ment not only in rheumatic fever and mumps but in other forms of generalized bacterial or virus infections as well. These implications and other aspects of the problem will be dealt with in greater detail in the final report.

Summary. 1. Two isolated cases of epidemic parotitis accompanied by electrocardiographic evidence of complete heart block are reported. 2. In a subsequent study of 104 consecutive cases of epidemic parotitis in adults, evidence of myocardial involvement was observed in 16 instances (15.4%). In all but 2 patients, the electrocardiographic changes were transitory and of short duration. The broad implications of these findings are discussed briefly.

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Inhibition of Drug Precipitation in the Urinary Tract by the Use of Sulfonamide Mixtures. I. Sulfathiazole-Sulfadiazine Mixture.*

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Serious toxic effects of sulfonamides upon the kidneys have appeared only after introduction of N^1-heterocyclic derivatives of sulfanilamide. Preference of these compounds over sulfanilamide in human therapy is based primarily on their wider range of antibacterial activity. Two representatives of this group, sulfathiazole and sulfadiazine, are employed at present as the "drugs of choice" whenever sulfonamide therapy seems indicated, despite their poor solubility if compared with the mother substance sulfanilamide. Hence renal concrement formation—a complication unknown from sulfanilamide—has become a serious problem worthy of the most careful attention.

The present investigation deals with the possibility of lessening the danger of renal concrement formation by the employment of sulfonamide mixtures. Solubility studies with N^1-heterocyclic derivatives of sulfanilamide revealed that these compounds are soluble in one and the same solution nearly to the extent of their separate solubilities; in other words, a saturated solution of sulfadiazine, for instance, can still be further almost fully saturated with sulfathiazole. This finding applies even to compounds which are structurally as closely related as sulfadiazine and its monomethyl and dimethyl derivatives (sulfamerazine and sulfamethazine). Table I illustrates these observations. Almost identical results were obtained in solubility studies with normal human urine.

Since even closely related sulfonamides, when present simultaneously in the same solution, do not influence each other appreciably with regard to their particular solubilities, the danger of intrarenal drug precipitation from the sulfonamides comprising the mixture should be only as great as if each compound had been administered alone, and in the partial dosage contained in the mixture. On the other hand, it seemed probable that in using combinations of different sulfonamides having similar or identical therapeutic indications, the antibacterial effect would largely correspond to the total concentration of free sulfonamide.

The validity of these contentions was investigated in toxicity experiments with albino rats and with the help of *in vitro* antibacterial studies. Sulfathiazole and sulfadiazine were selected for the initial series of experiments, because these compounds are at present most frequently employed, have almost the same therapeutic indications, and cause renal complications in about the same percentage of

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TABLE I.
Solubility of Sulfonamide Mixtures.*

Sulfathiazole (ST), sulfadiazine (SD), sulfamerazine (SMD), and sulfamethazine (SMMD), and mixtures of these compounds in powdered form were shaken in water for one hour at room temperature (20°C). The fluids, which always contained a safe excess of the drugs, were then filtered and the sulfonamide concentration in the filtrate was determined in a 1:200 dilution according to the method of Bratton and Marshall using a Klett Summerson Photo Colorimeter.

Drug	Reading	Sulfonamide dissolved, mg %	
		Found	Expected (Sum of solubilities of the single drugs)
SD	36	7.3	
SMD	89	20.2	
SMMD	163	43.0	
ST	159	34.4	
SD + SMD	120	25.6	27.5
SD + SMMD	200	50.3	50.3
SD + ST	180	38.3	41.7
SMD + SMMD	232	58.1	63.2
SMD + ST	230	50.7	54.6
SMMD + ST	300	72.0	77.4
SD + SMD + SMMD + ST	395	93.0	104.9

* Grateful acknowledgment for liberal supplies of the drugs used is made to the Schering Corporation, Bloomfield, N.J. (ST); the Lederle Laboratories, New York, N.Y. (SD and SMD); and to Sharp & Dohme, Philadelphia, Pa. (SMD and SMMD).

cases in experimental animals as well as in humans.[1-6]

Results. From previous experience it was known that both sulfathiazole and sulfadiazine are readily precipitated out in the urinary tract of albino rats if given in large amounts, and that renal obstruction from drug precipitate plays an important part in causing death from sulfathiazole or sulfadiazine intoxication.[7-9] It was expected, therefore, that joint administration of the two compounds, in amounts comparable in total weight to fatal dosages of either drug when administered separately, would reveal a significantly lower toxicity because of a diminished tendency to intrarenal precipitation.

Experimental results confirmed this viewpoint. It was found that the acute and chronic toxicity of sulfathiazole-sulfadiazine mixtures is strikingly low if compared with the toxicity of each of the two compounds when administered separately. The findings are briefly summarized in Table II.

Evidence derived from chemical studies pointed to a significant decrease of renal obstruction, following joint administration of the 2 sulfonamides, as the chief reason for the strikingly low toxicity of the mixture. This could be inferred in particular from a comparison of the nonprotein nitrogen levels in the blood and from comparative follow-up studies of the sulfonamide concentration in blood and urine at predetermined intervals. The sulfonamide blood levels obtained with the mixture were, as expected, much higher than from sulfathiazole and only slightly lower than from sulfadiazine. The average total sulfonamide values (mean of 10 animals) for the dosages used in the acute toxicity study (Table II) were, after 24 hours: for sulfadiazine 121 mg %, for sulfathiazole 45 mg %, and for sulfadiazine-sulfathiazole 85 mg %.

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TABLE II.
Comparative Toxicity in Albino Rats of the Sodium Salts of Sulfadiazine (NaSD), Sulfathiazole (NaST), and Mixtures of the Two Compounds.

Acute Toxicity.				
Drug, g per kg body wt				
Single intraperitoneal inj. of	Sulfonamide total amt	No. of animals	% death	Remarks
NaSD, 1.5	1.5	10	90	Died within 1 to 3 days
NaST, 1.1	1.1	15	67	" " 1 " 4 "
NaSD, 0.75 } NaST, 0.55 }	1.3	10	0	Mixture of ½ of each of above dosages. Complete recovery.

Chronic Toxicity.				
Drug, g per kg body wt				
*Daily intraperitoneal inj. of	Sulfonamide total amt daily	No. of animals	% death	Remarks
NaSD, 0.9	0.9	10	100	Died within 3 to 6 days
NaST, 0.9	0.9	10	100	" " 1 " 4 "
NaSD, 0.45 } NaST, 0.45 }	0.9	10	40	" " 3 " 7 "

* The animals were injected for a maximum of 6 consecutive days.

After the same interval, the urinary drug excretion per rat (mean of 10 animals) had reached 29 mg for sulfadiazine, 34 mg for sulfathiazole and *72 mg* for sulfadiazine-sulfathiazole. The strikingly high renal excretion of the mixture from blood levels distinctly lower than in the sulfadiazine group, suggested a diminution or even absence of renal obstruction in the animals receiving the sulfonamide combination. Further support for this viewpoint was derived from the marked difference in the nonprotein nitrogen values of the surviving rats 48 hours after the drug injection (mean values: sulfadiazine group 182 mg %, sulfathiazole group 120 mg %, sulfadiazine-sulfathiazole group *82 mg* %), and also from post-mortem examinations, especially of the urinary tract, which disclosed that the mixture animals showed little or no renal damage.

The *in vitro* antibacterial efficacy of solutions containing equal parts of sulfathiazole and sulfadiazine, as compared to those holding the same total concentrations of either drug alone, was tested thus far against strains of *Streptococcus hemolyticus, Staphylococcus aureus* and pneumococcus. Against the streptococcus the sulfadiazine-sulfathiazole combination was significantly more effective than either of the 2 drugs alone, whereas against the staphylococcus and pneumococcus, the mixture was more active than sulfadiazine but less active than sulfathiazole.

The results from the animal experiments and the *in vitro* studies suggest that the employment of combinations of sulfathiazole and sulfadiazine in human therapy (for instance, half the therapeutic dose of each), might considerably lessen the danger of concrement formation in the urinary tract, presumably to the extent as if only half the therapeutic dose of the one *or* the other of the 2 compounds had been administered. The *in vivo* bacteriostatic activity of the combination, however, will probably match the effectiveness of either sulfathiazole or sulfadiazine and might in some instances even surpass it. The clinical evaluation is under way. The merit of combining sulfadiazine and sulfathiazole in the treatment of pneumonia, for reasons of rapidly obtaining and maintaining satisfactory sulfonamide levels in the blood, has been demonstrated recently.[10]

The findings of the solubility study summarized in Table I indicate that many other sulfonamide combinations should be investigated as to their ratio of renal toxicity and bacteriostatic activity.

Summary. It was observed that N^1-hetero-

[10] Minetto, L. P., *New York State J. Med.*, 1944, **44**, 2022.

cyclic derivatives of sulfanilamide, even if closely related, are soluble in one and the same solution almost to the extent of their separate solubilities. Based on this observation, the toxicity and antibacterial activity of sulfadiazine-sulfathiazole mixtures was investigated. It was found that the acute and chronic toxicity of this drug combination for albino rats is strikingly low if compared with the effect of similar or identical total concentrations of either sulfathiazole or sulfadiazine alone. Evidence derived from chemical analyses and post-mortem examinations pointed to a diminution of intrarenal obstruction from drug precipitate as the chief reason for the low toxicity of the mixture. *In vitro* antibacterial studies showed that the effectiveness of the mixture corresponded largely to the total concentration of free sulfonamide. On the basis of these observations, the substitution at the bedside of sulfathiazole or sulfadiazine by combinations of these two compounds was suggested, because their application might decrease the danger of renal complications without interfering with the antibacterial efficacy. Clinical trials are in progress.

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Poliomyelitis Virus in the Blood Stream in the Experimental Disease.*

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Although most attempts to demonstrate poliomyelitis virus in the blood of experimentally-infected monkeys have been unsuccessful, four positive tests have been reported,[1,2,3,4] 3 of which were described more than 30 years ago. In all 4 instances the blood was drawn soon after the onset of paralysis. Furthermore the virus has long been sought in human blood but with the exception of a single instance, in spite of many trials,[5] such tests have been negative.[6]

The present data are placed on record to indicate some of the conditions under which poliomyelitis virus has been detected in the blood of monkeys during a recent series of experiments. In addition the virus has been looked for in the colon contents of many of these monkeys and the results of these tests are also presented.

Methods. Rhesus (*Macaca mulatta*) and capuchin (*Cebus capucina*) monkeys were used. The monkeys used as donors had been infected by the intracerebral, intracutaneous, and other routes. Three strains were used—all in their early passages. These strains originated in human stools of poliomyelitic patients from Texas (1942), Hartford (1942), and various sections of the country (1940-1941). The history of these strains in their early passages through monkeys has been described.[7]

Blood was collected from the heart and no attempt was made to prevent clotting. The whole blood was either stored on dry ice or it

* Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

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