This study of the effects of certain drugs, gas mixtures, and other stimuli on the cerebrospinal fluid pressure corroborates previous conclusions that alterations in cerebral blood flow are reflected by similar changes in the cerebrospinal fluid pressure in the same direction. The hypothesis is advanced that the elevations and depressions in cerebrospinal fluid pressure resulting from these agents are due to the respective increased and decreased volume of the vascular structures of the brain, expanding within its rigid container.

Changes in cerebrospinal fluid pressure are rather variable and are dependent upon a wide variety of physiologic stimuli. There has been some divergence of opinion concerning the possible relationships between changes in cerebral blood flow and spinal fluid pressure.

In earlier studies of the cerebral circulation, Wolff and Lennox observed alterations in the caliber of vessels of the pia in animals (as seen directly through a window in the skull) in response to variations in the oxygen and carbon dioxide content of the blood. Simultaneous changes in the spinal fluid pressure were recorded, an elevation of spinal fluid pressure occurring with dilatation, and a depression with constriction of the pial vessels. Similar observations of changes in the retinal vessels correlated with spinal fluid pressure were made by Cobb and Fremont-Smith. Ferris employed a method of measuring intracranial blood flow by displacement of spinal fluid using the bony cranium as a plethysmograph and obstructing the venous outflow from the cranium. There were certain obvious inherent disadvantages in measuring cerebral blood flow by such indirect and inferential methods. Recent studies, both in animals and in humans have demonstrated correlative changes in cerebrospinal fluid pressure accompanying alterations in cerebral blood flow, as measured by the nitrous oxide method.

The data obtained in our studies corroborate these findings and show additional evidence for this correlation.

METHODS

The subjects utilized in this study were young and middle-aged patients, free from cerebrovascular and neurologic disorders. Nembutal, 0.1 Gm., was administered on the previous evening at bedtime. An additional 0.2 to 0.3 Gm. Nembutal was given in the morning approximately one hour before the study was begun. All patients were in the basal state. There were no instances in which anxiety or muscle tension interfered with the measurements.

A lumbar puncture with an 18-gage needle was performed with the patient in the right lateral position, and a spinal pressure manometer was placed in position. A sufficient period of time was allowed to elapse after the puncture for stabilization of the pressure at a control level. Then the experimental study was begun.

Spinal fluid pressures were measured after intravenous administration of nicotinic acid, procaine hydrochloride, Priscoline, papaverine, and amphetamine, and after inhalation of mixtures of 10 per cent carbon dioxide and 90 per cent oxygen, 5 per cent carbon dioxide and 95 per cent oxygen, and 100 per cent oxygen. Nine hundred cc. of 3 per cent sodium bicarbonate solution were given intravenously, preceded and followed by venous blood pH determinations made on the Cambridge glass electrode, model R, pH meter at 33 C. corrected to 38 degrees by Rosenthal's factor. The effect of active hyperventilation with accompanying pH studies was observed. The spinal fluid pressure was recorded every 30 to 60 seconds during each procedure.

OBSERVATIONS

Nicotinic Acid. One hundred mg. of nicotinic acid given intravenously to eight patients in 30 to 60 seconds produced no measurable effect on...
the spinal fluid pressure. The usual intense facial blush caused by intravenous nicotinic acid was seen in every instance (fig. 1).

**Procaine Hydrochloride.** Spinal fluid pressure remained essentially unchanged in nine subjects after the intravenous infusion of 500 to 1000 mg. of procaine hydrochloride in 15 to 30 minutes. Mild headache, giddiness, blurring of vision, and anxiety occurred in a few patients, but these symptoms did not interfere with continued administration of the drug. No significant change in blood pressure or pulse was noted (fig. 2).

**Priscoline.** An intravenous injection of 100 mg. of Priscoline in one to two minutes failed to alter the spinal fluid pressure in five cases. Flushing of face and upper trunk, suffusion of the conjunctiva, and increased pilomotor activity were seen in each case. The pulse rate generally increased, and the blood pressure response was variable. No apparent change in spinal fluid pressure took place even with the greatest blood pressure increase (fig. 3).

**Papaverine.** The response to 180 mg. of papaverine hydrochloride diluted in 100 to 200 cc. of normal saline was variable. This solution was administered in 10 to 15 minutes, and only three patients experienced a flushing of the skin. Blood pressure in practically all cases showed a mean decline of 10 mm. Hg systolic and diastolic. Pulse rate did not change essentially. In four cases the spinal fluid pressure increased moderately (average 100 mm. water), and in five cases no obvious change was noted (fig. 4).

**Aminophylline.** A mean diminution of 40 mm. H_2O in spinal fluid pressure was evident in eight patients after 0.5 Gm. aminophylline was given intravenously in a period of five minutes. No change was detected in one additional patient (fig. 5).

**Carbon Dioxide (5 to 10 per cent).** The inhalation of mixture of 5 per cent carbon dioxide and 95 per cent oxygen in eight patients and 10 per cent carbon dioxide and 90 per cent oxygen in four patients uniformly caused an immediate marked rise in spinal fluid pressure, usually to levels of 400 to 500 mm. H_2O. There was a precipitous fall to the previous level as
soon as the gas was stopped. Ryder and associates have previously reported similar results (figs. 6 and 7).

One hundred per cent Oxygen. Four patients exhibited a mean fall of 60 mm. H$_2$O in spinal fluid pressure after the inhalation of 100 per cent oxygen, and in one patient there was no change (fig. 8).

Three per cent Sodium Bicarbonate Solution. Administration of 900 cc. of a 3 per cent solution of sodium bicarbonate in 30 to 60 minutes caused a mean elevation of 125 mm. H$_2$O of spinal fluid pressure in eight cases. Venous blood pH determinations were made in six cases immediately before and after the solution caused no alteration of spinal fluid pressure (figs. 9 and 10).

Hyperventilation. Spinal fluid pressure was lowered a mean of 60 mm. H$_2$O by active hyperventilation for a duration of three minutes in four cases, and in three patients no significant change took place. The drop in pressure occurred promptly after two or three deep breaths and reached its lowest point after the
From an analysis of the foregoing material it is believed that alterations in cerebral blood flow induce concomitant changes in the cerebrospinal fluid pressure.

Intravenous nicotinic acid causes no change in cerebral blood flow. No alteration of cerebral blood flow occurs after procaine intravenously in dosage similar to that utilized in this study, and cerebral vascular tone may actually increase. Priscoline by intravenous administration produces a slight decrease in cerebral blood flow. This slight decrease was not reflected by a diminution in spinal fluid pressure in our studies.

In the studies of cerebral blood flow with papaverine it is noted that of a total of 18 subjects 5 showed an actual decrease (attributed to experimental error in the procedure), and in an additional five the increase was minimal. Yet, the over-all mean of this group of 18 subjects reflected a 13 per cent increase in cerebral blood flow, a statistically significant increase. Thus, in calculating the mean per cent change in our spinal fluid pressure subjects, there appears to be an increase of 11 per
Aminophyllin exerts a depression of cerebral blood flow by causing a marked constriction of cerebral vessels. Aminophyllin likewise causes a statistically significant decrease in cerebrospinal fluid pressure ($p < .01$).

The dramatic rise in spinal fluid pressure resulting from inhalation of 5 to 10 per cent carbon dioxide exhibits a striking parallel to the increase in cerebral blood flow caused by this gas.

Kety and Schmidt found a decrease in cerebral blood flow during both active and passive hyperventilation attributable to cerebral vasoconstriction. The decrease in spinal fluid pressure observed in our studies after active hyperventilation is probably statistically significant ($p < .05$).

The alkalosis which results from administration of 3 per cent sodium bicarbonate solution results in a statistically significant ($p < 0.01$) elevation of spinal fluid pressure. This finding is noteworthy inasmuch as Schieve and Wilson

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**Fig. 9.** Patient E. M. Response to 900 cc. 3 per cent sodium bicarbonate.

**Fig. 10.** Patient K. B. Response to 1000 cc. normal saline.

**Fig. 11.** Patient E. H. Response to hyperventilation.
have recently observed a marked increase in cerebral blood flow (approximately 70 per cent) attendant to the intravenous administration of sodium bicarbonate. Accompanying this metabolic alkalosis, they found a rise in blood pH with an increase in arterial carbon dioxide content. A metabolic acidosis was produced by giving 0.3 per cent ammonium chloride intravenously, and a decrease in cerebral blood flow, pH, and arterial carbon dioxide content was evident. These changes in cerebral blood flow are the reverse of those reported in respiratory acidosis and alkalosis and appear to be related to changes in arterial carbon dioxide content rather than to pH. Schieve and Wilson conclude that these observations suggest that arterial carbon dioxide content is of greater importance than pH in the regulation of cerebrovascular tone.

It seems that changes in cerebral blood flow are reflected by similar changes in cerebrospinal fluid pressure in the same direction. The mechanisms by which this occurs are not yet completely elucidated. If increased and decreased cerebral blood flow are associated with cerebral vasodilation and vasoconstriction, respectively (and all available evidence tends to support this concept), it could be hypothesized that the elevations and depressions in spinal fluid pressure are due to the respective increased and decreased volume of the vascular structures of the brain, expanding within its rigid container.

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Relationship between Cerebrospinal Fluid Pressure Changes and Cerebral Blood Flow
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Circ Res. 1953;1:389-395
doi: 10.1161/01.RES.1.5.389

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