BINDING OF SULFONAMIDES BY PLASMA PROTEINS

CEREBROSPINAL fluid concentrations of sulfathiazole which occur during treatment of meningitis do not generally exceed 25 per cent. of the plasma concentrations; values for sulfanilamide in the cerebrospinal fluid may reach 100 per cent. of the plasma concentrations, whereas the values for sulfapyridine and sulfadiazine are intermediate. These differences in concentration have been ascribed to differences in the diffusibility of the drugs into the spinal fluid. An alternative explanation would be the existence of part of the drug in combination with plasma protein. Schonholzer[1] has demonstrated binding of the azo-dye of sulfanilamide, Prontosil, to serum albumin in electrophoresis experiments, but this technique does not furnish quantitative data for partial binding. The experiments reported in the present paper support the view that the sulfonamide drugs are bound to plasma proteins in varying proportions, the relative concentration of drug attained in the spinal fluid depending upon the extent to which the drug is bound in the blood.

Normal human plasma was dialyzed in Cellophane bags against 0.15 N. NaCl, buffered at pH 7.4 by the addition of 0.01 M. phosphate, with varying additions of a sulfonamide. At equilibrium the drug concentration was found to be higher in the plasma than in the buffer. While this distribution coefficient is not direct evidence of binding to protein, the data fit the Freundlich adsorption isotherm, as is the case with phenol red,[2] for which direct evidence of chemical binding has been furnished by absorption spectrophotometry.[3] Whether the phenomenon be due to adsorption, coordination, or simply depression of the activity coefficient by the protein is of less biological than chemical interest, for in any case, it is the value of the distribution coefficient which determines the distribution in the body. The binding (using the term in a very general sense) is due to albumin but not to globulin; lipid-free plasma behaves similarly. In normal plasma containing 7 per cent. protein, with drug concentrations of 10 mg per cent., the proportion of "free" (unacetylated) drug which is bound to protein is as follows:

Sulfanilamide	20 per cent.
Sulfapyridine	40 per cent.
Sulfadiazine	55 per cent.
Sulfathiazole	75 per cent.

These data can explain the observed distribution in body fluids and the greater solubility in plasma than in saline.

[1] G. Schonholzer, *Klin. Wchnschr.*, 19: 790, 1940.
[2] A. Grollman, *Jour. Biol. Chem.*, 64: 141, 1925.
[3] H. W. Robinson and C. G. Hogden, *Jour. Biol. Chem.*, 137: 239, 1941.

Preliminary bacteriostatic experiments were carried out with *B. coli* in a synthetic medium, with and without added albumin.[4] The results suggest that the concentration of unbound drug determines the level of bacteriostatic activity, the bound drug being apparently inactive. It was also noted that the order of increasing tendency to be bound to plasma albumin was identical with the order of increasing bacteriostatic effectiveness for the four sulfonamides studied.[5] This latter relationship may be of theoretical significance and is being studied further.

It has been demonstrated that the sulfonamide drugs behave as though bound in varying degree to plasma albumin or some fraction thereof, and it appears that the bound drug is not bacteriostatically effective. The effective level of the sulfonamides in the cerebrospinal fluid may therefore be as great as that in the blood stream, and the apparent level compared with the blood should not be used as a guide to the choice of a drug. Inasmuch as excellent therapeutic results have been reported with the use of sulfathiazole in meningococcic meningitis[6] it may be preferable to the more toxic sulfanilamide and sulfapyridine, which have often been favored because of the higher concentrations attained in the cerebrospinal fluid.

BERNARD D. DAVIS
CHEMICAL DIVISION, DEPARTMENT OF MEDICINE,
THE JOHNS HOPKINS HOSPITAL

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[5] (a) W. B. Wood, personal communication. (b) H. J. White, T. T. Litchfield, Jr., and E. K. Marshall, Jr., *Jour. Pharm. and Exp. Therap.*, 73: 104, 1941.
[6] (a) M. Finland and J. H. Dingle, *New Eng. Jour. Med.*, 225: 825, 1941. (b) H. S. Banks, *Lancet*, 1: 104, 1941.

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