frequent vomiting; sleepiness, dull mentality; neck rigidity +; Kernig's sign +; lt. external rectus palsy. Blood: W.B.C. 18,400 (N. 97%, L. 3%). L.P.: canary-yellow cloudy fluid released under high pressure; cells 5,060, G. +, S. —. Smear: N. predominate, no organisms found. Patient passed into coma, with weakening pulse, sluggish pupils, general flaccidity, and died.

Treatment.—Serum 200 ml. (195 ml. I.V., 5 ml. I.M.) first 6 days; after onset of meningitis, 10 ml. I.Th., 20 ml. I.V. Sulphath. 29 g. first 4 days; later 5 g.

Case VI: Inguinal Bubonic Plague; Secondary Plague Meningitis

Male aged 16; admitted 15/6/45, with history of 2 days' chill, fever, painful swelling rt. groin. T. 103° F. (39.4° C.), P. 120, R. 25; tender swollen rt. inguinal gland. Aspn.: *Past. pestis* found (few).

Course.—General condition gradually improved; bubo steadily enlarged. 24/6/45: T. 103° F., P. 90, R. 24; commencing suppuration in bubo. 27/6/45: T. 103° F., P. 90, R. 24; bubo incised, drained. 30/6/45: T. 102° F. (38.9° C.), P. 90, R. 24; headache, clouded mentality; neck rigidity +; Kernig's sign +. L.P.: cloudy fluid; cells 1,000, G. +, S. —. Smear: N. predominate, organisms not found. 1/7/45: Neck more rigid, with head retraction, opisthotonos; deafness.

2/7/45: Symptoms improved. L.P.: C.S.F. cloudy, yellow; S. —; C., no growth. Blood: W.B.C. 9,000 (N. 88%, L. 12%). 3/7/45: T. 98° F. (36.7° C.), P. 90, R. 24; further improvement. 5/7/45: T. 100° F. (37.8° C.), P. 100, R. 24. Patient insisted on leaving hospital, and died about a week later.

Treatment.—Serum 200 ml. I.V. in first 5 days; onset of meningitis onwards, 60 ml. I.Th., 20 ml. I.V. Sulphath. 52 g. in first 8 days; onset of meningitis onwards, 20 g.

Case VII: Epitrochlear and Axillary Bubonic Plague; Secondary Plague Meningitis

Female aged 39; admitted 28/7/44, with history of 2 days' high fever, painful swelling at lt. elbow and lt. axilla. T. 102.4° F. (39.1° C.), P. 104, R. 26; acute lt. epitrochlear and axillary adenitis with periadenitis. Epitrochlear gland aspn.: *Past. pestis* found +. Blood: W.B.C. 10,400 (N. 84%, L. 15%, M. 1%). Urine: moderate albuminuria, few pus cells.

Course.—Pyrexia maintained; buboes increased in size; oedema of whole limb down to fingers. 9/8/44: W.B.C. 16,900. 10/8/44: T. 103° F. (39.4° C.), P. 100, R. 30; buboes and oedema subsiding. Onset of painful stiff neck, headache, marked vertigo, relieved by keeping eyes shut, vomiting. Neck rigidity +; Kernig's sign +. Eyes: fine rotatory nystagmus on looking to lt., coarse jerking nystagmus on looking to rt. L.P.: clear fluid; cells 210, G. +, S. —. Smear: N. predominate; "Gram-negative diplococcus" (?) found. Urine: slight albuminuria. 12/8/44: Clouded mentality; irritability, nausea, severe vertigo, tinnitus; nystagmus pronounced, jerking, especially on lateral deviation; limbs flaccid; incoordination in finger–nose test on lt. L.P.: clear fluid; cells 500, G. +, S. —. Smear: N. predominate, no organisms found. Patient passed into coma and died.

Treatment.—Serum 200 ml. I.V. first 4 days. Sulphath. 37 g. 7 days beginning 31/7/44. Onset of meningitis: sulphath. 4 g., sulphap. 9 g., anti-meningococcal serum 20 ml. I.M.

Case VIII: Malaria; Primary Plague Meningitis

Male one month old; admitted 9/7/45, with history of 4 days' fever and slight convulsive movements. T. 104.4° F. (40.2° C.); irritable; fontanelle tense; slight neck rigidity; Kernig's sign equivocal. Blood: W.B.C. 17,000; film: *Plasmodium vivax* gametocytes found (few).

Course.—L.P. attempted many times without success. 12/7/45: T. 103° F. (39.4° C.); slight jaundice; neck rigidity +; Kernig's sign —. L.P.: few ml. turbid yellow fluid; cells 400, G. +, S. —. Smear: Gram-negative bacillus found (? *Past. pestis*). C.: *Past. pestis* isolated. 15/7/45: T. 99° F. (37.2° C.); head retraction; Kernig's sign +. 19/7/45: T. 100° F. (37.8° C.); pale, wasted; epileptiform convulsions, especially rt. face. 21/7/45: T. 101° F. (38.3° C.). L.P.: bead of pus at end of needle. Smear: Gram-negative bacillus found (? *Past. pestis*). (L.P. performed repeatedly from 12/7/45 onwards had only "dry" result.) Convulsions generalized, frequent; patient died 22/7/45.

Treatment.—Sulphap. 1.5 g. first 3 days, repeated last 2 days. Sulphath. 8.125 g., commencing 4th day, for 7 days. Serum 50 ml.

Summary

Eight cases of plague meningitis are described, occurring in a series of 203 cases of plague treated in South China during the years 1943–5.

The occurrence of a rare clinical form—primary plague meningitis—is recognized; one case is described and its pathogenesis discussed.

We wish to thank Dr. Robert Pollitzer, Senior Technical Expert, National Health Administration of China, for his advice and help in the compilation of this paper. We would also like to thank our Chinese colleagues, Drs. Wu, Ling, and Jao, for their help in treatment; the nursing staff of the hospital for their cheerful co-operation; and Mr. C. T. Lim for performing the laboratory examinations.

References

Burton, E., and Hennessy, R. S. F. (1940). *E. Afr. med. J.*, **17**, 266.
Lafont, A., Lecomte, A., and Heckenroth, F. (1915). *Bull. Soc. Path. exot.*, **8**, 92.
Lewillon, R., Devignat, R., and Schoetter, M. (1940). *Ann. Soc. belge Méd. trop.*, **20**, 79.
Meyer, K. F., Connor, C. L., Smyth, F. S., and Eddie, B. (1937). *Arch. intern. Med.*, **59**, 967.
Pollitzer, R. (1945). Paper on "The Clinical Aspects of Rural Plague," published in Chinese.
—— (1946). Personal information.
de Villafañe Lastra, T., and Rodeiro, M. (1942). *Prim. Congr. nac. Enferm. endemo-epidem.*, **1**, 579. [Cited in *Trop. Dis. Bull.*, 1944, **41**, 399.]
Wagle, P. M. (1944). *Indian med. Gaz.*, **79**, 585.
Williams, A. W. (1934). *E. Afr. med. J.*, **11**, 229.

"SULPHA-COMBINATION"—A NEW CHEMOTHERAPEUTIC PRINCIPLE

BY

A. RUNE FRISK, M.D.
GÖSTA HAGERMAN, M.D.
STURE HELANDER, M.D.
AND
BERTIL SJÖGREN

(From the IVth Medical Service of St. Erik's Hospital; the Dermato-venereological Clinic of St. Göran's Hospital; the Ist Medical Clinic of the Caroline Hospital, Stockholm; the Central Laboratories, Astra, Södertälje, Sweden)

The commonly used sulphonamides—sulphathiazole, sulphadiazine, and sulphamerazine—have on the whole the same effect when employed clinically. The two pyrimidine compounds, however, are less toxic than sulphathiazole, and are therefore better tolerated. From the therapeutic point of view sulphonamide treatment might be regarded as more or less perfect if it were not attended by the risk of damage to the blood and kidneys. Toxic effects on the blood are, however, extremely rare with the above-mentioned drugs. Renal complications are more common: they may have a toxic or allergic origin, but in most cases are due to a deposition of the sulphonamide compounds, or their acetyl derivatives, in the tubules from supersaturated solutions. This risk can be reduced by the introduction of acid-binding media and the maintenance of a high diuresis. With these precautions renal complications are rare, but the risk remains, and for this reason inadequate and ineffective doses are often given. Thus the importance of reducing concrement formation is evident.

Provided that the sulphonamides do not affect each other's solubility but dissolve independently, which is to be expected from the chemical point of view, the risk of concrement formation might be reduced if, for the attainment of a certain blood concentration or effect, not merely one compound but a mixture of several equivalent sulphonamides was employed. From the clinical standpoint it cannot make any difference if several compounds are used instead of one when all the drugs are equally effective. The risk of concrement formation will, however, be reduced in this case, since each drug in the mixture is present in a considerably lower degree of saturation than when a single compound is employed. This new therapeutic principle we have named the "sulpha-combination principle."

In cases where it is desired to increase the dose beyond the normal limits, resulting in higher blood concentration and better therapeutic outcome, the same principle can be applied. If in such cases a single compound is used the risk will be increased. On the other hand, when a mixture of several drugs is employed the risk will be reduced. The method has been used in a preliminary form (a mixture of equal parts of sulphathiazole and sulphadiazine) in Sweden for more than three years in the treatment of gonorrhoea (Hagerman, 1944; Herlitz, 1944; Werkö, 1945). In spite of the very high dosage (12 g. a day for four days) remarkably few renal complications occurred (Nilzén, 1946a).

The most important problem is how to avoid formation of renal obstruction with a normal dosage. A mixture of sulphathiazole and sulphadiazine, also suggested by Lehr (1945), is not, however, ideal. The chances of renal complications are admittedly reduced, but they are not eliminated, since some of the excretion products are still supersaturated. If this is to be avoided the two above-mentioned compounds must be complemented with a third—for example, sulphamerazine.

In the following account we discuss all the questions connected with "sulpha-combination" and describe experiments showing the practicability of the method. We also give an account of our final mixture, prepared according to this principle—"sulphadital"—which contains the three compounds sulphathiazole, sulphadiazine, and sulphamerazine, equally active in clinical practice. The present article is a condensation of a larger work which has already been published in Swedish (Frisk *et al.*, 1946).

Solubility

The solubility of sulphathiazole, sulphadiazine, sulphamerazine, and the corresponding acetyl derivatives was determined in solvents saturated with the substances separately and with mixtures of from two up to all six compounds. The solvents used were 1/30 molar potassium sodium phosphate buffer and urine varying in *p*H. The substances were brought into solution by even mechanical shaking for twenty-four hours at constant temperature—37° C.—and with the solutes present in excess. The concentrations were then determined in a photoelectric colorimeter according to Bratton and Marshall (1939). The solubility is given in mg. of dissolved substance per 100 ml. of solvent. The solubility curves are drawn to a logarithmic scale.

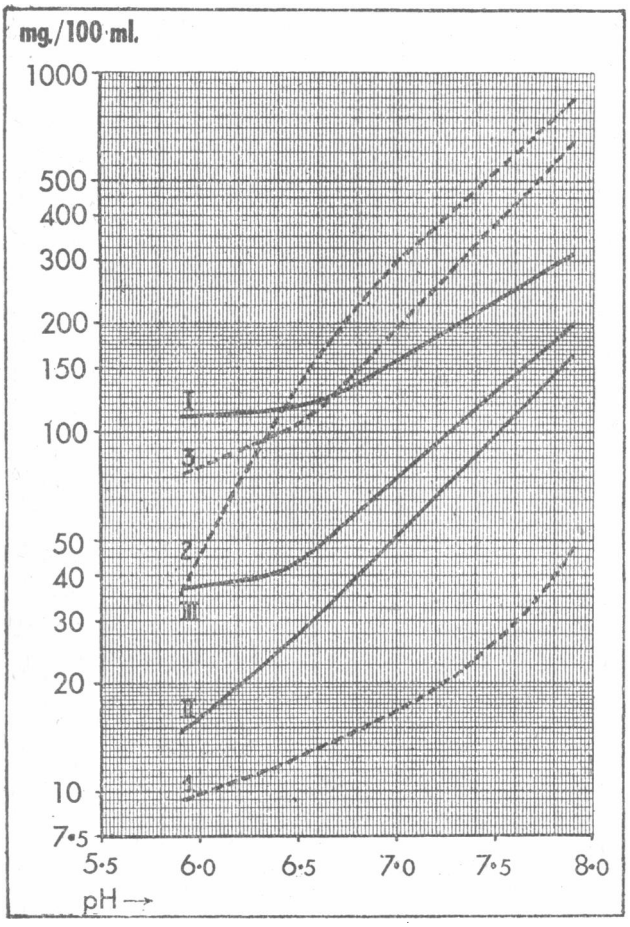

FIG. 1.—Solubility in urine at 37° C. over the *p*H range 5.9–7.9. I = sulphathiazole. II = sulphadiazine. III = sulphamerazine. 1 = acetylsulphathiazole. 2 = acetylsulphadiazine. 3 = acetylsulphamerazine.

For reasons of space we give here only the solubility in urine. Figs. 1 and 2 show the solubility at *p*H 5.9–7.9. From these it appears that the three sulphonamides, their acetyl derivatives, and all six compounds are, as expected, dissolving independently of one another.*

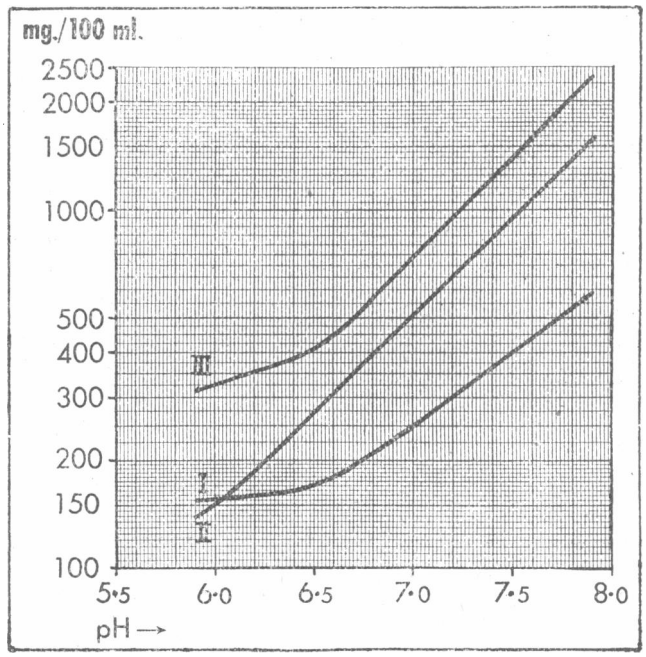

FIG. 2.—Solubility in urine at 37° C. of different mixtures over the *p*H range 5.9–7.9. I = sulphathiazole + sulphadiazine + sulphamerazine. II = acetylsulphathiazole + acetylsulphadiazine + acetylsulphamerazine. III = Σ sulphonamides + Σ acetyl derivatives.

Concrement Formation

We do not propose to review here the comprehensive literature on renal complications during sulphonamide treatment clinically observed or studied in animal experiments. Two main types of injury to the kidney can be distinguished—namely, those of toxic or allergic origin, and those due to the formation of calculi. In the first-mentioned type, which is more uncommon, small areas of focal necrosis are found not only in the tubular cells of the kidneys but also in other organs, as well as vascular changes, with fibrinoid degeneration of the media and voluminous intima proliferations.

The changes occurring after calculus formation are localized to the distal part of the kidney, and are characterized by distended tubules filled with masses consisting of protein precipitate, desquamated cells, and crystals of the sulphonamides or their acetyl derivatives. More detailed descriptions of the various anatomical changes have been given by Murphy *et al* (1944), Bergstrand (1946), and others.

In the present investigation the formation of renal calculi has been studied after the administration of sulphathiazole, sulphadiazine, and sulphamerazine. The dose and the blood concentration, as well as the time required to produce obstruction, have been determined for each compound. The composition of our mixture—"sulphadital"—was decided on the basis of these results, and with due respect to the solubility and pharmacological properties of the constituent compounds. This preparation was then subjected to the same investigation in order to ascertain whether the risk of concrement formation had been diminished by the combination.

Rabbits were used for the experiments. They were given a vegetable diet but no water. The urine was acid (*p*H 4–6). The compounds were administered intraperitoneally morning and evening (eight hours between the doses) every day except Sundays. The animals that did not die spontaneously were killed after about three weeks. Those dying spontaneously usually had concrements, which were the cause of death, but in some cases they died of injuries due to the injections. Twice a week free and total sulphonamide concentrations as well as non-protein nitrogen were determined.

* Further details to be published elsewhere; see also *Nord. Med.*, 1946, **29**, 639.

As soon as possible after death the kidneys were removed, fixed by freezing-drying according to Altmann, and then examined under a fluorescent microscope with the histological technique described by Sjöstrand (1944) and Helander (1945). With this procedure it is possible to make detailed studies of the preparations without staining. The crystals thus remain *in situ* in the preparations. It is also easy to detect the calculi, as they fluoresce in a characteristic manner (blue fluorescence).

With the method employed it was easy to produce renal obstructions. Their localization and the anatomical picture fully corresponded with previous descriptions. By the polarizing microscope it was also possible to verify the crystalline nature of the concrements. Melting-point determinations in polarized light showed that the sulphathiazole concrements consisted mainly of acetylsulphathiazole, and those of sulphamerazine of the unacetylated compound. As regards sulphadiazine, it was not possible to decide whether the crystals consisted of free or acetylated compound, the melting-points being too close together.

The results have been summarized in Table I. A daily dose of 0.8 g. of *sulphadiazine* per kg. body weight during a period

TABLE I.—*Summary of Results of Experiments on Concrement Formation*

Preparation	Daily Dose in g./kg.	No. of Experiments	Experimental Period in Days (mean)	Percentage Probability of Concrement	Blood Concentration during Experimental Period in mg./100 ml. (mean)	
					Free	Total
Sulphadiazine	0·8	5	9	100	18	38
	0·6	5	22	20	7	17
Sulphamerazine	0·6	5	10	100	6	28
	0·4	5	15	0	3	10
Sulphathiazole	0·8	6	16	67	6	11
	0·6	5	18	20	3	8
Sulphadital	2·0	10	12	40	41	63
	1·0	10	18	0	20	30

of nine days was necessary for provoking renal calculi in all the animals. A dose of 0.6 g./kg. seldom gave rise to concrements. In the case of *sulphamerazine* concrements were obtained in all the animals with a dose of 0.6 g./kg. in the course of only ten days, whereas a dose of 0.4 g./kg. was tolerated without any renal injuries. *Sulphathiazole* required a daily dose of 0.8 g./kg. for sixteen days (the blood concentration was remarkably low, presumably on account of the rapid excretion). In this series, however, only two-thirds of the animals died, even though a certain risk attended a dose of 0.6 g./kg. We have therefore considered this dose to be on the whole comparable to the dose of 0.6 g./kg. for sulphadiazine and 0.4 g./kg. for sulphamerazine. From this it follows that the last-mentioned compound should be present in the mixture in a smaller proportion than the two others.

Finally, it was possible with *sulphadital* to administer considerably higher doses without giving rise to concrements. With a daily dose of 2 g./kg. 60% of the animals escaped concrement formation during an experimental period of twelve days, despite the very high blood concentration. If the dose was reduced to 1 g./kg. no concrements appeared in any of the animals during an experimental period of eighteen days. The individual components of the mixture with this dosage gave rise to renal calculi in 100% of the cases.

Absorption and Excretion

With the dosage generally employed therapeutically the sulphonamides investigated here are absorbed almost completely; but with increasing oral doses the percentage absorbed becomes progressively less, as with other sulphonamides. The effect of the simultaneous administration of different sulphonamides on the absorption, excretion, and acetylation of the individual compounds was determined in the following way. Various single oral doses of sulphathiazole and sulphamerazine, separately and in a mixture, were administered to each of three healthy persons. The experimental procedure and method of determination earlier employed by Frisk (1943, 1945) were used.

Table II shows the mean blood concentrations in a typical experiment. A simultaneous administration of 2 g. of sulphathiazole and 2 g. of sulphamerazine gives a concentration that practically equals the sum of the separate values for the two compounds after a dose of 2 g.

TABLE II.—*Comparison between the Blood Concentrations after Single Oral Doses of Sulphathiazole and Sulphamerazine Separately and in Mixture*

Time in Hours	Blood Concentration in mg. per 100 ml.							
	Found						Calculated	
	After 2 g. Sulphathiazole		After 2 g. Sulphamerazine		After 2 g. Sulphathiazole + 2 g. Sulphamerazine		After 2 g. Sulphathiazole + 2 g. Sulphamerazine	
	Free	Total	Free	Total	Free	Total	Free	Total
1	2·4	2·7	2·0	2·1	5·6	5·9	4·4	4·8
2	2·8	3·2	3·0	3·0	6·3	7·0	5·8	6·2
4	2·4	3·2	3·8	4·0	7·2	8·2	6·2	7·2
6	2·1	2·7	4·1	4·7	6·6	7·6	6·2	7·4
10	1·0	1·4	3·4	3·9	4·1	5·6	4·4	5·3
24	—	—	1·8	2·4	2·0	2·7	1·8	2·4

TABLE III.—*Comparison between the Excretions through the Kidneys after Single Oral Doses of Sulphathiazole and Sulphamerazine Separately and in Mixture*

Time in Hours	Excreted Amount in Grammes (cumulative)							
	Found						Calculated	
	After 2 g. Sulphathiazole		After 2 g. Sulphamerazine		After 2 g. Sulphathiazole + 2 g. Sulphamerazine		After 2 g. Sulphathiazole + 2 g. Sulphamerazine	
	Free	Total	Free	Total	Free	Total	Free	Total
2	0·132	0·166	0·011	0·023	0·148	0·183	0·143	0·189
4	0·358	0·479	0·045	0·082	0·442	0·615	0·403	0·561
6	0·592	0·796	0·088	0·207	0·659	0·929	0·680	1·003
10	0·833	1·160	0·182	0·446	0·793	1·652	1·015	1·606
24	1·047	1·596	0·376	0·918	1·476	2·463	1·423	2·514
48	1·100	1·694	0·487	1·265	1·697	3·057	1·587	2·959
72	1·100	1·694	0·547	1·405	1·743	3·162	1·647	3·099

Table III shows the excretion of the drugs in the urine in one of these experiments. The excretion also takes place without the compounds influencing each other. Moreover, the acetylation is unaffected. For technical reasons these experiments were performed with only two drugs.

Composition of the Mixture, its Actions and Uses

Our results thus show that the sulphonamides examined, and their acetyl derivatives, do not affect each other's solubility, that a mixture of several compounds causes concrements to a considerably smaller degree than do the individual drugs at the same blood concentration, and that the compounds in a mixture are absorbed and excreted in the urine independently of each other. Since, as we have also been able to establish, the antibacterial effect of a mixture of several different sulphonamides is not affected but is the sum of the effects of the various compounds, the basis has been laid for the clinical use of the sulpha-combination principle.

A good mixture should contain a number of sulphonamides sufficient to maintain an adequate therapeutic concentration in the blood without risk of concrement formation. The compounds included in it must produce about the same antibacterial effect, be of low toxicity, and possess otherwise favourable pharmacological properties. In consideration of these factors, a mixture of sulphathiazole, sulphadiazine, and sulphamerazine is most suitable. The proportion of the different constituents depends upon their mode of absorption and excretion, their tendency to cause renal injuries, and the solubility of the compounds or their conversion products.

Sulphathiazole should not predominate in the mixture, as it is rapidly excreted and its acetyl derivative is not easily soluble. Sulphamerazine, owing to its slow excretion, gives rise to concrements in a somewhat lower dose than do sulphathiazole and sulphadiazine. The amount of sulphamerazine should therefore be less than that of the two others. The rapid excretion of sulphathiazole and the slow excretion of sulphamerazine can be compensated, however, if the drugs are present

in a certain proportion. We have sought for a mixture that has on the whole the same pharmacological properties as sulphadiazine, which involves no risk of accumulation, and which it should be possible to administer at intervals of four hours.

The final mixture (sulphadital) was given the following composition: sulphathiazole 37%, sulphadiazine 37%, and sulphamerazine 26%. The normal daily dose in the treatment of pneumonia, for example, is for sulphathiazole 6 g., for sulphadiazine 5–6 g., and for sulphamerazine 4–5 g. A daily dose of 6 g. of the above-mentioned mixture thus provides about one-third of the otherwise normal daily dose of each constituent.

Figs. 3 and 4 show the absorption, excretion, and acetylation of sulphadital after single oral doses of 2 and 4 g. (average

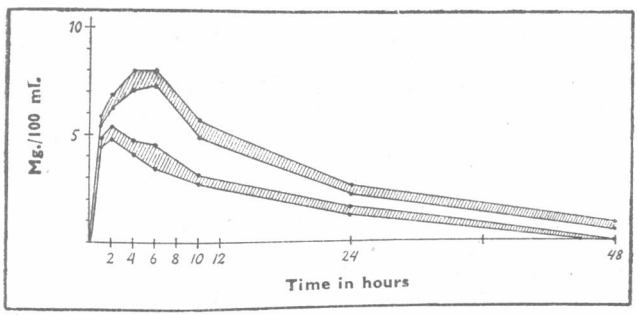

FIG. 3.—Blood concentration after single oral doses of sulphadital: the lower curves after 2 g., the upper curves after 4 g. The upper curve in each group shows the total amount of sulphadital, the lower curve the free sulphadital; the hatched area indicates the amount acetylated.

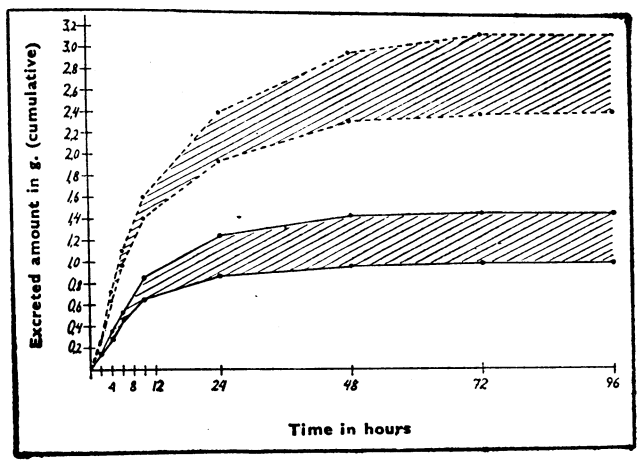

FIG. 4.—Excretion through the kidneys after single oral doses of sulphadital: the lower curves after 2 g., the upper curves after 4 g. In each group the upper curve shows the total amount of sulphadital, the lower curve that of free sulphadital; the hatched area indicates the amount acetylated.

of three experiments on the same persons). The blood concentration rises rapidly, reaching a maximum after 2–4 hours, whereafter it sinks slowly (Fig. 3). The excretion in the urine takes place relatively slowly, and after 48–72 hours is practically concluded (Fig. 4). Of the total dose administered 75–80% has then been recovered, 50–60% in an unaltered form. Thus in the urine about one-third of the amount excreted is present as acetyl derivatives.

With the following dosage—2 g. at 6 p.m., 2 g. at 10 p.m., and thereafter 1 g. four-hourly, the first dose being given at 6 a.m. and the last at 10 p.m.—the mean blood concentration (15 cases) of free sulphonamides after 15 hours was 7.8 ± 0.5 mg. per 100 ml. and that of total sulphonamides 8.5 ± 0.4 mg., the values after 39 hours being 8.0 ± 0.6 and 9.3 ± 0.7 mg., and after 63 hours 8.4 ± 0.8 and 9.1 ± 0.8 mg., respectively. These values agree well with the blood concentrations obtained when the same amounts of sulphadiazine are administered at the same times.

If the dose of sulphadital is increased to almost twice the amount—i.e., 4 g., 4 g., and thereafter 1.5 g. four-hourly—the means of the corresponding values (10 cases) are: after 15 hours 11.5 and 12.7 mg., after 39 hours 10.8 and 12.0 mg. per 100 ml., respectively. There is thus no risk of accumulation even with these high doses. Although the dose has been almost doubled the blood concentration does not increase by more than about 40%, owing to the fact that absorption is less complete when higher doses are given.

Calculation shows that the single sulphonamides at the usual pneumonia doses give such high concentrations of the free compounds and their acetyl derivatives in an acid urine that the compounds are always present in more or less supersaturated solutions. In a neutral urine this also holds for sulphathiazole, its acetyl derivative, and the free pyrimidine compounds, which may be present in concentrations two to three times greater than their solubility. At yet higher *p*H—e.g., 7.5—the risk is still less, but acetylsulphathiazole and free sulphadiazine may still be supersaturated. Considering these facts, it is surprising that renal complications appear in only a small percentage of the cases.

With the sulpha-combination drugs in the proposed normal dosage the risk of concrement formation is greatly reduced, as the components of the mixture are no longer excreted in the form of supersaturated solutions. This holds good if the reaction of the urine is neutral or approximately so. If, on the other hand, it is more acid, the concentrations of two of the excretion products—acetylsulphathiazole and sulphadiazine—may exceed their solubility. For safety's sake a high diuresis should therefore be maintained and the patient should be given acid-binding substances. We believe that if these precautionary measures are observed the risk of concrement formation in a normal kidney will be almost eliminated.

Hitherto the sulpha-combination in the form of sulphadital has been used in many hundreds of cases of acute pneumonia with good results and tolerance and without any known case of renal calculi, also with increased doses in many cases of gonorrhoea. Nilzén (1946b) has treated 105 cases of gonorrhoea with increased doses of sulphadital (9 g. daily for three days). Although he did not use any acid-binding substances no concrements were observed in any of the cases.

Summary

"Sulpha-combination," a new principle for treatment with sulphonamide drugs, is discussed, and an account is given of sulphadital, a preparation made according to this principle and composed of sulphathiazole, sulphadiazine, and sulphamerazine.

The results are given of a number of experiments illustrating the practicability of the method.

The importance of "sulpha-combination" is twofold. First and foremost, it appears to eliminate the risk of concrement formation at a normal dosage. Secondly, in cases with more resistant bacteria the doses may be considerably increased without greater risk of calculus formation than is possible with a single compound.

[Received originally on July 16, 1946]

REFERENCES

Bergstrand, H. (1946). *Acta med. scand.*, **124**, 309.
Bratton, A. C., and Marshall, E. K. (1939). *J. biol. Chem.*, **128**, 537.
Frisk, A. R. (1943). *Acta med. scand.*, Suppl., p. 142.
—— (1945). *Svenska Läkartidn.*, **42**, 3045.
—— Hagerman, G., Helander, S., and Sjögren, B. (1946). *Nord. Med.*, **29**, 639.
Hagerman, G. (1944). Ibid., **22**, 1093, 1223; **24**, 1944.
Helander, S. (1945). *Acta physiol. scand.*, Suppl., p. 29.
Herlitz, S. (1944). *Nord. Med.*, **22**, 1226.
Lehr, D. (1945). *Proc. Soc. exp. Biol.*, N.Y., **58**, 11.
Murphy, F. D., Kuzma, J. F., Polley, Th. Z., and Grill, J. (1944). *Arch. intern. Med.*, **73**, 433.
Nilzén, Å. (1946a). *Nord. Med.*, **32**, 2424.
—— (1946b). *Svenska Läkartidn.*, **43**, 1816.
Sjöstrand, F. (1944). *Über die Eigenfluorescenz tierischer Gewebe mit besonderer Berücksichtigung der Säugetiernieren*, Stockholm.
Werkö, L. (1945). *Svenska Läkartidn.*, **42**, 746.

Medical practitioners who are asked to give vaccinations and inoculations to intending air passengers are particularly requested to use the "International Certificate of Inoculation and Vaccination" (Form 3150) when recording them. These forms can be obtained by the passenger from the agency from which he receives his ticket and flight information. The use of any other form of certificate is liable to lead to delays and possibly to quarantine in foreign countries where the international certificate is the only certificate officially recognized.