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Prevention of Crystalluria During Sulfadiazine Therapy. Experimental and Clinical Studies.

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While with the increasing use of sulfadiazine the incidence of all toxic reactions has remained low, the seriousness of "renal irritation" has assumed greater importance ([1–7] and others). Most authorities agree that in the majority of, if not in all, instances this reaction is produced by the precipitation of sulfonamide compound in the kidneys and ureters. For this reason, it seemed important to make further studies of the solubilities of sulfadiazine and of acetyl sulfadiazine at varying pH levels, and to observe the effect of urinary pH on the incidence of crystalluria in patients receiving sulfadiazine.

Methods. An amount of sulfadiazine or acetyl sulfadiazine* in large excess of that to be dissolved was added to M/15 phosphate buffer solutions ranging in pH from 5.2 to 8.0. The mixtures were shaken for 18 hours in a water bath at 37°C, and filtered at the same temperature. The pH of the filtrate was measured immediately with a Beckman pH meter and appropriate temperature corrections were made. Similar solubility studies were made in M/10 citrate plus NaOH buffers, and in 2 concentrated, acid urines from normal subjects. These urines were divided in aliquots and adjusted in pH from 5.2 to 7.6 with small amounts of alkali. Free and acetylated sulfadiazine were measured according to Bratton and Marshall.[8]

First morning specimens of urine were collected on various services of the hospital from patients receiving sulfadiazine orally. The urines were kept at room temperature and examined within a few hours after they were voided. The urinary pH value was estimated with nitrazine paper, and the sediment after centrifugation was examined microscopically for the presence of crystals due to the drug.

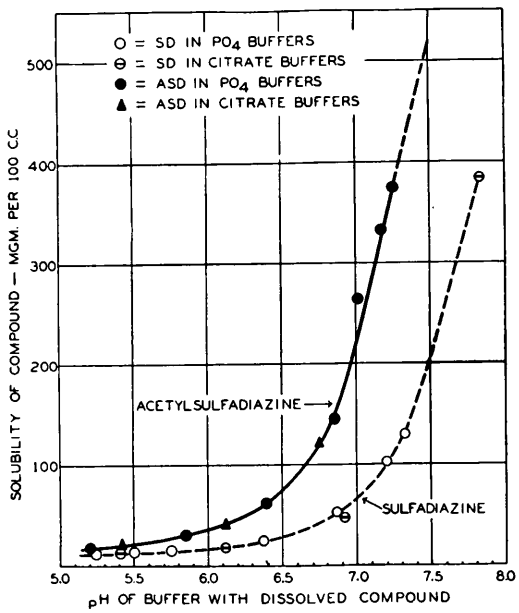

Fig. 1.

The curves of solubility of sulfadiazine and of acetyl sulfadiazine in phosphate and in citrate buffer solutions of varying pH's.

Results and Discussion. The solubilities of

1 Finland, Maxwell, Strauss, E., and Peterson, O. L., *J. A. M. A.*, 1941, **116**, 2641.

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5 Hellwig, C. A., and Reed, H. L., *J. A. M. A.*, 1942, **119**, 561.

6 Keitzer, W. A., and Campbell, J. A., *J. A. M. A.*, 1942, **119**, 701.

7 Plummer, Norman, and Wheeler, C., to be published.

* The sulfonamides were supplied by Lederle Laboratories, Inc.

8 Bratton, A. C., and Marshall, E. K., Jr., *J. Biol. Chem.*, 1939, **128**, 537.

sulfadiazine and of acetyl sulfadiazine increase markedly with rise in pH from 5.0 to 8.0. At a given pH the solubilities of these compounds are essentially the same in phosphate and citrate buffers (Fig. 1) and, under the express conditions of these experiments, in normal urine. Rose *et al.*[9] by varying the pH with addition of 0.1 N sodium hydroxide to the compounds dissolved in water have demonstrated also that the solubilities of sulfadiazine and acetyl sulfadiazine in water increase markedly between pH 5.5 and 7.5. Their experimental procedure yielded results somewhat different from ours, however. Urinary crystals and renal stones from patients receiving sulfadiazine orally appear from analysis to be chiefly acetyl sulfadiazine[3,6,10] and the solubility at varying pH's in phosphate buffers of the acetyl portion† of these urinary crystals is similar to that of pure acetyl sulfadiazine.[10] The large increase in solubility of acetyl sulfadiazine in buffers with increasing pH (Fig. 1) is to be contrasted with no change in solubility for acetyl sulfapyridine[9] and a comparatively small change for acetyl sulfathiazole[11] within the same pH range.

TABLE I.

Effect of Urinary pH on Incidence of Crystalluria from Sulfadiazine in 73 Patients Receiving 4-6 g of Sulfadiazine Orally per Day, with or without Varying Doses of Sodium Bicarbonate.

	Acid urines	Neutral or alkaline urines
No. of specimens	172	147*
No. of specimens with crystals	47	2
% of specimens with crystals	27	1.4

* 132 of these 147 urine specimens were from patients receiving alkali therapy.

Clinical studies which were suggested by the above solubility findings revealed the incidence of crystalluria following sulfadiazine therapy to be markedly higher in acid than in alkaline urines (Table I): 27% of 172 acid urines and only 1.4% of 147 neutral or alkaline urines. Factors other than pH which might affect the incidence of crystalluria—namely, the daily urinary volume, the specific gravity of the urine specimen examined, and the daily dose of sulfadiazine—were essentially the same in both groups. Nine patients who had had crystalluria in acid specimens no longer had crystals after sufficient sodium bicarbonate was administered to render the urine neutral or alkaline. In 2 patients showing crystals in acid urines, crystals were again found on the first morning the urine was rendered alkaline by alkali therapy, but were not present subsequently with a maintenance of alkaline urines. These 2 instances are the only ones in which we observed crystals in alkaline urine (Table I). It may be that these crystals were formed when the urine was acid and were being washed out of the urinary tract subsequently. Schwartz *et al.*[12] found an incidence of 25% crystalluria in 108 acid urines and 12% in 33 neutral or alkaline urines from patients receiving 4 g of sulfadiazine daily.

The dosage of sodium bicarbonate necessary to maintain the urine neutral or alkaline during sulfadiazine therapy is, of course, variable. With no alkali therapy, approximately 90% of the urine specimens are acid[12] (our data). Our experience to date, and the data of Schwartz *et al.*[12] indicate that less than 12 g daily of bicarbonate is usually insufficient. In a carefully controlled study of a group of 15 medical patients receiving an initial dose of 6 g of sodium bicarbonate followed by 19.5 g of the alkali daily, divided into 6 doses of 3.25 g (50 grains), all of the 44 urine specimens examined were pH 7.0 or over. In a similar study of 39 urines from 10 medical patients receiving an initial dose of 4 g of sodium bicarbonate followed by 13.7 g daily, divided into 6 doses of 2.3 g (35 grains), the urines were usually pH 7.0 or over but occasionally (6 specimens) were pH 6.3 to 6.8. No crystalluria was observed in either of these 2 groups. The alkali was well tolerated; none of the patients had gastrointestinal symptoms and there were no clinical evidences of alka-

[9] Rose, F. L., Martin, A. R., and Bevan, H. G. L., *J. Pharm. and Exp. Therap.*, 1943, **77**, 127.

[10] Unpublished data from this laboratory.

† The crystals studied yielded on analysis 93% acetyl sulfadiazine and 7% sulfadiazine.

[11] Climenko, D. R., Barlow, O. W., and Wright, A. W., *Arch. Path.*, 1941, **32**, 889.

[12] Schwartz, L., Flippin, H. F., Reinhold, J. G., and Domm, A. H., *J. A. M. A.*, 1941, **117**, 514.

losis. In some instances, such as in renal or cardiac insufficiency, sodium bicarbonate may be contraindicated. It must be emphasized that the purpose of this alkali therapy is to maintain the urine neutral or slightly alkaline, and not to produce alkalosis.

Conclusions. 1. The solubilities of sulfadiazine and particularly of acetyl sulfadiazine, in buffers and in normal urine, increase markedly with increasing pH within the physiological pH range of urine. 2. Examination of urine specimens from patients receiving sulfadiazine has demonstrated that crystalluria due to sulfadiazine can be prevented by maintaining the urine neutral or alkaline and the volume within limits generally considered optimum for patients with infection. 3. This study affords evidence that renal reactions due to the precipitation of sulfadiazine compounds can be prevented by appropriate alkali and fluid therapy. Our clinical findings to date accord with this assumption.

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Nutrition of the Golden Hamster.*

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Since several reports have indicated that the Golden or Syrian Hamster (*Cricetus auratus*) may be useful in studies involving human virus diseases,[1,2] we were interested in determining more specifically the nutritional requirements of this animal. It was immediately obvious that the hamster grew very poorly and failed to survive on synthetic diets which allow good growth and reproduction in the rat. The addition of liver extract did not improve the rate of growth appreciably and many animals failed on diets containing several natural products. The animals showed somewhat better growth when the synthetic diet was supplemented with whole liver substance or with preparations from grass.

We wish to report in this paper that one of the limiting factors in purified diets for the hamster is biotin and that when biotin is supplied in adequate amounts together with inositol and para-aminobenzoic acid excellent growth results. Under these conditions neither nicotinic acid nor vitamin C needs to be supplied in the diet.

Experimental. All the animals used were raised in our laboratory from a few stock animals originally obtained from Dr. A. F. Rasmussen, Department of Bacteriology. The stock ration was similar to that used for rats with additional greens and whole corn and wheat. The young were started on experiment at weaning when they weighed 25 to 35 g. The basal synthetic ration was similar to that used in our studies with rats and had the following composition: sucrose 72, casein 18, salts IV 5,[3†] corn oil 2, cod liver oil 2, and wheat germ oil 1. The ration was fed *ad libitum* and 1 drop of haliver oil was given to each animal every 2 weeks. All the vitamins were given in great excess in order to eliminate any possibility that the requirement of

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1 Lennette, E. H., PROC. SOC. EXP. BIOL. AND MED., 1941, **47**, 178.

2 Wheeler, A. H., and Nungester, W. J., *Science*, 1942, **96**, 92.

3 Phillips, P. H., and Hart, E. B., *J. Biol. Chem.*, 1935, **109**, 657.

† Salt mixture of Phillips and Hart modified by an addition of 5 g $MnSO_4$ per kilo.