References and Notes

1. H. G. Beeken and F. L. Dunn, *IRE Trans. on Med. Electronics* **PGME-12,** 53 (1958); H. Fischler, B. Blum, E. H. Frei, M. Streifler, *Bull. Research Council Israel* **E8,** 101 (1960).
2. D. E. Thomas and J. M. Klein, *Electronics World* **63,** 42 (1960).
3. S. Darlington, U.S. patent No. 2,663,806.

4. This investigation was supported by a research grant (No. B-2704) from the National Institute of Neurological Diseases and Blindness.

10 July 1961

Passage of Saccharides from Cerebrospinal Fluid to Blood

Abstract. Saccharides with a molecular weight ranging from 182 to 50,000, which enter the cerebrospinal fluid at extremely slow rates when administered intravenously, all pass readily at similar rates from cerebrospinal fluid to blood after injection into a lateral cerebral ventricle. The mechanism of transfer appears to be a filtration of cerebrospinal fluid across a sieve-like boundary possibly located at the arachnoid villi.

There is considerable evidence that drugs and other foreign organic compounds diffuse from plasma into cerebrospinal fluid at rates dependent on their lipid solubility. For example, organic acids and bases in general enter cerebrospinal fluid mainly in their undissociated form at rates roughly parallel to the lipid-water partition coefficients of these drug forms. Moreover lipid-insoluble organic ions such as quaternary ammonium compounds and sulfonic acids, as well as lipid-insoluble molecules such as sulfaguanidine and sucrose, penetrate into cerebrospinal fluid at very slow rates (*1*). In contrast, the transfer of drugs in the reverse direction—that is, from cerebrospinal fluid to plasma—does not appear to be highly dependent on lipid solubility. For example, Mayer *et al.* (*2*) have shown that, after intracisternal injection, compounds with low lipid solubilities leave the cerebrospinal fluid almost as rapidly as those with high lipid solubilities. Thus, drugs may pass from blood to cerebrospinal fluid by diffusion across a lipid-like boundary, but they appear to pass from cerebrospinal fluid to blood mainly in a different way.

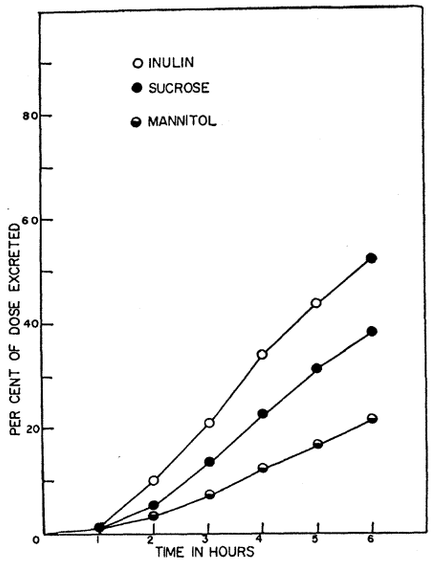

Fig. 1. Rates of appearance in urine of substances injected into a lateral cerebral ventricle of anesthetized rabbits. Each point represents the mean value for five animals. The standard errors for the points ranged from ± 1 to ± 3. The doses of the C^{14}-labeled substances in (mg/kg) were as follows: inulin, 0.15; sucrose, 0.20; mannitol, 0.05. The total radioactivity administered was 1 to 2 μc.

The investigation reported here is an attempt to describe the nature of the boundary across which substances pass from the cerebrospinal fluid into the blood stream. Lipid-insoluble foreign substances were investigated, since they would be unable to leave the cerebrospinal fluid by way of the lipid-like barrier between it and blood.

Five microliters of a solution of inulin-carboxyl-C^{14}, sucrose-C^{14}, or mannitol-1,6-C^{14} was injected into a lateral cerebral ventricle of male albino rabbits (2.1 to 2.3 kg) anesthetized with ether. Injections were made with the aid of a stereotaxic instrument which held the injection needle firmly in place throughout the experimental period, thereby preventing leakage of cerebrospinal fluid through the puncture. After the injection, the compounds moved rapidly toward the subarachnoid space, appearing in the cisterna magna within 5 minutes. Direct evidence that the compounds readily left the cerebrospinal fluid was provided by their detection in urine. The relative rates at which the compounds appeared in urine are shown in Fig. 1; 52 percent of the injected dose of inulin, 38 percent of the sucrose, and 23 percent of the mannitol were excreted in 6 hours.

To ascertain whether the appearance of the substances in urine was a measure of the rates of exit from the cerebrospinal fluid, the rates of urinary excretion of the substances were compared after a single intravenous injection in groups of three animals. Most of the inulin (92 to 95 percent) was excreted in 6 hours; sucrose was excreted to the extent of 82 to 94 percent, and mannitol, to the extent of only 76 to 82 percent. Little or no additional mannitol was recovered between the 6th and 7th hours after injection, suggesting that the compound may be metabolized or localized in the body. In any case, the incomplete recovery in urine of intravenously injected sucrose and mannitol suggests that these compounds had left the cerebrospinal fluid more rapidly than was apparent on the basis of their appearance in urine.

Evidence that sucrose, mannitol, and inulin leave the cerebrospinal fluid at similar rates was obtained on comparing the decline in concentration of the three saccharides in the fluid. The concentrations in cisternal cerebrospinal fluid 6 hours after intraventricular injection, expressed as a percentage of the dose in 1 ml of cerebrospinal fluid, were as follows: inulin, 10.1 (S.E., ± 0.6 in nine animals); sucrose, 10.2 (S.E., ± 1.0 in five animals); and mannitol, 8.1 (S.E., ± 0.4 in six animals). Preliminary experiments with dextran-carboxyl-C^{14} (molecular weight, 40,000 to 50,000) indicate that these large molecules pass from cerebrospinal fluid to blood at a rate almost the same as that of the other saccharides studied.

There is considerable evidence that cerebrospinal fluid flows from the cerebral ventricles toward the subarachnoid space and then filters across the arachnoid villi into the dural venous sinuses (*3*). This process of filtration or "bulk flow" into the blood stream would explain the essentially one-way transfer of lipid-insoluble molecules observed in the investigation reported here.

The results of this study suggest that drugs in general may pass from cerebrospinal fluid to plasma at similar rates by a nonspecific process of filtration across a porous boundary.

LEON D. PROCKOP
LEWIS S. SCHANKER
BERNARD B. BRODIE

Laboratory of Chemical Pharmacology, National Heart Institute, Bethesda, Maryland

References

1. H. Davson, *Physiology of the Ocular and Cerebrospinal Fluids* (Little, Brown, Boston, 1956); D. P. Rall, J. R. Stabenau, C. G. Zubrod, *J. Pharmacol. Exptl. Therap.* **125,** 185 (1959); S. Mayer, R. P. Maickel, B. B. Brodie, *ibid.* **127,** 205 (1959); B. B. Brodie, H. Kurz, L. S. Schanker, *ibid.* **130,** 20 (1960).
2. S. E. Mayer, R. P. Maickel, B. B. Brodie, *J. Pharmacol. Exptl. Therap.* **128,** 41 (1960).
3. H. Davson, *Handbook of Physiology, Section 1: Neurophysiology* (American Physiological Society, Washington, D.C., 1960), vol. 3.

3 July 1961