CHOICE OF SULPHONAMIDES FOR MIXTURE THERAPY*

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Extensive experimental and clinical studies of the last five years have established the advantages of sulphonamide mixture therapy.¹⁻¹⁷

In brief the rationale for the use of mixtures is as follows: The renal toxicity of most of the newer sulphonamides, if used singly, is due primarily to over-saturation of the tubular urine with a sparingly soluble sulphonamide and/or its metabolic product, resulting in the formation and deposition of drug crystals in the urinary pathways (crystaluria). This event may be followed by haematuria, oliguria, and complete renal shutdown. If instead of a single sulphonamide a combination of partial dosages of several therapeutically equivalent sulphonamides is employed, the danger of crystal formation in the kidney from the drugs comprising the mixture is significantly reduced. In fact, it will be only as great as if each compound had been administered alone and in the partial dosage contained in the mixture, since sulphonamides of different molecular structure, even if closely related, can be dissolved *simultaneously* to the full extent of their individual solubilities. At the same time full therapeutic potency is retained, since the antibacterial effect of such combinations is completely additive and may in many instances even show potentiation of action *in vitro* as well as at the bedside.^{1 2 15}

From the standpoint of renal protection, combinations of substantially equal partial dosages of at least *three* sulphonamides were considered adequate in routine therapy in the absence of alkalization.¹⁸ Some objection has been voiced against the use of mixed sulphonamides on theoretical grounds. It was intimated that the concomitant use of several drugs may lead to the simultaneous development of allergy against more than one component of the mixture.¹⁹ Thus the incidence of allergic reactions might be increased and the possibility of "switching" a sensitized patient to another sulphonamide drug might be eliminated.

This thought was based on the concept that the incidence of sensitization to sulphonamides is largely independent of the dosage used. However, this point of view is not borne out by practical experience. Critical evaluation of the vast literature on sulphonamide therapy¹² demonstrated that, in the dosage range employed in human prophylaxis and therapy, the incidence of sensitization increases in direct proportion with the dosage. Table I shows that, for example, at an oral dosage of not more than 2 to 4 g. of sulphanilamide, sulphathiazole, or sulphadiazine in 24 hours, none of these drugs appeared to produce rash or fever in any significant percentage of cases, even if used for prolonged periods and repeatedly in the same individuals. The incidence of allergic reactions assumed significant proportions only when the daily dosage was increased to more than 4 g. and reached even higher percentages with full therapeutic amounts of 6 g. or more,

TABLE I.—Relation of Dosage to Incidence of Sulphonamide Allergy

Drug	Daily Dosage (g.)	Days of Treatment	No. of Cases Treated	Incidence of Rash and Fever
Sulphanilamide ..	1-2 1.5-4 6-9	120-240 7-21 5-10 Routine therapy	188 1,687 1,407	% 1.0 0 >10.0 7.2*
Sulphathiazole ..	2-4 6 6-10	3-15 3-10 5-10 Routine therapy	3,584 2,475 529	0 >6.4 >10.0 11.2*
Sulphadiazine ..	1 2-4 4-6 6+	12-90 3-20 7-14 2-31 Routine therapy	664,840 18,185 500 2,791	<0.5 0.07 1.8 2.3 2.9*

* These figures are based on a comprehensive compilation of the incidence of rash and fever reported in the literature.

provided medication was maintained for a minimum of three to five days. These observations indicate that the production of sensitization reactions is dependent upon the repeated presence of certain minimal tissue concentrations of a sulphonamide for a minimum period of several days.

In most patients sensitization is specifically limited to the sulphonamide used. Hence the simultaneous administration of several sulphonamides in *partial* dosage may result in a reduced rather than an increased incidence of sensitization because mixtures permit "dilution" of individual drug concentrations below the level necessary for the production of allergy.

This concept appeared to be substantiated by our experience with more than 700 patients treated with combinations of two or three sulphonamides, including sulphadiazine, sulphamerazine, sulphapyrazine, sulphacetamide, and the "worst offender" sulphathiazole. The incidence of drug rash and fever at the full therapeutic dosage of 6 g. in 24 hours was impressively low and nowhere exceeded 2%.¹²

It has yet to be established whether closely related compounds such as isomers and homologues—e.g., sulphadiazine, sulphapyrazine, sulphamerazine, and sulphamezathine (sulphadimidine)—can be distinguished by the cells of the body as specific haptens. Should they prove indistinguishable, the danger of sensitization from their combined partial dosages could still not be greater than if the equal total amount of any one of these drugs had been employed. Hence no *increased* incidence of allergic reactions should result from any sulphonamide mixture, so long as individual drug concentrations in the tissues are kept well below the level usually necessary for the production of sensitization.

Theoretical Considerations

It seemed of interest to compare some properties of systemic sulphonamides which might help to determine their relative desirability as components of mixtures.

TABLE II.—Relation of Solubility to Renal Complications

Drug	Symbol	Solubility in Water 37° C.: pH 5.5 (Mg./100 ml.)		Blockage of Kidneys by Crystalline Deposits
		Free	N ₂ Acetyl	
Sulphadiazine ..	SD	13	20	Frequent
Sulphamerazine ..	SMD	37	79	"
Sulphamezathine ..	SMD	75	115	Rare
Sulphapyrazine ..	SPZ	5	5	Very frequent
Sulphathiazole ..	ST	98	7	"
Sulphacetamide ..	SAC	1,100	215	Not encountered
Sulphanilamide ..	SA	1,500	530	"

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Table II represents an enumeration of systemic sulphonamides which deserve consideration for possible use as combinations. (The symbols for the different drugs shown here will be used in all subsequent graphs and tables.)

It is readily apparent that a definite relationship exists between the solubility of the sulphonamides and their acetylated metabolites and the frequency of renal complications. From this point of view sulphapyrazine would seem to be about the least desirable and sulphacetamide and sulphanilamide the most advantageous compounds. However, the high solubility of sulphanilamide is outweighed by its considerable overall toxicity. For this reason sulphanilamide was not used in our studies.

The behaviour of the other six drugs in the human body, as gleaned from the extensive literature on this subject, is illustrated in Table III. The desirable features of each

TABLE III.—Comparison of the Behaviour of Six Sulphonamides in the Human Body

Drug	Average Blood Levels* Free Sulphonamide Mg./100 ml.	% Plasma-bound	Diffusion into C.S.F. (% of Blood Level)	% Acetylated in the Body
SD ..	8-15	17-56	50-75	20-40
SMD ..	10-20	39-84	30-60	30-60
SMD ..	5-12	39-84	30-60	50-80
SPZ ..	5-12	00-50	40-60	50-85
ST ..	4-7	60-75	10	10-30
SAC ..	5-10	13-20	60-85	20-40

* At a daily maintenance dose of 6 g. orally. Bold type = Advantages. Italic figures = Drawbacks.

drug are there stressed by bold print. Distinct drawbacks are indicated by italics. It can be seen that sulphadiazine is the least plasma-bound, best-diffusing, and least acetylated of the four "diazines." Hence, sulphadiazine rightfully maintains a therapeutic advantage over sulphamerazine and a definite superiority over sulphamezathine and sulphapyrazine. Sulphathiazole shares the disadvantage of excessive plasma-binding with the three last-named drugs and manifests in addition particularly poor diffusion into the cerebrospinal canal. Sulphacetamide, on the other hand, except for low blood levels due to rapid excretion, exceeds even the merits of sulphadiazine with regard to conjugation, diffusion, and plasma-binding.

No substantial differences seem to exist among systemic sulphonamides concerning their antibacterial spectrum. It should be remembered that various sulphonamides possessing a free para-amino group do not display appreciable differences in bacterial affinities. Molecular changes in the N_1 substituent serve to modify quantitative rather than qualitative antibacterial properties.²⁰

In the animal experiment sulphathiazole proved the most toxic of the group, closely followed by sulphapyrazine, and then sulphadiazine and its two methyl homologues, which are about equally as toxic, whereas sulphacetamide is about five times less toxic than sulphadiazine.²¹

From a clinical point of view it can be assumed as established that, on the basis of their excellent clinical record, sulphadiazine and sulphamerazine qualify at present for first and second place respectively as components of any mixture. The other four compounds deserve attention as possible *additional* members of a combination.

Experimental Results

With this view in mind, I compared various triple mixtures with regard to antibacterial activity, toxicity, and therapeutic effectiveness in the experimental animal and in man. The majority of the mixtures contained both sulphadiazine and sulphamerazine as constant com-

ponents, whereas the third component varied between sulphamezathine, sulphapyrazine, sulphathiazole, and sulphacetamide. Most experimental procedures used were closely similar to those outlined previously in detail.²⁷ For the sake of conciseness their description was eliminated from the present report.

No substantial differences were observed with any of the mixtures studied concerning *in vitro* antibacterial activity and efficacy against experimental infections of mice. On the whole the triple mixtures proved about equally as effective as sulphadiazine in identical total concentration or dosage.

Absorption, fate in the body, and excretion of these triple mixtures were investigated in rats, rabbits, and human beings. The results of representative experiments on tissue distribution in groups of albino rats are summarized in Figs. 1 and 2.

Fig. 1.—Concentrations of sulphonamide mixtures in tissues (single administration in albino rats).

Fig. 1 demonstrates the relationship of the drug concentrations in blood, lungs, and brain three hours after a single oral intubation of five triple mixtures (0.5 g./kg.). Although the sulphapyrazine and sulphamezathine combinations show higher blood levels, the sulphacetamide mixture, which is a close third in this respect, stands out as the one with excellent tissue distribution. In fact, the diffusion of this drug mixture into lungs and brain slightly surpasses that of the sulphapyrazine combination and is distinctly higher than that of the sulphamezathine or sulphathiazole mixture.

Similar results were achieved in 70 rabbits in studies of tissue distribution of sulphonamides from various routes of administration. In addition spinal fluid was obtained in these animals by occipital puncture, so that the blood-spinal-fluid ratio could be calculated. From the oral route of administration the diffusion of the sulphadiazine-sulphamerazine-sulphacetamide mixture through the haematocephalic barrier was as good as that of sulphadiazine, and the absolute concentration in the spinal fluid and blood even somewhat higher than that from sulphadiazine alone.

In the chronic study (Fig. 2), groups of rats were examined in a similar fashion after having been fed a standard diet containing 0.5% of four triple mixtures for 14 days. Here the mixture containing sulphamezathine as third component produced the lowest sulphonamide concentrations in lungs and brain, whereas there was no substantial difference between sulphathiazole, sulphapyrazine, and sulphacetamide in this respect. Since sulphathiazole

FIG. 2.—Concentrations of sulphonamide mixtures in tissues (chronic administration in albino rats).

has fallen into disfavour²² and sulphapyrazine possesses a rather high experimental and clinical toxicity,²³ the mixture containing sulphacetamide appeared the most desirable composition for immediate clinical application.

This viewpoint was strengthened in numerous studies of absorption and excretion in 60 human subjects, using single and multiple dosages of separate and mixed sulphonamides. Tables IV and V represent a summary of all single-dose experiments with separate drugs and drug mixtures.

TABLE IV.—Absorption and Excretion of Single Sulphonamides in Man*

Drug	Blood				Urine	
	Free Drug Mg./100 ml.				Total Drug Excreted After 24 Hours	
	1 Hr.	4 Hrs.	8 Hrs.	24 Hrs.	Mg.	% of Dose
SD ..	1.8	8.0	7.2	3.7	2,223	55.5
SMD ..	3.0	9.8	9.0	4.7	1,077	26.9
SMMD ..	4.2	7.8	5.1	2.6	1,233	30.4
ST ..	3.9	6.5	5.0	1.0	2,869	71.7
SAC ..	6.2	6.8	4.5	1.4	2,801	71.0

* Each figure represents the mean of the values of 4 or more male test subjects. The dose was 4 g. sulphonamide orally.

Table IV illustrates on the left the blood levels achieved in groups of four male subjects with five single sulphonamides and on the right the total amount of drug excreted in 24 hours in mg. and as percentages of the 4-g. dose. It is apparent that sulphacetamide and sulphathiazole show the fastest absorption and most complete excretion, and that within the four-hour interval the blood levels of sulphacetamide are better than those of sulphathiazole and not far behind those of sulphamezathine. This is the more significant since sulphamezathine, like sulphamerazine, shows very incomplete urinary excretion, a fact which could be partially accounted for by their greater retention in the blood stream (plasma-binding) and partially by poorer absorption after oral administration. The percentage of acetylation was highest for sulphamethazine (68%), followed by sulphamerazine (46%), sulphadiazine (33%), sulphacetamide (30%), and sulphathiazole (21%). The behaviour of three triple mixtures under identical experimental conditions is depicted in Table V.

It is apparent that the replacement of sulphathiazole by sulphacetamide as the third component tends to raise blood levels slightly within the first four hours and to lower them accordingly thereafter. Sulphamezathine in the same position assists, as expected, in the prolonged maintenance of high levels and greatly retards urinary excretion. Conjugation of all three mixtures within the first 24 hours was

TABLE V.—Absorption and Excretion of Sulphonamide Mixtures in Man*

Drug Mixture (Equal Parts)	Blood				Urine	
	Free Drug Mg./100 ml.				Total Drug Excreted After 24 Hours	
	1 Hr.	4 Hrs.	8 Hrs.	24 Hrs.	Mg.	% of Dose
SD+SMD+ST	4.4	11.4	9.2	3.5	2,350	58.7
SD + SMD + SMD ..	4.2	10.1	10.5	5.1	1,616	40.3
SD + SMD + SAC ..	6.3	9.2	7.1	3.2	2,431	60.7

* Each figure represents the mean of the values of 4 or more male test subjects. The dose was 4 g. sulphonamide orally.

around 30–40%, which was less than could be expected on the basis of mathematical computation using the figures of the single drugs. Since, in our hands, a combination of sulphadiazine–sulphamerazine–sulphathiazole had given excellent therapeutic results at the bedside, it was expected that the replacement of sulphathiazole by sulphacetamide would not interfere with the therapeutic efficiency of the triple mixture.

Clinical Application of Triple Mixtures

Clinical trials with a combination of equal partial amounts of sulphadiazine–sulphamerazine–sulphacetamide have been completed. A total of 170 unselected patients of all age groups with serious acute infections have undergone this therapy at the full routine dosage (in children: 0.15 to 0.2 g./kg. body weight daily; in adults: 3–4 g. initially, 4–6 g. daily thereafter; the lower maintenance dose of 4 g. daily proved adequate in most instances). Blood levels were excellent. They ranged as a rule between 10 and 25 mg. of free sulphonamide per 100 ml. Acetylation was low, rarely exceeding 20–25% in the blood and 40% in the urine. Although no alkalinizing agents were used, crystalluria of a moderate degree was encountered in only 12 instances, as a rule in connexion with excessive urine concentrations of sulphonamide. There were two cases of drug rash and fever occurring on the tenth and the thirteenth day of therapy, respectively, and two instances of fever alone, possibly due to sulphonamide administration. One patient with acute tonsillitis had severe nausea and vomiting on the third day of drug administration, requiring interruption of therapy, and another patient with pneumonia developed a moderate degree of “cyanosis” apparently due to the drug. No other serious untoward reactions were observed.

Therapeutic results were highly satisfactory, with deferescence usually occurring within the first 24 to 48 hours. The series comprised 55 cases of bacterial pneumonia, 23 of shigellosis (*Shigella sonnei*), six of pyelitis, five of bacterial meningitis, one of penicillin-resistant pneumococcal bacteraemia, and one of penicillin- and streptomycin-resistant staphylococcal septicaemia.

The experimental and clinical evaluation of other sulphonamide mixtures is continuing at present.

Summary

The simultaneous administration of several sulphonamides in *partial* dosage may result in a reduced rather than an increased incidence of sensitization, because mixtures permit “dilution” of individual drug concentrations below the level necessary for the production of allergy. Hence it is possible to enhance the renal protection afforded by sulphonamide mixtures by using additional components in proportionately smaller amounts, without the danger of increasing the incidence of allergic reactions.

Sulphadiazine and sulphamerazine qualify for first and second place, respectively, as mixture components. Sulphathiazole, sulphapyrazine, sulphamezathine, and sulphacetamide deserve attention as possible third and fourth members of a combination. Although sulphathiazole has fallen into disfavour in the U.S.A. because of its high clinical toxicity, mixtures containing this drug have shown a low overall toxicity. Sulphapyrazine, the most insoluble of these compounds, induces frequent renal and allergic reactions and therefore offers no advantages over sulphathiazole. Sulphamezathine has adequate solubility and low toxicity, but is subject to substantial conjugation and plasma-binding, which diminish its therapeutic efficiency. Sulphacetamide retains the high solubility of sulphanilamide and shares with the parent compound the improbability of renal concretion formation and the ready diffusibility into all tissues. In addition, it shows low figures for conjugation, plasma-binding, and sensitization.

The mixture sulphadiazine-sulphamerazine-sulphacetamide (equal amounts) revealed low toxicity in animals as well as excellent bacteriostatic activity *in vitro* and in experimental infections of mice. After oral administration, blood and spinal-fluid levels were similar to those from equal doses of sulphadiazine or sulphamerazine. Clinical trials of this mixture in 170 patients with acute systemic infections showed a high curative value and low toxicology.

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MEDICAL TREATMENT OF HYDATID CYSTS OF LUNG*

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Pulmonary hydatid cysts, apart from the rare cases which heal spontaneously after a single or repeated expectoration, are exclusively in the domain of surgery, varying only in the details of technique suited to each case.

Encouraged by the good results obtained in severe broncho-pulmonary suppurations, both localized and diffuse, by our method of transthoracic intrapulmonary injections of sulphonamides, antibiotics, and other drugs, we extended this treatment to suppurations due to the retention of hydatid membranes—that is, to suppurating cysts of the lung with incarcerated membranes. A few years later, in view of our favourable experience with infected cysts, we applied the same method of treatment to clean uninfected hydatid cysts.

Without exaggeration, and on the basis of our case records, we can now say that some cases can be treated medically. The importance and scope of this treatment remain to be established by further experience. Whilst the results in cases followed up have so far been successful, their number is too small to warrant definite conclusions. Nevertheless, we are optimistic, since we cannot believe that only the favourable cases came into our hands.

These cases fall into three categories: (1) suppurating pulmonary hydatid cysts, with retained membranes; (2) ruptured pulmonary hydatid cysts, with loss of fluid content and persistence of the parasitic cavity, whether air-containing or not; and (3) hyaline hydatid cysts—that is, closed and non-infected. We will outline the therapeutic procedures employed in each category, and give a single example of each kind to show the more salient clinical features.

Suppurating Pulmonary Hydatid Cysts, with Retained Membranes

These cases present two problems: broncho-pulmonary suppuration and the retention or incarceration of the parasitic membranes. The first problem is really a consequence of the second, since the membranes, except in rare instances of clean encystment or of calcification, behave as true foreign bodies, leading sooner or later to pus formation in the surrounding parenchyma.

We treat pulmonary suppuration locally by means of transthoracic injections of sulphonamides and antibiotics, choosing the drug according to the organism isolated, whenever possible, from the material aspirated, and adapting the dosage, interval of administration, etc., to the clinical and radiological progress of the patient.

The complete expulsion of the membranes, which is essential to end the suppuration, is achieved by a purely mechanical effect. The local congestion, partly hydrostatic and partly biochemical, created by the transthoracic injection provokes intense and repeated bouts of coughing, which directs the fluid current towards bronchi already dilated as a result of the suppuration. This flow carries along with it fragments of endocyst which have been

Over 200 Scottish nurses had their names added to the Register of the General Nursing Council for Scotland on June 21. New rules made by the Council provide for the transfer of these nurses from the 1943 Nurses' List to the Register without application or payment of fee. This allows these nurses, who have hitherto been known as State-listed nurses, to be classified as State-registered in the branch of nursing in which they are qualified. It also grants them the right to vote in the forthcoming elections for the new General Nursing Council. The rules provide that persons who would have been eligible for admission to the 1943 list but who did not apply within the prescribed period may also be admitted to the Register. In their case, however, application for admission must be made to the registrar of the council.

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