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Renal Function after Thyroidectomy and Parathyroid Hormone Administration

An Experimental Study in the Pig

B. Fåhraeus

Department of Urology, University of Umeå, Sweden

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Summary. Changes in renal function, measured by clearance determinations, and in serum electrolytes were studied in thyroidectomized pigs and after administration of PTH to thyroidectomized pigs. Thyroidectomy caused no changes in serum electrolytes or TRP but there was a significant decrease in Cl ^{51}Cr-EDTA-p and Tm_{PAH} and a slight decrease in Cl_{PAH} and Cl ^{125}I-hippuran. PTH administration after thyroidectomy caused a significant increase in serum calcium, and serum creatinine and an increase in urea-N, significant decreases in serum phosphates, all clearance values and a decrease in TRP. PTH administration also clearly affected the general condition of the pigs.

Key words: Clearance studies, serum electrolytes, thyroidectomy, PTH-administration, pigs

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The renal effects of parathyroid hormone (PTH) have been studied both clinically and experimentally in several investigations. Most experimental studies have dealt with the morphological changes in the kidneys or the changes in serum calcium, serum phosphate and serum magnesium values and with the tubular reabsorption of calcium, and phosphates. In some cases the maximum urine concentration capacity has also been studied (19, 21). Only a few investigations of the effects of PTH on renal function measured by clearance determinations have been published (20, 21, 26, 27, 46, 52).

It has been established that in hypothyroidism the clearance of inulin (Cl_{In}), the clearance of para-amino-hippuric acid (Cl_{PAH}) and the transfer maximum of PAH (Tm_{PAH}) are lower than normal (16, 28, 36, 51).

Calcitonin affects the serum calcium values (15) and also has renal effects, such as increased excretion of phosphates, calcium, magnesium, potassium and sodium (24, 41, 42), but its effect on renal function measured by clearance determinations has not been established.

In the present study the elimination of every conceivable effect of calcitonin on renal function was desired. Pigs were used as laboratory animals. In the pig the thyroid and the parathyroid glands are completely separated (35, 49). The production of calcitonin seems to occur only in the thyroid (1), although there are reports of an adrenal calcitonin-like principle in the pig (32). Thus in the pig calcitonin production is probably eliminated by thyroidectomy, but the effects of the thyroidectomy on renal function have to be taken into consideration.

Material and Methods

Laboratory animals. The investigations were performed in female pigs of either the Swedish Land race, Swedish Yorkshire race or crosses between these races, weighing between 16.5 and 28 kg at the beginning of the investigation.

Food. The pigs were given commercial pig food (Piggfor^{R}) and had free access to drinking water.

Surgical procedures. All operations were carried out under general anaesthesia (halothane, oxygen, nitrous oxide).
Implantation of central venous catheters and cystostomy were performed using techniques described earlier (22).
Thyroidectomy or a sham operation on the thyroid

was performed through a mid-ventral incision (44). Open kidney biopsy was carried out twice in each pig through an incision below the last rib.

Blood sampling. Blood samples were taken daily for the determination of serum electrolytes and calcium ion activity. The samples were collected before feeding.
The serum calcium and serum magnesium were determined using an atomic absorption spectrophotometer (Unicam SP 90 B).
An ionspecific flow-through electrode (Orion Research Corp.) was used to determine the calcium ion activity.
The other serum electrolytes were determined by means of standard clinical chemistry laboratory methods adapted to a multichannel auto analyzer (Technicon auto analyzer SMA 6/60).

Clearance studies. The technique for clearance studies in unsedated and unrestrained pigs has been described earlier (22).
The clearance of ^{51}chromium complexed with ethylenediamine-tetra-acetic acid calculated from the activity in plasma (Cl ^{51}Cr-EDTA-p) was used as the expression of GFR.
The clearance of ^{125}I-hippuran (Cl ^{125}I-hippuran) and Cl_{PAH} were used as the expression of the renal plasma flow (RPF).
Tm_{PAH} was also determined.
GFR was determined in 4 clearance periods, Cl ^{125}I-hippuran and Cl_{PAH} in 2 and Tm_{PAH} in 2.
Each clearance period lasted about 30 min (25-35 min) and the equilibration time was 45 min.

The plasma concentration of PAH varied during the clearance periods between 0.85 and 5.22 mg/100 ml. During the periods for determination of Tm_{PAH} it was 35 mg/100 ml or higher.

The extraction of PAH could not be determined and Tm_{PAH} was thus calculated from the formula

$$U_{PAH} \cdot V - 0.83 \cdot Cl\ ^{51}Cr\text{-}EDTA\text{-}p \cdot P_{PAH},$$

where U = urine concentration, V = volume of urine in ml/min and P = plasma concentration. 0.83 is a constant given by Reubi (43) to correct for the PAH bound to protein.

The tubular reabsorption of phosphates (TRP) was calculated from the formula 1 -

$$\frac{U_{Ph} \cdot V}{P_{Ph} \cdot Cl\ ^{51}Cr\text{-}EDTA\text{-}p}$$ where Ph = phosphates.

PAH was determined according to Brun (7).

A well-crystal scintillation detector (Landis & Gühr, Switzerland) was used to determine the isotope concentrations in blood, plasma and urine in 2 ml samples to a statistical precision of ± 1%.
A microhaematocrit centrifuge (No. 490, International Equipment Company) was used for the haematocrit determination.

Investigation procedures. The pigs were divided into 3 groups. A control group of 5 pigs (SHAM) was used to study possible effects of the surgical procedures, including anaesthesia, and the anaemia caused by blood sampling on the renal function. Another group of 6 pigs (TX) underwent thyroidectomy to demonstrate the effects of thyroidectomy on renal function. A third group of 5 pigs (TX + PTH) underwent thyroidectomy and were then given PTH.

The SHAM group underwent a sham thyroidectomy. In every other respect surgical and investigating procedures were identical in the 3 groups.

First an implantation of central venous catheters and cystostomy were performed in the pigs. Two or 3 days later the first clearance investigation (Cl 1) was carried out followed by thyroidectomy or a sham operation. 44 h after the thyroidectomy the first dose of PTH (Para-Thor-Mone, Lilly) was given to the pigs of the TX + PTH group. PTH was administered in subcutaneous injections 3 times daily, at 8 a.m., 3 p.m. and 10 p.m. in a total dose of 25 USP units/kg/day. 120 h after the first clearance investigation (i.e. 72 h after the first PTH injection) the second (Cl 2) was carried out followed by a left renal biopsy. After another 72 h the third and last clearance investigation (Cl 3) was performed and biopsies were taken from the right kidney.

In the TX + PTH group blood samples were taken daily 90 min after the morning injection of PTH. When clearance investigations were performed, they started with the first equilibration period, immediately after the blood sampling.

Statistical methods. The material was analysed using a two-factor analysis of variance design. F-tests were applied to judge if the changes were significant. If significant changes were found, further analyses were made using Scheffé's method for multiple comparisons (47).

Results

Serum electrolytes

No changes in sodium, potassium, magnesium, chlorides, bicarbonate or serum proteins were noted in any of the 3 groups.

In the SHAM and TX groups no changes in creatinine, urea-N, calcium or phosphates were noted.

In the TX + PTH group a significant ($p < 0.01$) increase in the serum calcium was found as well as a significant ($p < 0.01$) decrease in serum phosphates. A significant ($p < 0.01$) increase in serum creatinine and an increase in urea-N and the calcium ion activity ($p > 0.05$) were also noted (Figs. 1 and 2).

During the investigation the haematocrit decreased from 33% to 27%.

Clearance studies

The results of the clearance studies are shown in Table 1 and Figs. 3, 4 and 5.

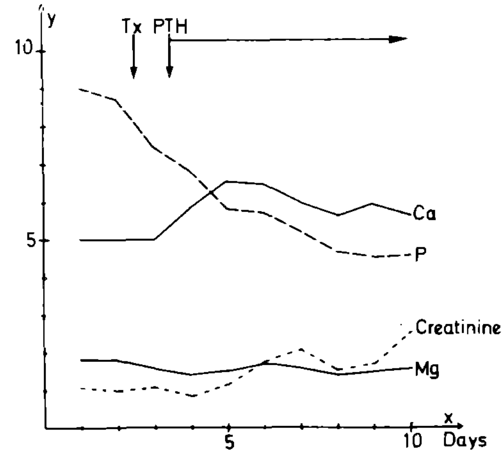

Fig. 1. Changes in Ca, P, Mg and creatinine after PTH administration. The values on the y-axis are for Ca and Mg in mEq/l and for P and creatinine in mg/100 ml. MSE (Mean square error, a measure of the uncontrolled variation) is for Ca 0.29, for P 0.81, for Mg 0.029 and for creatinine 0.482

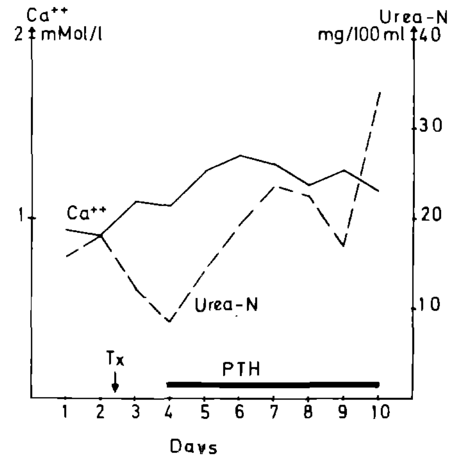

Fig. 2. Changes in urea-N and the calcium ion activity (Ca^{++}) after PTH administration. MSE is for urea-N 153.47 and for Ca^{++} 0.037

		Cl 1	Cl 2	Cl 3	$Cl\,1 - \frac{Cl\,2 + Cl\,3}{2}$	Cl 1-Cl 2	Cl 1-Cl 3	Cl 2-Cl 3
Cl ^{51}Cr-EDTA	SHAM	3.63	3.39	3.19	0.34	0.24	0.44	0.20
	TX	3.93	2.93	2.54	1.20$^{\circ\circ}$	1.00$^{\circ\circ}$	1.39$^{\circ\circ}$	0.39
	TX+PTH	2.87	1.39	1.22	1.57$^{\circ\circ}$	1.48$^{\circ\circ}$	1.65$^{\circ\circ}$	0.17
Cl ^{125}I-hippuran	SHAM	16.0	14.4	17.4	0.1	1.6	-1.4	-3.0
	TX	18.2	13.8	13.3	4.6	4.4	4.9	0.5
	TX+PTH	13.5	8.4	7.6	5.5$^{\circ\circ}$	5.1$^{\circ\circ}$	5.9$^{\circ\circ}$	0.8
Cl_{PAH}	SHAM	20.4	18.5	22.6	-0.2	1.9	-2.2	-4.1
	TX	23.5	17.2	13.7	8.0	6.3	9.8	3.5
	TX+PTH	15.6	10.0	8.7	6.2$^{\circ\circ}$	5.6$^{\circ\circ}$	6.9$^{\circ\circ}$	1.3
Tm_{PAH}	SHAM	4.31	4.49	4.24	-0.06	-0.18	0.7	0.25
	TX	4.69	3.75	3.27	1.18$^{\circ\circ}$	0.94$^{\circ\circ}$	1.42$^{\circ\circ}$	0.48
	TX+PTH	4.20	2.24	1.67	2.24$^{\circ\circ}$	1.96$^{\circ\circ}$	2.53$^{\circ\circ}$	0.57

Table 1. Clearance values in the 3 experimental groups. The values are expressed in ml (mg) / min / kg and are the mean values (Cl 1, Cl 2 and Cl 3). $Cl\,1 - \frac{Cl\,2 + Cl\,3}{2}$ is the average change after Cl 1. Cl 1 - Cl 2, Cl 1 - Cl 3 and Cl 2 - Cl 3 express the differences between the clearance investigations. $^{\circ\circ}$indicates significant ($p < 0.01$) changes. See also Figs. 3 and 4

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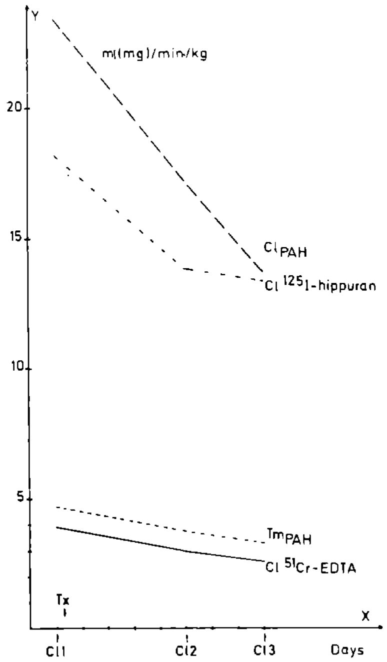

Fig. 3. Changes in clearance values in the TX group. MSE is for Cl ^{51}Cr-EDTA 0.13, Cl ^{125}I-hippuran 12.52, Cl_{PAH} 35.78 and for Tm_{PAH} 0.27

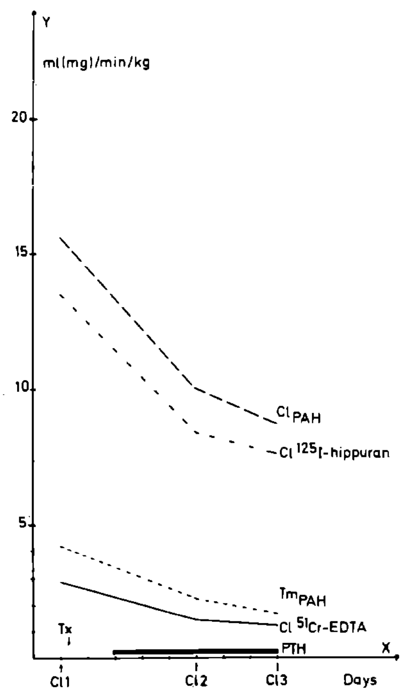

Fig. 4. Changes in clearance values in the TX + PTH group. MSE is for Cl ^{51}Cr-EDTA 0.18, Cl ^{125}-I hippuran 2.79, Cl_{PAH} 6.98 and for Tm_{PAH} 0.27

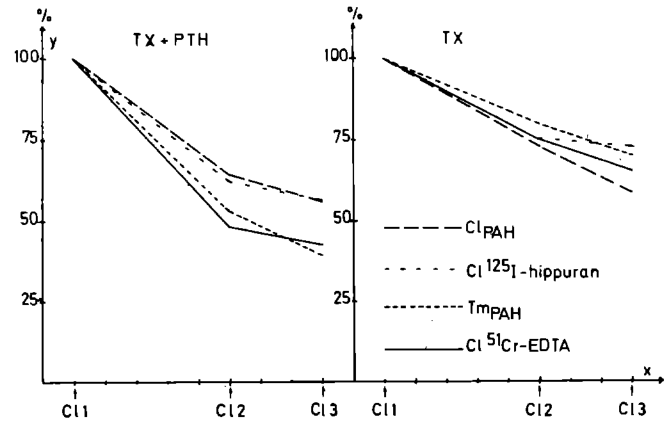

Fig. 5. Changes in clearance values in the TX and TX + PTH groups. The values are expressed in per cent of initial values (Cl 1)

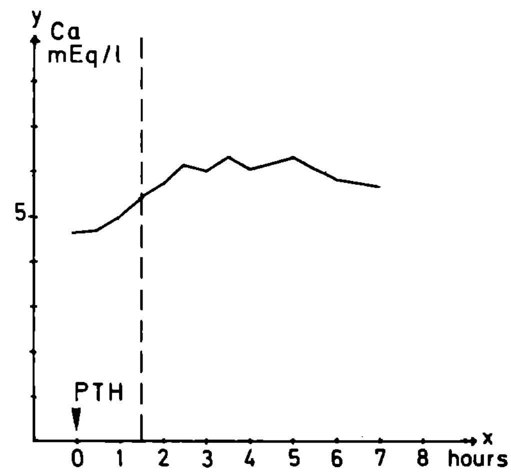

Fig. 6. Variations in the serum calcium values after injection of PTH. The highest values were found 3 1/2 and 5 h after the PTH injection. The broken line indicates the regular hour for blood sampling

In the SHAM group there were no significant ($p > 0.05$) changes in Cl ^{51}Cr-EDTA-p, Cl ^{125}I-hippuran, Cl_{PAH}, Tm_{PAH} or TRP.

In the TX group there was a significant ($p < 0.01$) decrease in Cl ^{51}Cr-EDTA-p and in Tm_{PAH} and a not significant ($p > 0.05$) decrease in Cl_{PAH} and in Cl ^{125}I-hippuran. TRP was unchanged (> 80 %).

In the TX + PTH group there were significant ($p < 0.01$) decreases in all clearance values. TRP was less than 80 %.

The differences found when comparing the mean values of the TX group with those of the TX + PTH group give the "true" effect of PTH on the renal function.

Discussion

Choice of laboratory animals

The pig is increasingly frequently used as a laboratory animal in medical research and it is considered by most authors to be very suitable for experiments (3, 17, 31, 34, 37). Kalich et al. (31) and Douglas (17) even consider the pig to be the most important laboratory animal next to the anthropoid ape, since the pig closely resembles man, e. g. in its metabolism.

The pig is especially suitable for studies on the interaction between PTH and calcitonin as the thyroid and the parathyroid glands are completely separated. The 2 parathyroids are located in the cranial part of the cervical portion of the thymus (35, 49) whereas the thyroid is found in the midline ventral to the trachea (44). The dog, which is generally used for studies of renal physiology, has 4 parathyroid glands, of which 2 are internal parathyroids located in the thyroid and 2 are external, usually closely connected to the thyroid. The internal parathyroids cannot be spared at thyroidectomy and there is also a risk of simultaneously damaging the external ones. This might lead to hypocalcaemia, which might affect GFR and RPF (33).

Another advantage that the pig has for studies on the interaction between PTH and calcitonin is the existence of specific radioimmunoassays for PTH and calcitonin (1). There are no such specific methods for determinations in dogs.

The dosage of PTH, 25 USP units/kg/day, was chosen on the basis of earlier reports, in which distinct but moderate morphological changes in the kidneys of dogs given this dose were described (4, 20) as well as a pronounced effect on renal function (20). After only 3 days administration of this dosage of PTH distinct morphological changes in the kidneys were observed (6).

Pilot studies showed that an obvious increase in serum calcium could be measured as early as 90 min after a PTH injection. The blood samples were therefore taken 90 min after the morning injection of PTH. In one case serum calcium samples were also taken every 30 min for 7 h, from the morning injection of PTH onwards. The highest serum calcium value was obtained after 210 min and was 0.9 mEq/l higher than that found after 90 min (Fig. 6).

The effects of anaesthesia, surgery and anaemia on the renal function

Several factors, such as anaesthetics, various drugs, stress and anaemia, can affect the renal function as measured by clearance determinations. In man, general anaesthesia usually causes a reduction in GFR and RPF (25, 39). In pigs, however, Gyrd-Hansen (23) could not establish that urethane sedation or pentobarbitone anaesthesia produced any changes in Cl_{In} or Cl_{PAH}.

In man, administration of corticosteroids causes an increase in GFR (36) and in the dog experimentally induced insufficiency of the adrenal cortex causes a decrease in Cl_{In}, the clearance of diodrast (Cl_D) and the transfer maximum of diodrast (Tm_D) (51).

Anaemia can also affect the renal function as measured by clearance determinations. Thus in anaemic children an increase in GFR and RPF is found, whereas in adults there is usually a reduction in GFR and RPF in chronic anaemia (50).

In the present experimental study the pigs underwent anaesthesia and surgery and became anaemic from repeated blood sampling. Throughout the investigation, i. e. for about 10 days, blood samples were drawn at least once every day and for the clearance studies there was further blood sampling. The blood loss at the operations was insignificant. The total blood loss amounted to 600-800 ml, which caused a decrease in the haematocrit from 33 % to 27 %.

Besides the anaesthetics and the test substances used for the clearance studies no other drugs were given to the pigs.

In the SHAM group no changes in serum electrolyte or clearance values were observed.

The effects of thyroidectomy on the renal function

In hypothyroidism in man, low values for Cl_{In} and Cl_{PAH} have been found (16, 28, 36). After only 6 days treatment with desiccated thyroid Hlad et al. (28) observed an increase in Cl_{In} and Cl_{PAH} to approx. normal values.

In dogs White et al. (51) found a decrease in Cl_{In}, Cl_D and Tm_D after thyroidectomy.

In spontaneous hypothyroidism there is a normal response to intravenous calcium administration, which implies that the calcitonin production in the thyroid is normal (38). Calcitonin plays an important part in the exact regulation of the serum level and elimination of calcitonin secretion causes increased sensitivity to administration of calcium or calcium-mobilizing substances (1, 2, 48). Administration of calcitonin to man (24, 41) or to laboratory animals (14, 42, 45, 53) causes increased urinary excretion of phosphates, calcium, magnesium, potassium and sodium. In thyroparathyroidectomized dogs given calcitonin, Pak et al. (42) found in several cases an increase in Cl_{In}, but this might have been caused by a decrease in the serum calcium level (33).

In the present study thyroidectomy was performed in order to eliminate all production of calcitonin and, consequently, also every possible effect of increased calcitonin secretion.

After the thyroidectomy no changes in serum electrolytes including serum calcium were observed.

The changes in the clearance values agreed with those of investigations published earlier.

In 2 pigs clearance studies were also performed 48 and 96 h after the thyroidectomy. These showed a reduction in renal function, to almost the same level as that found 120 h after the thyroidectomy, as early as 48 h after the thyroidectomy.

The effects of thyroidectomy and PTH administration on the renal function

In most previously published experimental works the studies on the effect of PTH on the renal function were performed immediately after the PTH administration; Handler et al. (26) found an increase of 37 % in Cl_{In} and of 51 % in Cl_{PAH} in anaesthetized dogs; Handler & Cohn (27) noted an increase of 12 % in the clearance of endogenous creatinine in dogs; Widrow & Levinsky (52) found an increase of 15-20 % in Cl_{In} in thyroparathyroidectomized dogs with normal serum calcium values. Samiy et al. (46), on the other hand, observed a considerable reduction in GFR, also in thyroparathyroidectomized dogs. However, as they gave no information about the serum calcium level at the clearance investigation before the PTH administration it is difficult to estimate their results, as hypocalcaemia causes an increase in GFR (33).

Epstein et al. (21) studied GFR in dogs 24 h after PTH administration. In most cases they found a decrease in Cl_{In}, but in some it was unchanged or even increased. The kidneys of these dogs were later examined microscopically and distinct alterations, e. g. changes of the tubular cells, calcified depots in the tubules and dilatation of the tubules were found (8).

In 5 reports Charbon (9, 10, 11, 12, 13) showed that PTH administration to dogs, even in small doses, produced an increase in the renal blood flow of approx. 40 %.

In dogs given PTH over a longer period of time, a decrease in Cl_{In}, Cl_{PAH} and Tm_{PAH} was found instead (20). Microscopic examination of kidney biopsies from these animals disclosed distinct morphological changes typical of hyperparathyroidism. It could also be established that Cl_{In} and Cl_{PAH} improved after the cessation of PTH administration, but there was no complete recovery, probably as a result of permanent morphological changes.

A decrease in Cl_{In}, Cl_{PAH} and Tm_{PAH} is also found in patients with hyperparathyroidism (5, 18, 29, 30, 40). In patients who were to be operated on because of hyperparathyroidism, Edwall (18) found relative renal hyperaemia, which disappeared after the operation. He also showed that there was a further decrease in Cl_{In} and Cl_{PAH} shortly after the operation.

In the TX + PTH group of the present study a significant ($p < 0.01$) decrease in all clearance values was found 72 and 144 h after the first PTH injection. This decrease was much more pronounced than that found after thyroidectomy alone (Table 1 and Figs. 3, 4 and 5).

As shown in Table 1 the initial values for Cl ^{51}Cr-EDTA-p, Cl ^{125}I-hippuran and Cl_{PAH} were lower in the TX + PTH group than in the SHAM and TX groups. This is due to the fact that 4 out of the 5 pigs in the TX + PTH group were deprived of water for studies on the maximum urine concentration capacity before the first clearance investigation. In young pigs thirst causes a decrease in these clearance values and sometimes even an increase in serum creatinine (22). In addition to these 5 pigs another 2 were initially included, but they are not accounted for as the investigation had to be interrupted because of technical complications. At the first clearance investigation these pigs had clearance values corresponding to those of the SHAM and TX groups. 120 h after the thyroidectomy (i. e. 72 h after the first PTH injection) their clearance values corresponded to those of the TX + PTH group on the same occasion.

The general condition of the pigs given PTH was clearly affected. They drank more, ate less and did not gain weight as did the pigs in the other 2 groups.

As has already been mentioned the administration of PTH caused a significant increase in serum calcium and serum creatinine, a significant decrease in serum phosphates, an increase in urea-N and a decrease in TRP to values below 80 %.

The present study has thus shown that thyroidectomy causes a reduction in the renal function measured by clearance determinations. This reduction can be observed as early as 48 h after the thyroidectomy. The study has also shown that PTH administration in a dose of 25 USP units/kg/day to thyroidectomized pigs causes an even more pronounced reduction in the renal function.

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Dr. Bengt Fåhraeus
Department of Urology
University of Umeå
Umeå
Sweden