cutan Rev., 42:880-881, Dec 1938.
(85) Rhoads, P. S., and Afremow, M. L.: Sulfanilamide in sore throat, J.A.M.A., 114:942-943, March 16, 1940.
(86) Hageman, P. O., and Blake, F. A.: Clinical experience with sulfanilamide in the treatment of beta hemolytic streptococcic infections, Am. J. M. Sc., 195:163-175, Febr 1938.
(87) McIntosh, R., Wilcox, D. A., and Wright, F. H.: Results of sulfanilamide treatment at Babies Hospital, New York City, J. Pediat., 11:167-182, Aug 1937.
(88) Bernstein, D. D.: Report on use of sulfanilamide at Children's Hospital of Michigan, J. Pediat., 11: 198-201, Aug., 1937.
(89)Hageman, and Blake, and Fleming, J. B.: Sulfanilamide in treatment of scarlet fever, Brit. M. J., 1:1281, June 19, 1937.
(90) Sako, W., Dwan, P. K., and Platon, E. S.: Sulfanilamide in treatment of scarlet fever, J.A.M.A., 111:995, Sept 10, 1938.
(91) Toomey, John A.: The management of scarlet fever and its complications, Pennsylvania M. J., 43:769, March 1940.
(92) Heintzelman, J.H.L., Hadley, P. B., and Mellon, R.R.: Use of p-aminobenzenesulfonamide in type 3 pneumonia from pneumococcus, Am. J. M. Sc., 193:759-763, June, 1937.
(93) Bullowa, J. G. M.: Pneumonias: Their management, Calif. and West Med. 46:368-372, June, 1937.
(94) Sadusk, J. F., Jr.: Observations on sulfanilamide therapy in pneumonia and meningitis due to type 3 pneumococci, New Eng. J. Med., 219:787, Nov. 17, 1938.

(95) Evans, G. M., and Gaisford, W. F.: Treatment of pneumonia with 2-(p-aminobenzenesulfanilamido) pyridine, Lancet 2:14, July 2, 1938.
(96) Telling, M., and Oliver, W. A.: Case of massive pneumonia, type III with massive collapse, treated with sulfapyridine, Lancet 1:1391, June 18, 1938.
(97) Christie, J. M.: Chemotherapy of pneumonia, Lancet 2:281, July 30, 1938.
(98) Flippin, H. and Pepper, D. S.: Use of sulfapyridine in treatment of pneumonia, Am. J. M. Sc., 196: 509, Oct 1938.
(99) Dyke, S. C. and Reid, G. C. K.: Treatment of lobar pneumonia with M&B 693, Lancet 2:1157, Nov 19, 1938.
(100) Hanssen, P.: Sulfapyridine in treatment of pneumonia, Lancet 1:61, Jan 1, 1938.
(101) Plummer, N., and Unsworth, H. K.: Sulfapyridine in the treatment of pneumonia, J.A.M.A., 113:1847, Nov 18, 1939.
(102) Whittemore, W. L., Royster, C. L., and Riedel, Paul A.: Administration of sulphapyridine in pneumococcic pneumonia, J.A.M.A., 114:940, March 16, 1940.
(103) Jensen, N. K., Johnsrud, Luverne W., Nelson, M. C.; The local implantation of sulphanilamide, Surgery 6:1, July 1939.
(104) Marshall, E. K., Emerson, K., and Cutting, W. D.: Para-aminobenzenesulfonamide-- absorption and excretion--, J.A.M.A., 108:953, March 20, 1937.
(105) Bohlman, H. R.: Gas gangrene treated with sulfanilamide, J.A.M.A., 109:254, July 24, 1937.
(106) Kennedy, W. C.: Therapy of gas gangrene, Illinois M. J., 73:260, March, 1938.
(107) Sadusk, Joseph F., Jr., and Manahon, C. P.: Sulfanilamide for puerperal infections due to Clostridium welchii, J.A.M.A., 113:14, July 1, 1939.
(108) Brown, W. H.: The use of sulfanilamide in clinical medicine, Canad. M. A. J., 39:15 July 1938.
(109) Bensley, E. H., and Wilen, B.: Methemaglobinemia and sulfhemoglobinemia due to sulfanilamide, Canad. M. A. J., 41:62-4, July 1939.
(110) Paton, J. P. J. and Eaton, J. C.: Sulfhemoglobinemia and methemoglobinemia following administration, Lancet 1:1159-1162, May 15, 1937.
(111) Archer, H. E., and Discombe, G.: Sulphaemoglobinemia; its cause and prevention, with special reference to treatment with sulfanilamide, Lancet 2:432-435, Aug 21, 1937.
(112) Discombe, G.: Sulfhemoglobinemia following treatment, Lancet 1:627- March 13, 1937.

(113) Frost, L. D. B.: Sulphemoglobinemia following antistreptococcal chemotherapy with benzyl-sulfanilamide and prontosil, sulfanilamide derivative, Lancet 1:510, Febr 27, 1937.
(114) Bensley, E. H., and Ross, J. B.: Methaemoglobinaemia due to sulphanilamide therapy, Canad. M. A. J., 37:62-64, July, 1937.
(115) Marshall, E. K., Jr., and Walzl, E. M.: On cyanosis from sulfanilamide, Bull. Johns Hopkins Hosp., 61:140-144, Aug 1937.
(116) Wendell, W. R.: Use of methylene-blue in methemoglobinemia from sulfanilamide poisoning, J.A.M.A., 109:1216, Oct 9, 1937.
(117) Chesley, L. C.: Cyanosis with sulf- or methemoglobinemia in patients receiving sulfanilamide treatment, J. Clin. Investigation, 17:445-447, July, 1938.
(118) Mull, J. W., and Smith, J. T.: Sulfanilamide, J.A.M.A., 110:539, Feb 12, 1938.
(119) Bigler, J. A., and Werner, M.: Cyanosis from use of sulfanilamide, Am. J. Dis. Child., 57:1338, June 1939.
(120) Archer, H. E., and Discombe, G.: Sulphaemoglobinemia, Lancet 2:432-435, Aug 21, 1937.
(121) Campbell, D., and Morgan, T. N.: Cyanosis (with methemoglobinemia or sulfhemoglobinemia) caused by sulfonamide compounds (sulfanilamide and sulfapyridine), Lancet 2:123-127, July 15, 1939.
(122) Hartmann, A. F., Perley, A. M., and Barnett, H. L.: A study of the physiological effects of sulfanilamide, J. Clin. Invest., 17:699, May 6, 1937.
(123) Ornsteen, A. M., and Furst, W.: Peripheral neuritis due to sulfanilamide, J.A.M.A., 111: 2103, Dec. 3, 1938.
(124) van Valkenburg, C. T., and Kreuzwendedich von dem Borne, G. A.: Polyneuritis after Uliron treatment, Lancet 2:889, Oct 15, 1938.
(125) Hogan, B. W., and McNamara, P. J.: Psychosis precipitated by sulfanilamide, U.S. Nav. M. Bull., 36:60-61, Jan 1938.
(126) Danziger, L.: Delayed toxic reaction to sulfanilamide, Bull. Johns Hopkins Hosp., 63:320-'4, Nov 1938.
(127) Bucy, P. C.: Toxic optic neuritis resulting from sulfanilamide, J.A.M.A., 109:1007-1008, Sept 25, 1937.
(128) Dozzi, J. L.: Transient nodal rhythm following use of sulfanilamide, Am. J. M. Sc., 195:771, June 1938.

(129) Fisher, J. H., and Gilmour, J. R.: Encephalomyelitis following administration of sulfanilamide with note on histologic findings, Lancet 2:301-305, Aug 5, 1939.
(130) Long, P. H., and Bliss, E. A.: p-aminobenzenesulfanilamide and its derivatives, Arch. Surg., 34: 351, 1937.
(131) Dees, J. E., and Colston, J. A. C.: The use of sulfanilamide in gonococcic infections, J.A.M.A., 108: 1855, May 29, 1937.
(132) Hageman, P. O., and Blake, F. G.: Specific febrile reaction; drug fever, J.A.M.A., 109:642-646, Aug 28, 1937.
(133) Gallagher, J. R.: Sulfanilamide drug fever: Second attack of sudden onset (case). New Eng. J. Med., 221:132, July 27, 1939.
(134) Schlesinger, E. R., and Mitchell, W. L., Jr.: Sulfanilamide eruption, Am. J. Dis of children, 56: 1256, Dec 1938.
(135) Cleveland, D. E. H.: Varioliform eruption from sulfanilamide, Arch. Derm and Syph., 39:693, April, 1939.
(136) Noun, M. H.: Erosions of oral mucosa and urticaria of body following small doses of sulfanilamide, Arch. Dermat. and Syph., 37:1044-1045, June 1938.
(137) Mathis, M. S., and McNamara, P. J.: Gonorrhea treated with sulfanilamide, U. S. Naval Bull., 37: 114, Jan, 1939.
(138) Davis, E.: Dermatitis and stomatitis in pneumonia treated with M&B 693, Lancet 1:1042, May 6, 1939.
(139) Myers, G. B., Vonder Heide, E. C., and Balcerski, M.: Exfoliative dermatitis following sulfanilamide, J.A.M.A., 109:1983-1984, Dec 11, 1937.
(140) Goodman, M. H., and Levy, C. S.: Development of cutaneous eruption (toxidermatosis) during administration; 2 cases, J.A.M.A., 109:1009-1011, Sept 25, 1937.
(141) Schonberg, I. L.: Purpuric and scarlitiniform eruption following sulfanilamide, J.A.M.A., 109:1035, Sept 25, 1937.
(142) Erskine, D.: --dermatitis, Brit. M. J., 2: 104-107, July 15, 1939.
(143) Wax, W. V.: Delayed photosensitization of the skin due to sulfanilamide, N. Y. St. M. J., 39:723, April 1, 1939.
(144) Schwentker, F. F., and Gelman, S.: Sulfanilamide rash, Bull. Johns Hopkins Hosp., 61:136, May 8, 1937.
(145) Stryker, Walter A.: The nature of the renal lesion with sulfapyridine therapy, J.A.M.A., 114:953, Mardh 16, 1940.

(146) Carroll, G., Shea, J., and Pike, G.: Complete anuria due to crystalline concretions following the use of sulfapyridine in pneumonia, J.A.M.A., 114:411, Feb 3, 1940.
(147) Gross, P., Cooper, F. B., and Lewis, M.: Urinary calculi from sulfapyridine, Urol. and Cut. Rev., 43: 299, May 1939.
(148) Rimington, C., and Hemmings, A. W.: Porphyrinuric action of drugs related to sulfanilamide- - -, Biochem. J., 33:960-977, June 1939.
(149) Rimington, C., and Hemmings, A. W.: Porphyrinuria following sulfanilamide, Lancet 1:770, April 2, 1938.
(150) Oakley, C. L.: Prontosil poisoning in mice, Biochem, J., 31:729-730, May 1937.
(151) Bensley, E. H., and Wilen, R.: Delayed excretion of sulfanilamide in case of pneumonia with renal failure, Canad. M. A. J., 41:184-185, August 1939.
(152) Ravel, V. M., and Curtis, W. R.: Hematuria and abdominal pain associated with sulfapyridine, South. Med., 23:264-265, Aug 1939.
(153) Gross, P., Cooper, F. B., and Lewis, M.: Fate of urinary calculi caused by sulfapyridine, Urol. and Cutan. Rev., 43:439-441, July 1939.
(154) Southworth, H., and Cooke, C.: Hematuria, abdominal pain and nitrogen retention associated with sulfapyridine, J.A.M.A., 112:1820, May 6, 1939.
(155) Kohn, S. E.: Acute hemolytic anemia during treatment, J.A.M.A., 109:1005-1006, Sept 25, 1937.
(156) Koletsky, S.: Fatal hemolytic anemia following administration of sulfanilamide, J.A.M.A., 113: 291-294, July 22, 1939.
(157) Rosenblum, P., and Rosenblum, A. H.: Severe hemolytic anemia due to sulfanilamide, Arch. Pediat., 55:511, Aug 1938.
(158) Wood, W. B., Jr.: Anemia during sulfanilamide therapy, J.A.M.A., 111:1916, Nov 19, 1938.
(159) Campbell, C. M., Jr.: Effects of sulfanilamide on blood picture, Lancet, I:247-248, Jan 29, 1938.
(160) Jennings, G. H., and Southwell-Sander: Anemia and agranulocytosis during therapy, Lancet 2: 898-901, Oct 16, 1937.
(161) Rosenthal, N., and Vogel, P.: Granulocytopenia caused by sulfapyridine in children, J.A.M.A., 113: 584-587, Aug 12, 1939.
(162) McGuire, P. R., and McGuire, J. P.: Agranulocytosis following the use of sulfanilamide, Illinois M. J., 73:425, May 1938.

(163) Allen, J. G., and Short, C. L.: Granulocytopenia associated with sulfanilamide therapy, New Eng. J. M., 219:6, July 7, 1938.
(164) Cutler, I. L., and Crane, E. J.: Agranulocytosis caused by sulfanilamide, New Eng. J. M., 221:231-233, Aug 10, 1939.
(165) Borst, J. G. G.: Death from agranulocytosis after treatment with prontosil flavum. Lancet 1: 1519-1520, June 26, 1937.
(166) Coxon, R. V., and Forbes, J. R.: Agranulocytic angina following administration of M&B 693, Lancet 2: 1412, Dec 17, 1938.
(167) Johnston, F. D.: Granulocytopenia, Lancet 2:1044, Nov 5, 1938.
(168) Sutherland, M. E.: Agranulocytosis following administration of M&B 693, Lancet 1:1208, May 27, 1939.
(169) Kracke, R. R.: Relation of drug therapy to neutropenic states, J.A.M.A., 111:1255, Oct 1, 1938.
(170) Schwartz, W. F., Curtis, F. G., and Koletsky, S.: Fatal granulocytopenia from sulfanilamide, J.A. M.A., 110:368-370, Jan 29, 1938.
(171) Berg, S., and Holtzman, M.: Fatal granulocytopenia following sulfanilamide therapy, J.A.M.A., 110: 370, Jan 29, 1938.
(172) Swift, H. F., Moen, J. K., and Hirst, G. K.: The action of sulfanilamide in rheumatic fever, J.A. M.A., 110:426, Febr 5, 1938.
(173) Corr, P., and Root, R. N.: Death from granulocytopenia after sulfanilamide therapy, J.A.M.A., 112: 1939, May 13, 1939.
(174) Shecket, H. A., and Price, A. E.: Fatal granulocytopenia following administration of sulfanilamide, J.A.M.A., 112:823, March 4, 1939.
(175) Dolgopol, V. B., and Hobart, H. M.: Granulocytopenia (and leukopenia) in sulfapyridine therapy, J.A. M.A., 113:1012-1017, Sept 9, 1939.
(176) Taub, J., and Lefkowitz, L.: Agranulocytosis due to sulfanilamide (case), N.Y.St. M.J., 39:1659-1661, Sept 1, 1939.
(177) Alpert, G. R., and Forbes, R. P.: Granulocytopenia and hyperleucocytosis following sulfanilamide therapy, J. Pediat., 12:605, May 1938.
(178) Young, C. J.: Agranulocytosis and para-aminobenzene-sulphonamide, Brit. M. J., 2:105, July 17, 1937.
(179) Bannick, E. G., Brown, A. E., andFoster, F. P.: Therapeutic effectiveness and toxicity of sulfanilamide, J.A.M.A., 111:770, Aug 27, 1938.

(180) Saphirstein, H.: Hepatitis and toxic erythema with desquamation due to sulfanilamide, Urol. and Cutan. Rev., 42:101, 1938 (Febr).
(181) Cline, F. W.: Acute yellow atrophy of the liver following sulfanilamide medication, J.A.M.A., 111: 2384, Dec 24, 1938.
(182) Garvin, C. F.: Toxic hepatitis due to sulfanilamide, J.A.M.A., 111:2283, Dec 17, 1938.
(183) Hogan, B. W., and McNamara, P. O.: Psychosis precipitated by sulfanilamide, U.S. Naval M. Bull, 36:60, Jan 1938.
(184) Fitzgibbon, P., and Silver, B.: Toxic necrosis of liver following use of sulfanilamide, Cal. and West. Med., 50:123, Feb 1939.