EVALUATION of the pathophysiology involved in the alteration of cerebrospinal fluid dynamics resulting in hydrocephalus has vexed observers for many years. More adequate means of investigation have been needed by the neurosurgeon, in particular, who must decide the feasibility of surgical intervention in each case encountered. Recognition of the effects of the disease presents no unusual problems. Marked ventricular dilatation and, in the infant, an enlarging head are common clinical entities. The problem arises in determining the activity of the disease. If active hydrocephalus is present, a shunting procedure may arrest destruction of the brain and result in actual regression of ventricular size. If the hydrocephalus is already arrested or compensated, surgical intervention may be contraindicated.

The dynamic nature of hydrocephalus requires serial contrast studies of the ventricles if anatomic indices of progression are to be used. The need for a test that would directly assess dynamics in hydrocephalus was appreciated by Dandy in 1914 when he studied the ventricular clearance of phenolsulfophthalein and its subsequent appearance in the urine of hydrocephalics. The advent of radioisotope techniques has permitted the study of the constituents of cerebrospinal fluid with increased precision. The interpretation of data obtained from the appearance or disappearance of an isotope in a particular compartment of fluid requires caution, however. The possibility of confusing permeability and active transport has been well stated by Selverstone.

The choice of radioactive iodinated serum albumin (RISA) as the tracer for study of cerebrospinal fluid dynamics is reasonable since albumin is a naturally occurring component of the biological system under study, and not a substance completely foreign to the system. Significant work on the dynamics of the cerebrospinal fluid system using RISA as the tracer has already been done involving clearance of RISA from cerebrospinal fluid, brain, blood and body depots with the tracer injected into the ventricles as well as the blood stream.

If we neglect the relationships between ependyma, neurones, glia, interstitial fluid and the physiologic significance of the various iodinated albumins (human, bovine, feline), our concept of RISA exchange can be diagrammed as in Fig. 1. The parameters used are in part the result of work by others and can be explained by reviewing the pathways designated by capital letters as follows:

A. Sweet and his co-workers found that the disappearance half-time of RISA placed in the ventricular system was about 2 hours in the normal human. This time was more than doubled in a patient with hydrocephalus.

B. The time required for equilibration of RISA from blood to cerebrospinal fluid was studied by Fishman and from cerebrospinal fluid to blood by van Wart. Both of these studies were carried out in laboratory animals and both showed an equilibration time of 16 to 20 hours.

C. Lee and Olszewski studied the uptake of radioiodinated bovine albumin from the
cerebrospinal fluid into the brain using radioautographs. They found the uptake of isotope by deeper structures most intense at 3 hours. There was decreased activity through the whole brain at 16 hours, and clearing occurred by 24 hours. They postulated entry of the tracer into the brain until the concentration in the cerebrospinal fluid was the same as that in the brain.

D. Storassli et al. studied the disappearance of RISA from the blood in humans. The concentration in blood decreased 10 per cent in 1 hour.

E. Storassli et al. also found the rate of urinary excretion was 8 to 12 per cent in 24 hours.

If RISA placed in the cerebrospinal fluid rapidly enters the brain, reaching equilibrium in about 3 hours, and the combined cerebrospinal fluid-brain compartment then reaches equilibrium with the blood about 20 hours following injection of RISA, the concentration of RISA in cerebrospinal fluid would decrease at a decreasing rate consistent with the data. Inherent in this model is the concept that the passage of RISA into the brain is more rapid than the passage of RISA into the blood from either cerebrospinal fluid or brain.

The present study was designed to provide information regarding the activity of the hydrocephalic process in patients being considered for various shunting procedures. Some limitations were imposed to keep the test simple enough to be of routine value in the hospital situation. The test measures the disappearance of RISA (radioiodinated human serum albumin) from the lateral ventricles and, in some cases, the appearance of the tracer in the blood.

MATERIALS AND METHODS

Studies were carried out in 22 patients ranging in age from 4½ months to 60 years. Of these studies, 21 evaluated transfer of RISA from ventricular cerebrospinal fluid into blood and 2 evaluated transfer from blood to cerebrospinal fluid. Lumbar and ventricular cerebrospinal fluid was studied in 3 patients. All patients studied had proven hydrocephalus (obstructed or communicating type) or were presumed to have hydrocephalus. None had neoplasm of the brain or meninges. Eleven had had ventriculo-atrial shunts (Pudenz-Heyer valves) placed from 3 years to 2 months prior to the study.

Following ventricular puncture through a twist-drill hole, 5 microcuries of RISA (0.1–0.2 ml. volume) were injected into the lateral ventricle. Samples of blood were taken at 5 minutes, 10 minutes, 1 hour, 4 hours, 12 hours and 24 hours. Samples of ventricular cerebrospinal fluid (1 ml.) were taken at 1 hour, 4 hours, and 24 hours. Samples of blood and cerebrospinal fluid were placed in sealed, previously weighed tubes. The tubes were weighed again to determine the amount of the sample to 1 per cent by weight. No correction was made for specific gravity in the conversion from weight to volume (approximate error less than 1 per cent). The samples were counted in a Picker model 2304 well-counter utilizing a thallium-activated sodium-iodide crystal. Corrections were made for isotope decay and background activity. No corrections were made from dependency of counting rate on sample volume since the count for a given amount of I131 varied only 2 per cent when the sample volume varied from 1 to 4 ml. Samples with counting rates less than twice the background rate were rejected.

The 1-hour sample proved to be an unreliable index of activity of transfer, possibly because of marked variation in volume of ventricular cerebrospinal fluid. The approximate mean activity of the 1-hour ventricular
cerebrospinal fluid samples was 10,000 cpm/ml. This is roughly the activity expected by dilution of the RISA sample in 500 ml.

In each study the specific activity of the 4- and 24-hour samples was determined and then expressed with respect to the 1-hour samples, i.e. $x = cpm/ml$. 4 or 24 hours/ cpm/ml. 1 hour. The mean and standard deviations were determined for each group (Fig. 2 and Table 1).

Clinical criteria were established for the four groups of patients studied: (i) normal, (ii) active hydrocephalus, (iii) arrested hydrocephalus, or (iv) functioning ventriculo-atrial shunt. Limits of data from the RISA studies which were present exclusively in each clinical group were then established. In effect, then, empirical limits were established for the data from the RISA studies for each group. These are limits that encompassed all but 1 of the patients studied.

RESULTS

As already indicated, the 1-hour samples of cerebrospinal fluid failed to delineate normal, active hydrocephalus, arrested hydrocephalus or functioning ventriculo-atrial shunt groups. The variations of the 4-hour samples were less than those of the 1-hour samples from group to group (Table 1) but still failed to provide adequate separation. Optimal information in this study was obtained from the 24-hour samples of cerebrospinal fluid. RISA levels in blood were too low to be useful except in the case of functioning ventriculo-atrial shunts, in which a sudden increase in activity in blood was associated with the time of function of the valves. These shunts apparently functioned intermittently rather than continuously.

The lumbar cerebrospinal fluid was an inaccurate index of ventricular RISA levels. With marked individual variation, the lumbar cerebrospinal fluid was 25 per cent as active as the ventricular fluid at 24 hours in patients with communicating hydrocephalus.

Activity in ventricular cerebrospinal fluid following intravenous injection of 5 micro-curies of RISA was too low to be measured accurately up through 24 hours.

The groups of patients studied had the following clinical criteria and characteristics of RISA clearance:

| TABLE 1 |
| Data on clearance of ventricular RISA with mean and standard deviations |

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Studies</th>
<th>4 hrs. CSF</th>
<th>24 hrs. CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>$\sigma$</td>
</tr>
<tr>
<td>Normal</td>
<td>3</td>
<td>.200</td>
<td>.141</td>
</tr>
<tr>
<td>Active hydrocephalus</td>
<td>7</td>
<td>.797</td>
<td>.308</td>
</tr>
<tr>
<td>Arrested hydrocephalus</td>
<td>7</td>
<td>.572</td>
<td>.242</td>
</tr>
<tr>
<td>Functioning ventriculo-atrial shunts</td>
<td>4</td>
<td>.262</td>
<td>.204</td>
</tr>
</tbody>
</table>
I. Normal Group.
A. Clinical Criteria. Communicating hydrocephalus was suspected as a cause of slow recovery following a head injury associated with bloody cerebrospinal fluid. Hydrocephalus was not verified by subsequent clinical course nor by contrast studies.
   1. Normal cerebrospinal fluid pressure and protein at the time of RISA study.
   2. No ventricular enlargement on serial contrast studies.
B. Limits of RISA Study.
   1. Ventricular clearance more than 0.65 at 4 hours.
   2. Ventricular clearance more than 0.97 at 24 hours.

II. Active Hydrocephalus Group.
A. Clinical Criteria (two or more criteria present in each case). These included cases of communicating hydrocephalus as well as obstructive hydrocephalus (aqueduct stenosis).
   1. Ventricular pressure greater than 180 mm. cerebrospinal fluid.
   2. Enlarging ventricles on serial contrast studies.
   3. Enlarging circumference of head (above 90 percentile); separated skull sutures.
   4. Tense, nonpulsatile fontanel.
B. Limits of RISA Study (two or more criteria present).
   1. Clearance less than 0.30 at 4 hours.
   2. Clearance less than 0.75 at 24 hours.
   3. Clearance from 4 to 24 hours less than 0.2.

III. Arrested Hydrocephalus Group.
A. Clinical Criteria. Seven patients were studied. Four had had ventriculo-atrial shunts placed previously, but none showed evidence that the shunts were functioning. The shunts were therefore removed;
   1. Ventricular dilatation on contrast studies.
   2. Increased cerebrospinal fluid pressure prior to RISA study but not elevated at time of study.
   3. No evidence of progression or resolution of ventricular dilatation on serial contrast studies.
   4. Stable size of head though enlarged; full but pulsatile fontanel.
B. Limits of RISA Study. Clearance inadequate to place in normal group but not impaired enough to place in the active hydrocephalus group.
   1. Clearance from 4 to 24 hours was greater than 0.2 and less than 0.65.
   2. Clearance of cerebrospinal fluid at 24 hours was 0.75 to 0.95.

IV. Functioning Ventriculo-Atrial Shunt Group.
A. Clinical Criteria.
   1. Evidence of active hydrocephalus prior to shunting procedure (done 3 years to 2 months prior to RISA study).
   2. Following shunting procedure:
      a. Decreased ventricular size or arrest of ventricular enlargement.
      b. Ventricular pressure less than 120 mm.
      c. Arrest of rapidly enlarging circumference of head; pulsatile, soft fontanel; or
      d. Active hydrocephalus when shunt obstructed.
B. RISA Study Criteria.
   1. Clearance greater than 0.97 at 24 hours.
   2. RISA in blood showed sudden dramatic rise, or no measurable activity.

The RISA study failed to give an accurate index of the hydrocephalic process in only 1 case. This was a 14-month-old white female who previously had had active hydrocephalus and had a ventriculo-atrial shunt proce-
“RISA” AS A DIAGNOSTIC AID IN HYDROCEPHALUS

The ventricular system is desirable, but proof of the patient’s ability to function without the shunt was needed. The shunt tube was ligated but not removed. Increasing ventricular pressure developed and the patient became obtunded. Another RISA study again demonstrated a clearance of more than 0.98 at 24 hours. The ligation was then removed from the shunt and the patient’s ventricular pressure dropped promptly and was associated with clinical improvement. The test failed, in this case, to differentiate active hydrocephalus from a functional ventriculo-atrial shunt. Conceivably the shunt functioned at such a low rate that clearance of cerebrospinal fluid approached normal rate and thus no surge of RISA in blood appeared.

DISCUSSION

While recognizing the rare possibility that hydrocephalus may be caused by excessive production of some or all components of the cerebrospinal fluid, the vast majority of cases apparently result from defective absorption. Serial samples of ventricular cerebrospinal fluid might be expected to show a decreased rate of egress of RISA from the ventricular system if the pathways from ventricular cerebrospinal fluid to brain or from the cerebrospinal fluid-brain compartment to blood were involved in the hydrocephalic process (Fig. 1, C and B). The sampling intervals chosen reflect the supposed behavior of the model. The samples of ventricular cerebrospinal fluid should be taken only frequently enough to provide adequate data since the hazards of serial ventricular puncture are significant.

The first samples of ventricular cerebrospinal fluid were taken 1 hour following injection of RISA since Lee’s data suggest reasonable diffusion through the cerebrospinal fluid over the cerebrospinal fluid-brain interfaces of the ependyma and subarachnoid space by that time. The rather long interval between injection and withdrawal of the first sample has a disadvantage in that a large part of the tracer is transported across the ependyma (Fig. 1, C) while waiting for mixing of the RISA and the cerebrospinal fluid. The second samples were taken at 4 hours at which time, in addition to adequate mixing of RISA and cerebrospinal fluid, equilibrium between brain and cerebrospinal fluid should have occurred. The third samples were taken at 24 hours at which time equilibrium between the brain-cerebrospinal fluid compartment and the blood should have been complete under normal circumstances (Fig. 1, B).

The rate of decrease in the concentration of RISA injected into the cerebrospinal fluid system has been shown to decrease with time. These data suggested the integrated effect of two exponential systems to Bowsher and he postulated two anatomic pathways to account for the “slow” and “fast” components of the curve of egress of RISA from cerebrospinal fluid. It is difficult to see why the “leptomeningovascular” route would cease functioning at a particular time so that only the “perineurymphatic” route would be left, resulting in a slower route of egress. Our proposed model seems consistent with the data above and does not require dual routes of egress from cerebrospinal fluid to blood with different rate constant.

The change in concentration of a tracer in a given compartment over a given time affords only a hazy appreciation of the basic processes involved. A change in concentration between compartments reflects the volume of the compartment, concentration of tracer in that volume, the surface area of the compartment and, most important, the rate constant (K) of the surface area (amount of tracer transferred/unit time/unit concentration gradient/unit area). If we let the transfer of RISA of cerebrospinal fluid to brain equal $k_1$ in the model depicted, and the transfer from brain to cerebrospinal fluid equal $k_2$, then the net transfer at equilibrium will be expressed by $K_1 = k_1/k_2$. At equilibrium $K_1 = $ concentration RISA in brain/concentration RISA in cerebrospinal fluid.
If $K_1$ is greater than unity, it can be shown that with a given total volume of the brain and cerebrospinal fluid, a higher concentration of tracer in cerebrospinal fluid will result in a patient with ventricular dilatation at equilibrium even if the rate constants between the cerebrospinal fluid and brain compartments are not altered.

Bering\(^1\) has studied the clearance of phenolsulfonphthalein via excretion in urine after ventricular injection in patients with hydrocephalus but concluded that this effect was caused primarily by dilution of the dye in the ventricles by increased volume of cerebrospinal fluid. If one accepts the assumptions required for the formulation of Bering’s mathematical model, i.e. that the transverse diameter of the lateral ventricles provides an accurate measure of ventricular volume, corrects a printer’s error,\(^2\) and states the equation in correct form, then:

1) \[ C_{esf} = C_0 \ e^{-x t} \]

\(t = \) time after injection of tracer into the ventricle

\(C_0 = \) maximum concentration of tracer at \(t = 0\)

\(C_{esf} = \) concentration of tracer at any time \(t\)

\(e = \) base of natural logarithms

\(x = \) a complex constant of exchange which includes the surface volume ratio \((s/v)\) of the ventricle and the exchange coefficient \((K)\).

\(x = K(s/v)\).

Bering then correctly derives the following equation:

\[ d \ \ln 2 = K T_{1/2} \]

in which \((d)\) is the transverse diameter of the ventricle, and concludes “\(\ln 2\) and \(K\) are constants, therefore a plot of \(d\) vs \(T_{1/2}\) should be linear with slope \(K/\ln 2\)”.

The data Bering presented do not appear to support the above conclusion. A plot of ventricular diameter vs. phenolsulfonphthalein concentration half-time is given in which the variability is striking. Unfortunately no correlation coefficients are given, but regression lines are plotted. Inspection of Bering’s scattergram suggests that the standard error of estimate might not differ significantly from the standard deviation of the ventricular-diameter distribution.\(^6\)

Exchange pneumoencephalography or ventriculography may be a dangerous procedure in advanced hydrocephalus. Instead, we have utilized “bubble studies” in which 5–10 cc. of air were introduced into the ventricular system to evaluate cortical thickness. By so doing, we have been unable to predict clearance of RISA or activity of the disease from cortical thickness (i.e., size of ventricle) in hydrocephalus, unless the “bubble study” is done serially with sufficient time intervals to show progressive change of cortical thickness.

There is a striking similarity in the clearance of RISA in the active hydrocephalus group and the normal group from 4 to 24 hours—0.189 and 0.186 (Table 1). This may be an artifact of sampling intervals or random similarities in small groups. This may also indicate that when the brain-cerebrospinal fluid compartments reach equilibrium, the process by which clearance occurs from the equilibrated compartments is not affected by the disease.

The clearance in the arrested hydrocephalus group was more than twice as great over this period—\(444\) (Table 1). This may represent failure to come to equilibrium by 4 hours. This may also indicate that at least a part of the mechanism whereby hydrocephalus becomes arrested involves more favorable transport of RISA from the cerebrospinal fluid-brain compartment to blood.

These tenuous hypotheses do not encompass any system other than transport of RISA which is at best a poor approximation of the complexities involved in hydrocephalus. They may be related, however, to other data to provide some insight into the mechanisms involved.

It is well known that the concentration of protein in the ventricular cerebrospinal fluid is less than that in the subarachnoid spaces. It is also well known that obstruction of the cerebrospinal fluid pathways from the ven-
tricles to the subarachnoid space of the cerebral hemispheres results in hydrocephalus. If the obstruction occurs at the level of the aqueduct of Sylvius "internal" hydrocephalus results. If the obstruction occurs in the basal cisterns "communicating" hydrocephalus develops. The results are the same in either case, i.e., ventricular dilatation and deteriorating clinical course terminating in death or arrest of the hydrocephalic process. In both cases the concentration of protein in the cerebrospinal fluid is usually normal. If the volume of cerebrospinal fluid produced in the ventricles is constant, either by filtration of a protein-poor fluid by the hydrostatic pressure across the choroid plexus between arterial blood and cerebrospinal fluid or by secretion of a hypertonic solution as Bowsher has proposed, the amount produced per unit time is apparently large with respect to the ability of the surface of the ventricles to absorb the fluid. The pressure of the cerebrospinal fluid-brain system then increases until the decreased hydrostatic gradient between arterial blood and cerebrospinal fluid or the increased gradient from cerebrospinal fluid-brain to venous blood pressure results in equilibrium with increased cerebrospinal fluid pressure.

Failure of the protein in cerebrospinal fluid to be elevated in hydrocephalus despite the decrease in available subarachnoid space for absorption of protein produced in the ventricles suggests that most of the protein in the cerebrospinal fluid may be produced at the subarachnoid cerebrospinal fluid-brain interface. If this were the case and the subarachnoid space available for water and absorption of protein were decreased, \( K_1 \) for protein would be unaltered for both \( k_1 \) and \( k_2 \) would be decreased simultaneously and concentration of protein would be normal. In the same case, if the greatest part of water and ionic solutes in cerebrospinal fluid were formed in the ventricles and absorbed in the subarachnoid space, hydrocephalus would result.

From the clinical standpoint this test can be used to determine patency of ventriculostriatral shunts in hydrocephalic children, though reliability must be considered based on experienced application and recognition of possible variables. Only clearance of the isotope in ventricular cerebrospinal fluid is needed over a 24-hour period though the levels in blood are very helpful if a sudden surge of isotope activity can be picked up to indicate functioning of the shunt. The small amount of tracer used is harmless but does tend to make interpretation of the sample of blood difficult because of counting rates in blood which approach background activity.

**SUMMARY AND CONCLUSIONS**

1. Twenty-five ventricular RISA studies were carried out in patients with suspected or proven hydrocephalus.
2. A technique is described for evaluating the activity of hydrocephalus by measurement of the decrease in RISA concentration in ventricular cerebrospinal fluid from the 1-hour level at 4 hours and 24 hours following injection of a 5-microcurie dose test. The technique was found satisfactory in classifying normal, active hydrocephalic, and arrested hydrocephalic patients.
3. Concentration of radioactivity in blood was found to be too low to be generally useful in this study. In patients with ventriculostrial shunts radioactivity in blood frequently showed a sudden surge indicating a functioning shunt. This variable finding depended apparently on time of sampling and rate of flow in the shunt.
4. One-hour concentration of RISA in ventricular cerebrospinal fluid was an unreliable index of activity of hydrocephalus.
5. Concentrations of RISA in lumbar cerebrospinal fluid were an unreliable index of concentration of RISA in ventricular cerebrospinal fluid.
6. A model is proposed for the dynamic characteristics of the cerebrospinal fluid protein system.
7. It is proposed that the most common basic defect in hydrocephalus is a critical reduction in area of available subarachnoid space where interfaces allow cerebrospinal fluid-brain mechanisms of transfer to take place.
REFERENCES

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