PHYSIOLOGIC EFFECTS FROM THE INTRODUCTION OF BLOOD AND OTHER SUBSTANCES INTO THE SUBARACHNOID SPACE OF DOGS*

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Solutions of normal saline, injected under pressure into the subarachnoid space, escape into the orbital tissues, producing proptosis and subconjunctival edema. When normal saline is injected at pressures in excess of 100 mm. Hg, drainage from the nostrils is often apparent. Solutions of dextran, plasma protein and colloidal gold also pass readily from the subarachnoid space, although more slowly than does normal saline. If erythrocytes or carbon particles from India ink are injected within the subarachnoid space in advance of an injection of normal saline, the flow of saline out of the subarachnoid space is blocked, and hence the flow of saline into the subarachnoid space also is impeded. Openings that can be blocked by erythrocytes or carbon particles are present about the optic nerves and about the olfactory nerves. In addition, spaces that permit the passage of fluid and particles have been demonstrated about the spinal nerves, and probably are present around other cranial nerves.

The arachnoid villi, whose importance was emphasized by Weed, have been shown experimentally by Welch and Pollay to permit perfusion of liquids and particles into the venous system in the monkey. Arachnoid villi in other species probably function in the same way. Simmons recovered erythrocytes labeled with P32 in the systemic circulation after their injection into the subarachnoid space of rabbits. Adams and Prawirohardjo recovered Cr51 labeled erythrocytes, and Bradford and Johnson recovered Fe59 labeled erythrocytes from the systemic circulation of dogs after their introduction into the subarachnoid space.

The brain and spinal cord become highly radioactive when radioactive colloidal gold is perfused into the subarachnoid space. The possibility of fluid and particles reaching the circulation of the brain or spinal cord by communication between the cerebrospinal-fluid spaces and the perivascular spaces must be kept in mind.

In this study there is little evidence to show which of the routes is followed by the bulk of a solution injected or just where the erythrocytes or carbon particles obstruct the flow of fluid from the subarachnoid space. However, it seems likely that all routes must be affected, since the degree of blocking of the passage of saline introduced into the subarachnoid space becomes quite high.

METHOD

Dogs weighing 14 kg. or more were anesthetized by intravenous injection of 30 mg./kg. of pentobarbital sodium. A lumbar laminectomy was performed and a polyethylene tube was introduced about 5 cm. cephalad into the lumbar subarachnoid space. Tight closure was made by tying the dura mater and the enclosed spinal cord and cauda equina firmly about the polyethylene catheter. A “T” connector was used so that 1 connection could be made to a pressure transducer and 1 to a container for injections by gravity or to a syringe for direct injections. In some of the more recent experiments 2 polyethylene tubes were tied into the subarachnoid space, 1 for pressure recordings and 1 for injections. Blood pressure was taken by cannulating the femoral artery and connecting it to a pressure transducer. For shunting procedures requiring blood at arterial pressure the other femoral artery was cannulated and poly-
ethylene tubing was used to make appropriate connections. Before a shunt was connected, the dog was heparinized with 2 mg. heparin/kg. Routine recording was done with a physiograph having channels for blood pressure, cerebrospinal-fluid pressure, respiration and time signal. Sixty-eight dogs, 2 cats and 2 rabbits were used in the experiments reported here.

**OBSERVATIONS**

**Subarachnoid Injection of Normal Saline.** The flow of normal saline into the subarachnoid space by gravity at approximately 135 mm. Hg pressure is variable, but usually quite free. The average rate is from 0.5 to 1.0 cc. per kg. of body weight per min. Occasional dogs will have much slower flow than others. The usual 20 kg. dog would accept 60 cc. of normal saline at 135 mm. Hg pressure in from 3 to 6 min. If the pressure is halved, the same amount of saline requires slightly less than 4 times as long to run in. If normal saline only is injected, succeeding 60 cc. quantities flow in the same or slightly less time. Edema can be noted in the orbital tissue after injection of 20 cc., and proptosis is apparent after 100 cc. or more. As a rule, vital functions are not altered appreciably by injections at a pressure of 135 mm. Hg lasting up to 12 min. Injections of from 30 to 50 cc. of normal saline by syringe at pressures of from 300 to 400 mm. Hg in 1 to 2 min. usually can be made. A marked rise in blood pressure occurs and occasional arrest of respiration, but the cerebrospinal-fluid pressure usually has returned to tolerated limits before any deterioration of the condition of the dog occurs. With a short rest between injections, many injections can be made without deterioration.

Two cats and 2 rabbits were tested with subarachnoid injections of saline. The rate of absorption, the collection of saline in orbital tissues and the dripping from the nostrils quite parallel the reactions observed in dogs.

In 3 dogs a catheter was tied into the lower end of the subarachnoid space at the 1st thoracic vertebra. Saline was accepted by this portion of the subarachnoid space with no access to the intracranial subarachnoid space. Absorption was quite slow, less than 10 per cent of that of the cranial subarachnoid space for pressures of from 200 to 400 mm. Hg and even slower for pressures of 100 mm. Hg or less.

**Subarachnoid Injection of Blood.** In his study of intracranial hematoma, Kabuki injected 1 cc. per kg. of autogenous blood into the subdural and epidural spaces of dogs without mortality. Mullan et al. injected blood into the subarachnoid and subdural spaces of dogs, finding the lethal dose under most circumstances between 1 and 2 cc./kg. If injected over a period of 45 min., a larger amount of blood was tolerated than if more rapid injection was made. Our findings upon injection of blood into the subarachnoid space were quite similar. It also was observed that saline, injected after blood in the amount of 1 cc./kg. or more, rapidly raised subarachnoid pressure. In fact, after the injection of blood, saline encountered as much resistance as would additional blood. Saline, injected after considerable blood had already been injected, was as lethal as further injection of blood. This effect was observed also in injections by gravity. Because of the free flow of saline from the subarachnoid space when injected by gravity at 6 feet (135 mm. Hg) the effective pressure was reduced. However, when flow was stopped by injection of blood preceding saline, further saline at the pressure of gravity at 6 feet caused more deleterious effects on vital functions. At one time it was thought that blood in the subarachnoid space had some specific lethal effect, but evidence gradually was accumulated that it was the almost complete arrest of flow from the subarachnoid space that produced the more formidable signs when additional saline was introduced by gravity or by injection.

After the injection of blood, if saline, in amounts just tolerated, is forced into the subarachnoid space, perhaps 60 cc. in the course of 1 hour, its passage through the subarachnoid space becomes easier, and subsequently moderately large quantities of saline can be injected in only a few minutes. Under such circumstances the subarachnoid space can be washed almost free from erythrocytes. During the "washing process"
erythrocytes were noted in the nasal drippings on several occasions, and on 3 occasions in which radioactive blood was administered into the subarachnoid space cells in the nasal drippings were radioactive.

After death, blood, if still present in the subarachnoid space, was noted extending in the meningeal sleeve to the back of the eye. There was diffusion of blood in variable degrees into areolar tissue near the back of the globe. Areolar tissue along the more proximal course of the optic nerve in the orbit usually was not stained. Papilledema was never observed in life, and no swelling or deformity of the papilla was noted after death. No hemorrhage in the retina, papilla or in any part of the eye was observed in any instance. In some dogs, when much saline had been injected after blood, there was admixture of blood in the diffuse edema of the orbital tissues and in the subconjunctival edema.

Subarachnoid Injection of India Ink. India ink, from 30 to 100 drops contained in 50 cc. of normal saline, had the same effect when introduced within the subarachnoid space of a dog as from 15 to 25 cc. of blood (Fig. 1). If saline, in amounts just tolerated, is forced into the subarachnoid space, this resistance to passage of saline gradually is overcome within the course of injection of 60 cc. of normal saline in approximately 1 hour. The effect of India ink is quite similar to that of blood.

Arteriosubarachnoid Shunts. To simulate the effect of rupture of a large subarachnoid artery, shunts were made with polyethylene tubing from femoral artery to spinal subarachnoid space. Animals were heparinized to prevent clotting in the shunt. When such a shunt was opened, a rapid rise in subarachnoid pressure occurred. A great rise in blood pressure then resulted, with a further rise in subarachnoid pressure, followed by respiratory arrest, dilatation of both pupils and death within 6 to 8 min.

When arterial blood is shunted into a sac contained within a bottle of saline so that it displaces saline at a somewhat dampened pulse pressure into the subarachnoid space, death may result quickly as from the direct arterial shunt. However, for the displaced saline to cause death, short and relatively large plastic tubing must be used. The rapid flow from the subarachnoid space of saline introduced under high pressure will prevent a fatal pressure unless provision is made for very free flow of saline at near arterial pressure into the subarachnoid space.

In a system in which arterial blood does not displace saline rapidly enough to cause death, blood will displace blood fast enough to cause death. Again, in the same system, after the tolerance of saline displaced into the subarachnoid space by arterial flow is established, 10 cc. of blood are injected by syringe into the subarachnoid space. Now, when saline again is displaced into the subarachnoid space, the same lethal course is followed as when there is a direct arteriosubarachnoid shunt (Fig. 2). It thus is apparent that blood blocks the outflow of saline from the subarachnoid space and makes the inflow of saline at a moderate rate (but at a sufficient pressure) more immediately lethal.

Subarachnoid Injection of Colloidal Gold. Radioactive colloidal gold solution (Au199) was administered within the subarachnoid space by lumbar catheter in 3 dogs and by cisternal puncture in 4 dogs. Difficulty was
experienced in balancing the account between radioactivity administered and that recovered, probably because of a tendency for the colloidal gold to settle to some extent so that solutions that had stood were not uniform in content of gold. Thorough mixing of all solutions before either further dilution or the taking of a sample probably would have prevented this discrepancy. Nevertheless, several interesting conclusions could be reached.

In the 3 dogs that received colloidal gold by lumbar catheter, saline that was injected afterward was accepted less readily into the subarachnoid space than when only saline was injected. The 2 dogs that received saline under pressures of 132 mm. Hg (by gravity) and 300 mm. Hg (by intermittent injection) dripped fluid from the nostrils which showed high counts of radioactivity. The count was higher in the dog that received undecayed colloidal gold than in the dog that received 5 times the amount of partially decayed gold, approximately equal in radioactive count. This suggests that if the particles are too numerous, a smaller per cent of the particles pass into nasal drippings. The dog given colloidal gold and saline at 50 mm. Hg pressure had no nasal dripping. These 3 dogs, sacrificed in from 1 3/4 to 3 hours, showed higher counts in the blood than did the 3 dogs sacrificed from 17 to 27 hours after cisternal injection. However, 1 dog sacrificed 5 hours after cisternal injection showed high radioactivity in the blood.

The tissue removed from about the optic nerve within the orbit was ballooned out with saline when saline had been injected but not when simple cisternal injection of from 1 to 2 cc. of colloidal gold solution was done. High counts of radioactivity were encountered in all specimens taken from the orbit.

Postmortem cisternal fluid always showed a high radioactive count. For this reason, specimens in contact with cerebrospinal fluid were washed freely with water before being counted.

Very high counts of radioactivity were encountered in cranial and spinal dura mater and in cerebrum and spinal cord. Lymph nodes from the neck gave high counts 17 and 20 hours after cisternal administration of Au\textsuperscript{198}. The maxilla, freed from brain and dura mater, showed a high count, the mandible a somewhat lower count.

The liver always showed a high count, higher when Au\textsuperscript{198} was administered under pressure than when administered intracisternally. The heart and spleen showed no increase in radioactive count.

Unfortunately, no thoracic or lumbar paravertebral lymph nodes were studied.

Other Observations. Dextran solution, 6 per cent in normal saline, acted very much the same as normal saline when introduced within the subarachnoid space, but the flow into the space (hence the flow from the space) was about 25 to 50 per cent slower than with normal saline. The nasal drippings after administration of dextran showed the presence of dextran in amounts comparable to those in the solution administered.

Dog plasma in amounts of from 50 to 100 cc. flowed readily into (hence out of) the subarachnoid space. Saline introduced by gravity after 50 cc. of plasma required about twice the time needed to run in before the plasma was administered.

Methylene-blue solution always stained the orbital tissues, but did not stain the nasal drippings.

Toluidine-blue solution stained both orbital tissues and nasal drippings. The entire
nasal mucosa was stained markedly after a
strong solution of toluidine blue was intro-
duced into the subarachnoid space. Vital
functions were disturbed, and the flow of
saline into the subarachnoid space after the
strong solution of toluidine blue was slowed
markedly.

Hyaluronidase, 150 U.S.P. units (Wydase
1 cc.), was injected in the course of injections
of saline and blood into the subarachnoid
space. One or 2 ampules generally increased
the flow of saline slightly. In 4 of 9 instances
of subarachnoid injection of heparinized
blood after 2 or 3 ampules of hyaluronidase
had been introduced into the subarachnoid
space, postmortem examination revealed a
startling amount of blood within the cone of
extra-ocular muscles outside the meninges of
the optic nerve on both sides. This type of
blood collection rarely was observed other-
wise.

REVERSIBILITY OF PHYSIOLOGIC CHANGES
RESULTING FROM SUBARACHNOID
INJECTIONS

Dogs subjected to repeated or prolonged
injections of solutions into the subarachnoid
space often had a clinical appearance suggest-
tive that changes had been brought about
that might not be reversible, even though the
level of blood pressure and the respiratory
exchange were satisfactory. The initial in-
travenous Nembutal anesthesia (30 mg./kg.)
ever required supplementation after sub-
arachnoid injection was well started, even if
the experiment was prolonged for several
hours.

To test reversibility, 2 dogs received more
than 300 cc. of normal saline into the sub-
arachnoid space by cisternal needle. The first
dog received in the course of 34 min. 18
injections of from 15 to 20 cc. of normal
saline, each of which produced a marked
rise in blood pressure. At the end of the
injection, blood pressure was 190/120 and
the respiratory rate was 34 per min.

In both dogs the character of respiration
appeared ominous because of depth and
rapidity. Both dogs had dripped saline freely
from the nostrils. Extreme proptosis was
present bilaterally in both dogs, but the
pupils were not dilated. Both dogs were
recovered fully the next morning.

Cessation of respiratory movements occurs
regularly within from 20 to 30 sec. after the
initiation of subarachnoid injections at pres-
ures higher than blood pressure. However,
the amount by which subarachnoid pressure
exceeds blood pressure seems to be of little
consequence if the injection is not too pro-
longed. The provoked rise in blood pressure
often causes a further rise in subarachnoid
pressure even though subarachnoid injection
is stopped before the rise in blood pressure
occurs. If subarachnoid pressure is main-
tained above blood pressure, artificial respi-
ration prolongs the period of response by
elevated blood pressure. Once the blood
pressure has dropped to shock level, artificial
respiration will not reverse the course to
circulatory failure and death. However, as
long as the terminal drop in blood pressure is
averted, the dog usually can be restored to a
state with satisfactory vital functions.

Bilateral maximal pupillary dilatation
occurs regularly during the period of maximal
elevation of blood pressure which results
from abrupt increase in subarachnoid pres-
sure. It occurs occasionally during prolonged
injections by gravity of fluid at a pressure of
135 mm. Hg. Maximal pupillary dilatation
is a sign of impending death, but is entirely
reversible if subarachnoid pressure is lowered
promptly. Initiation of artificial respiration
permits more delay in lowering subarachnoid
pressure.

SUMMARY AND CONCLUSIONS

Blood and particles of India ink block the
avenues of escape of saline from the sub-
arachnoid space. Spaces associated with the
optic and olfactory nerves and arachnoid
villi appear to be of special importance.
There is evidence that as particles pass
through these areas, escape of saline from the subarachnoid space is restored.

The cerebrospinal-fluid circulation in lower animals appears to be quite similar from species to species, and this circulation in man probably has much in common with lower animals. Blood in the subarachnoid space of man probably produces obstruction to absorption of cerebrospinal fluid as it does in animals to absorption of injected saline.

A test of the absorption potential of the subarachnoid space in man merely by injecting saline into the subarachnoid space under calibrated pressures appears possible. The test might determine in advance the chances of relieving an obstructive hydrocephalus by the Torkildsen procedure.

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