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.

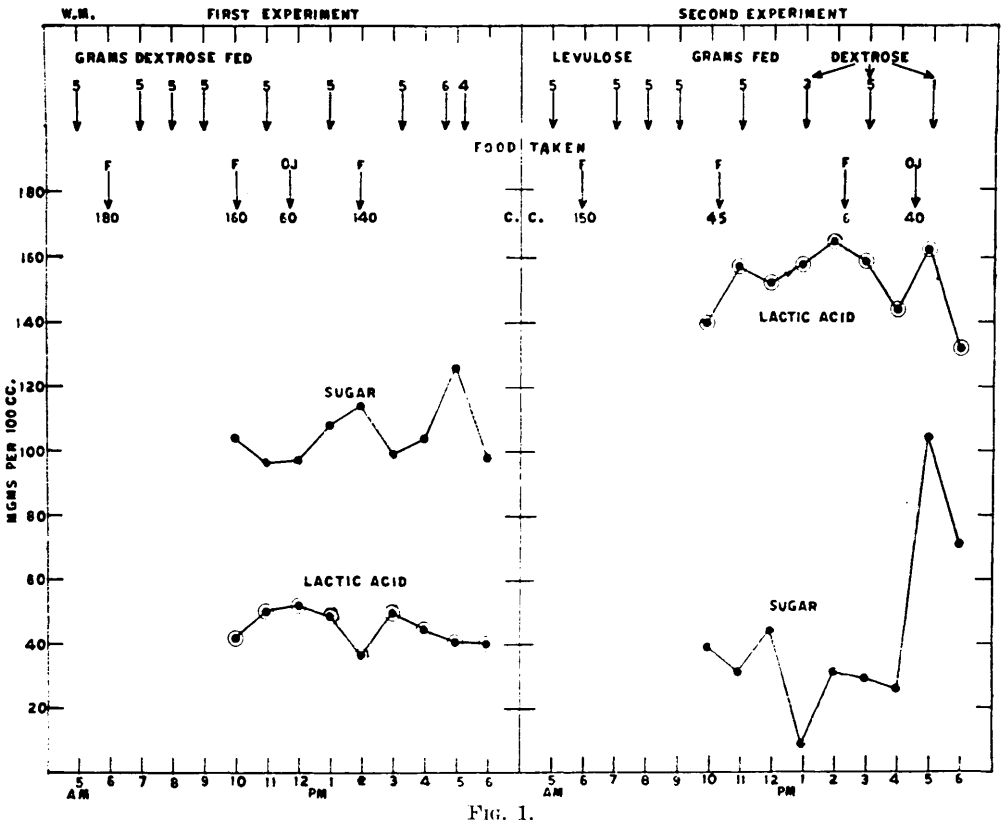

FIG. 1.

Blood sugar and lactic acid on 2 days. The blood lactic acid is nearly 3 times as high on the levulose day as on the glucose day. The feedings (F) were the same on both days. Each 100 cc contained soy bean flour 6 g, soy bean oil 3.2 g, glucose 1.8 g, sucrose 0.9 g, maltose 0.7 g, dextrine 1.2 g. Orange Juice (OJ) which contains 12% levulose, was fed on each day. On one day 5 g of glucose and on the other 5 g of levulose was offered each hour between the regular feedings. After 3 P.M. on the levulose day, glucose was fed because the infant refused the levulose and showed signs of hypoglycemic shock. This accounts for the sharp rise in blood sugar at the end of the observation.

The patients are female infants; one 6 months, the other 6½ months old. Both have very large livers. Neither shows any rise in blood sugar after the injection of epinephrine. Both tend to have very low blood sugar if not fed more frequently than a normal infant. Both have had convulsions due to hypoglycemia. Simultaneous determinations* of blood sugar and lactic acid have been made 110 times. An analysis of the correlation of these individual determinations shows no consistent relation between the height of the blood sugar and that of the lactic acid. When, however, these infants are fed soy bean mixture and corn syrup at the usual 4-hourly intervals and also given 30 to 50 cc of a 10% glucose solution every hour between feedings, the blood sugar stays at normal or slightly higher levels and the lactic acid remains at between 20 and 50 mg per 100 cc (Fig. 1). If levulose is substituted for glucose in the inter-

* All determinations were made on capillary blood. The skin was thoroughly washed with alcohol, then with ether. The first drop of blood was discarded. After precipitation of the proteins with tungstic acid,[4] sugar was determined on the filtrate by Benedict's[5] method and lactic acid by the method of Barker and Summerson.[6]

[4] Peters, J. P., and Van Slyke, D. D., *Quantitative Clinical Chemistry, II. Methods,* Baltimore, Williams and Wilkins Co., 1932, 461.

[5] Benedict, S. R., *J. Biol. Chem.*, 1931, **92**, 141.

[6] Barker, S. B., and Summerson, W. H., *J. Biol. Chem.*, 1941, **138**, 535.

vals between the regular feedings, the blood sugar remains much lower but the lactic acid reaches and maintains an abnormally high concentration.

In an individual with a normal liver both monosaccharides help to maintain the blood sugar at a normal level. In glycogen storage disease of the liver the two sugars behave differently. Absorbed levulose is quickly removed from the portal blood by the liver and stored there as glycogen or fat, but cannot be released later as glucose to sustain the falling blood sugar. Glucose, on the other hand, is removed with difficulty from the portal blood by the liver;[7] therefore, during the absorption of glucose the blood sugar rises to a high concentration and then falls rather rapidly, due to the removal of glucose from the blood by tissues other than the liver for combustion or storage. The only way to raise the low blood sugar in the postabsorptive state is to feed more glucose. This explains the hypoglycemia when the extra sugar fed is levulose and the normal or high blood sugar when the extra sugar is glucose. It does not explain the high blood lactic acid after the blood sugar has been low for some time, nor the much lower blood lactic acid after the blood sugar has been normal for a few hours.

Under the conditions of the test the lactic acid content of the blood is only slightly more than normal as long as the blood sugar is within the normal range, but increases several fold when the blood sugar is maintained at an abnormally low level. Neither patient shows any of the recognized causes of anoxia, nor any of the symptoms that characterize this condition, nor does either patient show any symptoms of hyperadrenalinemia.

The inference would appear to be that prolonged hypoglycemia causes the breakdown of liver glycogen in the cases reported as it does in the livers of normal individuals. However, in von Gierke's disease the liver is unable to dephosphorylate hexosemonophosphate and discharge glucose into the blood. Blocked at this point the breakdown takes the alternate route, namely, levulose-6-phosphate to levulosediphosphate, etc.[8] In this case one of the end products would be lactic acid.

[7] Mason, H. H., and Andersen, D. H., *Am. J. Dis. Child.*, 1941, **61**, 795.

[8] Cori, C. F., *Biol. Symposia*, 1941, **5**, 131.

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Effect of *p*-Aminobenzoate and Methyl *m*-Amino-*p*-hydroxybenzoate on Acute Toxicity of *m*-Amino-*p*-hydroxyphenylarsenoxide in Mice.

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p-Aminobenzoic acid (PAB) has been shown by Sandground[1] to antagonize the single-dose fatal toxicity of a number of pentavalent organic arsenicals in rats. That this antagonism was probably not due alone to phenomena dependent on close structural similarity was indicated by the fact that acetarsone (sodium *m*-acetylamino-*p*-hydroxyphenylarsonate) was one of the arsenicals antagonized. More recently, and coincidental with the completion of the work reported here, Sandground[2] reported success in antagonizing the toxicity of "at least one of the trivalent arsenical antisyphilis drugs" with PAB; the identity of the compound was not disclosed, however.

The toxic signs observed by Sandground, and which were attributable to the pentavalent arsonic acids antagonized by PAB, were of the neurotropic type characteristic of this class of compounds. Since it is clear that some

[1] Sandground, J. H., *Science*, 1943, **97**, 73.

[2] Sandground, J. H., PROC. SOC. EXP. BIOL. AND MED., 1943, **52**, 188.