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Comparative Solubilities of Sulfadiazine, Sulfamerizine and Sulfamethazine and Their N_4-Acetyl Derivatives at Varying pH Levels.

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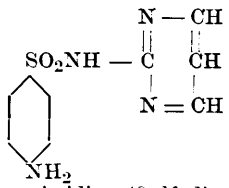
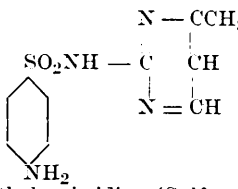
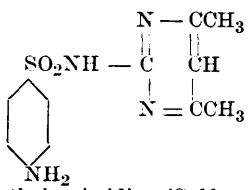
Monomethyl and dimethyl derivatives of sulfadiazine—namely, sulfamerizine and sulfamethazine—are currently receiving clinical trials.[1,2,3,4]



2-S*-pyrimidine (Sulfadiazine[6]†).



2-S-4-methylpyrimidine (Sulfamerizine[7]†).



2-S-4,6-dimethylpyrimidine (Sulfamethazine[8]†).

In vitro and *in vivo* studies have revealed that the bacteriostatic activities against several different organisms of these derivatives of sulfadiazine are quantitatively similar to those of sulfadiazine[6,9,10] and of sulfapyridine.[8]

It has been suggested that renal complications due to precipitation of the drugs or their acetyl derivatives‡ might be less frequent during therapy with sulfamerizine[3,4,7] and with sulfamethazine,[1,8] than with sulfadiazine. The different solubility characteristics of the three 2-sulfanilamidopyrimidine drugs and of their acetyl derivatives are therefore of particular interest. The solubilities of all of these compounds in buffer solutions of pH values within the physiological range of urinary pH are reported here; the findings for sulfadiazine and acetylsulfadiazine have also been presented elsewhere.[11]

Methods of Study. An excess of the compound§ to be dissolved was shaken in M/15 phosphate buffers and in M/10 citrate + NaOH buffers of various pH values for 18 hours in a water bath at 37°C and filtered in an incubator room at 37°C. The pH of the

1 Macartney, D. W., Smith, G. S., Luxton, R. W., Ramsay, W. A., and Goldman, J., *Lancet*, 1942, **1**, 639.

2 Jennings, P. A., and Patterson, W. H., *Lancet*, 1942, **2**, 308.

3 Goodwin, R. A., Jr., Peterson, O. L., and Finland, M., Proc. Soc. Exp. Biol. and Med., 1942, **51**, 262.

4 Murphy, F. D., Clark, J. K., and Flippin, H. F., *Am. J. Med. Sci.*, 1943, **205**, 717.

* S = Sulfanilamido; nomenclature by Crossley *et al.*[5]

† References to articles giving nomenclatures.

5 Crossley, M. L., Northey, E. H., and Hultquist, M. E., *J. Am. Chem. Soc.*, 1938, **60**, 2217.

6 Roblin, R. O., Jr., Williams, J. H., Winnek, P. S., and English, J. P., *J. Am. Chem. Soc.*, 1940, **62**, 2002.

7 Welch, A. D., Mattis, P. A., Latven, A. R., Benson, W. M., and Shiels, F. H., *J. Pharm. and Exp. Therap.*, 1943, **77**, 357.

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

9 Roblin, R. O., Jr., Winnek, P. S., and English, J. P., *J. Am. Chem. Soc.*, 1942, **64**, 567.

10 Bell, P. H., and Roblin, R. O., Jr., *J. Am. Chem. Soc.*, 1942, **64**, 2905.

‡ Throughout this report, "acetyl derivative" refers to the N_4-acetyl derivative.

11 Gilligan, D. R., Garb, S., and Plummer, N., Proc. Soc. Exp. Biol. and Med., 1943, **52**, 248.

§ The sulfonamide compounds were supplied by Lederle Laboratories, Inc.

filtrate was measured immediately at room temperature with a Beckman glass electrode pH meter and appropriate corrections for the differences between room temperature and 37°C were applied. The amounts of dissolved compounds were measured according to the method of Bratton and Marshall.[12] Studies of the amounts of the drugs and of their acetyl derivatives dissolved in M/15 PO_4 buffer of pH 6.98 after 18 and 42 hours of shaking at 37°C showed that saturation had been reached in 18 hours. The results were calculated in terms of molar concentrations and sulfadiazine equivalents in mg per 100 cc for the purpose of ease of comparison. (Fig. 1, 2).

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

Results. The solubilities of all of the compounds studied increase with increasing pH over the range of 5.0 to 8.0 (Fig. 1, 2). The solubilities in citrate buffers accord with those in phosphate buffers.

Both in terms of molar concentrations and weights of compounds dissolved per unit volume the acetyl derivatives of sulfadiazine and of sulfamethazine are more soluble than the parent drugs, respectively, throughout the range of urinary pH (Fig. 1,2). Similarly acetylsulfamerizine is more soluble than is sulfamerizine in terms of weight of compound dissolved; in terms of molar concentration, however, these two compounds have practically the same solubilities between pH 5.2 and 6.4 (Fig. 1, 2).

Sulfamethazine is the most soluble of the 3

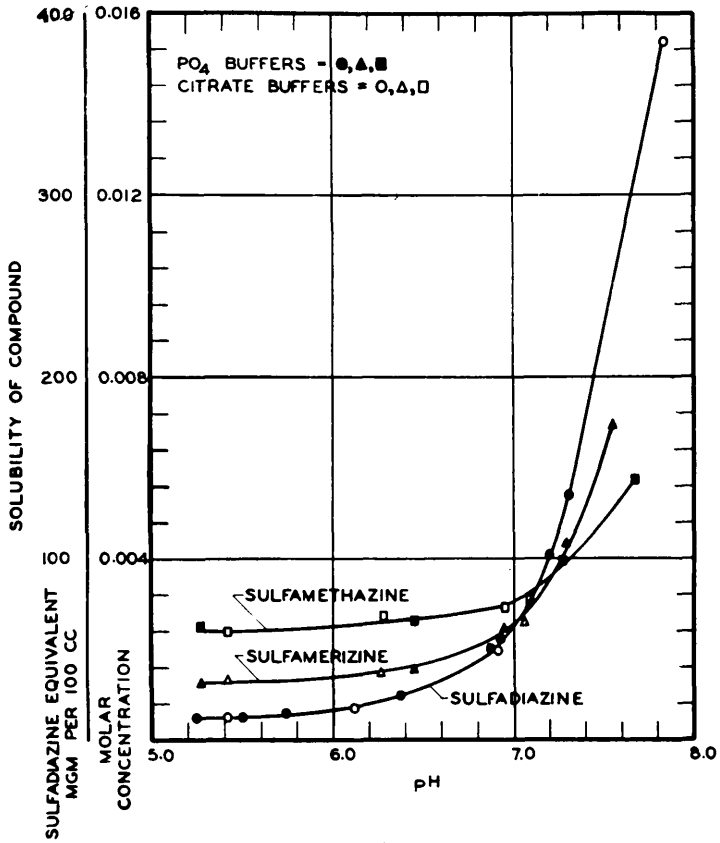


FIG. 1.
Curves of Solubility of Sulfadiazine, Sulfamerizine, and Sulfamethazine in Buffer Solutions.
The solid circles, triangles and squares represent measurements in phosphate buffers for sulfadiazine, sulfamerizine, and sulfamethazine, respectively. The open symbols represent measurements in citrate buffers.

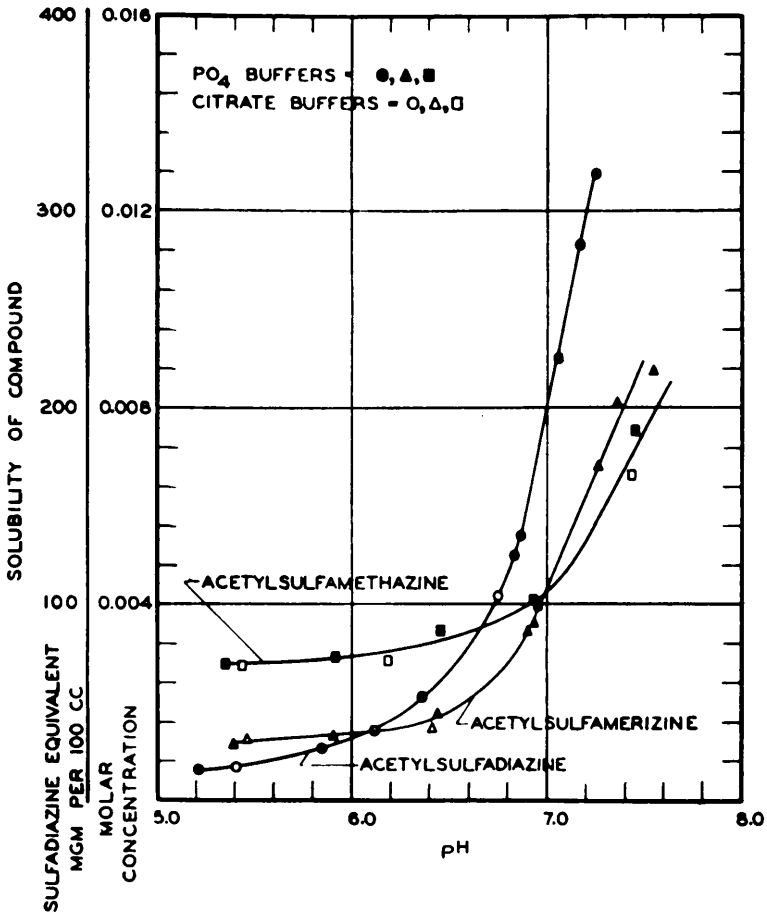


FIG. 2.
Curves of Solubility of Acetylsulfadiazine, Acetylsulfamerizine, and Acetylsulfamethazine in Buffer Solutions.
The solid circles, triangles and squares represent measurements in phosphate buffers for acetylsulfadiazine, acetylsulfamerizine, and acetylsulfamethazine, respectively. The open symbols represent measurements in citrate buffers.

drugs in the acid range of urinary pH, and sulfadiazine is the most soluble in the alkaline range (Fig. 1). Acetylsulfamethazine is more soluble than acetylsulfamerizine in the whole acid range of urinary pH and is more soluble than acetylsulfadiazine up to pH 6.65; acetylsulfadiazine is the most soluble of the 3 compounds in the alkaline range (Fig. 2).

Discussion. The data presented here accord in general with other recently published findings on the solubilities of some of these compounds in normal urine of varying pH,[7,13] or in H_2O plus varying amounts of NaOH.[1,8] It is to be noted that Rose *et al.*[8] and Macartney *et al.*[1] reported solubility data for "sulfamethazine hemihydrate," a meta-stable compound with lower melting point (178°-180°C) and much higher solubility[1,3] than those of sulfamethazine (Fig. 1). This "sulfamethazine hemihydrate" was the original sulfamethazine preparation produced by Imperial Chemical Ltd. (England), and which they subsequently have been unable to reproduce.[8] The sulfamethazine compound now produced

[13] Jensen, O. J., Jr., and Fox, C. L., Jr., *J. Urol.*, 1943, **49**, 334.

‖ This information was gained through a courteous personal communication, dated April 19, 1943, from Drs. H. R. Martin and F. L. Rose of Imperial Chemical, Ltd.

and distributed for clinical use[14] by them has the same melting point (197°-198°C) as that (198°-199°) produced for Lederle Laboratories, Inc., and used in our studies. We were able to study a sample of this later sulfamethazine product of Imperial Chemical Ltd., and found its solubility at varying pH levels to be the same as that of the sulfamethazine (Fig. 1) from Lederle Laboratories, Inc.

It was found recently that no crystalluria or renal complications occurred in a series of over 150 patients who had received sulfadiazine together with sufficient adjuvant alkali therapy to maintain the urine neutral or alkaline.[11,14] These clinical findings accord with the markedly increased solubilities of sulfadiazine and acetylsulfadiazine in alkaline solutions (Fig. 1, 2). Whether the incidence of renal complications from sulfamerizine or sulfamethazine will be sufficiently low to warrant the use of these drugs with no adjuvant alkali therapy awaits answer from further clinical trials. The daily amounts of the drug excreted in the urine on appropriate therapeutic doses, together with the extent to which the drug in the urine is acetylated, are factors of great importance. Since the urinary precipitates from all of the sulfonamide drugs are usually chiefly composed of the acetyl derivatives of the drugs,[14,15,16] it is of particular interest to note that the mean solubility of acetylsulfamerizine in the acid range of urinary pH is no greater than that of acetylsulfadiazine, whereas the mean solubility of acetylsulfamethazine in the acid range is considerably higher than that of acetylsulfadiazine (Fig. 2).

Summary. Comparative data are presented on the solubilities of sulfadiazine, sulfamerizine and sulfamethazine and their N_4-acetyl derivatives in buffer solutions at varying pH levels within the physiological range of urinary pH. The findings have been discussed briefly in reference to their possible bearing on renal complications from therapy with these drugs.

[14] Gilligan, D. R., Garb, S., Wheeler, C., and Plummer, N., *J. A. M. A.*, in press.

[15] Stewart, J. D., Rourke, G. M., and Allen, J. G., *J. A. M. A.*, 1938, **110**, 1885.

[16] Prien, E. L., and Frondel, C., *J. Urol.*, 1941, **46**, 748.

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Blood Lactic Acid in Liver Glycogen Disease.

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An increase in the amount of circulating lactic acid is generally attributed to anoxia.[1] This is the cause of the high values obtained during muscular work, in cardiac decompensation, anemia, pneumonia, and shock. The concentration of lactic acid in the blood can, however, be raised above the normal fasting level by the injection of epinephrine.[2] Cori[3] has demonstrated that in this case the lactic acid comes largely from the breakdown of muscle glycogen. This phenomenon is apparently not associated with anoxia.

We have recently had the opportunity to observe 2 infants with a singular disease, in which the high blood lactic acid would seem to be due to some other mechanism than that postulated. The disease in question, commonly known as hepatic glycogen disease or von Gierke's disease, is characterized by a defect in liver metabolism, in consequence of which the liver accumulates abnormally large stores of glycogen which it is unable to transform into glucose and excrete into the blood as a normal liver does during hypoglycemia.

[1] Jervell, O., *Acta Med. Skand.*, 1928, **24**, 1.

[2] Loeb, R. F., *J. Clin. Invest.*, 1931, **10**, 19.

[3] Cori, C. F., and Cori, G. T., *J. Biol. Chem.*, 1928, **79**, 309.