CXC. ON THE ACTION OF PARATHORMONE. III

By HECTOR KENNETH GOADBY

From the Medical Unit Laboratories, St Thomas's Hospital, London

(*Received 22 July 1937*)

Since the original description by Allbright *et al.* [1929] of increased phosphate excretion following the injection of parathormone, numerous investigators have been searching for the site of this action; evidence has gradually been accumulating that it is the phosphate excretory mechanism in the kidneys which is acted upon by parathormone.

Using cross-transfusion experiments in animals Brull [1936] concluded that parathormone lowers the renal threshold for phosphate, as suggested by Ellsworth [1932], although there is no definite evidence that such a threshold exists. Brull's experiments show that when the same blood is transfused through two kidneys, one of which is in a normal animal, the other in an animal that has previously had an injection of parathormone, the second kidney excretes phosphate at a considerably greater rate than the first; this difference persists for some time after the parathormone has ceased to circulate in the blood of the injected animal.

Further evidence for the renal action of parathormone is put forward by Tweedy *et al.* [1935; 1936; 1937] who show that in nephrectomized dogs there is no such rise in serum calcium in 24 hr. following the parathormone injection as occurs in normal animals. Later experiments by the same authors [1936] confirm these results, which are however at variance with those of Ellsworth & Futcher [1935]: Collip *et al.* [1934] also maintained that the bones of nephrectomized dogs were depleted of calcium to the same degree as normals.

Goadby & Stacey [1935] demonstrated that in cases of severe renal damage the phosphate diuresis following parathormone injection was much less than in normals: in one case of acute nephritis it was low during the acute illness, after recovery it was increased fourfold and was comparable with normals.

This present paper gives the findings in six further cases of acute nephritis, during the acute stage and after recovery.

Methods

All the patients were on a standard low protein diet, the protein being restricted to 2/3 g. per kg. body weight per day; they were allowed their meals and fluids during the experiments; the conditions during the experiments in the acute stages and after recovery were the same.

Owing to the very greatly increased phosphate excretion after parathormone it was considered unnecessary to do phosphate excretion curves; the total phosphate excretion in the urine was therefore estimated in two 6-hr. periods, from 6 a.m. to 12 noon (the control period), from 12 noon to 6 p.m., the subject having received an intramuscular injection of 60 units of parathormone (Lilley) at 12 noon.

Urinary inorganic phosphate. Albumin when present was precipitated by adding an equal volume of 20 % trichloroacetic acid to an aliquot portion of the urine. The estimation was done on the filtrate by the Youngburg [1930] technique using a photoelectric instrument devised by the author for the colorimetry.

Discussion

From the figures given in Table I it is clear that the effect of parathormone on phosphate excretion was far less when the patients were suffering from the clinical condition of acute nephritis than it was when they had recovered.

Table I

	Clinical					Urine		Experimental		
Case	Age	Oedema	B.P.	B.U.	U.C.T.	alb.	casts	Extra phosphate excretion in 6 hr. mg.	Phosphate concentration change + or − mg./100 ml.	Urine volume change + or − ml./6 hr.
	Response of individuals with acute nephritis to 60 units parathormone during acute stage									
1	14	+	128/82	33	1·2	+ +	+	206	+65·8	+ 5
2	14	+	172/102	72	—	+ + +	+	30	+30·9	−345
3	61	+ + +	135/100	56	2·9	+ + +	+	18	−32·0	+ 60
4	16	0	120/68	25	—	+ +	+	120	+ 5·0	+250
5	13	0	112/74	40	—	+	+	16	+ 2·7	+ 15
6	17	+	145/90	—	—	+	Few	85·3	+19·5	+ 88
	Response of individuals with acute nephritis to 60 units parathormone after recovery									
1	—	0	122/62	—	2·4	0	0	349·6	+41·0	+355
2	—	0	120/44	25	2·2	Trace	0	335·0	+84·0	+ 62
3	—	0	110/60	—	1·6	Trace	0	201·7	+17·5	+675
4	—	0	106/60	26	2·5	0	0	287·0	+73·8	− 5
5	—	0	120/74	—	—	+	0	259·0	+39·9	−100
6	—	0	—	28	—	0	0	389·0	+60·0	+195

B.P. = blood pressure in mm. Hg. B.U. = blood urea in mg./100 ml. U.C.T. = maximum concentration of urine-urea in urea concentration test. alb. = albumin.

Some control experiments were done on various cases under the same conditions of diet, fluids etc.; in these the phosphate excretion in the two 6-hr. periods was estimated without the midday injection of parathormone: the results are given in Table II and can be seen to be very irregular: usually there

Table II. *Extra phosphate excretion in second 6 hr.*

Case	mg. + or − Without parathormone	With parathormone
1. Acute nephritis	+190·6	+206
2. Acute nephritis	+ 61·0	+ 30
7. Acute nephritis, recovered	+ 75·0	+180·5
8. Acute nephritis, recovered	+ 11·9	+350·6
9. Congenital cystic kidneys. Uraemia	+ 69·8	− 2·6
10. Acute nephritis	− 73·0	+ 4·5
11. Acute nephritis	+ 34	− 99·0

is rather more phosphate excretion in the second period than in the first: in two cases of acute nephritis and one of congenital cystic kidneys with gross renal failure there was actually less extra phosphate excretion after parathormone than occurred naturally.

It seems doubtful in view of these control experiments whether the small extra phosphate excretion in the acute stages of acute nephritis (Table I) can be attributed to the parathormone at all.

If then parathormone has little or no effect on phosphate excretion during acute nephritis, and on the patient's recovery a normal phosphate diuresis is found, the hypothesis that one action at least of parathormone is directly on the kidneys is greatly strengthened. Goadby & Stacey [1935] showed that it is not a rise in the blood phosphate that produces the extra phosphate excretion.

The main hypothesis is further strengthened by the fact that the effect of parathormone is more reduced the more severe is the impairment of renal function as shown by the blood urea etc. Thus in cases 1 and 4 where the nephritis was relatively mild there was quite a considerable phosphate diuresis after parathormone, the excretion being raised to three times and twice that of the control period; on recovery, it was raised to six times and four times respectively. In the two severe cases, 2 and 3, parathormone increased the excretion only by one-third and one-tenth during the acute illness, whereas on recovery the rise was to nine times and fourteen times the control period excretion.

Parathormone usually, but not always, produces a water diuresis, but this is very variable and the extra excretion of phosphate is independent of this, as was shown originally by Goadby & Stacey and has since been confirmed by Ellsworth & Nicholson [1935].

The degree of parathormone effect does not run parallel with the natural rate of phosphate excretion as shown by the control period beforehand: in fact during the acute stage the natural phosphate excretion rate in the control period was in four cases out of six higher than after recovery.

Parathormone produces an increased phosphate excretion independent of water diuresis (case 5 recovered) or of increased concentration in the urine (case 3 acute). Presumably the magnitude of one effect is nearly always sufficient to overcome even a diminution in the other: that this hypothesis may be true is supported by the results from two cases of acute nephritis, not in this series, in both of which there was less phosphate excretion after parathormone than before (Table III).

Table III

	Control period			After parathormone			
Case	Urine volume ml./6 hr.	Phosphate concentration mg./100 ml.	Phosphate excretion mg./100 ml.	Urine volume ml./6 hr.	Phosphate concentration mg./100 ml.	Phosphate excretion mg./6 hr.	Phosphate excretion variation mg./6 hr.
A	186	90·3	168	171	40·4	69·0	−99·0
B	348	23·5	82	158	27·7	43·7	−38·3

Unfortunately there was no opportunity to test these patients after recovery.

The exact mechanism of the action of parathormone remains yet to be discovered. Ellsworth & Nicholson have observed an increased excretion of Na and K ions after parathormone and suggest that this is its primary effect, the phosphate diuresis being secondary.

Summary

1. In persons suffering from acute nephritis parathormone produces a much smaller phosphate diuresis than when they have recovered.

2. The hypothesis that parathormone acts directly on the kidneys to produce an increase of phosphate excretion is thus confirmed.

My thanks are due to the Physicians of St Thomas's Hospital for permission to use their cases.

REFERENCES

Allbright, Bauer, Ropes & Aub (1929). *J. clin. Invest.* **7**, 139.
Brull (1936). *Arch. int. Physiol.* **43**, 253.
Collip, Pugsley, Selye & Thompson (1934). *Brit. J. exp. Path.* **15**, 335.
Ellsworth (1932). *J. clin. Invest.* **11**, 211.
—— & Futcher (1935). *Johns Hopk. Hosp. Bull.* **57**, 91.
—— & Nicholson (1935). *J. clin. Invest.* **14**, 823.
Goadby & Stacey (1935). *Biochem. J.* **30**, 269.
Tweedy, Templeton & McJunkin (1935). *J. biol. Chem.* **109**, xcii.
—— —— —— (1936). *Amer. J. Physiol.* **115**, 514.
—— —— —— (1937). *Endocrinology*, **21**, 55.
Youngburg & Youngburg (1930). *J. Lab. clin. Med.* **16**, 158.