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THE SIGNIFICANCE OF BLOOD AND CEREBROSPINAL FLUID UREA LEVELS ESTIMATED AFTER DEATH

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Doubt exists regarding the significance and diagnostic value of raised urea levels found in blood and cerebrospinal fluid after death. Harrison (1947), for instance, considers that in the present state of knowledge of post-mortem chemistry such estimations are without value, as high results are often obtained in moribund patients without kidney disease, and he also suggested that post-mortem changes occur which might influence the urea level. Some workers found post-mortem blood and C.S.F. urea estimations of limited value (Polayes, Hershey, and Lederer, 1930; Hamilton, 1938; Naumann, 1949, 1950; Tarsitano, 1950), but none of them attempted to determine by repeated estimations the degree of change in the blood urea level during the important agonal period.

It may be of value when considering a cause of death to know whether a high post-mortem urea level represents an agonal rise, a post-mortem change, or urea retention during life with or without renal damage.

This paper concerns the relationship of the pre-agonal and agonal blood urea levels to the post-mortem blood and C.S.F. levels, and an interpretation of the results in the light of the clinical and full post-mortem findings. The conclusion reached is that post-mortem urea levels, particularly those in C.S.F., are of value in diagnosis.

Material

Thirty-eight cases were investigated. Most of them came from the wards of a general hospital, and many of these were studied during life, up to and including the moment of death. Further study was then made at necropsy. Other cases came to post-mortem examination via the coroner, and full details of previous health and mode of death were available.

Cerebrospinal fluid was obtained after removal of the brain by inserting a Pasteur pipette through the infundibulum into the third ventricle and applying gentle suction. In two cases a succession of post-mortem samples of C.S.F. was obtained by cisternal puncture followed by the usual sample from the third ventricle later.

In 17 instances a sample of blood was also removed from the right ventricle of the heart at the time of necropsy, and the urea content estimated. On 12 occasions arm vein samples of blood were taken for urea estimation within the first few minutes after death.

Methods

All urea estimations were performed by the urease-nesslerization technique using a Klett colorimeter. Samples of blood and C.S.F. were refrigerated until the test could be performed, which was always within 24 hours of the time of collection.

Results

The cases are divided into four groups. The first is a control group of six sudden deaths in apparently healthy persons. The second consists of 19 cases of uraemia. The third is composed of nine instances of pre-renal urea retention. The fourth is a miscellaneous group of four cases.

Group 1: Sudden Death in Presumed Non-azotaemic Individuals.—In order to ascertain whether a normal C.S.F. urea level alters appreciably after death, six cases of sudden death were investigated in which, on clinical and pathological evidence, normal ante-mortem levels could confidently be inferred. Two were the result of road accidents, three were due to coronary occlusion, and one was a homicidal cut throat.

Some of the cadavers were examined in the summer and some in the winter, and none of them had been placed in a refrigerator until at least eight hours after death.

The urea levels found in the C.S.F. in these cases were 50, 33, 34, 38, 36, and 22 mg. per 100

ml. respectively at times from 19 to 72 hours after death. All these figures were normal for the respective ages.

Group 2 : Renal Uraemia.—This group consists of 19 cases where uraemia from kidney disease had been given as a cause of death by other observers on clinical and pathological grounds.

From Table I it will be seen that the post-mortem C.S.F. urea levels agreed well with the ante-mortem blood levels where the latter had been estimated within three days of death. The post-mortem blood levels, when known, were always higher than the corresponding C.S.F. figures.

Correlation is good in every case in spite of the fact that the times between death and the taking of samples of C.S.F. had varied from nine hours to four days, and that the bodies had been stored at different temperatures after death.

In four of the seven cases where blood levels were estimated within a few minutes after death, the levels in the blood taken from the right ventricle of the heart at necropsy, from 13 to 37 hours later, showed an increase of as much as 54 mg. per 100 ml.

TABLE I

UREA LEVELS (MG. PER 100 ML.) IN RENAL URAEMIA

Case No.	Ante-mortem Blood	Agonal Blood	Post-mortem Level		Cause of Death
			Blood	C.S.F.	
7	325 (3 days)*	—	—	290 (24 hrs.)†	Amyloid spleen and kidneys with T.B. of lung and intestine
8	235 (3 ,,) 400 (1 day)	—	—	360 (60 ,,)	Chronic pyelonephritis in a sole kidney
9	392 (4 days) 512 (1 day)	—	—	390 (72 ,,)	Chronic glomerulonephritis
10	178 (2 days)	242	296	238 (13 ,,)	Cardiac failure and acute nephritis
11	375 (1 day)	—	—	400 (48 ,,)	Malignant hypertension
12	173 (10 days)	—	—	400 (96 ,,)	Pyelonephritis
13	290 (6 ,,) 390 (2 ,,)	—	—	323 (48 ,,)	Chronic pyelonephritis
14	490 (3 hrs.)	560	600	570 (21 ,,)	Chronic glomerulonephritis
15	395 (5 days) 720 (2 ,,)	—	—	880 (38 ,,)	Chronic glomerulonephritis
16	466 (6 ,,)	—	520	440 (9 ,,)	Diabetic glomerulosclerosis
17	560 (9 hrs.)	—	540	450 (14 ,,)	Hydronephrosis
18	736 (1 day)	924	—	900 (20 ,,)	Chronic pyelonephritis
19	261 (3 days) 371 (15 hrs.)	—	378	350 (13 ,,)	Pyelonephritis
20	412 (1 day) 410 (10 hrs.)	400	— — 440	395 (13 ,,) 393 (17 ,,) 438 (37 ,,)	Chronic glomerulonephritis
21	210 (3 days)	390	394	344 (20 ,,)	Hydronephrosis
22	394 (2 ,,) 576 (9 hrs.)	—	596	422 (14 ,,)	Chronic glomerulonephritis
23	379 (3 days)	580	576	498 (52 ,,)	Malignant hypertension
24	494 (3 ,,) 580 (1 day)	668	682	536 (13 ,,)	Uraemia due to polyarteritis nodosa
25	440 (½ hr.)	—	—	440 (24 ,,)	Chronic nephritis

* Figures in brackets represent time before death.
† Figures in brackets represent time after death.

Four cases have been placed in this group when on clinical grounds a raised urea level could be attributed to pre-renal causes and where necropsy showed the kidneys to be normal. Cases where both renal and pre-renal factors operated are included in the miscellaneous Group 4.

Nine cases were investigated and the results are shown in Table II. The post-mortem C.S.F. levels varied between 56 and 300. The wide variation of results is similar to the variation observed in this type of case when investigated during life.

TABLE II

UREA LEVELS (MG. PER 100 ML.) IN PRE-RENAL UREA RETENTION

Case No	Ante-mortem Blood	Agonal Blood	Post-mortem Levels		Cause of Death
			Blood	C.S.F.	
26	46 (2 days)	—	—	80 (36 hrs.)	Paralytic ileus following colostomy for carcinoma of rectum
27	220 (5 hrs.)	—	—	300 (15 ,,)	Perforation at site of gastroenterostomy; paralytic ileus
28	46 (17 days)	—	—	188 (52 ,,)	Paralytic ileus after transplantation of ureters
29	66 (2 ,,) 101 (19 hrs.)	142	154	114 (24 ,,)	Cardiac failure due to coronary atheroma
30	88 (2 days)	—	—	150 (10 ,,)	Cirrhosis of liver; gross ascites and oedema
31	86 (9 hrs.)	132	—	98 (17 ,,)	Carcinoma of lung with secondaries
32	53 (9 ,,)	—	54	56 (14 ,,)	Cardiac failure; mitral stenosis
33	49 (6 days)	70	82	58 (15 ,,)	Cardiac failure; coronary atheroma
34	67 (6 ,,)	126	140	94 (24 ,,)	Hypostatic pneumonia; hypoplastic anaemia

Case 29 shows a terminal rise in blood urea of 41 mg. per 100 ml. within the last 19 hours of life, and 24 hours after death an even further rise of 12 mg. per 100 ml. in the blood, whereas the C.S.F. level is similar to the pre-agonal blood level.

Likewise, Cases 31 and 33 do not show the agonal increase in the post-mortem C.S.F. urea levels which have occurred in the blood. In Case 30 death was due to liver failure, and we should therefore expect to find a normal or low urea level. That a level of 150 was found in the C.S.F. after death is probably explained by the fact that there had been a gross accumulation of fluid in the abdominal cavity necessitating frequently repeated paracenteses before death with resulting severe diversion of fluid from the kidneys, and, therefore, pre-renal urea retention of a moderate degree.

Group 4: Miscellaneous Conditions.—These cases, for various reasons, do not fit into any of the preceding groups. The results are shown in Table III.

TABLE III
MISCELLANEOUS CASES

Case No.	Ante-mortem* Blood	Agonal Blood	Post-mortem Levels		Cause of Death
			Blood	C.S.F.	
35	40 (2 days)	—	28	28 (10 hrs.)	Haemochromatosis; liver failure
36	136 (1 day)	—	144	151 (14 ,,)	Diabetic coma; benign hypertensive changes in kidneys
37	73 (1 ,,)	—	—	132 (12 ,,)	Pulmonary embolism; chronic pyelonephritis and hypertension
38	135 (10 days) 137 (1 day) 134 (5 hrs.)	170	— — 198	132 (24 ,,) 142 (48 ,,) 120 (72 ,,)	Cerebellar haemorrhage; diabetic glomerulosclerosis and hypertension

* Urea levels expressed as mg. per 100 ml.

Case 35 is one of liver failure showing a drop in urea level from 40 in the blood two days before death to 28 in the blood and C.S.F. 10 hours after death.

Case 36 is considered to be one of extra-renal uraemia in a man dying in diabetic coma. The case could not be placed in Group 3, however, because mild benign hypertensive changes were found in the kidneys histologically. There is no evidence of diabetic glomerulosclerosis.

Cases 37 and 38 showed a severe degree of renal damage with evidence, during life, of kidney failure. The progress of the kidney disease in each instance was terminated unexpectedly by death from pulmonary embolism in the former and by cerebellar haemorrhage in the latter. The post-mortem C.S.F. urea levels record, fairly accurately, the degree of renal failure existing before death. In Case 38 it was possible to follow urea levels in the blood right up to the time of death. An agonal rise of nearly 40 mg. per 100 ml. occurred in the blood within the last five hours of life. There was also a rise in the urea content in the blood after death amounting to 28 mg. per 100 ml. in 72 hours. However, the C.S.F. urea levels after death bear close relation to those found in the blood during life before the agonal rise took effect. The small differences in the daily post-mortem C.S.F. urea levels arose because the first two specimens obtained by cisternal puncture were contaminated with blood, whereas the third specimen procured directly from the infundibulum was not so contaminated.

Discussion

Urea is an easily diffusible non-electrolyte (Eggleton, 1930; Folin and Berglund, 1922) and is thus found in fairly uniform concentration in most tissues and fluids of the body during life.

Studies on the C.S.F. and aqueous humour of the eye led Walker (1933) to the conclusion that the choroidal and ciliary epithelia exhibit selective qualities with regard to urea and that neither the C.S.F. nor the aqueous humour urea levels are controlled by a simple process of filtration. On the other hand, Fremont-Smith, Dailey, Merritt, Carroll, and Thomas (1931) found the C.S.F. to be in osmotic equilibrium with the plasma, but state that after any change in the blood there is a latent period of perhaps many hours before the C.S.F. regains equilibrium. Many other investigators who uphold this diffusion theory (Myers and Fine, 1919; Cullen and Ellis, 1915) agree that there is a considerable lag in the attainment of equilibrium after a change in the plasma content.

During the moribund state, when the renal circulation is failing, with consequent urea retention, it is conceivable that a simultaneous failure of the circulation in the choroidal plexus prevents the raised blood level being "transmitted" to the C.S.F.

On three occasions specimens of blood were obtained within a matter of hours before death followed by a further specimen taken within the first few minutes after death in the same patient. The ante-mortem values of 490, 86, and 134 mg. per 100 ml. rose to 560, 132, and 170 mg. per 100 ml. respectively at death. The post-mortem C.S.F.

values of 570, 98, and 120 did not show the agonal rise in two cases.

Increases in the blood urea levels were found to occur between the time of death and the time of necropsy in seven cases. They ranged from 2% to 22% of the blood levels at death, but bore no quantitative relationship to the time after death at which they were estimated or to the degree of urea retention existing at the time of death. Such increases might be due to continued urea production by the liver after death or to the formation of ammonia (which is included as urea in the test) from protein breakdown by enzyme or bacterial activity.

The post-mortem C.S.F. urea levels in these cases were the same as, or somewhat lower than, the blood levels at death. It is therefore suggested that the C.S.F. is shielded by its secluded situation from the post-mortem increases of urea in the blood. The post-mortem C.S.F. urea level can therefore be taken as a reliable guide of the state of ante-mortem urea retention in the phase of the illness immediately preceding the moribund state, provided the latter state is not very prolonged.

Even where the blood or C.S.F. figures at necropsy have shown a change from the pre-agonal blood level, the differences have been so small in this series that not once would they have misled the pathologist in his interpretation of the case.

The values in the renal failure group have a much higher average than those in the pre-renal urea retention group, but there is such a marked overlap that the segregation of cases into one or other of these groups on post-mortem urea levels alone cannot be recommended. Naumann (1949) has shown that when a high post-mortem C.S.F. urea level is found in the absence of comparable kidney disease a post-mortem urinary analysis will often help to rule out renal causes. In such cases, one of the several causes of pre-renal azotaemia should be found.

In 10 cases in this series urea retention had no bearing on the cause of death, as judged by both the clinician and pathologist. These cases gave much lower post-mortem C.S.F. urea levels, varying from normal to 151, with an average of 64.

This investigation suggests that a normal C.S.F. urea level found at necropsy will rule out uraemia as a cause of death.

Allen (1951), quoting from the work of Naumann, agrees that the C.S.F. appears more dependable than the blood for urea determinations but remarks that the former is not so easily secured. No such difficulty was encountered in this investigation, but a further advantage is that the C.S.F. is still readily available towards the end of a post-mortem examination, when other findings may have led one to consider uraemia as a cause of death.

Summary

Post-mortem C.S.F. urea levels at varying periods after death were found to correlate closely with ante-mortem blood levels and with the clinical and pathological features of the case.

The post-mortem blood levels, though agreeing fairly well with the ante-mortem blood levels, were found to be less reliable than those of the C.S.F.

No anomalous results were found in a series of 38 cases.

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References

Allen, A. C. (1951). *The Kidney*, p. 76. Grune and Stratton, New York.
Cullen, G. E., and Ellis, A. W. M. (1915). *J. biol. Chem.*, **20**, 511.
Eggleton, P. (1930). *J. Physiol., Lond.*, **70**, 294.
Folin, O., and Berglund, H. (1922). *J. biol. Chem.*, **51**, 395.
Fremont-Smith, F., Dailey, M. E., Merritt, H. H., Carroll, M. P., and Thomas, G. W. (1931). *Arch. Neurol. Psychiat., Chicago*, **25**, 1271.
Hamilton, R. C. (1938). *Arch. Path., Chicago*, **26**, 1135.
Harrison, G. A. (1947). *Chemical Methods in Clinical Medicine*, 3rd ed., p. 99. Churchill, London.
Myers, V. C., and Fine, M. S. (1919). *J. biol. Chem.*, **37**, 239.
Naumann, H. N. (1949). *Arch. Path., Chicago*, **47**, 70.
—— (1950). *Amer. J. clin. Path.*, **20**, 314.
Polayes, S. H., Hershey, E., and Lederer, M. (1930). *Arch. intern. Med.*, **46**, 283.
Tarsitano, F. (1950). *Folia med., Napoli*, **33**, 310.
Walker, A. M. (1933). *J. biol. Chem.*, **101**, 269.