BODY WATER IN EPILEPSY*

BY

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Epilepsy, one of the first maladies to be described, still remains a subject for investigation. Experimentally, fits have been produced in animals by overhydration and controlled by dehydration. Moreover, dehydration has been used with some success as a therapeutic measure in epilepsy, the electroencephalogram showing improvement as a result.

Although previous work indicates that disturbance of body fluid distribution plays an important part in the production and prevention of fits, the relation between the distribution of extracellular water and total body water in epilepsy is not so well established. In the present work, with the object of elucidating this problem further, a comparison has been made of the values found for extracellular water and total body water in a group of epileptic and non-epileptic subjects in the same age range.

All those investigated were males whose ages ranged from 18 to 66 years, 18 were epileptic and 38 non-epileptic. In the epileptics the length of history varied from 2½ to 40 years.

The subjects were prepared for the test by giving a low protein diet and ample fluid the day before. On the morning of the test, after recording the height and weight, a self-retaining catheter was passed, the bladder emptied completely, and the time noted. The urine was discarded and all further samples were related to this zero time.

Methods

Total body water was measured by the urea method (McCance and Widdowson, 1951). In 17 patients we found good agreement ($r=0.94$) between this method and that using N.A.A.P. (N-acetyl-4-aminoantipyrine) (Brodie *et al.*, 1949), measurements with N.A.A.P. having been found to correspond closely with those made with deuterium oxide. The extracellular space was measured with sodium thiosulphate (Cardozo and Edelman, 1952). When this method was compared with inulin for measurement of extracellular space, the correlation was also highly significant ($p=0.96$). Serum sodium was estimated by flame photometry.

Measurement of Extracellular Space.—A blank sample of 10 ml. of venous blood is collected, the skin having been anaesthetized with 2% procaine solution. An intravenous drip of 1 litre of 5% dextrose in water is then set up to run at 120 drops per minute. Into the tubing of the drip is injected 10 g. of 50% sodium thiosulphate, taking 10 minutes

over the injection. The exact time is noted at the beginning and on completion of the injection. A further 100–120 ml. of glucose is then run through the drip at the same rate to wash through the sodium thiosulphate; thereafter the drip can be dismantled. Blood samples, taken if possible without venous stasis, are collected through a heparinized Gordh needle, at 10-minute intervals, rejecting the first 2 ml., the first sample being taken 10 minutes after the injection of sodium thiosulphate.

Urine samples are collected at 30, 60, and 90 minutes after the injection for determination of thiosulphate excretion rate and for use as blanks in the determination of basic urea excretion rate for estimation of total body water.

Measurement of Total Body Water.—As soon as the two blank urine samples have been collected, 2.5 g. of urea per stone (0.4 g. per kg.) body weight is given orally. The time is noted when all the urea has been taken. Urine is collected 90, 150, and 210 minutes after giving the urea, and venous blood samples are taken half-hourly for two hours to ensure that the peak concentration of urea in the blood is obtained, thereafter one or two more blood samples are taken at hourly intervals.

Results

The mean weight of the epileptic subjects was 65.6 kg. and of the non-epileptics 64.0 kg.

The mean total body water, expressed as percentage of body weight, was $70.3\% \pm 7.7\%$, with a range of 50.1–86.4%, in the non-epileptics (Table I), and $66.6\% \pm 7.5\%$,

TABLE I.—*Extracellular Water (Litres) and Total Body Water (Litres) as Percentage of Body Weight (kg.) in Normal and Epileptic Subjects*

	Normals (38 Cases)	Epileptics (18 Cases)	"t" Test
E.C.W. Body wt. % { Mean Range	17.8 S.D. ± 3.1 15.3–23.8	19.4 S.D. ± 3.7 13.3–28.7	} $p=1.74$. Not significant at 0.05 level
T.B.W. Body wt. % { Mean Range	70.3 S.D. ± 7.7 50.1–86.4	66.6 S.D. ± 7.5 52.4–84.8	

with a range of 52.4–84.8%, in the epileptics. According to Student's "t" test this difference between the means is not significant ($p=1.75$). The mean value for extracellular water, expressed as percentage of body weight, in the non-epileptic group was $17.8\% \pm 3.1\%$, with a range of 15.3–23.8%, and in the epileptic group $19.4\% \pm 3.7\%$, with a range of 13.3–28.7%. The difference is not significant ($p=1.74$).

Absolute values for total body water also do not differ significantly in the two groups (Table II). In the non-epileptics the mean for total body water was $44.9 \text{ l.} \pm 6.4 \text{ l.}$,

TABLE II.—*Extracellular Water and Total Body Water in Normal and Epileptic Subjects*

	Normal (38 Cases)	Epileptics (18 Cases)	"t" Test
E.C.W. (litres) { Mean Range	11.30 S.D. ± 1.76 7.9–15.1	12.49 S.D. ± 3.1 10.6–18.0	} $p=2.3$. Significant at 0.05 level
T.B.W. (litres) { Mean Range	44.9 S.D. ± 6.4 32.1–60.3	43.4 S.D. ± 6.8 35.1–53.6	

range 32.1–60.3 l., and in the epileptics the mean was $43.4 \text{ l.} \pm 6.8 \text{ l.}$, the range being 35.1–53.6 l. The difference between the absolute values for extracellular water was found to be significant. In the normal group the extracellular water in litres measured 11.3 ± 1.76 , with a range of 7.9–15.1 l. In the epileptics the mean was $12.5 \text{ l.} \pm 3.1 \text{ l.}$, with a range of 10.6–18.0 l., the difference being significant at the 0.05 level ($p=2.3$).

When the ratio of extracellular water to total body water expressed as a percentage was compared in the non-epileptic and epileptic groups, the significance of the difference between the two groups becomes more evident (Table III). In the non-epileptic group the mean E.C.W./T.B.W.% was

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TABLE III.—*Extracellular Water (Litres) as Percentage of Total Body Water (Litres) in Normal and Epileptic Subjects*

	Normal (38 Cases)	Epileptics (18 Cases)
E.C.W./T.B.W. % { Mean	25.3 S.D. $\pm$ 3.4	29.0 S.D. $\pm$ 5.1
T.B.W. % { Range	18.9–32.8	22.7–35.9

"t" test: $p=3.7$. Significant at 0.01 level

25.3 ± 3.4 , range 18.9–32.8, whereas in the epileptics it was 29.0 ± 5.1 , range 22.7–35.9. This difference is significant at the 0.01 level ($p=3.7$).

Of the epileptic patients 10 were in the age group 18–45 and 8 were between the ages of 46 and 66 (Table IV). The mean E.C.W./T.B.W.% in the 10 epileptics aged 18–45 was 29.7, range 22.7–35.9, and in the 8 aged 46–66 it was 29.2, with a range of 24.5–32.6. No significant difference was found between the means in these two age groups.

The epileptics have also been grouped according to the frequency of fits: six had fits once a week to once a month, eight had fits once every few months, and four had fits

TABLE IV.—*Extracellular Water (Litres) as Percentage of Total Body Water (Litres) in Epileptics Aged 18–45 Years and 46–66 Years*

	Epileptics Aged 18–45 Years (10 Cases)	Epileptics Aged 46–66 Years (8 Cases)
E.C.W./T.B.W. % { Mean	29.7	29.2
T.B.W. % { Range	22.7–35.9	24.5–32.6

"t" test: $p=0.124$. Not significant at 0.05 level.

TABLE V.—*Extracellular Water (Litres) as Percentage Total Body Water (Litres) in Epileptics With (a) Frequent Fits, (b) Moderately Frequent Fits, and (c) Infrequent Fits*

	Group A (6 Cases)	Group B (8 Cases)	Group C (4 Cases)
E.C.W./T.B.W. % { Mean	32.5	28.2	25.0
T.B.W. % { Range	31.0–33.6	22.7–35.9	23.8–27.5

"t" test (A–B): $p=2.7$. Significant at 0.02 level.

"t" test (A–C): $p=3.9$. Significant at 0.01 level.

rarely (Table V). In these groups the mean value found for E.C.W./T.B.W.% was 32.5, 28.2, and 25.0 respectively. Applying the "t" test, a significant difference was found at the 0.02 level ($p=2.7$) between the means of the group with frequent fits and the group with moderately frequent fits, and a more highly significant difference at the 0.01 level ($p=3.9$) was found when the group with frequent fits was compared with the group who rarely had fits or with normals.

The average total sodium in the extracellular space of epileptic and non-epileptic patients was 1,416 and 1,216 mEq respectively.

Comment

For comparative study, data concerning body fluid measurements are usually related to body weight or surface area; that this is not satisfactory, owing to the individual variation in fat mass, is discussed in other work under preparation. A more accurate baseline is the lean body mass.

Pace and Rathbun (1945) have shown that, irrespective of the species of animal investigated, the total body water calculated on a fat-free basis is approximately constant at 73%. From this it follows that the lean body mass (fat-free) can be calculated from the total body water (T.B.W./0.73 = L.B.M.). As the lean body mass bears a constant relationship to the total body water, the ratio E.C.W./T.B.W. should provide a more valuable index of normality in regard to body fluid distribution than data related to body weight, in which the relatively anhydrous fat mass comes into consideration.

Our findings confirm this observation; thus when values for extracellular water in the epileptic and non-epileptic series are related to body weight no significant difference was found between the means of the two groups owing to the fact that the epileptic patients were, on average, 1.6 kg. heavier than the non-epileptic subjects.

The ratio E.C.W./T.B.W., however, was found to be significantly different in the epileptics as compared with the non-epileptics; moreover, this difference was more significant in the epileptics with frequent fits, indicating a greater increase in extracellular water in these patients as compared with those who had fewer seizures. Age was not a factor in producing this change.

The significant difference found in the absolute quantity of extracellular water, and in the ratio E.C.W./T.B.W., between the epileptic and non-epileptic group was not due to a difference in the "variance ratio" in the two groups, and can be regarded as representing a real increase of extracellular fluid in epileptic patients as compared with non-epileptic subjects. Since the total body water in litres does not differ significantly in either group, there must also be a relative intracellular dehydration in the epileptics, the degree varying with the amount of extracellular water.

The total increase of sodium found in the extracellular fluid in the epileptic group is associated with the increase of fluid in the extracellular space in epileptics as compared with the non-epileptics.

As all the epileptics were investigated in the interval between attacks our results suggest that an increase of extracellular fluid is always present in epileptics, and it is this which predisposes them to seizures, a finding which is in agreement with the observation of Dandy (1923), who noted in chronic epilepsy abnormal deposition of fluid, especially over the frontoparietal areas of the brain. Furthermore, Pancoast and Fay (1929), in encephalographic studies on epileptics, also found increase of supracortical fluid to be a constant feature in the well-established case of epilepsy.

The beneficial results reported from treatment such as starvation (Guelpa and Marie, 1911), dehydration (Gamble, 1930; Fay, 1930), ion-exchange resins (Klingman, 1954), and acetazolamide (Ansell and Clark, 1956), which probably also depend to some extent on the loss of fluid and sodium from the extracellular space, add further support to our findings.

In conclusion, as an increase of extracellular fluid has been found a constant feature in epilepsy, it would seem that restriction of sodium in the diet is a rational approach in the treatment of this malady.

Summary

The total body water and extracellular water has been measured in 18 epileptics and 38 non-epileptic patients. The total body water did not differ significantly in the two groups. A significant difference was found in the amount of extracellular water, and in the ratio E.C.W./T.B.W. in epileptics as compared with non-epileptics. There is a relative intracellular dehydration in epileptics. The significance of these findings in relation to treatment is commented upon.

REFERENCES

- Ansell, Barbara, and Clark, E. (1956). *Brit. med. J.*, 1, 650.
 Brodie, B. B., Axelrod, J., Soberman, R., and Levy, B. B. (1949). *J. biol. Chem.*, 179, 25.
 Cardozo, R. H., and Edelman, I. S. (1952). *J. clin. Invest.*, 34, 245.
 Dandy, W. E. (1923). *Bull. Johns Hopk. Hosp.*, 34, 245.
 Fay, T. (1930). *Arch. Neurol. Psychiat.* (Chicago), 23, 920.
 Gamble, J. L. (1930). *Ibid.*, 23, 915.
 Guelpa, G., and Marie, A. (1911). *Rev. Thér. méd.-chir.*, 78, 8.
 Klingman, W. O. (1954). *Amer. J. Psychiat.*, 111, 184.
 McCance, R. A., and Widdowson, E. M. (1951). *Proc. roy. Soc. B*, 138, 115.
 Pace, N., and Rathbun, F. N. (1945). *J. biol. Chem.*, 158, 685.
 Pancoast, H. K., and Fay, T. (1929). *Amer. J. Roentgenol.*, 21, 421.