EXPERIMENTAL STUDIES ON THE CIRCULATION OF THE CEREBROSPINAL FLUID

AND METHODS OF PRODUCING COMMUNICATING HYDROCEPHALUS IN THE DOG

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Much of the experimental work that has been done on the physiology of the cerebrospinal fluid has been performed on laboratory animals and the results have then been applied to man. The purpose of the present work was to discover any differences that might exist among the cerebrospinal fluid (CSF) circulations of the dog, the cat, and the Rhesus monkey, so that the comparisons that have been made between these circulations and that of man might be evaluated. A further objective was to find a satisfactory preparation for the study of communicating hydrocephalus in animals.

Our concept of the circulation of the CSF is essentially that which was described by Weed, as far as the flow and absorption are concerned. In our experiments we have not been concerned with the origin of the fluid, or with following the course of the ionized constituents, about which there is controversy and in which differences may be found to exist between various species and man. Our studies have been to determine the main pathways of flow and absorption beyond the ventricular system in the animals under consideration. At this stage of the circulation the fluid passes into the extracerebral subarachnoid spaces, where it is partly absorbed by arachno
dal villi situated not only along the superior sagittal sinus but also in conjunction with the cavernous and other sinuses. An additional route of absorption exists along the arachno
dal sheaths of certain cranial nerves, from which the fluid passes into intercellular tissue spaces and then into the lymphatic system. For the purposes of this study any fluid and ion exchange which may take place between the CSF and brain substance has been disre
garded.

CSF Absorption in the Dog. The existence of pathways along the cranial nerves of dogs was shown by Key and Retzius using a subarachnoid injection of gelatine containing Berlin blue, and later by Weed with potassium

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ferrocyanide. Other substances such as India ink have been used for the same purpose. The perineural channels of the optic and olfactory nerves were demonstrated radiologically by Stuck and Reeves using Thorotrast\(^*\) and by Strain, French and Jones\(^2\) using Pantopaque.\(^\dagger\)

In our preliminary studies we repeated the work of Strain, French and Jones\(^2\) and confirmed their observations. Five cc. of Pantopaque were injected into the cisterna magna of a dog under intravenous Nembutal anesthesia; the animal was then kept prone for 5 to 6 hours and x-rays were taken of the head at 30–minute intervals. The contrast medium passes in about 90 minutes into the fila olfactoria. These are arachnoidal tubes sur-

![Lateral view (dog) 6½ hours after cisternal injection of 5 cc. of Pantopaque, with the animal prone. Contrast medium is seen in the optic nerve sheaths and in the fila olfactoria. Lymphatic glands behind the mandible are visible.](image)

rounding the olfactory nerves which connect the olfactory bulbs through the cribriform plate with the submucous tissues of the nose. From the fila olfactoria the Pantopaque passes into the submucous spaces and into lymphatic channels through which it travels to lymph glands behind the mandible and in the neck (Fig. 1). The contrast substance also enters the sheaths of the optic nerves and passes into the epichoroidal and episcleral spaces from which it reaches the filtration angle of the eye and traverses the facial lymphatics to the anterior lymph glands of the neck\(^4\) (Fig. 2). After 5 days most of the Pantopaque has left the nerve sheaths, and the remainder is scattered into droplets over the base of the cerebral hemispheres. The amount of Pantopaque seen there slowly decreases, and after 19 days the

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* Colloidal Thorium Dioxide.
† Ethyl Iodophenylundecylate.
glands are almost free, only scattered intracranial droplets remaining which are still visible after 3 1/2 months. As in the experiments of previous investigators, the animal was in a prone position.

In our next studies a cisternal injection of 3 cc. of Pantopaque was given under intravenous Nembutal anesthesia with the animal supine and the head and neck extended. As expected, the Pantopaque passes over the surface of the cerebral hemispheres and along the borders of the superior sagittal sinus. However, it still enters the nasal tissues and optic nerve sheaths, although it now takes 5 hours to reach them. It is still visible in these situations 19 hours later (Fig. 3), after which it gradually disappears except for a few droplets over the cerebral hemispheres.

**Fig. 2.** Lateral view (dog) showing Pantopaque surrounding the globe of the eye 24 hours after cisternal injection. Anterior lymphatic glands are visible in the neck as well as those behind the mandible.


Comparison with Other Animals. In the cat, maintained in a prone position under intraperitoneal Nembutal anesthesia, it was found that the contrast does not enter the nasal tissues or optic nerve sheaths, although it flows into a suitable position for this to occur; the same thing was found in the kitten. However, in the Rhesus monkey it appears in the optic nerve sheaths in 15 minutes, although at no time does it enter the nasal tissues (Fig. 4).

Since Pantopaque is more viscous than CSF, these experiments were repeated in a cat and a monkey with Thorotrast, which has a relatively low viscosity. The results were the same except that a faint trace of contrast medium was seen in the optic nerve sheaths of the cat. These findings were in agreement with those of Stuck and Reeves\(^3\) except that we did not observe any development of hydrocephalus in these animals after 4 months.

Significant differences therefore exist in the CSF circulations of these three animals. In each the arachnoidal villi are of importance, and in the cat and monkey they are certainly the chief route of absorption. In the dog,
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Fig. 3. Lateral view (dog) 24 hours after cisternal injection of 3 cc. of Pantopaque with the animal supine. Contrast substance is seen over the surface of the cerebral hemispheres, in the fila olfactoria, and in the sheaths of the optic nerves.

However, there are also important fluid exits through the nasal tissues and optic nerve sheaths, while in the cat the optic nerve sheaths are of but slight significance and the olfactory pathways of none at all. In the Rhesus monkey the optic nerve sheaths, but not the nasal channels, achieve an important role.

The Relative Importance of the CSF Pathways of the Dog. The effects of interruption of the main absorptive channels of the dog were investigated, in order to establish their relative importance.

Pantopaque will produce a fairly intense inflammatory reaction in the cerebral subarachnoid spaces of the dog (Fig. 5). This is confirmed during life by the failure of a second cisternal injection to pass into the olfactory and optic nerve sheaths. Instead, the Pantopaque is diverted by the basal obstructive process into the ventricles and over the cerebral hemispheres where the remaining absorptive pathways are occluded. That these barriers are also effective against the passage of

Fig. 4. Lateral view (Rhesus monkey) showing Pantopaque outlining the optic nerves 15 minutes after cisternal injection of 2.5 cc. Some of the contrast medium has also entered the 3rd and lateral ventricles. There is none in the nasal region.
CSF is shown by subsequent progressive ventricular enlargement and elevated intracranial pressure. The effect is the same whether 3 1/2 months or 7 days separate the 2 injections (Fig. 6). This experiment was carried out in 5 dogs with the same findings each time (2 dogs received 3 injections, but the ventricles were already enlarged when the third was given).

A single injection of 3 cc. of Pantopaque will not alone induce hydrocephalus (3 control animals) whether the animal has been kept prone or supine after it has been given. This indicates that if most of either the perineural or villous pathways are occluded the others are still sufficient to absorb enough CSF to prevent symptoms and signs of obstruction. The volume of Pantopaque used is not the operative factor, since there was no enlargement of the ventricles of a dog 5 weeks after a cisternal injection of 6 cc. of the substance.

Obstruction in the interpeduncular and neighboring cisterns was produced in dogs by the following method. A polyethylene tube was introduced
into the interpeduncular region through a subtemporal craniotomy under intravenous Nembutal anesthesia. The animals were then kept in a prone position while injections of a suspension of 250 mg. of kaolin* in 2 cc. of normal saline were given in 0.5 cc. doses over a period of 3 to 4 hours. It does not matter if some of the kaolin enters the subdural space. A subarachnoid fibrosis occurs which prevents the forward passage of CSF beyond the obstruction (Fig. 7). With kaolin a diffuse inflammatory response is produced, in contrast to the response to Pantopaque which is concentrated in zones beneath the arachnoidal surface and especially about the blood vessels.

Obstruction of the interpeduncular cistern of 12 dogs by this method caused only a minimal degree of ventricular enlargement or none at all. This indicated, as in our previous experiments, that a satisfactory alternative route of absorption still remained. The basal obstruction then prevented a subsequent cisternal injection of Pantopaque from entering the sheaths of the olfactory and optic nerves of 7 dogs. Following the Pantopaque injection, the remaining pathways were occluded by inflammatory reaction in the meninges and hydrocephalus resulted (Fig. 8).

Obstruction of the ambient cistern has been produced by means of a suspension of kaolin introduced through a tube in 2 dogs, and the effects were similar to those of interpeduncular obstruction.

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* Hydrated Aluminum Silicate.
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The olfactory CSF pathways were divided surgically in 2 dogs. No ventricular enlargement because of deficient absorption occurred. One of these received an injection of 3 cc. of Pantopaque into the cisterna magna; this was followed by enlargement of the ventricles—a hydrocephalus which was demonstrated to be communicating in type by the intraventricular injection of phenolsulphonphthalein (PSP) which appeared at the cisterna magna in 30 seconds.

Obliteration of 50 per cent of the subarachnoid pathways over the surface of the cerebral hemispheres can be brought about by an arachnoiditis induced by covering the brain with cellophane or iodinated gauze; this causes a very dense fibrosis of the meninges. Despite this reduction of absorptive channels, there are no signs of hydrocephalus until the optic and olfactory routes are also obstructed by a Pantopaque arachnoiditis. When this occurs hydrocephalus rapidly develops.

CONCLUSIONS

In the dog there are three main paths of CSF absorption: the arachnoid villi leading to the blood stream, and the perineural channels of the optic and olfactory nerves leading to the lymphatic system. Weed using ferrocyanide found granules of Prussian blue from the vagus nerve sheath in the middle of the neck; from the spinal accessory sheath they traveled 1 to 2 cm. and from the hypoglossal nerve sheath they reached the tongue. However, these experiments were done under raised pressure, and we consider that the contribution of nerve sheaths other than the optic and olfactory is not significant. Each of the three main routes described appears to be of almost equal importance in the dog, a state of affairs that does not exist.

Fig. 6C. Brain slices showing the degree of hydrocephalus in the same animal as in Figs. 6A and B, 4 months after injection.
in the cat or Rhesus monkey. This amplifies the differences among these animals which we earlier demonstrated radiologically. There is reason to believe that similar differences exist between the CSF circulations of dog and man. Great care must therefore be exercised in drawing conclusions based on evidence from the lower animals about this circulation in man, and it follows that the dog is not suitable for comparative experimental work on the absorptive aspect of the CSF circulation.

In view of the inflammatory reaction that we have seen with Pantopaque,
Fig. 8. (Upper) Lateral view (dog) 38 hours after a cisternal injection of 3 cc. of Pantopaque given 3 weeks after obstruction of the interpeduncular cistern with kaolin. No contrast medium has passed beyond the obstruction in a forward direction. The ventricles are outlined and show slight enlargement. (Lower) Brain slices of the same animal showing the degree of hydrocephalus 2 months later.

we must emphasize that we do not consider it unsuitable for clinical use in myelography. In our experiments we employed a greater amount relative to the total CSF volume than is used clinically. However, our findings show the need for removing as much as possible and for keeping it away from the cerebral subarachnoid spaces, since it causes subarachnoid fibrosis when used in dogs.

EXPERIMENTAL COMMUNICATING HYDROCEPHALUS

In the course of our experiments various types of obstruction of the CSF
pathways have produced enlargement of the ventricles. This hydrocephalus is almost always of communicating type.

Five dogs were each given 2 cisternal injections (2 dogs had 3 injections) of Pantopaque, one prone and the other supine. The basal pathways and the channels over the cerebral hemispheres were thus obliterated. We found 1 or 2 weeks to be a suitable interval between injections. In all these animals communicating hydrocephalus developed. After 3 injections in 1 animal a block developed in the cisterna magna, which later re-opened. Three control animals received only 1 injection and did not become hydrocephalic. There were no deaths in this series.

Seven animals received interpeduncular kaolin suspension followed by cisternal Pantopaque. Two weeks elapsed between the 2 procedures. In 6 of these communicating hydrocephalus developed which was of considerable degree in 5 (Fig. 9). There was 1 death 4 days after Pantopaque injection, the cause of which was not clear. Proof of communication was afforded by combined cisternal and ventricular taps, with or without the injection of PSP or other dye. This method has not been so successful in Rhesus monkeys; hydrocephalus developed in only 1 out of 3.

In 2 dogs that received cisternal injections of 2 cc. of Lipiodol* com-

![FIG. 9. Brain slices (dog) showing considerable ventricular enlargement 1 month after occlusion of the remaining subarachnoid CSF pathways with Pantopaque following interpeduncular obstruction with kaolin.](image)

* Lipiodol Lafay.
municating hydrocephalus developed but the rate of development was too slow for the method to be of experimental use.

In the animals in which the olfactory pathways were divided or the cerebral hemispheres covered to produce fibrosis, communicating hydrocephalus developed, but owing to the extent of the operative damage the preparation would be unsuitable for some experiments.

Two satisfactory methods of producing communicating hydrocephalus have therefore been found. However, after 2 injections of 3 cc. of Pantopaque a small amount of the contrast medium remains in the CSF and cannot be absorbed, at least for several months, whereas following an interpeduncular injection of kaolin hydrocephalus may be produced with as little as 1 cc. of Pantopaque. This has almost all disappeared by the time hydrocephalus has developed to a satisfactory degree, which takes about 3 weeks.

Interpeduncular injection of kaolin suspension followed by cisternal injection of Pantopaque is therefore the most satisfactory method for the experimental production of communicating hydrocephalus. The technique has been used chiefly on dogs, but since the absorptive channels are obstructed, the differences in CSF absorption between dogs and other animals are not a consideration when using it for comparative studies.

SUMMARY

1. Significant differences in the mechanisms of absorption of CSF are shown in the dog, cat and Rhesus monkey by following the course of a cisternal injection of Pantopaque.

2. Pantopaque will produce arachnoidal fibrosis when injected into the subarachnoid space of the dog.

3. Obstruction of arachnoid villi, and the perineural subarachnoid pathways in the dog, show both to be of importance in the absorption of CSF in this animal. This is not true in the cat or Rhesus monkey.

4. Care should be exercised in comparing the CSF absorption mechanisms of lower animals with those of man.

5. Methods of producing experimental communicating hydrocephalus in the dog are described.

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REFERENCES


