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# Evaluation of Acetylation of Sulfanilamide as a Test of Liver Function.*

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In a study of the excretion of sulfanilamide by the digestive glands the possibility was considered that a test of liver function might be evolved.[1]

It is a known fact that in certain animals, including man, the body detoxicates aromatic amines by means of acetylation. This is the mechanism employed in the case of sulfanilamide.[2-7] This process has been studied extensively by investigators using p-aminobenzoic acid and sulfanilamide, and evidence presented would indicate that the liver is the sole organ in which this chemical change takes place.[3, 8]

As sulfanilamide in the urine is excreted in a state of only partial acetylation in man,[9] it was thought that varying percentages in the amount of the acetylated drug might reflect the state of liver function.

In accordance with this idea, small amounts of sulfanilamide were given to normal subjects and to subjects known by accepted tests of liver function and by other means such as peritoneoscopy and surgical exploration to have hepatic disease. In some cases the diagnosis of hepatic disease was confirmed later at necropsy. The amounts of sulfanilamide were considered to be sufficiently small not to cause any injurious results in the subjects tested. Urine was collected for 24 hours following the administration of the drug. Samples from this urine

* This work was started in the Northwestern University Medical School laboratories of Dr. A. C. Ivy. It was completed in the clinical pathology laboratories of the Mayo Clinic.

1 Carryer, H. M., and Ivy, A. C., *J. Pharm. and Exp. Therap.*, 1939, **66**, 302.

2 Ellinger, Alexander, and Hensel, Marie, *Z. f. physiol. Chem.*, 1914, **91**, 21.

3 Ambrose, A. M., and Sherwin, C. P., *Ann. Rev. Biochem.*, 1933, **2**, 377.

4 Sherwin, C. P., *Physiol. Rev.*, 1922, **2**, 238.

5 Muenzen, J. B., Cereedo, L. R., and Sherwin, C. P., *J. Biol. Chem.*, 1926, **67**, 469.

6 Harrow, Benjamin, and Sherwin, C. P., *Ann. Rev. Chem.*, 1935, **4**, 263.

7 Harrow, Benjamin, Power, F. W., and Sherwin, C. P., PROC. SOC. EXP. BIOL. AND MED., 1927, **24**, 422.

8 Harris, J. S., and Klein, J. R., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 78.

9 Marshall, E. K., Jr., Cutting, W. C., and Emerson, Kendall, Jr., *Science*, 1937, **85**, 202.

were analyzed for their percentage content of acetylated and non-acetylated sulfanilamide by the method of Marshall and his associates.[10, 11] Portions of urine were hydrolyzed and analyzed in duplicate.

Nineteen healthy subjects were given from 5 to 30 grains (0.3 to 2 g) of sulfanilamide. The drug was given from one to 6 times to the various subjects. Analysis of the following 24-hour specimen of urine revealed that from 40 to 59% of the drug was acetylated, the average being 48%. Sixteen patients, 15 of whom had an elevated concentration of serum bilirubin with a direct van den Bergh reaction resulting from portal cirrhosis, disease of the biliary tract or carcinoma of the pancreas, were given 15 grains (1 g) of the drug. In these patients from 21 to 61% of the drug was acetylated. The data obtained did not correlate with the severity of the disease as indicated by the serum bilirubin, bromsulfalein elimination, prothrombin time and hippuric acid elimination tests. Five other patients, who did not have jaundice but did have cardiac cirrhosis of the liver (one patient), carcinomatosis (2 patients) or severe thyrotoxicosis (2 patients), were given 15 grains (1 g) of the drug. These patients acetylated normal amounts of the drug.

It was evident that the proposed test did not have any definitely apparent value in the determination of liver function or in the detection of hepatic disease. A possible explanation for the failure of this test may be found in the fact that ingestion of relatively small amounts of several substances will increase acetylation in the liver greatly. These substances include many of the amino acids, ethyl ester of diacetic acid, sodium acetate, beta-oxybutyric acid, pyruvic acid, glyceric aldehyde, glycerol, acetic aldehyde, and other compounds. It is probable that the metabolism of many of these is changed greatly with advanced liver disease.

Also, it has been shown recently that the body can deacetylate certain compounds.[12]

*Summary.* The extent to which sulfanilamide is acetylated by the liver was found not to be of any definite value as a test of liver function.

[10] Marshall, E. K., Jr., Cutting, W. C., and Emerson, Kendall, Jr., *J. A. M. A.*, 1938, **110**, 252.

[11] Marshall, E. K., Jr., and Litchfield, J. T., Jr., *Science*, 1938, **88**, 85.

[12] Henderson, E., (Schering Corporation), personal communication to Northey, E. H.; *Chem. Rev.*, 1940, **27**, 85.