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THE TREATMENT OF HEMOLYTIC STREPTOCOCCUS INFECTIONS AND THE NEWER APPLICATIONS OF SULPHANILAMIDE*

REUBEN OTTENBERG

THE HEMOLYTIC streptococcus ranks among the prime causes of disease. Perhaps second to the pneumococcus as a direct cause of death, it probably is more frequently responsible for acute infections than any other germ. This is particularly true if one includes not only the diseases directly due to it, such as scarlet fever, tonsillitis, erysipelas, suppuration, puerperal fever, but the possible indirect effects attributed to it, such as glomerulonephritis and the recrudescences of rheumatic fever. It is responsible for at least one fifth of all cases of septicemia.[1]

Within recent years there has been great progress in knowledge of the biology of the hemolytic streptococcus, and in the past two years, with the advent of a remarkable and highly effective chemotherapy there has been renewed activity in the study of these infections with perhaps an unfortunate tendency to think that sulphanilamide has closed the chapter. This is far from being the case. And it is important not to lose sight of the valuable advances of recent years in the biology and immunology of the streptococcus. For this reason I will discuss this subject first.

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Classification of Streptococci

The hemolytic streptococci form a large group of closely related organisms.[2] They are of great viability, remaining alive in air and dust for long periods of time and from five to thirty per cent of adults are carriers. The importance of the hemolytic property as a unifying biological characteristic began to be stressed at the turn of the century when blood cultures came into use for diagnosis. Brown, in his monograph of 1919,[3] used the hemolytic character as a chief differential point, classifying streptococci into alpha or viridans, beta or hemolytic, and gamma or non-hemolytic. In blood plates the clear rings of hemolysis around the colonies are characteristic. The red cells undergo complete clearing.

A great number of the earlier attempts at subdivision of the hemolytic streptococci failed because the cultural and biological characters of the sub-groups did not correspond to clinical divisions and so many separate strains were found that no grouping was possible.

In recent years, however, many of these difficulties have been circumvented by new immunological studies. Two important new classifications have been introduced, based on different principles, not mutually exclusive but supplementing each other.

The first of these, introduced by Lancefield[4] and her co-workers, is based on a simple precipitin reaction; as antigen is used a carbohydrate (often called substance C) extracted from the bacteria themselves with hot hydrochloric acid; as antibody, the serum of rabbits immunized with formolized bacteria. With this method hemolytic streptococci from all sources are found to fall readily into seven sharp groups.

Cutting across and supplementing this classification is typing by the method of agglutination. Unsatisfactory attempts to type hemolytic streptococci have been made for years. But recently by a slight simplification of technic Griffith[5] has shown that hemolytic streptococci derived from human sources can be classified by agglutination with immunized rabbit's sera into twenty-eight (or perhaps more) fixed types analogous in many ways with the fixed types of pneumococci. These strains maintain their specificity for years; certain of them have special pathological or epidemiological peculiarities.[6] Four of the types (Nos. 7, 16, 20 and 21) have now been eliminated[7] as not belonging to Lancefield's group A. The others are all pathogenic for man and are found with varying incidence in all kinds of hemolytic streptococcus

affections. It is of the greatest importance that one and the same strain may be responsible for entirely different clinical diseases.[8] Already grouping (A to G) and typing of strains (within Group A) are helping to clear up many epidemiological problems.

Before going into the hotly debated and still not entirely settled question of the specificity of certain streptococci it is necessary to say a few words about the five known toxins of the hemolytic streptococcus.

TABLE I

CLASSIFICATION OF STREPTOCOCCI

BROWN 1919 *Culture on Blood*	LANCEFIELD 1933 *Specific Precipitation*	GRIFFITH 1935 *Specific Agglutination*
Alpha (α) Viridans		
Beta (β) (Hemolytic)	A—Pathogenic; of human origin — but causing mastitis in cows by contact with human carriers — hence milk borne epidemics of sore throat and scarlet fever	Twenty-four or more permanent types, numbered between 1 and 28
	B—Chiefly bovine C—In various animals Cause disease in animals — may be harbored in human throat, vagina or intestines, but as a rule without causing disease	Four or more types known (Nos. 7, 16, 20, 21)
	D, E, F, G — Usually saprophytic found chiefly in foods	
Gamma (γ) (Non-Hemolytic)		

TOXINS

The hemolysin (often called streptolysin) is the toxin which has been known longest. It is liberated in culture media and can be assayed quantitatively. It is not limited in its action to human red blood cells but acts on the cells of many different animals. An antibody to it (antistreptolysin) frequently occurs in human disease particularly of course in hemolytic streptococcus diseases and has recently become of clinical importance.[9] Antibodies to streptolysin have been difficult to produce in animals but recently Todd[10] has shown that streptococci from human infections (Group A) have two lysins; one of these is a true toxin whose

injection leads to the production of neutralizing antibodies in animals: it is labile in the presence of oxygen. The other, like the hemolysins produced by the non-human streptococci of groups B, C, D and E, is oxygen stable and non-antigenic.

The second known toxin of hemolytic streptococci, a leukocidin, has been little studied because of difficulties of technique. It probably plays an important rôle in killing not only leukocytes but also other cells and hence probably in the local (pyogenic) effects of hemolytic streptococci.

A third toxin (if it deserves the name) is a ferment-like substance, fibrinolysin,[11] capable of dissolving fibrin. It is specific for human fibrin and is formed only by Group A streptococci. There is no evidence that it plays a rôle in the spread of streptococci through the tissues unless it does so by influencing the character of the exudate.

Until recently a soluble toxin fatal to animals had not been demonstrated in culture filtrates. But in 1934 Weld[12] succeeded in extracting such a toxin of great potency from the surface of young organisms. This lethal principle always accompanies hemolysin but is not identical with it.

The fifth and most important (from the practical view) is the erythrogenic toxin. The study of this has played a large rôle in the question of the specificity of certain strains of streptococci. While the existence of an erythrogenic toxin was presumed after the discovery of the Schultz-Charlton reaction in 1918 (blanching of the scarlet fever eruption locally on intracutaneous injection of convalescent scarlet fever serum), proof of the definite existence of a soluble exotoxin capable of producing erythema only when injected into the skin of susceptible humans was the result of the work of G. F. and Gladys Dick.[13] It is often spoken of as the "Dick Toxin". It has had the most widespread application in the prevention and treatment of scarlet fever, an application which I cannot discuss here.

The great question of the specificity of the scarlet or erysipelas toxins is still in dispute[14] with the best of authorities and arguments on each side. Since the experts cannot agree it would seem best for the outsider to accept some intermediate view, such as that put forward by Hooker[15] and by Gay;[16] all hemolytic streptococci produce more or less erythrogenic toxin, each toxin being a mixture containing different quantities of different toxin moieties. An antitoxin formed against a strain of broad polyvalency and high toxin production (such as most

strains from scarlet fever) may neutralize erythrogenic toxin from many other sources.

Such a view is capable of explaining many otherwise irreconcilable observations such as the immunity of some individuals to certain scarlet fever toxins but not to others,[17] the failure of commercial antitoxin to neutralize the toxin of some scarlet fever strains, the occurrence of scarlet fever in Dick negative persons, the permanence of immunity to scarlet fever and the impermanence of immunity to erysipelas, the undoubted efficacy of scarlet antitoxin and scarlet convalescent serum in some cases of erysipelas and other streptococcus infections, and so forth.

Serum Treatment

The multiplicity of hemolytic streptococcus strains probably forms only a partial explanation for the failure of most polyvalent antistreptococcus sera in human infections in the past. It is not very difficult to produce in horses sera which will influence streptococcus bacteremia in laboratory animals if the bacteremia is due to strains similar to those used for immunization. Such sera are usually phagocytosis-promoting rather than bactericidal or antitoxic. Even if the promotion of phagocytosis should turn out to be of great importance, the experience of recent years with type specific antipneumococcus sera shows how unlikely it is that any polyvalent antibacterial serum as yet produced can have enough antibody to be of more than occasional and accidental efficacy for organisms of such widely different serological strains as the streptococci.

What place has serum treatment then (since the introduction of sulphanilamide) in the treatment of hemolytic streptococcus infections other than scarlet fever? In actual practice ordinary polyvalent antistreptococcus serum has too little value to be further considered. In erysipelas the specific antitoxin[18] (and equally scarlet antitoxin) has considerable therapeutic effect although probably less than has sulphanilamide. The trend of recent clinical opinion is that scarlet fever convalescent serum is superior (despite lower antibody content) to the animal derived antitoxin,[19] not only in scarlet fever but in all sorts of other hemolytic streptococcus infections.[20] Such convalescent sera are not available everywhere but most of our large cities now have serum centers where convalescent sera are carefully gathered.[21] New York is fortunate in having such a center under charge of William Thalhimer.

Some may think the advent of sulphanilamide has made sera superfluous but this is not so. There are cases in which sulphanilamide has to be stopped because of idiosyncrasies. There are cases in which it is ineffective. There is also evidence that the drug and serum supplement each other: the serum is antitoxic and the drug is antibacterial: certainly they do not interfere with each other. For this reason in every desperate case of hemolytic streptococcus infection it would seem wise to supplement the drug with the serum—by preference convalescent scarlet fever serum when available.

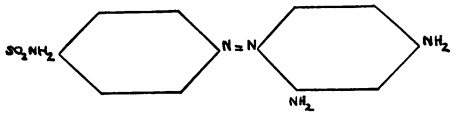
Chemotherapy

When I was asked over a year ago to give the present lecture the request was that I should discuss the then new chemotherapy for streptococcus infections. At that time the status of the new drugs was less certain than it is now and I hesitated to commit myself to present the subject a year later. For this reason I chose the non-committal title "Treatment of Hemolytic Streptococcus Infections".

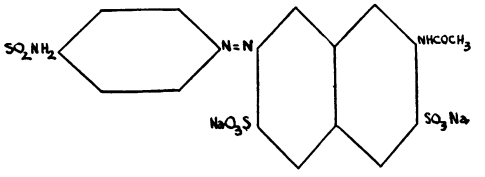
However, within the past year I have had an opportunity to follow over a hundred treated cases myself, and the literature has presented an enormous amount of new information. It is perfectly clear now that for the first time a successful bacterial chemotherapy has been found. And it promises to have a far wider usefulness than originally appeared probable. In fact it is one of the major advances of our generation.

The curious round about course of progress in this field is interesting.[22] Before 1935 there had been innumerable attempts to find a chemical which would have a specific effect on various kinds of bacteria. None of these had been successful. In the majority a start had been made with some substance known to have bacterial killing properties in the test tube. Heidelberger and Jacobs[23] had pointed out that there was a certain chemotherapeutic effect from molecules containing the azo coupling, for example para-amino-benzene-sulphonamide-azo-hydrocupreine. Whether it was this or pure chance that led Domagk in 1935[24] to try the effect of the dye, prontosil (though it had no bactericidal effect in the test tube) is not known. At any rate his experiments on the hemolytic streptococcus sepsis of mice and rabbits were clear cut and conclusive and were immediately confirmed by Levaditi and Vaisman,[25] and at once led to effective use of this dye by oral administration in the treatment of streptococcus infections.[26]

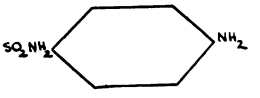
CHART I



THE *ORIGINAL* PRONTOSIL
(Prontosil rubrum Prontosil flavum Sulphonamide-chrysoidin)
A red crystalline substance no longer in use.



PRONTOSIL SOLUBLE
Now generally called *PRONTOSIL*
A red solid usually supplied in 2½% solution (formerly known also as Streptozon)



SULPHANILAMIDE
(Prontylin, etc.)
Para-amino-benzene-sulphonamide

The original dye, prontosil, is a very insoluble substance and has the property of staining the entire body intensely. A related dye, of a much more complex structure but very much more soluble and convenient, known as prontosil soluble or prontosil solution soon replaced it. This could be given by intramuscular or, if necessary, even by the intravenous route. It had the same peculiar properties, having no effect on bacteria in the test tube but nevertheless curing experimental and clinical infections.

Within a few months a further simplification was introduced by Tréfouel[27] and associates. They found that para-amino-benzene-sulphonamide was the common factor not only in prontosil but in a large series of other more or less active compounds. With this drug, which has now been given the name of sulphanilamide, they obtained both in mice and rabbits results quite as good as those obtained with prontosil. Their work was quickly confirmed.[28]

Sulphanilamide represents about one half of the molecule of the more complex drugs, and the azo linkage which was originally thought to be essential to the therapeutic effect is not present. Sulphanilamide (intro-

duced under the trade name, prontylin), unlike prontosil, is not a new drug covered by patents, but is a long-known chemical compound which any competent chemist can make. It is now produced by a great many different pharmaceutical houses under different names. The Council on Pharmacy of the American Medical Association has recommended[29] that the name sulphanilamide be used; while a shorter name might perhaps be desirable it seems best to adhere to this name. The term prontosil when used now refers to soluble prontosil.

Fuller[30] in England and Marshall[31] and associates in the United States have cleared up some of the mystery about the effect of prontosil; both of the original forms of prontosil liberate sulphanilamide in the body and it is possible that their therapeutic effect is due entirely to the sulphanilamide liberated. Soluble prontosil liberates about one-third of its weight of sulphanilamide.

Sulphanilamide

Sulphanilamide is a colorless solid, somewhat soluble in water (0.8 per cent) but most conveniently given by mouth in the solid form. Its easy solubility in fat may turn out to have considerable significance.[32] The study of its mode of action and practical use have led to certain very important observations. In the presence of a very limited number of bacteria and a suitable environment the drug is slightly bactericidal. It is, however, unmistakably bacteriostatic; that is to say, provided the number of bacteria is not too great, it definitely slows down the rate of growth of hemolytic streptococci. It was claimed by Levaditi[33] at the very beginning that its major effect was not only on the bacteria but on the specific hemolysin and leukocidin (and by inference the other toxins of the streptococci). This has received confirmation in a recent remarkable piece of research by Osgood and Brownlee[34] in which the effect of the drug was observed on infected cultures of human bone marrow. When dissolved in broth or in salt water the drug has little killing effect on streptococci. When dissolved in the serum of such animals as the mouse or the guinea pig, which have slight natural resistance to streptococci, the drug has a distinct inhibitory effect on growth but is unable to accomplish sterilization. When dissolved in serum such as that of man and monkey which in itself has considerable bactericidal power for streptococci, the drug greatly enhances this bactericidal power so that numbers of organisms such as may occur in human infections, namely

up to 500 per cubic centimeter, are completely killed.

According to earlier work of Buttle, Colebrook and associates[35] in England and Long and Bliss[36] in this country, fairly high concentrations (1/10,000 or 10 mg. per 100 cc.) in serum are necessary to accomplish sterilization; and dosage has accordingly been adjusted to bring about such a concentration. But if the recent work of Osgood and Brownlee[34] is correct the drug is effective at a much higher dilution in human serum, only 1/100,000 (or 1 mg. per 100 cc. of serum). If this turns out to be true (and its confirmation will require further clinical as well as experimental studies) we shall require much smaller doses than we have been using.

It is probable from all the recent work that the drug does not work in the body only by direct killing of bacteria but also by neutralizing the aggressive poisons of the bacteria. Colebrook[37] at first thought that the effect depended on stimulation of phagocytosis. But the drug is bactericidal in the test tube when added to human blood from which practically all of the leukocytes had been filtered (method of Flemming). Mellon and his group have shown that even when it appears to cure infection the drug does not kill all the bacteria in the tissues. This explains the observation made almost at the beginning of the work by Levaditi[38] that in mice which had apparently recovered, recurrence of the infection and death might occur at any time from one to thirty days after administration of the drug had been stopped. Similar clinical observations have been made in man. For this reason the appropriate procedure is to continue treatment for at least four or five days after the apparent cessation of infection. Fortunately in man these recrudescences are much less frequent and serious than in mice because man has a very much higher immunity to hemolytic streptococci.

Absorption and Excretion

Within the past year careful work on absorption and excretion of the drug by Fuller[39] and by Marshall[31] have taught us much concerning the best method of administration. Absorption of sulphanilamide from the gastrointestinal tract is very rapid. In ordinary dosage most of the drug administered is absorbed in four hours. If it be possible to use the gastrointestinal tract there is no advantage in parenteral administration. By repeated administration at intervals of three or four hours the concentration of sulphanilamide in the blood can be steadily raised to five, ten,

fifteen or even more milligrams per 100 cc. of serum. Long and his associates[36] believe the blood level should be kept at ten milligrams per 100 cc. but many others[40] have obtained excellent results with lower concentrations (4-7 mg. per 100 cc.). Marshall[31] has shown that in patients with large daily divided doses it takes three days for the blood level to reach an equilibrium and a blood concentration of ten to fifteen milligrams per 100 cc. can be maintained easily. It takes about three days after the drug is discontinued for the blood to free itself if such a level has been reached.

Marshall has devised a simple clinical method of determining the concentration of the drug in the blood. Such determinations ought to be made occasionally in most cases and frequently in critical cases. Long and Bliss[36] pointed out on clinical grounds and Osgood[34] and others have shown on experimental grounds that continuous treatment is essential. The drug must not be omitted during the night. The continuous presence of low concentration in the blood is more important than intermittent high concentration. The drug penetrates well into tissue fluids, into pleural exudates, cerebrospinal fluid and hence into all the tissues but in none of these places does it reach as high a concentration as in the blood. For this reason it is frequently advisable to inject 0.8 per cent sulphanilamide (made from the pure crystalline product) in normal sodium chloride solution into the spinal fluid in meningitis and into the pleura in empyema cases.[41] In patients to whom the drug for any reason can not be administered by mouth, one has a choice between intramuscular administration of the dye solution prontosil, or the subcutaneous infusion of 0.8 per cent sulphanilamide. The question of the relative effectiveness of these two procedures is not yet settled. Certainly prontosil administration leads to a much lower concentration of sulphanilamide in the blood than does the administration of sulphanilamide directly; but it seems nevertheless to be clinically about as effective. Both drugs are rapidly absorbed when given intramuscularly or subcutaneously and it is probably never advisable to give either drug intravenously.

Both soluble prontosil and sulphanilamide are excreted rapidly in the urine; the latter is certainly excreted in the bile. This has led to valuable applications of these drugs particularly in the treatment of infections of the genito-urinary and biliary tracts. In treatment of urinary infections the concentration of the drug in the urine is important. Marshall[42] has shown that in man and the rabbit a part of the drug is excreted in

conjugation as a para-acetyl derivative while in dogs it is all excreted in its original form, that is as sulphanilamide. The important thing is probably the concentration of unaltered sulphanilamide which is easily determined by Marshall's method. With renal impairment of course the excretion of the drug is slower and the effect to be expected in urinary infections is not so great; hence the administration of the drug must be more cautious and must be checked by more frequent blood examinations on account of the possibility of its accumulating in the blood.

Dosage

It is quite possible that on the basis of Osgood and Brownlee's[34] recent work a smaller dosage than at present used will be found satisfactory. But for the present at least it will be best to adhere to the dosage worked out by Colebrook[35] and by Long[36] on essentially clinical grounds. It is important to attain the desirable concentration in the blood as rapidly as possible; for this reason a large amount of the drug should be given during the first twenty-four hours. The usual dosage of sulphanilamide is figured at approximately one gram for each twenty pounds of body weight in twenty-four hours with an average upper limit for adults of five or six grams. But during the first day of treatment in any serious case and during many days of treatment in very desperately serious cases, considerably larger doses up to a total of ten or even fifteen grams per day have been given with success.[43]

The danger of toxic effects or idiosyncrasy seems to be no more with large than with ordinary doses. After the first few days, if the symptoms are abating and there is no bacteriemia, the dosage may be reduced. Half dosage is continued for four or five days after the infection has apparently subsided.

When prontosil is used the dosage for twenty-four hours can be calculated most conveniently as one cubic centimeter of the 2½ per cent solution (obtained in ampoules on the market) for each pound of body weight except that for persons over one hundred and fifty pounds in weight it is better to reckon on three quarters of a cubic centimeter per pound. As in the case of sulphanilamide the daily dosage should be divided and given at from four to six hour intervals. When prontosil and sulphanilamide are given together a gram of sulphanilamide can be taken as approximately equivalent to twenty cubic centimeters of prontosil.

CHART II

AVERAGE DOSAGE OF PRONTOSIL OR SULPHANILAMIDE FOR SEVERE INFECTIONS

In twenty-four hours, *For every twenty pounds body weight up to 120 pounds,*

SULPHANILAMIDE 1 gram (15 grains) by mouth or subcutaneously, or interchangeably,

PRONTOSIL 20 cc. intramuscularly.

Dose should be distributed as uniformly as possible throughout the twenty-four hours, e.g., for an average adult 1 gram sulphanilamide (or 20 cc. prontosil) every four hours *day and night.*

For the first twenty-four hours in particularly dangerous infections 50 per cent or 100 per cent more may be given.

After temperature is normal half dosage is continued for five to fourteen days according to severity of the case.

Toxic Effects

The drug on the whole is remarkably non-toxic. In animals it is necessary to give almost incredibly large doses[44] to produce toxic effects or death. In human beings any toxic effect other than minor inconveniences is extremely rare.

The cyanosis which occurs with the use of the drug can hardly be regarded as a toxic effect. It occurs in over 60 per cent of all patients and is not accompanied by dyspnea or diminished oxygen carrying capacity of the blood.[45] Sulphemoglobinemia or methemoglobinemia was at first thought to be the cause of the cyanosis[46] but now is believed to be extremely rare.[47] It has been thought that the sulphemoglobinemia was due to administration of sulphates,[46] generally in the form of magnesium sulphate. The real cause of the cyanosis is unknown; it may be some black oxidation product of the drug on the surface of the red cells.[45] In general it is important to remember that cyanosis is to be expected; unless other symptoms appear it is not to be regarded as a reason for discontinuing the drug.

Certain subjective symptoms frequently occur. These are nausea, vomiting, headache, slight dizziness and mental confusion. In rare cases these symptoms are enough to prevent administration of the drug. I have the impression that they occur chiefly in nervous individuals who expect them or realize that they are getting an unusual form of treatment. They are almost never the precursors of more serious toxic symptoms and can as a rule be disregarded. They are just as likely to occur after very small doses as after large doses.

A common but not serious effect is a mild degree of acidosis.[48] This can usually be relieved by mere administration of bicarbonate of soda and in fact it is wise to give bicarbonate of soda, one gram for each gram of the drug administered as a routine in all cases.

Both in animals and in man long continued administration of the drug does not produce any delayed toxicity or late secondary effects. When the drug has been given a considerable number of days and the patient's temperature has come to normal, there is occasionally a secondary rise of temperature without further symptoms of infection. This "secondary fever" is probably due directly to the drug itself and the temperature returns to normal when the drug is stopped.[49] I have seen this phenomenon a number of times. It is very puzzling and the decision to stop the drug calls for a nice clinical discrimination.

All the other described toxic effects of the drug must be classified as idiosyncrasies, that is, as abnormal results which cannot be produced in the vast majority of cases even by very large doses. The possibility of these idiosyncrasies is important to keep in mind although they are very rare indeed; when they occur some of them are very serious.

Anemia is commonly regarded as the most important idiosyncrasy. Severe degrees of anemia are so common in almost all the infections for which the drug is used that it is often questionable whether an anemia which occurs is really due to the drug. However, there have been a considerable number of cases of acute hemolytic anemia reported.[50] Jaundice or hemoglobinuria may accompany the anemia. I have seen only one such severe case with hemoglobinuria. These cases have almost all recovered when the drug was stopped and one or two blood transfusions given but there probably have been some deaths. Anemia of the aplastic type has been described. It is extremely rare but is much more dangerous than the hemolytic anemia. Agranulocytosis must be extremely rare also, but there have been several cases attributed to the drug.[51] In animal experiments and clinical observations the drug seems to have only a very slight if any depressing effect on the leukocyte count or the bone marrow. Anemia can develop in two or three days and it is important in all cases under treatment to repeat blood counts frequently. One case of a transient optic neuritis[52] has been ascribed to the drug and one case of apparent generalized allergy (urticaria, sneezing and dyspnea).[53] There have been a considerable number of cases of a peculiar widespread dermatitis.[53,54] Rather definitely the drug sensitizes the skin to light and

dermatitis has occurred chiefly in ambulant patients who exposed themselves to direct sunlight. The discovery of porphyrin[55] (a hemoglobin degradation product capable of sensitizing to light) in the urine of these cases may explain this and perhaps other idiosyncrasies. The eruption is morbiliform, does not affect the mucous membranes, is often accompanied by fever up to 103° and usually does not persist longer than about three days even if the drug be continued. Persons who have once had the eruption are likely to get it again if the drug be resumed.[56] Some of the patients have developed it after a single small dose. Schwenkter[53] saw it in ten of 180 patients, a large proportion of them ambulant. We have seen three cases in approximately 150 hospitalized patients. On account of the rare idiosyncrasies sulphanilamide in spite of its vast usefulness must be considered a dangerous drug. Most of the accidents have occurred after small doses which shows how great a rôle special susceptibility plays. It is important that druggists should not supply this drug to the public for self medication. All patients receiving it should be under daily medical supervision, especially for the first few days of administration.

CHART III

PRECAUTIONS TO BE TAKEN DURING TREATMENT WITH SULPHANILAMIDE AND PRONTOSIL

1. Patient must be examined in a good daylight at least once a day, (for jaundice, anemia, eruptions).
2. Urine must be watched daily for hemoglobin or bile.
3. Blood count must be made every day for first three days then every two days.
4. Bicarbonate of soda must be given (in a dose about equivalent to sulphanilamide) to prevent acidosis.

PUERPERAL INFECTIONS

The earliest practical application of sulphanilamide was in the treatment of puerperal hemolytic streptococcus infections. Colebrook and his co-workers, who made the first comprehensive report in 1936,[57] have recently reviewed one hundred cases[58] and show a striking reduction in mortality, from 22.8 per cent for 495 cases in the preceding five years, to 8 per cent in the last one hundred cases. Their series included fifteen patients with positive blood cultures and six with general peritonitis, and one half or more of both these groups recovered. Not only were the recoveries greater in number but the secondary develop-

ment of parametritis (almost the rule in puerperal sepsis cases before this) was very rare, 5 per cent. It is interesting that not all the streptococci were killed off, as 48 per cent of the cases still showed them in vaginal smears at the time of discharge from the hospital. Their work has been confirmed by other workers[59] and there is no doubt that sulphanilamide represents an immensely valuable remedy in puerperal infections. It is possible that routine use of small doses after childbirth, especially in cases exposed to infection, might greatly reduce the incidence of puerperal infections since the experimental work all indicates that the drug is far more effective against incipient than well developed infections.

Meningitis

There is no field in which the effects of sulphanilamide therapy have been so dramatic and conclusive as in the treatment of streptococcus meningitis. The mortality before the advent of this drug was 95 per cent to 97 per cent according to the statistics of Neal[60] and of Gray.[61] The first recovery with prontosil treatment was reported by Caussé in February 1936 and this was followed by reports by Schwenkter, Vitenson, Neal and others.[62] Neal and Applebaum[63] reported the largest series of cases personally observed: of seventeen cases in which there was no question of the diagnosis thirteen recovered. Bliss and Long[64] reported recovery in twenty-four out of twenty-eight cases of hemolytic streptococcus meningitis with which they had had contact. This confirms the experience of other reports in the literature and indicates a recovery of something like 75 per cent of the cases.

In the treatment of streptococcus meningitis the administration of the drug must be prompt and vigorous and it is advisable (although not all authors agree that it is necessary) to give the drug intraspinally as well as by mouth or intramuscular injection. In the intraspinal administration it is important to use only the 0.8 per cent solution in saline made up with pure crystaline sulphanilamide (which can be obtained from Winthrop or from Du Pont). Prontosil has been tried intraspinally but Schwenkter[62] warns against it as it seems to be irritating and less effective than sulphanilamide. The intraspinal treatment is carried out by replacing about ten to twenty cubic centimeters of spinal fluid with sulphanilamide about twice in twenty-four hours until the spinal fluid becomes cleared of streptococci on smear and culture. Oral or intra-

muscular treatment is continued for a considerable period longer, for ten to fourteen days, or until the patient is entirely well; but for the latter part of the period the dosage can be reduced to one-half or one-third. It is important that the surgical indications should be met despite the advent of the new drug. If a suppurating focus such as mastoiditis or sinusitis requires surgical drainage, this should be carried out. It is very likely that prophylactic administration of sulphanilamide in cases in which meningitis is to be feared, such as mastoiditis or brain injuries, may reduce the incidence of this form of meningitis.

Streptococcus Infections of Other Serous Membranes

In streptococcus infections of the eye, the peritoneum, the pleura, joints and other serous surfaces, sulphanilamide has yielded extraordinarily good results. I have seen two cases of streptococcus peritonitis which recovered promptly with the drug. Three out of four cases of streptococcus pleurisy in the stage in which there was not yet frank pus have recovered under sulphanilamide therapy.[65] As streptococcus pleurisy most commonly occurs as a complication of streptococcus bronchial pneumonia, the sputum in every case of bronchial pneumonia ought to be more carefully studied for the presence of Streptococcus hemolyticus than it has been in the past. It would seem indicated to treat streptococcus bronchial pneumonia such as so commonly follows measles and influenza with sulphanilamide both because it is a streptococcus infection of the lungs and for the prevention of the frequently occurring empyema.[66] It is no longer therefore enough to get a laboratory report that there are or are not pneumococci present in the sputum but the presence of hemolytic streptococci should also be determined and acted on.

Erysipelas

From the very beginning the reports of treatment of erysipelas with the new drug have been very striking and it might safely be said that although there are occasional cases that do not respond to it, its use is the optimal method of treating the disease. Peters and Havard[66] reported on forty-seven cases in every one of which the spread of the disease was arrested in twenty-four hours and in forty-three of which the temperature was normal in forty-eight hours. The duration of the disease is regularly shortened by the drug.[67] One of the most important

uses is in the erysipelas of very young infants[65] in whom there is usually bacteriemia and a very high mortality (94 per cent). On account of the synergistic action of specific serum and sulphanilamide reported in other connections it would seem wise in severe cases of erysipelas to use both the antitoxic serum and the drug.

Scarlet Fever

There is very little evidence that sulphanilamide has any effect in scarlet fever.[65] Peters and Havard[66] reviewed 150 cases and were not able to find sufficient differences between the treated and untreated cases to demonstrate any effect of the drug on the toxic phase of the disease. However, there was a slight difference in the development of suppurative complications; 56 per cent of the untreated and only 35 per cent of the treated patients developed such complications. It is therefore possible that sulphanilamide will be of use in the more severe cases of scarlet fever as a preventive of suppurative complications. If so used, of course it should be in addition to antitoxic or convalescent serum.

Rheumatic Fever

In spite of the well established association of hemolytic streptococci with recrudescences of rheumatic fever, all the evidence at hand is that sulphanilamide and the allied compounds not only have no therapeutic effect on rheumatic fever itself[68] but also according to a recent small but very carefully studied series of cases,[69] have no effect in preventing recrudescences when used for the streptococcus infection. Indeed the toxic effects of the drug seem to be increased in rheumatic fever. In chronic arthritis likewise the drug has been disappointing.[70]

Tonsillitis and Septic Sore Throat

Every one has reported excellent results in severe cases of tonsillitis and septic sore throat as well as in suppurative sinus infections due to the hemolytic streptococcus. However, on account of the possibility of untoward reactions the drug should not be used as a routine for ordinary sore throats but should be reserved for more menacing infections. True, the idiosyncrasies are of very rare occurrence but if one were to produce an aplastic anemia or an agranulocytosis, even though only once out of ten thousand times, as the result of the treatment of a disease in itself

relatively harmless, one would be open to blame. On the other hand in a serious infection the chance of an idiosyncrasy is very small as compared with the danger of the disease.

Streptococcus Surgical Infections and Septicemia

In all varieties of surgical infections due to hemolytic streptococcus, sulphanilamide is indicated and should be used vigorously. In septicemia (for example, in sinus thrombosis) the drug has accomplished results such as have never been seen before. However, although recoveries have been reported with sulphanilamide and without operation,[71] it does not yet seem so certain that the drug will cure any given case that one is justified in omitting surgical removal of the infected focus (e.g., the infected thrombus in the lateral sinus).

The Use of Sulphanilamide in Infections Other Than by Hemolytic Streptococcus

Sulphanilamide was originally introduced as a specific for hemolytic streptococcus infections. Further laboratory and clinical investigation has shown it to have a much wider field of usefulness.

Concerning other forms of streptococci than the typical hemolytic streptococcus (beta) of Lancefield's group A, occasional infections do occur with organisms from animal sources and it is interesting that there have been reports of successful use of the drug in cases of group B but failures in groups D and G.[72] There has also been a report of the effective use of the drug in guinea pigs against a streptococcus of group C which produces a natural acute disease in these animals.[73] The drug promises great economic usefulness in bovine mastitis.[74] In infection with Streptococcus viridans and other non-hemolytic streptococci nearly all observers have reported clinical failure although the drug in the test tube is stated by Long to have an effect on some strains of the organism. Neal reported having seen one recovery in Streptococcus viridans meningitis among three cases of meningitis due to non-hemolytic streptococci for which the drug was tried. In subacute bacterial endocarditis the results have been uniformly unfavorable.

Sulphanilamide has so far had little trial for anaerobic infections. It protects mice against intraperitoneal inoculation with Clostridium welchii[75] and I have seen one striking recovery in postabortal septicemia due to the anaerobic Streptococcus foetidus of Viellon (later described

by Schottmuller as Streptococcus putridus). Good results have also been reported in gas gangrene.[75]

With Staphylococcus aureus infections there have been almost no reports of definite favorable therapeutic effects. Our own attempts with the drug in staphylococcus septicemia were all ineffective.

Pneumococcus

In pneumococcus infections Sanford Rosenthal[77] and others have shown sulphanilamide is well worth using. It has a distinct effect on the highly virulent type III[78] as well as some effect on type I[79] and other types.[80] It has a greater effect in animals than in man. In pneumococcus meningitis Neal[63] reports three recoveries among twenty clinical cases. This is not a large proportion but as these were the only recoveries seen in her twenty years' experience, the drug is worth trying. The drug and the specific serum, experimentally at least, have an additive result.[79] Hence, it would seem worth using the drug alone for pneumococcus infections for which no serum is obtainable, particularly the very virulent type III, and perhaps along with serum for other severe cases. In the use of the drug for pneumonia there is one inconvenience, namely, the pseudocyanosis due to the drug. In severe cases it is necessary to judge the degree of anoxemia by the respiratory rate and determinations of the oxygen saturation of the arterial blood rather than as usual by the appearance of the patient.

Meningococcus

Until recently animal experimentation with meningococci was rather unsatisfactory but by the new method (C. P. Miller) of injecting the organisms suspended in a protecting solution of mucin a virulent form of meningococcus peritonitis can be produced in mice. With this method Proom showed that the drug protects mice against otherwise overwhelming infections.[81] With the meningococcus (as with the pneumococcus) the drug and the immune serum combined have a greater effect than the sum of the individual effect of the two agents.[82] The use in clinical meningococcus meningitis has been so recent that there is not yet at hand a report of a large series of cases but Long reports[83] that Schwenkter has observed fifty-five cases treated with the drug with a mortality of 19 per cent as compared with a mortality of 30 per cent in a control group treated with serum. Neal[76] reports eighteen meningitis cases of which

thirteen recovered. While the case fatality is not strikingly reduced she has the clinical impression particularly in a few very malignant cases that the drug has an unmistakably beneficial effect. Its method of administration in meningitis was discussed earlier in the present paper. Recent workers however find the intraspinal administration of sulphanilamide unnecessary: this simplifies the treatment greatly.

Other Gram Negative Organisms

Concerning the influenza bacillus, Neal[63] reports the work of Provitzky who found prontosil combined with immune serum to have some curative action on the otherwise fatal infection of mice with influenza bacilli. Neal and Applebaum report recovery in one out of ten cases of influenza bacillus meningitis so treated.

The protective effect of sulphanilamide against gram negative bacilli was first demonstrated by Buttle and co-workers.[84] They showed that the drug in relatively small doses protects mice against one hundred to one thousand otherwise fatal doses of typhoid or paratyphoid bacilli. With Friedländer bacilli experimental work by Buttle was discouraging.

Helmholz[85] showed that sulphanilamide is active against B. coli, B. capsulatus aerogenes and the proteus bacillus. He pointed out in fact that the drug is effective against practically all the common urinary infections except that with the Streptococcus fecalis (variety of non-hemolytic streptococcus) and it is fortunate that we have in mandelic acid a drug which has a very pronounced effect on the Streptococcus fecalis. Sulphanilamide is peculiarly adapted to be of aid in the very common and stubborn urinary infections with bacilli of the proteus group. These organisms resist many of the ordinary urinary antiseptics because of the strong alkaline reaction which they create but the effectiveness of sulphanilamide is greatly enhanced by this very alkalinity.

The latest gram negative organism to succumb to sulphanilamide is the Ducrey bacillus. Boris Kornblith[86] has reported highly favorable results in twenty-two of twenty-three cases of chancroid.

The use of sulphanilamide in gonococcus infections is also a matter of relatively recent discovery. Surprisingly prompt cures were shown in thirteen of nineteen cases reported by Dees and Colston[87] from Johns Hopkins Hospital in May 1937, and there has been wide experimentation with the drug in practically all genito-urinary clinics since then.[88] The consensus of opinion seems to be that with oral administration of sul-

phanilamide without any other therapy a rapid cure can be expected in about half the cases. Good results have been reported in prostatitis, arthritis, ophthalmia and other complications.[89] A certain proportion of the cases seem to be resistant to the drug. What factors cause this uneven response is not yet known. Due to the fact that gonococcus cases are usually ambulant, while most of the other diseases for which sulphanilamide has been used are not, and that exposure to sunlight undoubtedly increases the susceptibility to skin eruptions, the majority of the cases which have shown skin idiosyncrasies have been reported from genito-urinary clinics. Gonorrhea is a disease which is generally curable by other means and it is possible that the drug will in the future be reserved for systemic, complicated or otherwise resistant cases of gonococcus infections.

Urinary Infections

In the genito-urinary organs the drug acts not only in virtue of its already recognized effect in the tissues, but also because of its excretion, in far higher concentrations in the urine than it ever reaches in the blood. Fuller[30] early in 1937 showed that when prontosil is given by injections, sulphanilamide is excreted in the urine (along with prontosil). In this case sulphanilamide appears in the urine only from four to six hours after the injection of prontosil. On the other hand when sulphanilamide is given by mouth it appears as such in the urine very rapidly and in very high concentrations. Marshall and his co-workers[31] showed that whereas in the dog all the drug is excreted as sulphanilamide, in man as well as in the rabbit about one-half is excreted in a conjugated form as a para-acetyl derivative and this acetylated form is stated to be almost inactive. Marshall's very delicate method of quantitative testing enables one to estimate the quantity of sulphanilamide in the urine with considerable accuracy. Helmholz and his associates[85] and Long and his associates[36] found that a concentration of 75 to 200 mg. per 100 cc. of the free drug is needed for a satisfactory bactericidal effect in the urine. It was found by Helmholz clinically[90] that the drug shows distinctly increased effectiveness in alkaline solution. The administration of sodium bicarbonate should never be omitted when the drug is given as a urinary antiseptic. The total volume of urine is naturally of importance when determining the bactericidal efficiency. Long recommends that the twenty-four hour volume be kept as nearly as possible eighteen hundred

cubic centimeters by the administration of fifteen hundred cubic centimeters of milk and four hundred cubic centimeters of orange juice. The concentration which the drug reaches in the urine will depend to a considerable extent on renal function. If optimal results are to be expected it is necessary to test this concentration frequently.

Aside from bacterial infections the drug has been tried with no success in syphilis but with definite curative results in malaria.[91]

Infections of Unknown Nature

In the future undoubtedly many more uses will be found for sulphanilamide. Modifications of it or of other drugs of greater potency or specificity will probably be discovered. In its use great stress has been laid on accuracy of bacteriologic diagnosis but on account of the unexpected versatility of the drug it seems worth using at present in any very grave infection of unknown nature. For example, I have recently seen recovery in two cases of pyelophlebitis. This is a disease the bacteriology of which is seldom discovered except at the postmortem table: then the organisms found are commonly some intestinal inhabitant such as streptococci, colon bacilli or anaerobes. In desperate cases of this kind, although the bacteriology cannot be determined, the drug is well worth a trial.

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