SPECIAL ARTICLES

BRAIN WATER MOVEMENT DURING ANESTHESIA

ALTHOUGH dehydration has for nearly half a century[1] been considered a probable accompaniment of anesthesia, apparently direct confirmation of this fact on nerve cells has never been reported. Suggestive analogies, however, have been brought forward in connection with the narcosis of plants. Furthermore Knaffl-Lenz[2] has shown that the swelling of red blood cells in hypertonic saline solutions is prevented by low concentrations of alcohol. He confirmed this with other anesthetics which also dehydrated gelatin plates. Similarly, Kochmann[3] inhibited the acid swelling of fibrin particles by anesthetics. This investigator further found the narcosis of frogs' gastrocnemii by chloroform, chloral and a series of alcohols accompanied in each case by reversible dehydration.

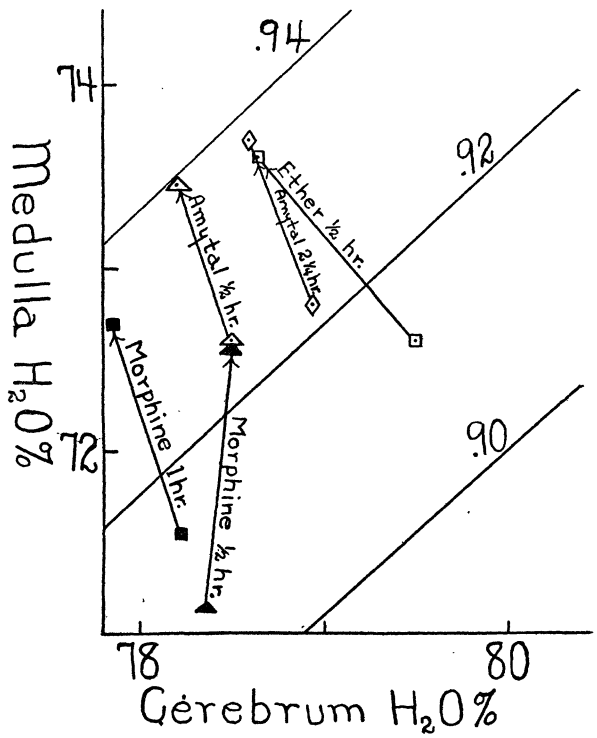
The water content of nerve centers is difficult of investigation, owing to the fact that each determination must be made on a new individual, and statistical data built up for the particular age and conditions of the animals. Apparently this type of investigation has hitherto been attempted only by Haldi[4] who, with Larkin and Wright, obtained results indicating that various anesthetics differ among themselves as to their effect upon the water content of the brain as a whole and of certain subdivisions. Both ether and morphine in three- or four-hour experiments on rabbits increased rather than decreased the water content of the various parts of the brain.

Brain hydration was found on withdrawal of morphine from young adult rats and dogs by Flowers and Dunham[5] working with the writer; this led to an attempt to learn more of the relations of brain water to narcosis. In our first experiments when a single dose of morphine was given to rats, the cerebrum was found somewhat dehydrated after two hours. A year ago, Dunham, Ellerbrook and I, in confirming this fact, showed that several hours after morphine injection the dehydration occurred both in cerebrum and medulla; but *during the first two hours* a marked difference was noted in that while the cerebrum usually lost water, the primary effect upon the medulla was *hydration*. Thus we have in early morphine narcosis a condition in which the ratio medulla H_2O/cerebrum H_2O is markedly increased.

[1] V. E. Henderson, *Physiol. Rev.*, 10: 176, 1930.
[2] E. von Knaffl-Lenz, Pfluger's Arch. Physiol., 171: 51, 1918.
[3] M. Kochmann, *Biochem. Zeitsch.*, 136: 49, 1923.
[4] J. Haldi, J. Larkin and P. Wright, *Amer. J. Physiol.*, 88: 112, 1929.
[5] S. H. Flowers, E. S. Dunham and H. G. Barbour, Proc. Soc. Exper. Biol. and Med., 26: 572, 1929.
H. G. Barbour, B. E. Russell, S. H. Flowers, E. S. Dunham and L. G. Hunter, *Amer. J. Physiol.*, 90: 273, 1929.

The use of the medulla H_2O/cerebrum H_2O ratio tends to minimize individual variations between animals. For example, one rat as a whole might be wetter than another without a change in this ratio. When it does change a possible shift of water from one part of the brain to another is thereby suggested.

Recently Flowers and I have extended the anesthetic work to include amytal and ether, and have confirmed the increase in the medulla H_2O/cerebrum H_2O ratio in rats, and in the case of ether in young rabbits as well. While this ratio is normally around .92, it may rise to nearly .94 in early anesthesia, as shown by the diagonals in the accompanying figure.



The medulla water percentage is plotted as ordinate against the cerebrum water percentage as abscissa, and the dehydration of the cerebrum shown in four out of five cases is quite overshadowed by the hydration of the medulla.

While all the anesthetics mentioned tend to increase the general muscle tone of rats, a true "stage of excitement" occurs only after ether. In the above-mentioned experiments it was brief. Ether excitement intentionally prolonged for half an hour in one rat and two rabbits produced no significant increase in the medulla H_2O/cerebrum H_2O ratio. Furthermore, one half hour muscular activity in an unanesthetized rat gave only a normal figure. Hence the water shift described appears directly associated with the process of *narcosis*, not with preliminary stimulation of any sort.

The results are summarized in the following table where fifteen control rats are seen to have given an average medulla H_2O/cerebrum H_2O ratio of .922 ± .003, while thirteen morphinized rats gave an average ratio of .939 ± .007.

TABLE

Condition	Duration	Average Medulla H_2O / Cerebrum H_2O	
		Rats (No.)	Rabbits (No.)
Anesthesia:			
Morphine sulfate	½–2½ hrs.	(13) .939 ± .007*	
Amytal	½–2½ hrs.	(5) .931	
Ether	½ hr.	(1) .936	(2) .933
Excitement:			
Ether	½ hr.	(1) .928	(2) .920
Muscular activity	½ hr.	(1) .924	
Controls (normal)		(15) .922 ± .003*	(3) .926

* Standard deviation of the average.

The above findings (which we plan to report more completely in *The American Journal of Physiology*) are entirely consistent with the conception that anesthesia in mammals is associated with the dehydration of nerve cell bodies. It is conceivable that early in narcosis the colloidal condition of the cells is altered in such a way as to extrude water (*cf.* Claude Bernard's semi-coagulation theory[6] or Hirschfelder's[7] demonstration of lessened lipoid dispersion).

Dehydration of the cerebrum is the rule, at least in rats. The extra water taken on by the medulla not only may be located entirely outside of the nerve cells but may even be derived from the nerve cells of both medulla and cerebrum. The interfibrillar spaces may well serve as a temporary storehouse for water during readjustments of brain pressure and the like. At all events our results indicate that the first accompaniment of brain narcosis is a temporary storage of water in the medulla, partly at the expense of the cerebrum.

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METALLIZED FOOD IN THE REGENERATION OF HEMOGLOBIN IN RAT AND MAN

To eliminate the acidity of salt solutions used in the regeneration of hemoglobin in animals made anemic by deficient diets, Fe, Co, Mn and Cu were dissolved directly in milk while in the ice box.[1,2,3] After 12 hours half the milk was used after being shaken, and the balance was shaken and used 12 hours later. The metals were washed and placed in fresh milk for the next day and so on. In this way enough of the metals dissolve in milk to supply the requirements for rapid hemoglobin regeneration in rat and man, as seen below.

On April 22, 1929, two dozen young white rats, reduced to 75 per cent. hemoglobin by feeding on pure raw milk, were equally divided in two identical cages, A and B, Fig. 1, and each rat was then fed

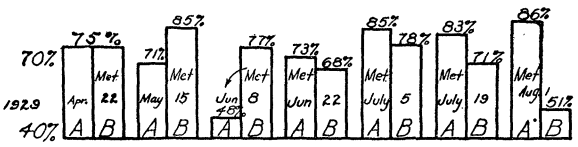

FIG. 1

50 cc of raw milk per day, free from metallic contact in its production and storage.[4] Into the 600 cc of milk for group B 181 gms of Fe, Co, Mn and Cu in alloy form were placed each day for the two feedings. A was the first and B the latter control. All hemoglobin is reported in percentage (Newcomer). The second and third graphs of Fig. 1 show the percentage *differences* after three and six weeks, being respectively 14 per cent. and 29 per cent. on May 15 and June 8. On June 8 the alloys were transferred from the milk for B to that for A. In 14 days group A average hemoglobin had risen from 48 per cent. to 73 per cent., while that of B had fallen from 77 per cent. to 68 per cent. as per the fourth graph. Progressive, average percentage differences increased as seen in the fifth, sixth and last graphs, when on August 1, 6 per cent. beyond a complete reversal appeared in average per cent. hemoglobin of the two groups. Tangents drawn to A and B of the third group and to B and A of the last group meet almost at right angles. Note that B on May 15 equals A on August 1, both with metals. Group B shows evidence of some metal retention by a very gradual decline in hemoglobin during 8 weeks. Fig. 1 shows remarkable hemoglobin control by a metallized diet.

In order to compare the hemoglobin regenerative effects of direct metallization with salt effects, the tests of Fig. 2 were made. The average hemoglobin of the rats studied in the 7 cages of Fig. 2 had dropped on a pure milk diet to 38 per cent., and all

[6] The current work of Bancroft and Richter (Proc. Nat. Acad. Sci., 16: 573, 1930., and *J. Phys. Chem.*, January, 1931) contributes striking evidence that narcotics produce a reversible semi-coagulation.

[7] A. D. Hirschfelder, *J. Pharmacol. and Exper. Therap.*, 37: 399, 1929.

[1] Clarice M. Burns, *Biochem. Jnl.*, 32: 5, 860.

[2] Elvehjem and Hart, *J. Biolog. Chem.*, 84: 131, 1929.

[3] Waddell and Steenbock, *J. Biolog. Chem.*, 84: 115, 1929.

[4] Lewis, Weischelbaum and McGhee, *Proc. Soc. Exp. Biol. and Med.*, 27: 329, 1930.