

## Hyperparathyroidism after Bilateral Nephrectomy in Dogs

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**Summary.** Bilateral nephrectomy was performed in 6 dogs. During the first 2 days after the operation the serum calcium level remained normal, but there were significant increases of serum phosphorus, creatinine and BUN. Light

and electron microscope evidence of parathyroid hypertrophy and hyperplasia were found.

**Key words:** Hyperparathyroidism, renal failure, dogs, light and electron microscopy.

In previous work (Boquist et al., 1973) the development of hyperparathyroidism was reported in dogs subjected to heminephrectomy on one side and nephrectomy on the other in order to produce persistent (chronic) renal failure. Bilateral nephrectomy in man and laboratory animals is known to elicit rapid hyperplasia of the parathyroid glands (Baker, 1945; Hansson et al., 1971). Although dogs have often been used for physiological studies of calcium and phosphorus metabolism in experimental renal failure (Tweedy et al., 1937; Winthernitz et al., 1940; Rodbard, 1945; Houck, 1954), there appear to have been no reports of the ultrastructure of the canine parathyroid gland after nephrectomy. Studies of this type have been performed in rats (Davis and Enders, 1961; Mazzochi et al., 1967). A significant increase of the serum calcium level has been recorded only 24 h after bilateral nephrectomy in dogs (Freeman and Change, 1950). Hypercalcaemia has also been reported in acute renal failure in man (Gossmann and Lange, 1968; Leonard and Eichner, 1970).

The aim of the present work was to supplement the previous study of the effect of chronic

renal impairment on parathyroid morphology and function by examining the effect of acute renal failure. Dogs were subjected to bilateral nephrectomy in order to evoke acute renal failure.

### Material and Methods

**Animals.** Six dogs (3 males and 3 females), aged 6 months to 2 years, with body weights of 21 to 30 kg were used. The animals were healthy clinically; and no signs of chondrodystrophy or rachitis were found. During the experimental period (48 h) they were not fed but had free access to water. The postoperative course was uneventful apart from the few dogs that vomited after drinking.

**Operative Technique.** The animals were anaesthetized with Pentobarbitalum Mebumal 6% (ACO, Stockholm), 0.5 ml/kg body weight intravenously. After intubation, bilateral nephrectomy was carried out under aseptic conditions through an upper midline incision. The kidneys were saved for pathological examination. No postoperative complications occurred. Forty-eight hours after operation the animals were anaesthetized again and their necks were explored. The parathyroid glands were identified and the upper left and lower right glands taken for light microscopy and the upper right and lower left glands were taken for electron microscopy. Then the animals were killed.

**Statistical Methods.** The volumetric data were tested statistically by non-parametric methods

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(Wilcoxon and Mann-Whitney). The difference test was used for the biochemical data.

The details of the laboratory methods, volumetric determinations and light and electron microscope techniques were the same as reported previously (Boquist et al., 1973).

## Results

**Laboratory Findings.** The dogs developed marked uraemia with elevation of BUN from a mean of 18.8 mg/100 ml at the beginning of the experiments to a mean of 90.8 mg/100 ml after 24 h, and 167.6 mg/100 ml after 48 h (Fig. 1). Serum creatinine also rose from a mean of 1.1 mg/100 ml at the beginning of the experiments to 6.2 mg/100 ml at 24 h and 12.3 mg/100 ml at 48 h (Fig. 2).

The mean value of serum calcium was 5.3 mEq/l before the operation, 5.4 mEq/l at 24 h and 5.1 mEq/l at 48 h (Fig. 3). These values did not differ ( $p > 0.05$ ) significantly. The mean serum phosphorous concentration was 4.8 mg/100 ml before the operation and it had risen significantly ( $p < 0.05$ ) at both 24 and 48 h (Fig. 4). The serum phosphorous level showed considerable variations in the different dogs.

**Light Microscope Findings.** The kidneys removed at operation appeared normal.

The parathyroid glands from all the dogs showed essentially similar morphological features. There was no obvious structural difference between the superior and inferior glands. The glands were moderately enlarged, rounded or oval and were surrounded by a thin connective tissue capsule. There appeared to be both diffuse hyperplasia and hypertrophy of the parenchymal cells. They did not contain fat cells. Light (Fig. 5) and dark chief cells were found in solid cords and sheets in a delicate stroma that consisted of oc-

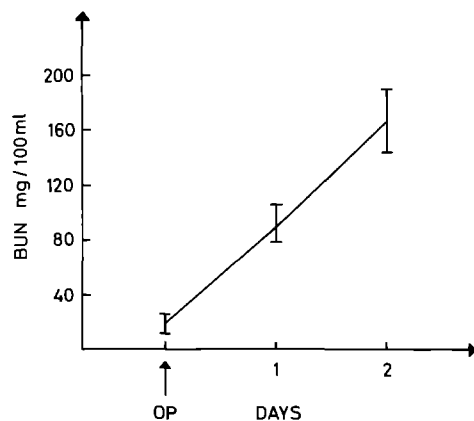


Fig. 1. Mean blood urea nitrogen concentration in 6 dogs after bilateral nephrectomy. Vertical bars indicate the range

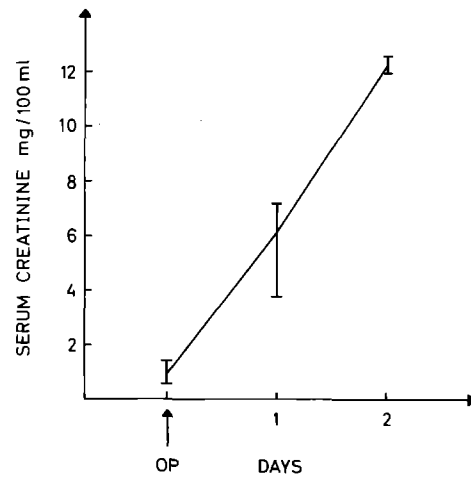


Fig. 2. Mean serum creatinine level in 6 dogs after bilateral nephrectomy. Vertical bars indicate the range

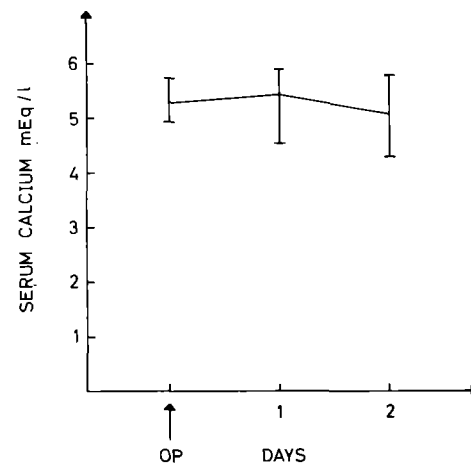


Fig. 3. Mean serum calcium level in 6 dogs after bilateral nephrectomy. Vertical bars indicate the range

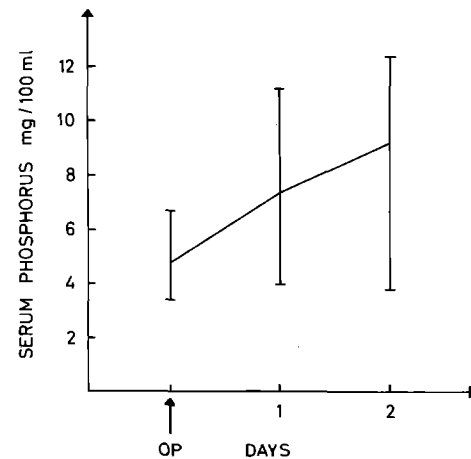


Fig. 4. Mean serum phosphorus level in 6 dogs after bilateral nephrectomy. Vertical bars indicate the range

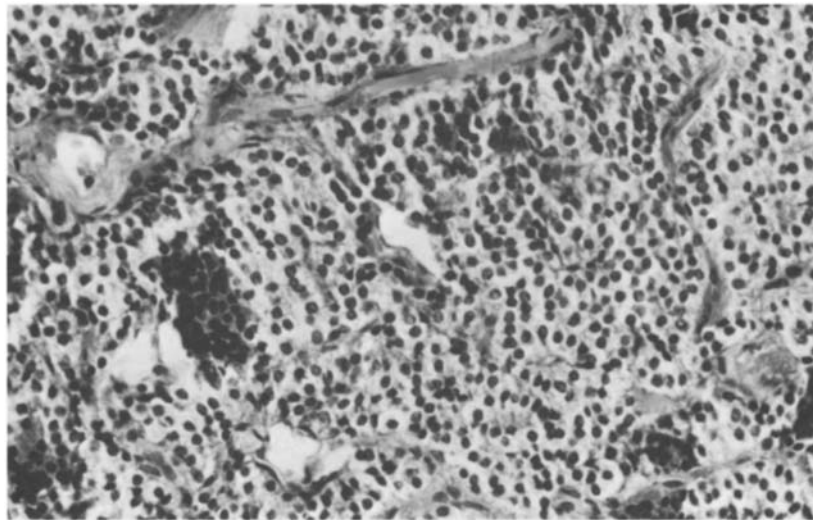


Fig. 5. Photomicrograph of hyperplastic parathyroid gland of dog two days after bilateral nephrectomy showing light chief cells and small aggregates of dark cells. Haematoxylin and eosin. X 63

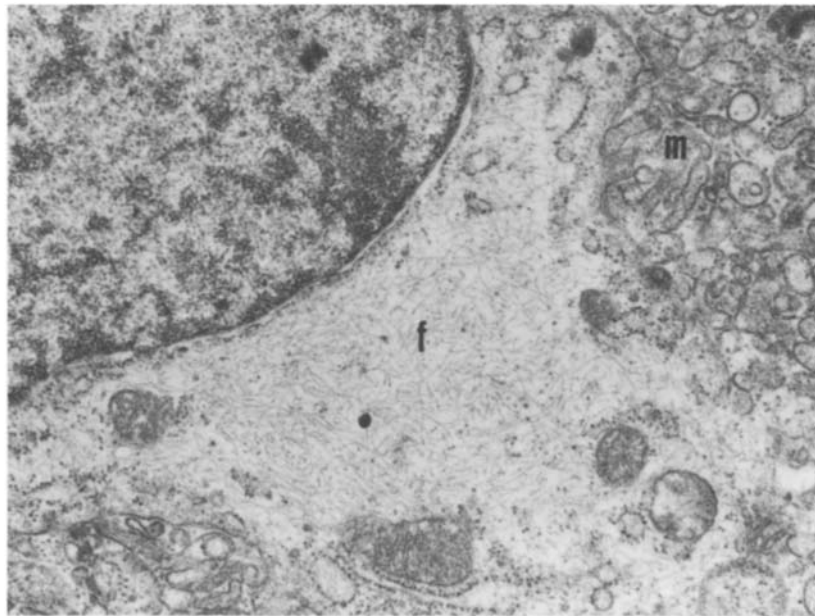


Fig. 6. Electron micrograph of parathyroid chief cell showing delicate cytoplasmic fibrils (f) and microvilli (m). X 15,000

casional strands of collagenous connective tissue. Sometimes a slight tendency to a follicular arrangement of the chief cells was seen. Cellular aggregates of small chief cells and syncytial cells were found and were similar to those in normal dogs. Few oxyphil cells were identified. Vacuolated chief cells were found but no obvious water-clear cells.

Volumetric Determinations. The mean number of nuclear hits in the parathyroids of the experimental dogs was  $422.5 \pm 24.3$  as compared with  $321 \pm 4$  in normal animals (Bergdahl and Boquist, 1973). The difference was significant ( $p < 0.05$ ).

Measurements of the nuclei showed a mean produce ( $D_1 \times D_2$ ) of  $24.2 \pm 2.5$  as compared with  $15.6 \pm 1.4$  in normal dogs (Bergdahl and Boquist, 1973). The difference was significant ( $p < 0.05$ ).

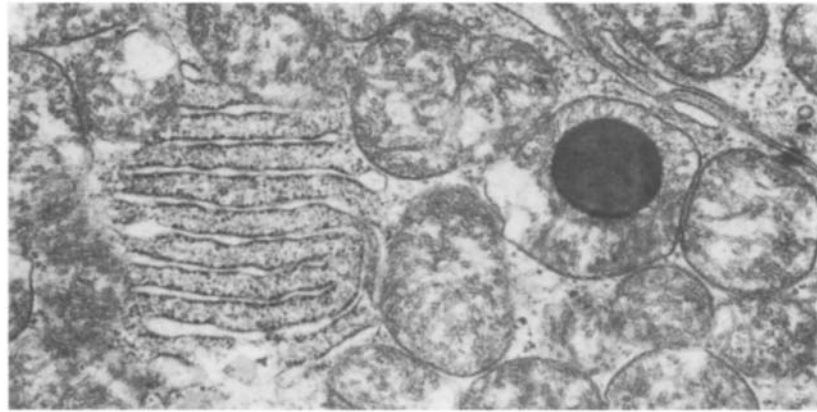


Fig. 7. Portion of oxyphil cell showing lamellar endoplasmic reticulum and mitochondria. One intramitochondrial dense body is seen. X 19.000

Electron Microscope Findings. The chief cells both of the light and dark variants possessed large nuclei, often with well developed nucleoli, and a prominent Golgi complex and endoplasmic reticulum. The number of secretory granules in these cells varied and often only a few were found in the cytoplasm. Glycogen accumulation was seldom seen. Scattered lipoid bodies were found. Delicate cytoplasmic fibrils were observed in a few light chief cells (Fig. 6). Cilia were occasionally seen, but no annulate lamellae. Most chief cells possessed numerous mitochondria. The cell membranes showed microvilli and interdigitations.

The oxyphil cells often had a distinct Golgi complex and endoplasmic reticulum. Occasional intramitochondrial dense granules were observed (Fig. 7).

The syncytial cells were similar to those seen in normal dogs. The small chief cells possessed occasional dense cytoplasmic bodies and a moderately developed Golgi complex. The endoplasmic reticulum was inconspicuous or moderately developed.

The follicles and the other structural details in the parathyroid glands were similar to those seen in normal dogs (Bergdahl and Boquist, 1973).

#### Discussion

After bilateral nephrectomy in dogs a post-operative survival of 4 to 10 days has been reported (Winternitz et al., 1940). Rodbard (1945) found a mean survival time of 3 1/2 days if bilateral nephrectomy were performed as an one-stage operation, and a mean survival of 5 days if a two-stage operation was done at an interval of 1 to 4

weeks. The dogs in the present study were in a fairly healthy condition until the end of the period of observation 2 days after the operation.

In the present study the BUN-level rose by about 70 mg/100 ml per day. In man, the increase of BUN in acute anuria seldom exceeds 50 mg/100 ml per day, unless there is extensive damage to the tissues. The development of increasing uraemia was associated with quite rapidly progressive hyperphosphataemia, the serum calcium level remained within normal limits. These findings are in agreement with those of Monahan and Freeman (1944), but are contrary to the results of Freeman and Chang (1950), who reported hypercalcaemia in three dogs at 24 hours after bilateral nephrectomy. Schønau Jørgensen (1972) found the maximum serum calcium in rats 4 h after bilateral nephrectomy and a decrease to sub-normal levels after 24 h.

The volumetric and light microscope findings have shown hyperplasia of the parenchymal cells of the parathyroids and the histological changes have also suggested hypertrophy of these cells. The ultrastructural changes in the chief cells were consistent with great functional activity. There appear to be no previous ultrastructural studies of canine parathyroids after bilateral nephrectomy. In nephrectomised rats, ultrastructural signs of increased cellular activity have been found (Mazzocchi et al., 1976).

These results indicate that parathyroid hyperfunction (hyperparathyroidism) develops very rapidly in dogs after bilateral nephrectomy. In a previous study of dogs in chronic renal failure it was found that hyperparathyroidism developed in the absence of hypocalcaemia and even in the presence of hypercalcaemia (Boquist et al., 1973). The present observations show that hyperparathyroidism may also develop in the absence of

hypocalcaemia in dogs suffering from acute renal failure.

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