PHOSPHATE RETENTION AS A FACTOR IN THE PRODUCTION OF ACIDOSIS IN NEPHRITIS *

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It is now a well-known and generally recognized fact that acidosis may occur in the course of nephritis, particularly in the terminal stages. Among the evidences of acidosis are a diminished carbon dioxid tension of the alveolar air, an increased hydrogen ion concentration of the blood or serum, a diminution of the alkali reserve and of the oxygen combining power of the hemoglobin.

It is not yet clear on what this acidosis depends. It is surely not due to an accumulation of the acetone bodies, for they do not appear in the urine nor are they increased in the blood. It has been suggested that lactic acid may be responsible for the acidosis. The studies of Lewis, Ryffell and others[1] have shown that lactic acid is not increased in the blood in sufficient amount to account for the acidosis. There is no direct evidence nor, so far as we are aware, is there any indirect evidence that other organic acids can be held responsible. There is a diminished ammonia excretion in many cases of severe nephritis, as Henderson and Palmer[2] have shown. A diminished ammonia production might well be a factor in producing acidosis. A reasonable explanation for the acidosis and one that has been suggested by a number of different writers is that the kidney fails to play its part in excreting the acid substances ordinarily formed.

The regulation of the acid base equilibrium of the body is largely brought about by the ability of the kidney to excrete acid phosphate. This regulation of reaction is one of the most important of the kidney's functions. If this function is interfered with, the normal acid base equilibrium must be disturbed and eventually acidosis is inevitable. In order to prove the failure of this function of the kidney it is neces-

*Submitted for publication July 25, 1916.

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*We have been led to the investigation of patients outside our immediate field on account of the difficulty of obtaining a sufficient number of cases of severe nephritis in children. We are much indebted to the members of the staff of the Johns Hopkins and Bay View Hospitals for furnishing us with the blood and urine of adult patients and for the use of the histories.

1. Lewis, Ryffell and others: Heart, 1913, v, 45.

2. Henderson and Palmer: Jour. Biol. Chem., 1915, xxi, 37; THE ARCHIVES INT. MED., 1915, xvi, 109.

sary to demonstrate an accumulation of inorganic phosphates in the blood serum.

Greenwald[3] has determined an increase of total phosphorus in the blood serum in some cases of nephritis and with this there was often an increase in his so-called acid soluble fraction, which he believed represented chiefly inorganic phosphates. He suggested no connection between his results and the possibility of acidosis.

It has been necessary to devise a method sufficiently accurate and delicate enough to determine the inorganic phosphates in a small quantity of serum. This we have done.[4] With this method we have determined the inorganic phosphates in the serum of a series of normal adults and older children and then of patients with nephritis, both without and with acidosis.

TABLE 1.—NEPHRITIS WITHOUT ACIDOSIS *

Case No.	Mg. per 100 C.c. P	Mg. per 100 C.c. Ca	Remarks
1	5	8.3	Chronic diffuse nephritis; phenolsulphonephthalein 41 per cent in two hours; nonprotein nitrogen of blood 35 mg.; RpH of serum 8.5; Ambard 0.146.
2	5	10	Chronic diffuse nephritis; fatal; no hyperpnea; RpH 8.5; plasma CO_2 61.4; Ambard 0.137; urea nitrogen in blood 19 mg.
3	4	8	Chronic diffuse nephritis; fatal; phenolsulphonephthalein trace in two hours; RpH 8.5; urea nitrogen in the blood 98 mg.; Ambard 0.775; plasma CO_2 86.
4	2.7	...	Chronic diffuse nephritis; hypertension; condition good; phenolsulphonephthalein 32 per cent. in two hours; RpH 8.5

* The plasma carbon dioxid was determined by the Van Slyke method (Proc. Soc. Exper. Biol. and Med., 1915, xii, 165). The RpH of the serum (alkali reserve) was determined by the Marriott method (The Archives Int. Med., 1915, xvi, 390). Phenolsulphonephthalein determinations were made on two-hour specimens. The nonprotein nitrogen and urea are expressed in terms of mg. of nitrogen per 100 gm. of blood. Chlorids are expressed in terms of sodium chlorid in grams per 100 gm. of blood. Ambard s constant is the urea constant.

The inorganic phosphate, expressed in terms of phosphorus, was low in thirty-five normal persons. The amount varied from 1 to 3.5 mg. per 100 c.c. of blood. In the great majority the amount was less than 2 mg. With marked nephritis there was a tendency for the inorganic phosphate to be slightly increased, but death from nephritis occurred in a number of patients without an increase of the phosphorus and without any evidence of acidosis.

We have determined (Table 2) the inorganic phosphate in the serum of patients with acidosis occurring in nephritis. In every instance there was an increase in the phosphorus to many times the normal amount, that is, to from 8 to 23 mg. per 100 c.c. of blood.

3. Greenwald: Jour. Biol. Chem., 1915, xxi, 29.
4. Howland, Haessler and Marriott: Jour. Biol. Chem., 1916, xxiv; Proc. xviii.

Simultaneous determinations (Table 2) of the combined carbon dioxid of the serum showed that in certain instances the phosphoric acid was combined with twice as much of the available base as was carbonic acid, in striking contrast to the normal conditions in which the base combined with phosphoric acid is only from one tenth to one fifteenth of that combined with carbonic acid.

TABLE 2.—NEPHRITIS WITH ACIDOSIS *

Case No.	Mg. per 100 C.c. P	Mg. per 100 C.c. Ca	Remarks
1	22	4	Chronic diffuse nephritis; fatal; uremia; hyperpnea; RpH 7.8; alveolar CO_2 tension 21 mm.; nonprotein nitrogen of blood 189 mg.; Ambard 1.23; phenolsulphonephthalein 0.
2	11.3	9	Congenital polycystic kidney; improved; hyperpnea; RpH 7.8; plasma CO_2 21; alveolar CO_2 tension 25 mm.; phenolsulphonephthalein trace.
3	19	5.3	Double pyonephrosis; uremia; fatal; hyperpnea; phenolsulsulphonephthalein 0; urea nitrogen in blood 193 mg.; chlorids 0.538; before alkali; RpH 7.35; plasma CO_2 14.7; alveolar CO_2 tension 10.7 mm.
	12	1	After alkali: RpH 7.9; plasma CO_2 36.6.
4	10.3	7.2	Chronic diffuse nephritis; fatal; nonprotein nitrogen of blood 212 mg.; hyperpnea; RpH 7.95; plasma CO_2 40.
5	13	1.5	Chronic nephritis; lead poisoning; uremia; fatal; hyperpnea; phenolsulphonephthalein 0; before alkali; RpH 7.4; plasma CO_2 11.
	23	4	After alkali; PpH 7.9; plasma CO_2 28.
6	9	6.3	Chronic diffuse nephritis; uremia; fatal; phenolsulphonephthalein 0; RpH 7.9; plasma CO_2 34.
7	8	3.3	Arteriosclerotic kidney; pneumonia; phenolsulphonephthalein 3 per cent.; fatal; RpH 7.8; plasma CO_2 19.
8	9	...	Acute and chronic nephritis; fatal; hyperpnea; phenolsulphonephthalein 32 per cent.; RpH 7.9.
9	18	3	Polycystic kidney; uremia; fatal; hyperpnea; urea in blood 332 mg.; alveolar CO_2 6.4 mg.; Ambard 34.8.
10	9	10	Chronic diffuse nephritis; hypertension; hyperpnea; RpH 7.9; plasma CO_2 33; nonprotein nitrogen in blood 136; chlorids 0.475; Ambard 157.

* See note to Table 1.

The retention of acid phosphate (for approximately 90 per cent. of the phosphate in an average urine is acid phosphate) would seem to be sufficient to account for the degree of acidosis observed. We are not prepared to say that it is the sole factor in producing it.

The retention of acid phosphate in nephritis is not part of a general salt retention; it seems due to a certain specificity of retention, for we have found the inorganic phosphate much increased when there was no increase of sodium chlorid. It is also not necessarily proportional to the total nitrogen and urea retention. The phosphate retention is

not a result of acidosis per se, for we have failed to find an accumulation of phosphates in the serum of severe cases of acidosis in diabetes and other forms of acetone body acidosis. That the high phosphate content is due to interference with a specific function of the kidney and not to increased phosphate production in the body or increased absorption from the intestinal tract is shown by the fact that the urinary output of phosphate is not increased and indeed may be diminished. It is possible to determine a constant for phosphate excretion analogous to Ambard's constant for urea. If, as we believe, the retained phosphate is capable of doing much harm, the constant for phosphate should be of great clinical significance.

The acidosis itself may be overcome by alkali therapy, but it is a matter of experience that little besides this is accomplished. The disease usually progresses to a fatal termination. We have found that the administration of alkali generally fails to bring about a marked reduction of the accumulated phosphate; we have even observed an increase after the administration of sodium bicarbonate.

The accumulated phosphates of the serum, even though neutralized, are capable of doing serious harm to the organism. The amount is sufficient to have a definite influence on the osmotic pressure. This suggests a possible connection with the phenomena of edema and hydremia.

We have found, further, in most of the cases studied a marked reduction in the calcium of the serum. In one case this was only 1.5 mg. per 100 c.c. of serum, as compared with the normal of from 10 to 11 mg. What influence this low calcium content may have on the production of such symptoms as convulsions and hemorrhages can only be suggested. The low calcium content is to be referred to the excess of phosphates in the plasma. It has repeatedly been shown that phosphates administered in any form cause an increased elimination of calcium, chiefly by way of the intestines. The converse is also true. The administration of calcium leads to an increased elimination of phosphate, also by the bowel. This fact offers a suggestion for a rational therapeutic procedure.