CC. ON THE MECHANISM OF ACIDOSIS IN EXPERIMENTAL URANIUM NEPHRITIS.

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IN a series of publications concerned with the mechanism of changes in the blood and urine in experimental uranium nephritis, which were studied by the method of double-crossed circulation of Brull [1931], it was stated: (1) that the glycosuria and albuminuria of this nephritis are of purely renal origin [Brull and Fanielle, 1931; Weekers, 1934], (2) that the initial polyuria is due to substances transmitted by the blood [Brull and Fanielle, 1931], (3) that this polyuria is independent of the increased blood-flow which generally occurs [Brull and Roersch, 1933, 1, 2], (4) finally, that the nephritic blood is not immediately toxic for the kidney, since this blood is able to induce considerable hyperactivity in normal kidneys which it perfuses [Brull and Fanielle, 1931].

The present part of our research relates to the mechanism of the profound acidosis noticed by all investigators who have studied the alterations of acid-base equilibrium in acute uranium nephritis.

In a recent series of papers Csapo and co-workers [1932] concluded that the acidosis after ligation of the ureters is due to accumulation of organic acids in the blood. Similar findings were made by Brühl [1933] in human nephritis. The old question of acidosis produced by accumulation of organic acids was thus revived, but we shall not here discuss this matter further [*cf.* Straub and Schleyer, 1912; Poulton and Ryffel, 1913].

The present publication deals with a series of experiments performed in order to discriminate between the relative parts of nephritic retention on the one hand, and of eventual toxic overproduction of acids on the other, in the causation of the acidosis.

Technique.

Dogs were kept in metabolism cages on a known diet, urine and in one case faeces and vomited matter and also intake being analysed every day for acids and bases. Blood was taken before injection of uranium nitrate (6 mg./kg.) and at the end of the experiments (6 or 7 days after intoxication).

Chemical methods. p_H of blood by Cullen's method, with electrometric control (electrode of Vlès and Vellinger [1927]); of urine with Sb electrode of the same authors. CO_2 of true plasma by Van Slyke's manometric method; in urine no CO_2 determinations were made (the low p_H excluding significant amounts). Total bases as described by Van Slyke and Peters [1932], the precipitates being collected on Jena glass filters. Cl by Rusznyak's [1921] method. Sulphate in serum gravimetrically as $BaSO_4$; in urine by the benzidine method. Inorganic phosphate in blood and urine either by Bell and Doisy's colorimetric method or micro-gravimetrically as strychnine phosphomolybdate. Protein and non-protein-nitrogen by micro-Kjeldahl. Ammonia in urine by Yovanovitch's method [1925]. The biscuit given in one experiment was analysed for N, Ca, Mg, SO_4 after slow dry combustion in the electric oven and for Cl and P by wet combustion.

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EXPERIMENTAL.

Three dogs were used. Nos. I and II weighing 14.5 and 18 kg. received respectively every day 500 and 750 g. raw meat and distilled water *ad lib.* No vomiting occurred.

No. III received 160 g. biscuit, 15 g. fresh butter, 3 drops of lemon juice and distilled water. This food was taken regularly up to the second day after injection. A little vomiting occurred during the two following days. The next day only half of the daily intake was given and 22.6 g. dry matter were vomited. On the last day nothing was given. The daily intake contained 1.25 g. N, 36 milliequiv. Ca, 17.4 milliequiv. Mg, 3 milliequiv. Cl, traces of S and 46 milliequiv. P.

In the two first experiments urine was analysed alone, in the last one faeces were examined. The average daily faecal output before uranium was: 8.8 g. dry matter with 0.16 g. N, and, in milliequiv., 22 Ca, 6.8 Mg, 0.003 Cl and 11.2 P. After intoxication the figures were 13.8 dry matter, 0.22 g. N, and, in milliequiv., 25 Ca, 6.2 Mg, 0.004 Cl and 22 P. Together with the increase of faecal output, phosphate output goes up. As a result the excess of Ca + Mg over P drops from 17.6 to 9.1 milliequiv. which might mean an average saving of bases of 8.5 milliequiv. a day (unless S excretion changes). On the whole the faecal changes seem to be of secondary importance.

Urine analysis in milliequivalents per 24 hours for acids and bases, the average figures being given only. Separate determinations were made every day.

No. of exp.	Period	Volume ml.	N	NH ₃	NH ₃ -N %	Fixed bases	Cl	P	S	Total inorganic acids	Organic acids
I	Before uranium, 5 days	385	16.5	34.5	3.2	36.8	7.4	49.7	25.0	82.1	44.3
	After uranium, 7 days	830	8.3	14.7	2.6	47.0	6.5	76.3	32.7	105.5	67.1
	Variations, m. equiv.	+355	- 8.2	-19.3	—	+10.2	-0.9	+26.6	+ 7.7	+23.4	+22.7
II	Before uranium, 8 days	514	26.8	60.0	3.09	76.0	13.6	63.0	44.9	121.5	63.0
	After uranium, 5 days	1015	13.5	24.0	3.01	91.0	14.2	85.4	39.6	139.2	64.0
	Variation, m. equiv.	+501	-13.3	-36.0	—	+15.0	+0.8	+12.4	- 5.3	+17.7	+ 1.0
III	Before uranium, 7 days	188	0.30	9.0	5.3	6.0	4.9	7.9	3.5	16.3	11.0
	After uranium, 6 days	144	0.14	3.2	1.2	9.2	6.2	5.2	3.2	14.6	4.8
	Variation, m. equiv.	- 44	-0.16	- 5.8	—	+ 3.2	+1.3	- 2.7	- 0.3	- 1.7	- 6.2

Blood analysis.

In Exp. I the p_H drops from 7.30 before to 6.98 seven days after the injection and in Exp. II from 7.40 before to 7.12 five days after. In Exp. III a full analysis of the blood is available. To give a more general idea of the alteration of the blood, we give below, together with Exp. III, the results of two other experiments.

Blood analysis (in milliequivalents).

	Exp. III		Exp. IV		Exp. V	
	Before uranium	After uranium	Control	Nephritic	Control	Nephritic
Fixed base	166.0	157.0	144.0	150.0	149.0	164.0
Cl	103.0	85.0	98.2	108.0	106.0	127.0
P	2.1	9.0	1.0	1.7	3.9	3.0
Bicarbonate	17.2	9.35	18.0	9.4	18.0	8.3
S	?	1.45	—	—	?	2.04
Base bound by serum-prot.	10.8	8.2	11.2	8.6	10.0	8.4
Undetermined acids	32.9	47.45 (without S)	15.6	22.0	10.2	17.3 (2.04 S)
p_H	7.30	7.02	7.32	7.0	7.3	6.95

DISCUSSION.

The first two experiments, with high protein intake, give similar results. Ammonia output is lowered by about 50–60 %. Nevertheless the inorganic and organic acid excretions rise, probably owing to the influence of polyuria. Fixed bases behave in the same way. Although no acid retention or relative loss of bases occurs, a deep acidosis sets in after uranium nitrate.

In the third experiment, with low nitrogen intake, the ammonia excretion which is much smaller, undergoes the same decrease, with the result that its absolute output becomes very low. Oliguria sets in instead of polyuria. The inorganic acid output is not lowered, owing partly to vomiting. A relative rise of fixed bases occurs, tending to compensate the fall in ammonia. The inorganic acid output falls from 11 to 4.8 milliequiv. In this case the acidosis may be due more or less to a loss of fixed bases and perhaps to retention of organic acids.

When one considers the blood analysis, it is obvious that the rises of phosphate and sulphate are not sufficient to account for the drop of bicarbonate. The eventual rise of Cl is largely compensated by a parallel increase of bases. It seems difficult to avoid the hypothesis of an organic acid acidosis. On the other hand this hypothesis is confirmed by the results of unpublished experiments in which it was found that normal kidneys, when transferred from the circulation of a normal dog to that of a nephritic animal, show an enormous increase of organic acid output.

These findings agree with the experiments of Csapo and of Brühl referred to above.

The question, whether the acidosis is a result of toxic overproduction of acids or of a lack of catabolism owing to the general intoxication, is now being studied.

It must be said that it is very probable that the kidneys, had they retained a normal power of excretion, would have overcome by an increased excretory activity the overproduction of acids, as is shown by the crossed circulation experiments just referred to, but this would not exclude an overproduction of acids.

CONCLUSIONS.

Acid-base balance study of experimental uranium nitrate acidosis leads to the conclusion that there is an accumulation of organic acids in the blood. This accumulation may occur independently of any retention phenomenon. It may even be found when the inorganic and organic acid output is increased, without any relative loss of fixed base.

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