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# REVIEW PAPERS

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(Papers appearing in this section are invited reviews of subjects of wide current interest.)

## A REVIEW OF THE PROBLEMS OF SULFONAMIDE CHEMOTHERAPY

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Every since the development of systematic bacteriology and the rapid growth of the germ theory of disease, man has been engaged in an untiring search for agents which would specifically destroy the offending organisms. Up to the time of Ehrlich, that search had been more or less fruitless. Ehrlich approached the problem from a fresh point of view, and it is to him that we owe our modern concept of the chemotherapy of disease. His theory was expressed as "therapia sterilisans magna." He chose to direct this "sterilizing therapy" at the dread scourge of syphilis, and in 1907 he announced the discovery of salvarsan. Ehrlich's was the first planned attack upon a specific organism by means of a specific drug. Up to that time, quinine was the only specific therapeutic agent known to medicine, and it had been used empirically. This date, 1907, then marks the beginning of the modern clinical attack upon disease-producing microorganisms.

In the next year, an obscure Australian chemist, Gelmo, synthesized p-aminobenzenesulfonamide. Chemotherapy was the farthest thing from his mind. He was searching for dye intermediates, and the astounding potentialities of his new compound remained unknown for more than twenty-five years. It was not until 1932 that two German workers, Meitzsch and Klarer, experimenting with the possibilities of various dyes as antiseptics, noted that Gelmo's compound was very effective in preventing death in mice infected with the  $\beta$ -hemolytic streptococcus. Little further work was done along the lines suggested by this discovery until 1935 when another German worker confirmed and extended the earlier observations and a new era in chemotherapy was opened. The compound with which he worked was not Gelmo's original p-aminobenzenesulfonamide but a derivative known as prontosil. It was shortly learned that the extra chemical group in prontosil was not necessary for its activity against the streptococcus and he named the parent group (Gelmo's original compound) sulfanilamide. The German scientist who thus opened the door to modern chemotherapy was named Domagk. In the same year three English workers, Buttles, Grey and Stephenson, confirmed these observations and made them known to the world. Domagk was awarded the Nobel Prize and it is a significant comment on trends then prominent in Germany that Hitler refused to permit Domagk to receive the award.

When we examine the structure of sulfanilamide, we see at once that a host of substitution products are possible from a strictly chemical point of view. It has been estimated that some 7,000 different compounds related to this nucleus have been prepared and tested biologically. Out of this huge amount of work has come a number of observations of fundamental importance with reference to the activity of the substitution products of sulfanilamide. Then it was learned that neither substitutions on the ring other than the p-amino group nor modifications of the sulfoxide radical would yield compounds which were effective against the bacteria. There remained then only the possibility of substituting the amide nitrogen. A large number of amido-substitution products have been prepared

but only a few of these have come into the practice of medicine. The first one of any importance was sulfapyridine, introduced in England in 1939. It was sulfapyridine which really established the value of this group of drugs in medicine, for sulfapyridine was effective against the pneumococcus, the most dramatic and one of the worst scourges of mankind. In 1940 American chemists gave us sulfathiazole, and in 1941 sulfadiazine appeared. Since 1941 there have been but few additions to the sulfonamide group of drugs. The substituted nucleus of sulfadiazine has been slightly modified and two of its relatives, sulfamethazine and sulfamerazine, are receiving the tests of their clinical value today.

It was further noted that substitution on the amino nitrogen made the compounds difficult to absorb from the gastrointestinal tract. Such compounds were found, however, to be effective against many types of bacteria which are either

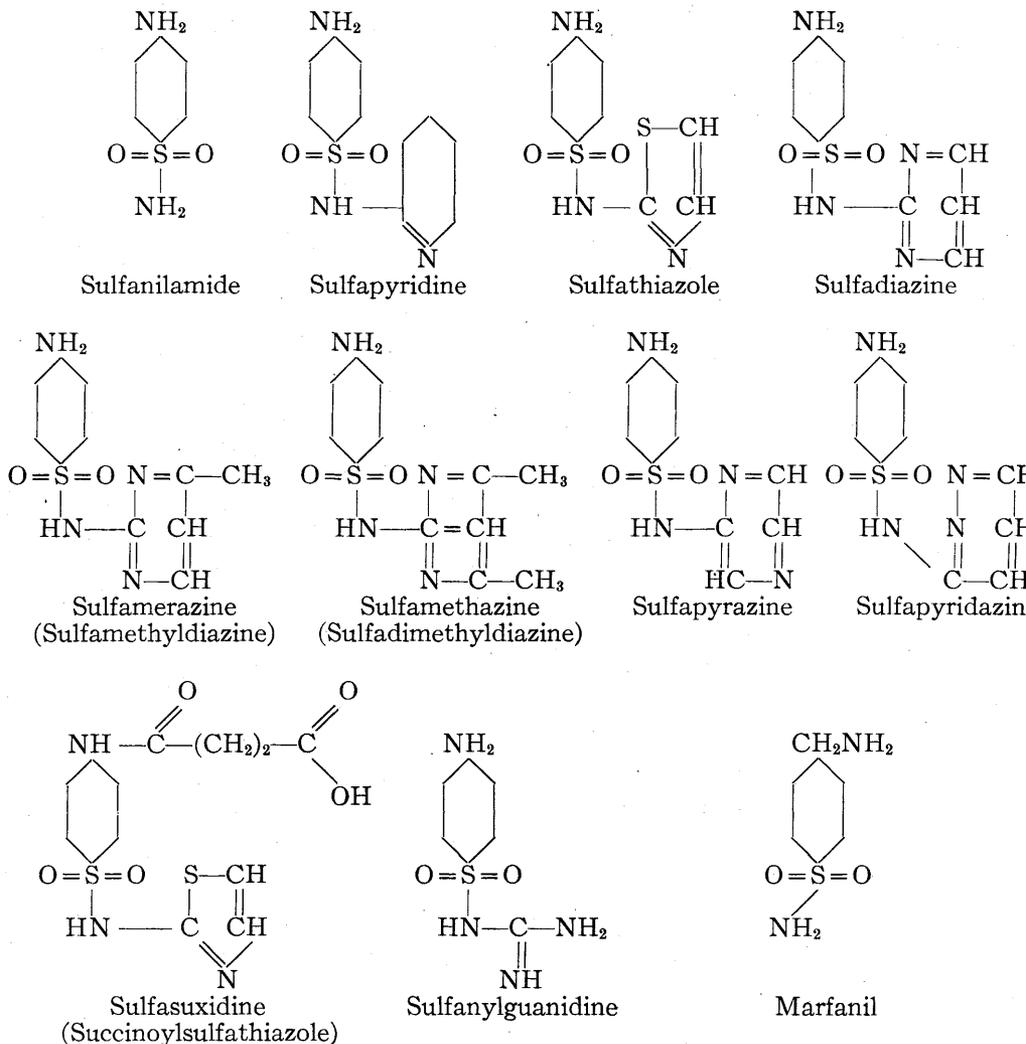


FIGURE 1. THE STRUCTURAL RELATIONSHIPS OF THE SULFONAMIDES

normal inhabitants of the gastrointestinal tract or produce diseases peculiar to that system. Two of these compounds have been of some use in medicine. They are sulfasuxidine and sulfanylguanidine. A third compound of this latter type known as marfanil has been employed by the Germans in the prevention and treatment of wound infections. Captured samples of this drug have been studied and its structure is known. Preliminary reports indicate that marfanil is more effective for the use noted than any of the previously known sulfonamides.

The structural relationships of all of these drugs are indicated in Figure 1.

#### PHARMACOLOGY

##### A. ABSORPTION AND FATE OF THE SULFONAMIDES.

All of the sulfonamides in which there is no modification of the amino nitrogen are relatively rapidly absorbed from the intestine. Maximum blood levels are attained in from 3 to 6 hours, following a single dose of any of the group. For this reason it is seldom necessary to administer the drugs by any other route than the oral. In certain specific cases, as, for example, when the patient is vomiting or in the presence of an overwhelming infection demanding heroic treatment, it is sometimes desirable to administer the drugs parenterally. With the exception of sulfanilimide, all of the free compounds are too insoluble for parenteral administration but for this purpose there are available soluble sodium salts of sulfapyridine, sulfathiazole and sulfadiazine.

All of the sulfonamides after absorption are rapidly distributed to all organs and tissues and to all of the extra-vascular fluid compartments. Concentrations attained are, in general, approximately 20 per cent lower than the concentration in the blood. One important exception to this general statement should be noted in the case of sulfathiazole. For some unknown reason, the concentration of sulfathiazole in the cerebrospinal fluid of the normal individual remains at a level represented by 10 per cent or less of the level in the blood. Recognition of this fact is important in the selection of a drug in the treatment of meningitis.

After the sulfonamides have been distributed throughout the body as noted above, very little happens to alter their chemical nature. All of them are acetylated by the liver to the extent of about 15 per cent of the total concentration in the blood. Recently it has been noted that certain members of the group tend to combine to a greater or lesser degree with the plasma. This action is spoken of as plasma-binding capacity. With sulfathiazole this occurs to the extent of about 25 per cent of the total plasma concentration; with sulfadiazine, to the extent of about 50 per cent; and with sulfamethazine, about 75 per cent. The variations in the plasma-binding capacity may be of significance with reference to the effective blood level in any given infection but the exact significance is not fully understood at the present time. Certain conditions existing in areas where infection is present or is likely to occur operate to lessen the effectiveness of the drugs. Among these must be mentioned collections of serum and the presence of pus. How these extraneous factors affect the metabolism of the sulfonamides is not known.

The chief route of excretion for all of the sulfonamides is via the urinary tract. Certain complications of great significance in the therapeutic use of the sulfonamides may occur as a result of this pathway of excretion. More detailed reference to this phenomenon will be made below.

##### B. MECHANISM OF ACTION.

The mechanism by which the sulfonamide drugs act to combat infectious processes presented a very difficult but interesting problem in bacteriology. Certain fundamental observations with reference to the classical theories of antibacterial action were soon made. They were as follows:

1. The drugs act by slowing the growth of the bacteria rather than by killing them outright; their action is bacteriostatic rather than bacteriocidal.

2. The drugs cause no potentiation nor inhibition of immunologic responses nor of the phagocytic mechanisms of the host.

3. The sulfonamides have no effect which could be interpreted as concerned with the neutralization of bacterial toxins.

In the light of these negative findings, it was necessary to postulate and study other possible mechanisms. The results of such studies may be briefly summarized as follows: The sulfonamides compete in the metabolism of the bacterium with some substance which is essential to the normal growth and multiplication of the organism. This hypothetical substance was definitely found to be p-aminobenzoic acid, known to the elect as PAB. Upon comparing the sulfonamides and PAB, it might be said somewhat facetiously, that the poor bacteria, never having had a college course in organic chemistry, are unable to distinguish between p-aminobenzoic acid and p-aminobenzene sulfonamide, and in attempting to utilize the former starve to death in the process. It is probably unwise to treat such an important discovery so lightly for, if it is possible to confuse the bacteria in this respect, then it is equally possible that a little research may disclose other substances which are essential to the well-being of the organisms. Synthetic compounds resembling these essential metabolites may then be developed and offered as ineffective substitutes for the essential metabolites to the detriment of the bacteria. The possibilities inherent in such an idea are so far-reaching that they stagger the imagination. Suffice it to say that already a great deal of research has been done along the lines suggested here. It is indeed fortunate that such a fundamental discovery has been made for it has been suggested only recently that the sulfonamides have probably been developed to their maximum extent. On the basis of certain careful physico-chemical observations, it has been predicted that sulfadiazine exhibits the maximum antibacterial action which can be developed by any derivative of the parent sulfonamide nucleus.

#### CLINICAL APPLICATION

##### A. ORGANISMS AFFECTED:

Following the initial wave of enthusiasm which greeted the introduction of the sulfonamides into the practice of medicine, it became quickly apparent that these new compounds were not panaceas. It was shortly learned that the sulfonamides were effective against a definitely limited number of organisms and that all of them were not equally effective against even these. Among the diseases which are most adequately controlled by the sulfonamides are those which are caused by the  $\beta$ -hemolytic streptococcus, the pneumococcus and the gonococcus. Among those diseases which may be fairly satisfactorily treated by the sulfonamides are those caused by the meningococcus, the staphylococcus, and the  $\alpha$ -hemolytic streptococcus (*viridans*). It is thus apparent that the field of usefulness is limited almost entirely to the coccal infections. Infections in which the etiologic agent is a bacillus and which respond to the administration of the sulfonamides are uncommon. Chief among them are infections produced by *Escherichia coli*, and by the dysentery bacilli. The gas gangrene group of bacilli are only moderately susceptible. It must be emphasized that the sulfonamide drugs are totally ineffective against the causative agent of rheumatic fever and against the organisms causing typhoid fever, typhus, diphtheria, tuberculosis and syphilis. In addition to these, furthermore, none of the known virus infections responds to sulfonamide therapy. These include influenza, "virus" pneumonia, measles, smallpox and many others. Table I compares their relative effectiveness against the common organisms.

## B. SPECIAL CASES:

## 1. Streptococcal Infections.

a. *β-Hemolytic Streptococcus*.—This organism is responsible for so-called strep throat; for one of the dreaded forms of blood poisoning; and very probably for scarlet fever. Once it has taken hold in a susceptible individual it goes like wild-fire and the patient when first seen is usually acutely and dangerously ill. Complication follows complication and, if the patient is able to withstand the onslaught and survive, he must usually face a long period of debility.

b. *α-Hemolytic Streptococcus*.—This organism commonly known as *Streptococcus viridans*, or the "green-producing" streptococcus, is a common cause of upper respiratory infections of the type usually associated with the common cold and its sequellae. We have already noted that the sulfonamides are of limited value in the management of infections caused by this organism, and the use of these drugs in the common cold is generally of little value.

TABLE I

THE COMPARATIVE SUSCEPTIBILITY OF THE COMMON ORGANISMS TO THE VARIOUS SULFONAMIDES

Organism	Sulfanila- mide	Sulfapyra- dine	Sulfathia- sole	Sulfadia- zine
<i>β-hemolytic Streptococcus</i> .....	++++	+++	+++	++++
<i>α-hemolytic Streptococcus</i> .....	++	++	++	++
<i>Diplococcus pneumoniae</i> (pneumococcus) ..	=	++++	++++	++++
<i>Neisseria intracellularis</i> (meningococcus) ..	++	++	++	++
<i>Neisseria gonorrhoeae</i> (gonococcus).....	++	++	+++	+++
<i>Staphylococcus</i> .....	=	++	++	+++
<i>Escherichia coli</i> (urinary tract).....	+++	++	+++	+++

One of the most terrible diseases known to medicine (fortunately, a relatively uncommon disease) is subacute bacterial endocarditis. This is a slowly progressive disease which nearly always attacks only those whose hearts have been damaged by rheumatic fever. It has been, up to the present era, a uniformly fatal infection. As one famous pathologist puts it, "The heart is beating muffled marches to the grave." Great hopes were held for its treatment when the sulfonamides became available, but disappointment and despair have followed their use. In one outstanding paper discussing the treatment of 67 cases of this disease, in which all of the sulfonamides and all adjuvant forms of therapy were used, the concluding sentence reads, "All sixty-seven patients are dead."

## 2. Pneumococcal Infections.

Prior to the advent of sulfapyridine, somewhere between 30 and 50 per cent of patients suffering from pneumonia died. Sulfapyridine alone reduced this appalling mortality to about 12 per cent and it was at once hailed as the "miracle drug." If no other benefits had resulted from the use of the sulfonamides, this victory alone would have been sufficient reward for the tremendous effort which has been expended in the development of these drugs. Sulfapyridine is no longer used in medicine, because both sulfathiazole and sulfadiazine are equally effective, and both of the latter are much less toxic to the patient than is sulfapyridine. In addition to the tremendous reduction in mortality it is apparent at once from this clinical picture that the morbidity has also been strikingly decreased. In a word, the fortunate patient who recovered from pneumonia in the pre-sulfonamide era was destined to spend long weeks of convalescence before he was able to return to anything resembling normal existence. Today he may be as "good as new" in as short a time as three weeks after the onset of the illness.

### 3. Gonococcal Infections.

Gonorrhoea has always been held somewhat lightly in the minds of men. This attitude has prevailed in spite of the fact that gonorrhoea rendered thousands upon thousands of women incapable of child-bearing. The misery, both physical and mental—and spiritual—produced by the gonococcus must forever remain incalculable. The sulfonamides have gone far in reducing this scourge, but the very nature of the disease and the circumstances surrounding its transmission work continuously against any method of treatment. We shall have occasion under another heading to refer again to the gonococcus.

Prior to the availability of the sulfonamides, an uncomplicated case of gonorrhoea which was given the best therapy available could be cured in a matter of weeks. When the sulfonamides are used in a similar case today, the cure is literally a matter of hours. Here again we see strikingly illustrated the tremendous importance of these drugs.

### C. PROPHYLACTIC USE.

It was natural that drugs which were so effective in the cure of certain diseases should be tried for the purpose of preventing these diseases from developing. For a long period of time after the introduction of the sulfonamides, their prophylactic use belonged in the category of "armchair" therapeutics. No one had any real information as to their efficiency in the prevention of disease and such use aroused a small storm of protest from those who were already beginning to realize the complications which might arise from the development of fastness in the organism and sensitivity in the patients. These men argued that before prophylactic use was justifiable, it must first be demonstrated that a sufficiently high degree of morbidity could be prevented to justify the danger of the production of sensitivity in those receiving the drugs, and to justify the development of "carriers" of sulfonamide-fast organisms. The multitude of variables presented in the consideration of these two problems has thus far defied analysis. The war with its consequent crowding together of large groups of men under conditions which have long been realized to be ideal for the development and spread of epidemics, made the prophylactic use of the sulfonamides under certain circumstances mandatory. For example, an epidemic of scarlet fever began on Navy Pier in New York City. At once a large section of the personnel was given sulfadiazine in small daily doses. The case incidence of scarlet fever in the treated group promptly fell to zero. Another trial of prophylactic value was made in a Southern army camp. Sulfathiazole was administered to each man who "signed out" in the evening, and a similar dose was given when he returned to camp. In this camp, prior to the introduction of routine sulfathiazole administration, the incidence of gonorrhoea was 171 cases per 1,000 men per year. Following the prophylactic use of sulfathiazole, the case incidence dropped to 8 per 1,000 men per year. Many more such instances could be cited. However, they all point toward the same conclusion. It is possible by the controlled prophylactic administration of a sulfonamide to reduce materially the incidence of infection by any bacterial agent which is ordinarily susceptible to the sulfonamides. Thus the fact of prophylaxis is established. It must be emphasized, however, that the two dangers inherent in sulfonamide prophylaxis have not been adequately evaluated.

### D. TOXICITY

#### 1. General Incidence of Toxic Reactions.

In the early years of sulfonamide chemotherapy, it was difficult to evaluate the incidence of total toxic reactions to the administration of these drugs. However, with the passing years it has become possible to give what is believed to be

a reasonably correct estimation of reaction incidence. The over-all reactions may be summarized roughly as follows (excluding the "mild" group in Table II):

Sulfathiazole.....	18 per cent
Sulfapyridine.....	16 per cent
Sulfanilamide.....	12 per cent
Sulfadiazine.....	10 per cent

In certain clinics it has been possible by meticulous attention to all details of therapy to reduce the over-all incidence of toxic reactions to figures appreciably below those cited. Table II gives a detailed analysis of the reactions which have been reported, together with an estimate of their distribution among the various sulfonamides. In general, those labeled "mild" do not contraindicate the further administration of the drugs; the label "moderately severe" should give reason

TABLE II  
THE PERCENTAGE DISTRIBUTION OF THE MORE COMMON REACTIONS TO THE SULFONAMIDES

	Sulfanila- mide	Sulfapyra- dine	Sulfathia- zole	Sulfadia- zine
	%	%	%	%
<b>MILD</b>				
Nausea and vomiting.....	25-40	40-60	6	0.7
Dizziness.....	50-60	50-60	5	rare
Mild hemolytic anemia.....	3	rare	rare	rare
Cyanosis.....	90-100	50	rare	none
<b>MODERATELY SEVERE</b>				
Acidosis.....	2	rare	rare	rare
Fever.....	10	4	6	3
Rash.....	2	2	6	2.1
Hematuria (microscopic).....	?	-	4	5
<b>SEVERE</b>				
Leukopenia.....	0.3	0.6	1.6	1.2
Agranulocytosis.....	0.1	0.3	rare	rare
Anuria or oliguria.....	none	0.3	0.7	1.5
Jaundice.....	1.8	0.6	rare	rare

for stopping the drug unless to do so would endanger the patient's life; the appearance of these reactions called "severe" makes the cessation of administration mandatory.

Sulfadiazine is the most important of the sulfonamides today and has for most infections supplanted all the rest.

It is unwise to try to draw many conclusions with reference to the significance of these toxic phenomena from the bare figures given here. The severity of a reaction varies directly with the seriousness of the disease process which instituted the administration of the drug in the first place. These tables and figures are included merely to permit a general concept of the extent and type of toxic effects which may be anticipated.

It should be pointed out that the actual numbers of individuals receiving the drugs are so great that some of the figures given in the tables fade into insignificance. Only those reactions in which there may be a large element of sensitivity involved, and those reactions referable to the kidney will be considered in any detail. The significance of the "sensitivity" group is discussed in the section dealing with the limitations of the sulfonamides.

Those reactions referable to the kidney are of sufficient importance to merit further comment. These reactions are of two types. The first type is entirely mechanical in character. As the sulfonamides are excreted, both in their free

and acetylated forms, they are concentrated in the kidney. As that concentration rises they tend to be precipitated, and crystalline compounds thus formed act to produce mechanical damage to the kidney tubules. This damage may range from slight irritation of the tubules with the appearance of a little blood in the urine, to the complete blocking of the tubules followed by the loss of the ability of the kidney to function. In addition to these mechanical effects, the sulfonamides (especially sulfadiazine) produce a chemical action on the walls of the kidney tubules. This cellular damage may also result in serious derangement of kidney function.

The greatest attention has been paid to these reactions and, if the proper precautions are taken, the incidence of serious kidney damage can be reduced almost to zero. The precautions are simple indeed and involve, first of all, careful observation of the patient's urinary output, which should be at least 1000 cc. daily. In the second place, some effort should be made to keep the urine alkaline by the administration of an alkaline salt, such as sodium bicarbonate. An alkaline urine helps to insure maximum solubility of the drug and reduces the danger of damage by crystal formation.

It should be mentioned that the "dizziness" noted in the tables may make it unsafe for the patient to carry our skilled tasks, such as driving a car or piloting an airplane. For this reason, in the Air Forces, any pilot receiving a sulfonamide is "grounded" until his treatment is finished.

#### E. THE LIMITATIONS OF SULFONAMIDE THERAPY.

##### 1. Organisms Not Affected.

In a previous section, the sulfonamide susceptibility of the various organisms which commonly cause disease was discussed. Little more need be said here, except to point out that the use of the sulfonamides in diseases caused by unsusceptible organisms is to be unhesitatingly condemned.

##### 2. Sulfonamide "Fastness."

In the early days of the sulfonamide therapy of gonorrhea, it was not uncommon to see reports indicating an incidence of cure as high as 90 per cent. As time has passed, this figure has further decreased until today one is likely to be depressed by the fact that rates of cure are being reported as low as 30 per cent. These carefully controlled case-studies are supported by the passing observations of many physicians who have not studied the problem in detail. For example, one prominent urologist in a Midwestern city told me in 1941 that he had long since cured all of the gonorrhea which was curable by sulfonamide and by sulfapyridine, and that he was then working on sulfathiazole. He remarked that he hoped a new sulfonamide would soon make its appearance else he would have to resort to the old pre-sulfonamide methods. These observations with reference to the gonococcus raised the question of the development of resistance by the organisms to the action of these drugs. This problem of resistance has been studied in great detail using all of the organisms which are known to be originally susceptible to sulfonamides. As a result of such studies, it is now known that most of the susceptible organisms under the proper conditions may become completely resistant to the action of the drugs. Such resistant organisms then are said to be sulfonamide-fast.

The conditions for the development of fastness have not been completely established. It seems, however, that prolonged exposure to concentrations of sulfonamide somewhat lower than those used therapeutically, is extremely effective in producing strains of resistant organisms. It is clear this phenomenon of fastness may be especially significant, if one takes the long term view. It is at once apparent that we must consider the definite possibility of the ascendancy of a whole new order of sulfonamide-resistant bacteria.

It has been shown that about 40 per cent of persons who recover from pneumonia serve as carriers of the infecting organisms for a long period of time. Many of these organisms have undoubtedly become resistant to sulfonamides during the treatment of the active disease and it has been shown that even now the incidence of sulfonamide-resistant pneumococcal pneumonia is increasing.

The illustrations afforded by the gonococcus and the pneumococcus serve as a grave warning with reference to the future of sulfonamide therapy. The possibility of the development of resistant organisms constitutes one of the chief contraindications to the indiscriminate use of the sulfonamide drugs.

### 3. The Problem of Sensitivity.

A number of the toxic reactions discussed above have been found to be the result of the development within the individual of special sensitivity to the sulfonamides. This sensitivity is related in some fashion to the general problem of allergy. The exact mechanism of the development of sensitivity is not well understood. It is, however, assumed that the sulfonamides react in some fashion with certain protein elements in the blood-stream, and antibodies for this new compound are then developed. The result of these complex changes is a repetition of the toxic response following immediately upon the administration of the next dose of the sulfonamide which caused the original reaction. Here again, as in the case of fastness, all the factors producing such sensitivity have not been fully determined. It is the consensus of opinion, however, that both the size of the dose and the duration of the administration are involved. Some of the reactions presumed to be sensitivity phenomena, are fever, skin rashes, agranulocytosis, and hemolytic jaundice. Some of the other reactions may also belong in this category but there is sufficient question as to their being so classified that we shall omit them from this discussion.

In the case of fever it has been noted that it is most likely to occur between the 5th and 7th days of administration. When a patient who has developed a fever receives a second course of sulfonamide drugs within the next year, he is very likely to develop a drug fever within the first 24 hours. Now the relation of duration of administration to the development of the sensitivity reaction may be pointed out. If a first course of sulfonamide therapy does not extend into the period when the fever would ordinarily be manifest, then no sensitivity would be developed so far as fever is concerned. This conclusion is not entirely valid for exceptions to it have frequently been noted. The second major factor (the size of the dose) is difficult to evaluate. The use of the sulfonamides in the prophylaxis of infectious diseases necessitates the administration of smaller doses over a long period of time. In such circumstances the incidence of reactions of all kinds is very low, generally in the neighborhood of 1 to 2 per cent. However, following the cessation of prophylactic course, it has been suggested that the incidence of these reactions believed to be sensitivity phenomena is much higher whenever it becomes necessary to give those patients full therapeutic doses of the drugs. This observation suggests that it is possible to develop sensitivity by continuous small doses without any overt toxic manifestations during such a prophylactic course. In summarizing, it may be said that there is little doubt that some of the toxic reactions to the sulfonamides are sensitivity phenomena. The exact significance of such phenomena with reference to the future of sulfonamide chemotherapy is not yet apparent. Nevertheless, the possibilities are sufficiently alarming to discourage the indiscriminate administration of the sulfonamides.

### THE FUTURE OF SULFONAMIDE CHEMOTHERAPY

As time goes on and we recover somewhat from the effects of our enthusiasm with respect to the sulfonamides, their value in the practice of medicine becomes more clearly defined. This group of drugs will continue to hold an important

place in therapeutics. The indications for their use have been clearly defined but the contraindications are still somewhat debatable. It is with the latter that we must be more concerned in the future. Obviously, the use of sulfonamides in the treatment of an infection caused by an organism which is known not to be susceptible to the sulfonamides constitutes a contraindication. Among the other contraindications, may be mentioned inadequate therapy, indiscriminate prophylactic use, and administration prior to an attempt to discover the nature of the offending organism. These three errors of application invite the development of "fast strains" of organisms. They also favor the development of sensitivity phenomena in the patients receiving them. If we are to keep the development of sensitivity and the development of fastness at a minimum, then it behooves us to use the sulfonamides sparingly and only after weighing carefully all of the dangerous possibilities which may, and inevitably will, accrue from their indiscriminate use.

It is probably justifiable to say that the sulfonamides themselves have served their greatest purpose in the treatment of human ills, not by virtue of their effect upon certain specific organisms, but because they have introduced us to a new approach to the problem of bacterial infection in general—the so-called metabolic theory of bacteriostasis. There is every reason to believe that other substances essential to the welfare of a given organism will be discovered. Then compounds may be prepared which will compete with that essential metabolite to the detriment of the organism in question. From this point of view, the outlook for the future of chemotherapy is indeed bright and it is not inconceivable that some time in the near future we may hope for drugs which will rid us of all infectious diseases.

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