Hydrocephalus: Changes in Formation and Absorption of Cerebrospinal Fluid Within the Cerebral Ventricles*

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This paper presents a study designed to measure accurately the changes that occur in the formation and absorption of cerebrospinal fluid within the cerebral ventricles during the development of hydrocephalus. The results of these experiments are considered in relation to the evaluation of the hydrocephalic patient.

A hydrocephalic infant on ventricular drainage will produce several hundred cc. of cerebrospinal fluid per day, but the ventricular rate of growth in rapidly progressing hydrocephalus is only of the order of 10 to 15 cc. a day, only a small fraction of the amount of fluid being formed. Clearly, therefore, there must be intraventricular absorption of fluid. Attempts have been made to measure absorption of cerebrospinal fluid for the evaluation of hydrocephalus by measuring the disappearance of tracers from the fluid, but this method has been shown to be wrong fundamentally. The data required to evaluate the outflow of cerebrospinal fluid or absorptive mechanism must include information about the rate of formation of the bulk of the fluid and how it can change. What is the maximum production of cerebrospinal fluid that the system of outflow must handle? There also must be information about the resistance to outflow of the bulk of cerebrospinal fluid (or absorption) and the total absorptive capacity. With these data an accurate assessment can be made of the absorptive mechanism and its ability to handle the cerebrospinal fluid produced.

Recently, methods have been developed for measuring accurately the formation and absorption of cerebrospinal fluid. These have been applied to a large group of normal dogs and dogs with acute and chronic progressive hydrocephalus. This provided data about the physiology of cerebrospinal fluid, and an opportunity to test this type of data for the evaluation of hydrocephalus.

Material and Methods

These studies were done on male mongrel dogs weighing 12 to 17 kg. anesthetized with intravenous pentobarbital. The animals were prone with the head slightly elevated so that the external auditory meatus was 20 cm. above the top of the table. All procedures were carried out aseptically.

The experimental data were obtained from perfusion of the ventricular system with artificial cerebrospinal fluid by the method described in detail by Pappenheimer et al. but with some modifications to adapt it to dogs. Ventricular punctures were made percutaneously through needle guides imbedded previously in the skull and the scalp was closed over them. Cisternal punctures were made percutaneously through the foramen magnum. The rates of perfusion were in the range of 0.23 to 0.33 ml./min., but constant for any one experiment to ± 0.002 ml./min. Intraventricular pressure was measured continuously at the inflow needle with a Statham strain gauge feeding into a Grass polygraph. Other physiological events (electrocardiograms, electroencephalograms and arterial and venous blood pressures) also were monitored on the polygraph. The system was tested for leaks at the time of sacrifice by perfusion with a mixture of 10 per cent formalin, isotonic saline and methylene blue. Then the calvarium was removed and the brain was inspected for leaks or the animal was decapitated and the head was frozen and cut in the frozen state. The presence of dye outside the desired area was considered to constitute a leak and the

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experiment was discarded. Other animals were sacrificed with intravenous Nembutal, and the brain was removed and fixed in formalin or other appropriate fixatives for anatomical studies.

The perfusive fluid was made up to the average composition of cerebrospinal fluid of the dog found in this laboratory and adjusted for pH and content of CO\textsubscript{2} as described. Various tracers were added in small amounts which did not affect its osmotic concentration.

Determinations of creatinine were done by the alkaline picrate method; inulin by the resorcinol method; albumin tagged with T\textsuperscript{38} (RISA) was counted in a well-scintillation counter; and the C\textsuperscript{14} urea was counted in a liquid-scintillation or a continuous gas-flow counter. The rates of inflow and outflow were measured gravimetrically to ±.002 gm. and ±.00002 gm. per min.

The interpretation of the results of these experiments involved small difference between relatively large quantities so that accuracy of all measurements was extremely important and considerable effort was made to reduce all errors to less than 2 per cent both by attention to technique and by multiple determinations.

The notation to be used in the description of the results will follow that used by Heisey \textit{et al.}\textsuperscript{11}

\[ \dot{V} = \text{rate of flow mL./min.} \]
\[ i, o, p = \text{subscripts referring to inflow, outflow, and plasma respectively.} \]
\[ f, a = \text{subscripts referring to formation and bulk absorption of fluid.} \]
\[ c = \text{concentration of quantity/mL.} \]
\[ \bar{c} = \text{mean concentration in ventricular system = c}_{0} + 0.37 (c_{1} - c_{0}) \]
\[ h_{x} = \text{steady-state transport of any substance} \]
\[ x = \text{from the perfusion of cerebrospinal fluid to the blood =} \]
\[ V_{c} \dot{c}_{1} - V_{c} \dot{c}_{0} \]
\[ C_{x} = \text{steady-state clearance of x =} h_{x}/\bar{c}. \]
\[ C_{o} \bar{c}_{0} \]
\[ C_{0} \bar{c}_{0} \]
\[ C_{1} = \text{can be used as well as the} \]

This gives a slightly higher figure and is correct for the subarachnoid space.

Four types of perfusion were done in the normal dogs: subarachnoid-cisternal perfusion, ventriculocisternal perfusion, ventriculo-aqueduct perfusion, and lateral ventricle-lateral ventricle perfusion with the aqueduct of Sylvius blocked.

There were three groups of perfusions in hydrocephalic dogs. Lateral ventricle-4th ventricle and lateral ventricle-lateral ventricle perfusions in dogs made hydrocephalic by cisternal kaolin, and lateral-ventricle to lateral-ventricle perfusion in dogs made hydrocephalic by plugging the aqueduct of Sylvius.

During perfusion, the pressure of perfusion was regulated by the height of the outflow, where a proportional drop counter recorded the outflow. Perfusion was carried on at any one pressure for 45 min., then 15-min. samples were taken until two successive samples had rates of inflow and outflow constant within 2 per cent. When the tracers were first added the 45-min. period was broken up into three 15-min. intervals so that the volume of distribution could be calculated. Several pressures were used in any one experiment, usually at increments of 100 mm. H\textsubscript{2}O. The resistance of the inflow needle was determined separately for each experiment and the appropriate correction in pressure was made.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Substance & Volume of Distribution & Calculation Formula \\
\hline
Inulin & VIT & \[ V_{IT} = \frac{\Sigma_{1}^{n} [\dot{V}_{1}c_{1} - \dot{V}_{o}c_{o(t)} - C_{x} \bar{c}_{o(t)}] \Delta t}{\dot{c}} \] \\
\hline
\end{tabular}
\end{table}

where:

\( V_{IT} = \text{volume of distribution of the test substance x.} \)
\( n = \text{number of samples.} \)
\( i, o = \text{subscripts referring to inflow and outflow.} \)
\( c_{o(t)}, \bar{c}_{o(t)} = \text{the concentrations at time t.} \)
\( C_{x} = \text{steady-state concentration of outflow.} \)
\( VIT = \text{volume of inflow tubes.} \)
\( VOT = \text{volume of outflow tubes.} \)
\( C_{x} = \text{the steady-state flux or clearance in mL./min. of x out of the ventricular system per unit concentration =} \)
\( \left( V_{cc} - V_{o}c_{o} \right)/\dot{c} \)

In the normal dog, the volume of distribution of subarachnoid (parietal)-cisterna magna perfusion was 7.9 ml. for creatinine and 5.8 ml. for inulin. The mean volumes of distribution found in ventriculocisternal