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HYPERVITAMINOSIS D IN SHEEP

AN EXPERIMENTAL STUDY

By

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SIMESEN, M. G., T. HÄNICHEN and K. DÄMMRICH: *Hypervitaminosis D in sheep. An experimental study.* Acta vet. scand. 1978, *19*, 588—600. — A comparison of the picture of vitamin D intoxication in sheep caused by injection of vitamin D_3 and the picture caused by injection of 1α-OH-cholecalciferol was made. The clinical symptoms were moderate. Unwillingness to move and sensitivity to palpation of the flexor tendons of the forelegs were found during the last week of life. The clinical-chemical picture was characterized by a pronounced increase in inorg. P values and a less pronounced increase in Ca values. In the vitamin D_3-treated animals these increases appeared later and were less pronounced.

At necropsy, vascular calcifications were found (Table 3). No macroscopical or histological differences between the effect of vitamin D_3 and of 1α-OH-cholecalciferol were demonstrated.

vitamin D_3; 1α-OH-cholecalciferol; hyperphosphataemia; hypercalcaemia; toxicity; sheep.

Recent investigations concerning the metabolism of vitamin D have yielded important new information and concepts in the fields of Ca and P metabolism, clinical medicine related to mineral metabolism, and skeletal pathology (*Wasserman* 1975). Hypervitaminosis D has been studied in cattle, swine, horses, dogs, cats and several other animals (*Dämmrich* 1963, *Capen et*

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al. 1966, *Chineme et al.* 1976). Several investigations were carried out before modern concepts of the metabolism and the metabolic transformations of vitamin D were known.

In sheep apparently no experimental vitamin D intoxication trials have been carried out in the last 25 years or more. One or 2 large doses of vitamin D have been used to prevent rickets in young sheep, so far without notable ill effect (*Jubb & Kennedy* 1970). The only data designed expressly to determine the vitamin D requirement for growing sheep are those of *Andrews & Cunningham* (1945). Their results indicate a minimal requirement about 4 i. u./kg body weight/day. Available data, on the other hand, on the toxicity of massive doses of vitamin D to sheep indicate that healthy sheep can tolerate a single dose of 2 mill. i. u. vitamin D (*Grant* 1955). *Greig* (cit. ARC 1965) found that a single dose of 10 mill. i. u. vitamin D given intravenously produced marked vascular (metastatic) calcifications. Apart from these reports it is generally known (*Jubb & Kennedy*) that administration of vitamin D does promote hypercalcaemia and hyperphosphataemia, but the levels of these elements, or the blood urea as a reflection of a renal injury, do not correlate very well with the severity of the clinical signs.

In the present study it was the purpose to compare the picture of vitamin D intoxication caused by the injection of vitamin D_3 with that caused by injection of 1α-OH-cholecalciferol* in sheep.

MATERIAL

The study included 2 trials with a total of 4 healthy, approx. 6 months old sheep (2 male and 2 female). The sheep were kept indoors. They were fed good quality hay free choice.

The sheep were injected weekly. Two sheep were given 2 mill. i. u. vitamin D_3 (∞ 40,000 i. u./kg body weight i. m.), and 2 sheep were given 50 µg 1α-OH-cholecalciferol (∞ 1 µg/kg body weight i. m.) in the posterior thigh musculature (Table 1).

Blood samples were collected 3 days before the first treatment, and from then on blood samples were drawn at regular intervals as follows: In the first trial (sheep Nos. 21 and 26) at

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* The 1α-OH-cholecalciferol was placed at our disposal by Leo Pharmaceutical Products, Copenhagen, who also most kindly sponsored the colour plate.

Table 1. Survey of animals, treatment, body weight and duration of experiment.

Sheep No.	Breed	Age	Sex	Treatment*, in week No.					Body weight, kg at beginning	Body weight, kg at termination	Duration of experiment, days
				1	2	3	4	5			
26	Merino	ab. 6 months	♂	vit. D_3	vit. D_3	vit. D_3	none	vit. D_3	43.0	40.0	37
21	Merino	ab. 6 months	♂	1α-OH	1α-OH	1α-OH	none	1α-OH	43.5	34.7	37
2	Merino	ab. 6 months	♀	vit. D_3	vit. D_3	vit. D_3			49.5	45.3	21
1	Merino	ab. 6 months	♀	1α-OH	1α-OH	1α-OH			45.5	45.0	21

Dose: Vitamin D_3: 2 000 000 i.u., i.m.
1α-OH-cholecalciferol: 50 μg, i.m.

0, 1, 3, 5, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144 and 168 hrs. during the first and second weeks; 9 samples in the third week; 3 samples in the fourth week (without treatment); and 9 samples in the fifth week. In the second trial (sheep Nos. 1 and 2) blood samples were drawn at 0, 3, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144 and 168 hrs. during the first and second weeks; blood samples were collected daily in the third week. The first trial terminated after 37 days, the second trial after 21 days.

The sheep were weighed weekly; the body weights at the beginning and at the termination of the trials are shown in Table 1.

METHODS

Serum Ca was determined directly by flame photometry (Eppendorf flame photometer). Inorg. P was determined by the Fa ASID method (Ammonium-molybdenum blue). Serum Mg was determined photometrically by the Ingotest (Xylidinblau Fa Boehringer method from Fa Haury). Alkaline phosphatase activity was estimated by the 1—2—3 min. method (Fa Boehringer).

The animals were necropsied after the termination of the experiment. The macroscopic and microscopic examinations were carried out at the Institute for Animal Pathology, University of München. The changes in the skeleton were examined at the Institute for Veterinary Pathology at Freie Universität, Berlin.

Routine Paraplast® sections of heart, carotid artery, mesenteric artery, lung and kidney were stained by the H & E and Von Kossa methods. Thyroid glands were embedded in Epon® and sectioned for electron microscopical study of the C-cells.

RESULTS

Clinical observations

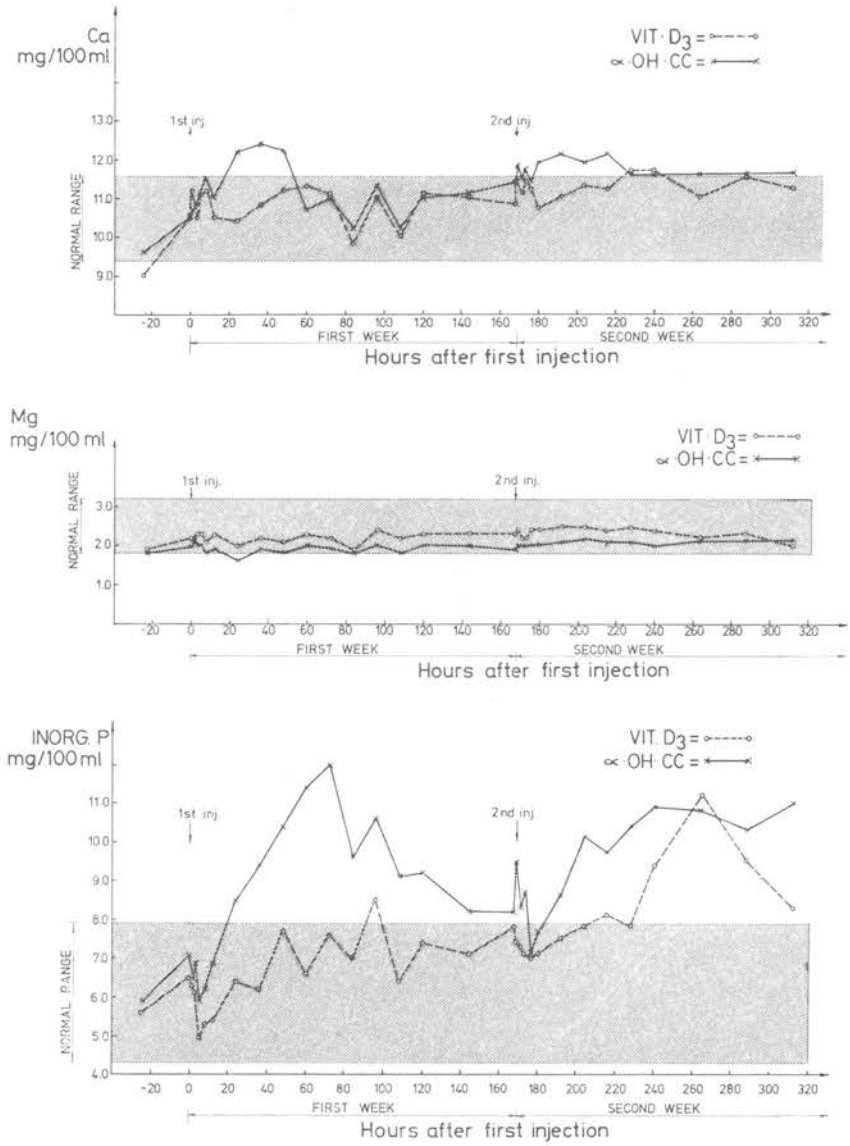
The 4 sheep remained clinically healthy throughout the trials. The general condition was very little influenced. They all showed a loss of weight during the trials (Table 1), most pronounced in the last 2 weeks of the trial in sheep Nos. 21 and 26. Towards the end of the 5 weeks' experimental period, sheep No. 21 showed increasing unwillingness to move. This sheep became very sensitive to palpation of the flexor tendons and the suspensory ligaments of the forelegs. The animal had a tendency to place itself in a protracted kneeling posture when rising. In sheep Nos. 21 and 26 the jugular vein appeared indurated in both sides during the last few days before they were slaughtered. In sheep Nos. 1 and 2 this was not the case.

The body temperature, heart rate at rest, respiration, rumination, defecation and urination were checked daily and found normal. From the third week of the experimental period the pulse rate (heart rate) increased considerably, merely because of the effort when the sheep got up and moved a little around in the pen (from 60—70 to 100—120/min.). The heart sounds, however, were normal and regular.

Clinical-chemical picture

In Figs. 1, 2 and 3 the clinical-chemical changes with regard to average values of Ca, inorg. P and Mg after vitamin D_3 or 1α-OH-cholecalciferol injections are shown. In serum Ca an increase is seen in both groups. The increase after the 1α-OH-cholecalciferol injection was, however, more pronounced and appeared sooner than after the vitamin D_3 injection. Only in the 1α-OH-cholecalciferol-treated group did the increase exceed the upper normal value (28—48 hrs. after the injection). After the second and the third injections almost the same picture was seen. The fluctuations in serum Ca as well as in inorg. P seemed, however, a little less pronounced than after the first injection.

The clinical-chemical picture following the treatment was



Figures 1, 2 and 3. Changes following the 2 first injections of vitamin D_3 (○ – – – ○) and 1α-OH-cholecalciferol (× —— ×) in serum Ca, Mg and inorg. P.

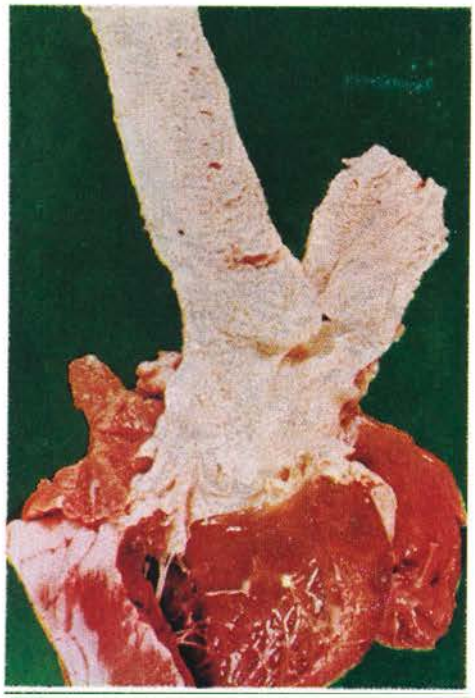


Fig. 4.

Figure 4. Left ventricle and inside of aorta. Subintimal calcifications with washboard-like contours.

Figure 5. Capsular surface of kidney with vascular calcifications.

Figure 6. Sagittal, cut surface of kidney with vascular calcifications.

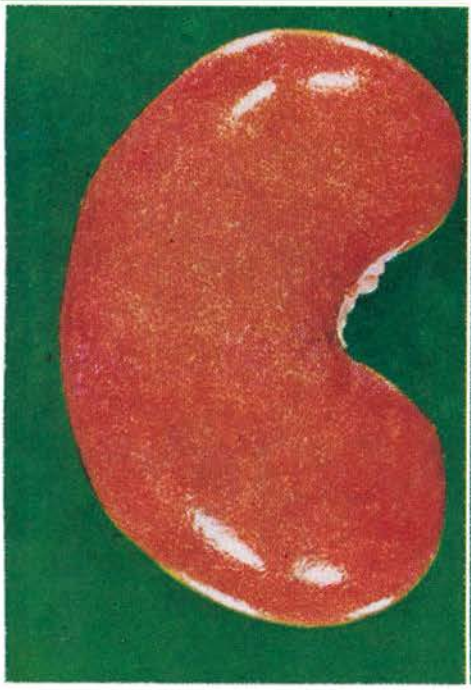


Fig. 5.

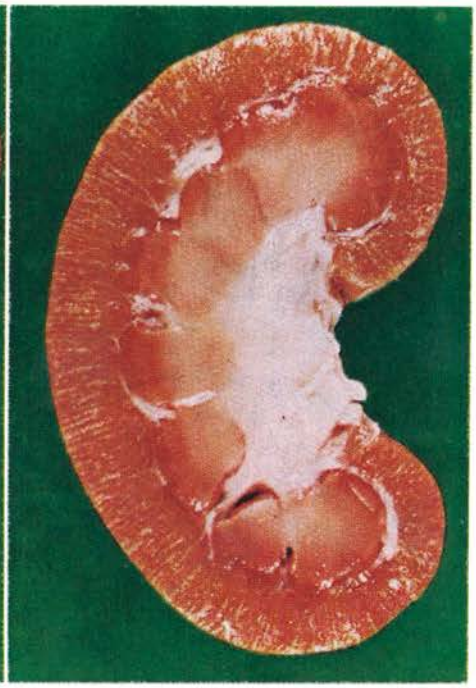


Fig. 6.

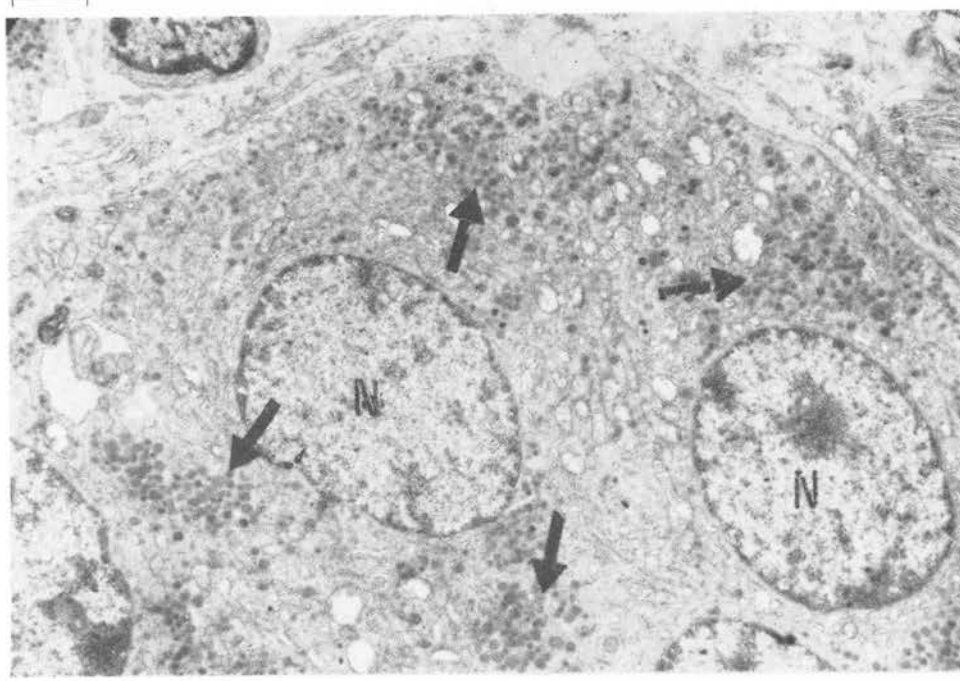


Figure 7. Electron micrograph of normal C-cell granules (arrows) from a sheep. N = nucleus. × 5000.

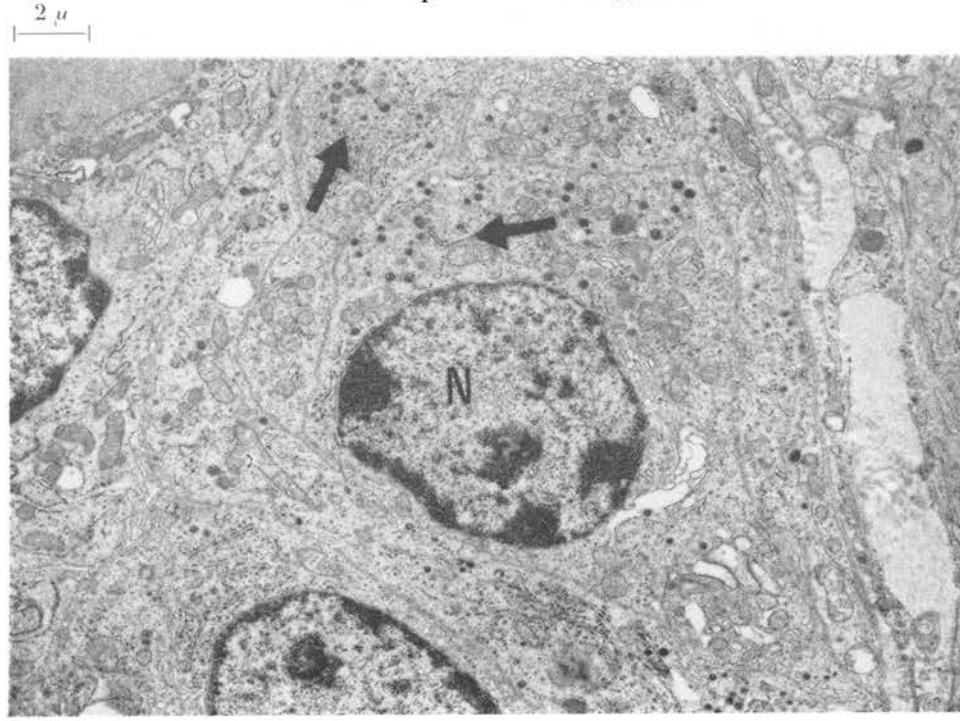


Figure 8. Electron micrograph of degranulated C-cells (arrows) from a sheep treated with 1α-OH-cholecalciferol and vitamin D_3. N = nucleus. × 5000.

especially characterized by a strong increase in the blood values of inorg. P. These values increased from about 5—7 mg/100 ml to values around 11—12 mg/100 ml. The increase reached its summit about 72 hrs. after the injection of 1α-OH-cholecalciferol. The increase after the first vitamin D_3 injection was less pronounced (max. value 8.5 mg/100 ml) and appeared almost 24 hrs. later than after 1α-OH-cholecalciferol injection. Neither after 1α-OH-cholecalciferol nor after vitamin D_3 injection did the values for inorg. P return completely to their starting levels prior to the following injection 1 week later.

After 1 week's pause, the fourth injection was given to 1 animal in each group. Following this injection the fluctuations in serum Ca seemed a little more pronounced (values exceeding 12 mg/100 ml) in both groups. For inorg. P the max. increase was to about 12 mg/100 ml in both groups. Average weekly values are given in Table 2.

Table 2. Average weekly values of serum calcium and inorg. phosphorus during the trials (mg/100 ml).

Sheep No.	Av. value before 1st injection	Treatment, in week No. 1	2	3	4	5
Calcium						
		vit. D_3	vit. D_3	vit. D_3	none	vit. D_3
26	10.7	11.0±0.7	11.3±0.8	11.6±0.7	11.2(n=3)	11.9±1.3
		1α-OH	1α-OH	1α-OH	none	1α-OH
21	11.1	11.4±1.8	11.7±0.8	11.1±1.2	11.2(n=3)	12.1±0.8
		vit. D_3	vit. D_3	vit. D_3		
2	9.2	9.8±1.0	10.9±1.4	12.2(n=3)		
		1α-OH	1α-OH	1α-OH		
1	9.8	10.6±1.5	11.7±0.9	11.9±1.1		
Inorg. phosphorus						
		vit. D_3	vit. D_3	vit. D_3	none	vit. D_3
26	6.2	6.6±1.6	7.7±2.2	9.1±1.7	9.7(n=3)	9.9±1.3
		1α-OH	1α-OH	1α-OH	none	1α-OH
21	9.8	8.5±4.4	9.8±2.8	10.0±1.9	9.8(n=3)	9.8±1.5
		vit. D_3	vit. D_3	vit. D_3		
2	6.5	7.4±2.5	9.0±3.2	9.6(n=3)		
		1α-OH	1α-OH	1α-OH		
1	6.6	8.5±3.4	8.7±2.8	9.9±1.1		

Normal values (n=25): Calcium = 10.5±1.1
Inorg. phosphorus = 6.1±1.8

Normal values for Ca and inorg. P ($\bar{x} \pm 2$ s) calculated from blood samples from 25 sheep in the same herd given the same diet and analyzed by the same methods are shown in Table 2.

The values for serum Mg are characterized by being almost constant during the whole period. Only for the 1α-OH-cholecalciferol group a slight tendency to a decrease was observed in weeks 1 and 4. The Mg values, however, were never below 1.50 mg/100 ml.

The levels of serum alkaline phosphatase showed great variations in the 4 animals. For the individual animal, however, the level seemed to stay at a more constant level. In both groups of sheep the treatment caused a decrease in the individual levels. The lowest values (about 50 %) were reached in the third week of the trials.

The values for blood urea stayed constant between 25 and 60 mg/100 ml in all animals during the trials.

Post-mortem observations

At necropsy all animals showed vascular calcifications, varying only in the extent of the mineral deposits and the vessels involved (Figs. 4, 5 and 6).

The degree of vascular calcifications in the individual animals is shown in Table 3. After 4 injections of 1α-OH-cholecalciferol (sheep No. 21) additional calcification of the endocardium and interstice of the lung occurred.

The C-cells of the 4 animals were almost completely degranulated, compared with those of normal sheep from another experiment used as control (Fig. 7). Only a few granules and the less electrondense progranules could be seen, and the cytoplasm appeared much lighter. The C-cells were difficult to detect between the follicular thyroid epithelium. There was no evident difference between these 4 animals. Two other sheep, not included in this study, which had received vitamin D_3 and 1α-OH-cholecalciferol alternately, developed less severe calcifications and also showed less degranulation (Fig. 8). The C-cells from these 2 sheep could, as normally, be found easily and had abundant electrondense granules.

The histological examination of metatarsal and metacarpal bones from sheep Nos. 1 and 2 showed identical changes and were characterized by endosteal as well as periosteal break-down of the bone. The catabolism (osteocytic osteolysis) of the bone

Table 3. Macroscopic and histopathologic* observations.

Sheep No.	Sex	Treatment	Aorta			Pulmonary artery	Carotid artery*	Left ventricle* and left lung*	Mesenteric artery*	Lung*	Kidney*		
			proximal A	thoracic A	abdominal A						cortex	medulla	papillae
2	♀	3 × vit. D_3	—	—	—	—	—	(+)	—	—	—	+++	—
26	♂	4 × vit. D_3	++	+++	+++/++++	—	+	—	+	—	+[1]	+++	—
1	♀	3 × 1α-OH	++	+++	++	++	+++	—	+	—	+[2]	—	+++
21	♂	4 × 1α-OH	++++	++++	++++	+++	+++	+	+	+	+++[2]	—	+

[1] Vascular deposits. [2] Vascular deposits and deposits in the renal tubules.

The degree of vascular calcification in the individual animals is graded as follows: — negative (normal); (+) very weak; + distinct; ++ moderate; +++ abundant; ++++ extensive.

tissue had been followed by a filling up of the lacunae with connective tissue. These changes were most prominently seen on the spongiosal trabeculae and on the surface of the metaphyseal cortex. The number of regular cartilage columns and primordial spongiosal trabeculae at the normally non-conspicuous epiphyseal lines was diminished, giving room for sporadically intensified myelofibrosis in the area. This subsiding phase of enhanced bone break-down was succeeded by formation of a basophilic bone matrix, which covered the spongiosal trabeculae as thin basophilic lines, and which lined the Haversian canals and to a lesser extent the periosteal surface of the cortex.

The histological examination of ribs and metacarpal bones from sheep Nos. 21 and 26 showed similar changes.

Endosteal as well as periosteal bone matrices were formed and characterized by basophilia. This tissue covered the spongiosal trabeculae as well as the Haversian canals as a fine stratification. A similar stratification was observed under the periosteum. In this location, it radiated as a crumbled-granular seclusion as far as the connective tissue of the cambium. It was thus shown, especially at the rib, that this layer of basophilic bone matrix was covered by newly formed bone trabeculae. The epiphyseal lines were not clearly marked in any way. Only around the cartilage columns and the primordial spongiosal trabeculae cartilage columns, the spongiosal net appeared condensed as a consequence of the diminution of the modelling break-down.

DISCUSSION

Injections of vitamin D_3, 40,000 i.u./kg body weight, or of 1α-OH-cholecalciferol, 1 μg/kg body weight, were given to 4 young sheep weekly for 3 and 4 weeks during the 5 weeks' experimental period. In week 4 no injections were given. Both treatments caused extensive calcinotic changes in the cardiovascular system. As seen from Table 3 the macroscopic and microscopic calcifications were more pronounced after treatment with 1α-OH-cholecalciferol than after vitamin D_3 (sheep Nos. 1 and 21 >< sheep Nos. 2 and 26). The calcifications were in both groups heavier after 5 weeks (4 injections) than after 3 weeks (3 injections).

In spite of this, clinical symptoms were almost absent. All sheep remained clinically unaffected throughout the first 3

weeks. At the end of the 5 weeks' experimental period the jugular veins could be palpated latero-ventrally on both sides of the neck. In the last week of life 1 sheep (No. 21) treated 4 times with 1α-OH-cholecalciferol showed unwillingness to move and was sensitive to palpation of the flexor tendons of the forelegs, i.e. showed symptoms almost like those observed in cows with enzootic calcinosis (*Dirksen et al.* 1970).

The clinical-chemical picture was especially characterized by a pronounced increase of inorg. P values. In the 1α-OH-cholecalciferol-treated group this increase appeared about 72 hrs. after the first injection. In the vitamin D_3-treated group the increase in inorg. P appeared later and was less pronounced. After the second 1α-OH-cholecalciferol injection the increase in inorg. P was almost as marked as after the first treatment.

Hypercalcaemia appeared 20—50 hrs. after the first 1α-OH-cholecalciferol injection as well as after the following injections. In the vitamin D_3-treated group the increase in Ca was less pronounced and appeared several hours later, and the Ca values did not reach hypercalcaemic values in the first week. In the following weeks the response in serum Ca seemed to increase after each vitamin D_3 injection.

In dairy heifers *Sansom et al.* (1976) have reported a similar Ca and inorg. P blood picture after 1α-OH-cholecalciferol and vitamin D_3 injections.

Following the modern concept of vitamin D metabolism it has been demonstrated that in the liver vitamin D is transformed to a biologically significant intermediate, 25-hydroxycholecalciferol, which is then transported to the kidney, where the metabolically active form is produced (*Holick et al.* 1971). It has been shown that 1α-OH-cholecalciferol in animals produces a response which in time course is almost identical to the response to 1,25-$(OH)_2$-cholecalciferol, the most active vitamin D derivative (*DeLuca et al.* 1976). According to the current concepts on the biochemical mode of action of vitamin D and its metabolites it was to be expected that the 1α-OH-cholecalciferol-treated group should react sooner than the vitamin D_3-treated group (*Norman* 1974).

In sheep and other herbivorous animals vitamin D and vitamin D metabolites characteristically cause a hyperphosphataemia and to a lesser degree a hypercalcaemia. This is not the

case in omnivorous animals as the pig (*Stepp et al.* 1957, *Dämmrich* 1963, *Bille* 1970, *Chineme et al.* 1976).

The degranulation of the C-cells, observed in our sheep treated with vitamin D_3 or 1α-OH-cholecalciferol, is in accordance with the findings of *Capen & Young* (1969). *Collins et al.* (1976) described the same rapid effect in cattle fed with Solanum malacoxylon. *Reisinger* (1977) observed degranulation of the C-cells in rats treated with dihydrotachysterol. This is usually interpreted as a response to hypercalcaemia. Also in the present experiment there was a rise in serum Ca levels. Decreased activity of the parathyroid glands can be assumed.

From the results of microscopic studies we shall emphasize the differences in the localization of the mineral deposits in the kidney. In the vitamin D_3-treated sheep the lesions mainly involved the tubuli of the renal medulla, whereas in sheep treated with 1α-OH-cholecalciferol only the tubules of the cortex were involved.

This fact and the lower extent of calcifications after combined treatment with vitamin D_3 plus 1α-OH-cholecalciferol are striking. So far we have no explanation for this and we just want to present the results. Individual susceptibility of the animals has to be considered.

In the cow, calcifications similar to those observed in this experiment have been observed after treatment parenterally with 1α-OH-cholecalciferol in doses corresponding to those used in this experiment (*Björklund et al.* 1976).

The changes demonstrated in ribs, metacarpal and metatarsal bones are similar to the changes observed after hypercalcaemia as a consequence of long-term treatment with toxic doses of vitamin D_3 or after poisoning with plants such as Solanum malacoxylon (enzootic calcinosis). No difference was established between the effect of vitamin D_3 and 1α-OH-cholecalciferol. The histological picture observed in sheep Nos. 1 and 2 demonstrated lesions less advanced than those present in sheep Nos. 21 and 26, in which the increased formation of stratified bone tissue mirrored the chronic hypercalcaemic condition. Differences thus appear only to be a consequence of the duration of the treatments.

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SAMMENDRAG

Vitamin D_3 hypervitaminose hos får. En eksperimentel undersøgelse.

Der er foretaget en sammenligning mellem billedet af vitamin D-forgiftning forårsaget af injektion med vitamin D_3 og det billede, som fremkaldes ved injektion af 1α-OH-D_3.

De kliniske symptomer var i begge tilfælde meget moderate. Uvillighed til bevægelse og ømhed ved palpering af forbenenes bøjesener blev påvist i sidste leveuge. Klinisk-kemisk var billedet karakteriseret af en udtalt stigning i værdierne for uorg. P og en mindre udtalt stigning i serum Ca værdierne. Hos de vitamin D_3 behandlede får indtraf stigningerne senere og var mindre udtalte.

Ved obduktionen påvistes subintimale forkalkninger i hjertet og de store karstammer (tabel 3). Der kunne ikke påvises makroskopiske eller histologiske forskelle imellem effekten af vitamin D_3 og 1α-OH-D_3.

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