HYPOTHYROIDISM IN THE SHEEP

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Summary

The effect of the oral administration of methyl thiouracil at three dose rates to pregnant ewes has been studied. Observations were made on foetal skeletal growth and maturity, foetal and maternal thyroid iodine, plasma-protein-bound iodine (PBI), cholesterol, phospholipid, total esterified fatty acids, and calcium. A retardation of osseous growth and a significantly greater retardation of osseous maturity was found. The thyroid iodine concentration in both ewes and foetuses and the maternal total thyroid iodine in all treated groups were decreased but the *foetal* total thyroid iodine was reduced only in the two highest dose rates. Significant reduction in the foetal PBI was found only with the two highest dose rates and no significant changes were found in the maternal PBI concentration. Increases in all lipid fractions and a decrease in calcium concentration were found in the foetal plasma in the treated groups.

I. INTRODUCTION

Hypothyroidism induced by various goitrogens is known to be associated with perinatal mortality in lambs. The disease was first reported in New Zealand by Gilruth (1901) who described hypertrophy in the thyroid glands in calves, lambs, and foals. Hopkirk *et al.* (1930) considered that the goitres were due to iodine deficiency. Sinclair and Andrews (1954) described the occurrence of congenital goitre in lambs when the pregnant ewes had been grazed on kale. Subsequently Wright and Sinclair (1958) presented evidence which suggested that the goitrogenic substance in kale belonged to the thiouracil group. Thiouracil is known to inhibit the organic binding of iodine as thyroglobulin (Vanderlaan and Vanderlaan 1947; Stanley and Astwood 1948; Berson and Yalow 1955). Flux *et al.* (1956) suggested that level of thiocyanate in the sera of animals fed clovers containing cyanogenetic glucosides was sufficient to produce goitre. Thiocyanate is known to be goitrogenic by inhibiting thyroidal accumulation of iodine (Astwood 1943; Rawson, Tannheimer, and Peacock 1944; Wolf *et al.* 1946; Barker, Lindberg, and Wald 1941; Brown-Grant and Gibson 1955).

Todd, Wharton, and Todd (1938) described the effect of thyroidectomy in the lamb, and noted defective development of the epiphyses and adjacent shafts. The present study was undertaken to examine the effects of hypothyroidism on ossification and growth in the foetal appendicular skeleton. Also biochemical observations on plasma-protein-bound iodine (PBI), lipid, calcium, and thyroid iodine concentrations were made.

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II. Materials and Methods

(a) *General*

Fifty Peppin-type Merino ewes were paddock-mated at Trangie Experimental Farm, N.S.W., between April 8 and 28, 1958. Twenty-four of those which did not return to service were transported to Sydney, arriving at the Veterinary School on May 25. The ewes were randomly divided into four groups of six ewes and were suitably identified. Following weighing, the 24 ewes were housed at random, three per pen. At each subsequent weekly weighing the ewes were re-randomized to the pens in order to prevent development of intra-pen correlations in the final results. The cardinal signs of each ewe were recorded daily and heparinized blood samples were collected at intervals of 5–6 weeks throughout pregnancy, the first sample being collected on May 27. The plasma was separated by centrifugation and stored at −20°C until analysed. Treatment of the ewes with methyl thiouracil commenced on June 3, three groups receiving respectively 0·5, 1·5, and 4·5 g of methyl thiouracil in 30 ml of water per day, by oesophageal tube. The ewes of the fourth group (i.e. controls) were given 30 ml of water. This dose range was based on the doses fed to young rams by Hall and Harvey (1952).

Soon after parturition, plasma samples were collected from both ewe and lamb. Each lamb was weighed and the body length measured by placing a piece of string along the mid-dorsal line from a line joining the medial canthi of the eyes to the tip of the tail (Dun 1955). The string was marked at the appropriate point and then compared with a fixed scale.

Post-mortem examination of each ewe and lamb was carried out. The thyroid glands were weighed. A small slice (approx. 0·5 g) was taken from each gland for total thyroid iodine estimations. The slice was weighed and placed in 10 ml of 12·5 per cent. formol–saline in a jar which was tightly stoppered.

Both dorsal and lateral radiographs of the left fore and hind limbs of each lamb were taken, using non-screen film (Ilford) at 50–55 kV, 30 mA, with 0·5 sec exposure and 36-in. anode film distance. By means of calipers the length of the tibial diaphysis was measured using the lateral radiograph, the proximal and distal landmarks taken being points midway between the anterior and posterior aspects of the bone. The degree of osseous maturity of lambs at birth was assessed by counting the number of appendicular epiphyseal and round bone centres of ossification, ignoring the lesser trochanter and the talus (Lascelles 1959).

(b) *Biochemical Methods*

PBI was determined by the method of Grossman and Grossman (1955) as modified by Setchell (1959). Ten simultaneous analyses on a single sample of plasma yielded a mean value of 4·51 μg PBI/100 ml with a standard error of the mean of $\pm$ 0·29. Eight analyses on the same plasma sample to which 5 μg of inorganic iodine/100 ml had been added immediately before drying and ashing gave the value of 9·35 μg/100 ml with a standard error of the mean of $\pm$0·38. This indicates a recovery rate of 97 per cent., a satisfactorily high value.

Thyroid iodine was determined by digesting the weighed slice of thyroid gland in 5 ml ethanol and 10 ml of 1·8N KOH (Franklin 1931). During digestion, the volume was reduced by evaporation to about 5 ml to make the KOH approximately 4N. The volume was then made up to 50 ml in a volumetric flask with 4N Na_2CO_3. If necessary, further dilutions with 4N Na_2CO_3 were made; 1-ml portions of a suitable dilution were dried, incinerated, and the iodine determined by the above method for PBI. Dry weight of thyroids was taken as 20 per cent. of the fresh weight.

Plasma cholesterol was determined by the method of Pijoan and Walters (1937). Plasma total esterified fatty acids were determined by the method of Stern and Shapiro (1953). Phospholipids were determined in the extract for fatty acids, a 7-ml portion of which was evaporated to dryness in a microKjeldahl flask and digested with 1·2 ml 7N $HClO_4$. The inorganic phosphate was determined in the digest by the vanado-molybdate method of Simonsen *et al.* (1946).

Plasma calcium concentrations were determined by the spectrophotometric murexide method of Harper (1959). All readings were made on a Beckman spectrophotometer using 1-cm cells.

III. Results

(*a*) *Clinical Effects and Post-mortem Observations*

After a few weeks of treatment the ewes receiving the 1·5-g and the 4·5-g doses became noticeably lethargic. These animals rested for long periods and consumed less food than those in the other groups. Only two ewes from the 1·5-g group survived until parturition. The sheep that died showed characteristic symptoms, namely, progressive loss in weight, profound depression, and inappetance. The symptoms increased in severity until the ewe was unable to stand. Three of the ewes developed pneumonic symptoms in the terminal stages and areas of consolidation were found in the lungs at post-mortem examination.

All the lambs carried to full term were born alive but those in the treatment groups were weak and with few exceptions died soon after birth.

The mean length of the gestation period of each group was estimated by using the mid-range of the mating period as the date of conception. Since the groups were randomly formed this estimate is not biased, and a significant difference ($P < 0·001$) is found between the length of the gestation period in the control and treated groups (cf. Sinclair and Andrews 1954).

The administration of the goitrogen did not affect the weight of the pregnant ewes surviving the gestation period. Although the body length of the lambs was significantly smaller in the treated groups ($P < 0·05$) the difference in body weight just failed to be significant.

At autopsy, the most outstanding feature was the enlarged thyroid glands in those that had been treated with methyl thiouracil. However, the weight of the thyroid glands of the ewes in the 0·5- and 1·5-g groups was much greater than that of the only surviving ewe in the 4·5-g group. This particular gland had a

TABLE 1

DETAILS OF POST-MORTEM AND RADIOLOGICAL DETAILS OF EWES AND LAMBS TREATED WITH METHYL THIOURACIL AND OF CONTROL GROUPS AT BIRTH

Values given are means and standard deviations of the means. Number of animals in each group given in parenthesis

Dose Rate of Methyl Thiouracil (g/day)	Estimated Length of Gestation Period (days)	Weight of Ewes (lb)	Weight of Lambs (lb)	Body Length of Lambs (in.)	Length of Ossified Tibial Diaphysis of Lambs (in.)	Age of Lambs (length method) (days)	Osseous Maturity Score (units)	Age of Lambs (maturity method) (days)	Weight of Thyroid Glands of Ewes (g)	Weight of Thyroid Glands of Lambs (g)
0	146·6 ±2·2 (6)	120·0 ±2·5 (6)	7·63 ±0·67 (9)	27·12 ±0·81 (9)	3·73 ±0·12 (9)	147 ±4·0 (9)	39 ±0 (9)	143 ±0 (9)	3·55 ±0·03 (6)	0·93 ±0·12 (9)
0·5	156·8 ±1·1 (6)	129·0 ±3·6 (6)	6·69 ±0·41 (9)	25·53 ±0·58 (9)	3·27 ±0·13 (9)	132 ±2·7 (9)	22·8 ±2·5 (9)	122 ±3·2 (9)	33·7 ±6·5 (6)	69·8 ±14·3 (9)
1·5	169·5 ±3·5 (2)	124·5 ±0·5 (2)	6·72 ±0·04 (2)	25·35 ±0·15 (2)	3·25 ±0·01 (2)	131 ±0·2 (2)	13·0 ±1·0 (2)	109 ±1·2 (2)	34·0 ±8·1 (2)	56·5 ±16·9 (2)
4·5	161 (1)	112 (1)	4·38 ±0·30 (2)	23 ±1 (2)	2·42 ±0·02 (2)	113 ±0·6 (2)	8 ±0 (2)	103 ±0 (2)	11·8 (1)	18·15 ±8·15 (2)

woody texture compatible with the complete acinar collapse which was observed histologically. Van Gieson staining did not demonstrate any differences in collagen content.

Macroscopically the goitrous thyroid glands were deep red in colour and fleshy in texture and microscopically the epithelial cells were enormously hypertrophied; the acini had lost their normal shape and had become convoluted as a result of cellular crowding. Colloid which was abundant in the thyroid glands of the controls was present in small amounts only or completely absent in the glands of the treated groups. The other outstanding and constant features found at the autopsy were the enlarged fatty livers and kidneys.

The lambs in the treated groups showed more pronounced goitres than their dams. The goitrous thyroids of lambs differed from those of the ewes in that gross cystic changes had occurred; other histological changes were similar. The tongue and neck were usually somewhat oedematous in the lambs of the treated groups, and the jugular veins were engorged with blood. In addition, the trachea and larynx were distinctly compressed by the goitre and the pericardial sac usually contained a little fluid.

The wool covering of the lambs in the 0·5- and 1·5-g groups was coarse and hairy. In some cases the skin was only sparsely covered with hair, particularly in the dorsal half of the body, ears, face, and inguinal region. The two lambs of the surviving ewe from the 4·5-g group were hairless except for a few hairs on the muzzle, eyelids, horn buds, ventral aspect of the neck and underline to the umbilicus, plantar aspect of the tarsus and metatarsus, dorsal aspect of the carpus, and around the coronets. These findings are in accord with those of Ferguson *et al.* (1956) who described a delay in the maturity of secondary wool follicles in thyroidectomized lambs. The coarser wool observed in the lambs in the present study would indicate the presence of a higher proportion of primary follicles than normal.

(*b*) *Radiological Observations*

The length of the ossified tibial diaphysis was significantly smaller ($P < 0 \cdot 01$) in the treated groups.

There was a pronounced delay in the appearance of ossification centres in the treated lambs (Plates 1 and 2) and this is also represented in Table 1 under the heading "Osseous Maturity Score". Osseous maturity as assessed by counting the centres of ossification (Lascelles 1959) has a maximum score of 39 which is attained in the average normal Peppin-type Merino several days before birth. Thus it is not surprising to find that in the present data the lambs in the control group all have an osseous maturity score of 39. The difference between the scores of the controls and the treated groups is very large and is highly significant ($P < 0 \cdot 001$).

The epiphyseal and round bone centres of ossification in the hypothyroid lambs often first appeared as irregular fragmented areas of opacity on the radiograph, whereas in the normal lamb the centres appeared as distinct areas of uniform opacity.

TABLE 2

BIOCHEMICAL ESTIMATES MADE ON PLASMA SAMPLES TAKEN DURING PREGNANCY FROM EWES TREATED WITH METHYL THIOURACIL AND FROM CONTROL EWES

Values given are means and standard deviations of the means. Numbers of animals in each group given in parenthesis

Date of Collection of Blood	Dose Rate of Methyl Thiouracil (g/day)	PBI (mg/100 ml)	Cholesterol (mg/100 ml)	Phospholipid (mg/100 ml)	Total Esterified Fatty Acids (μ-equiv/ml)	Calcium (mg/100 ml)
27.v.58	0	11·2 ± 1·0 (6)	85 ± 7 (6)	88 ± 11 (6)	4·1 ± 0·5 (6)	11·2 ± 0·5 (6)
	0·5	10·2 ± 1·1 (6)	92 ± 14 (6)	91 ± 4 (6)	3·6 ± 0·4 (6)	10·0 ± 0·3 (6)
	1·5	9·8 ± 0·7 (6)	101 ± 6 (6)	79 ± 6 (6)	4·8 ± 0·6 (6)	10·2 ± 0·5 (6)
	4·5	11·0 ± 1·6 (6)	86 ± 6 (6)	78 ± 3 (6)	4·5 ± 0·4 (6)	10·9 ± 0·9 (6)
4.vii.58	0	8·0 ± 0·5 (6)	73 ± 6 (6)	66 ± 7 (6)	3·5 ± 0·3 (6)	12·9 ± 0·2 (6)
	0·5	5·1 ± 0·6 (5)	70 ± 6 (6)	63 ± 10 (5)	2·7 ± 0·3 (5)	12·7 ± 1·0 (5)
	1·5	6·6 ± 1·2 (5)	72 ± 8 (5)	82 ± 7 (4)	3·6 ± 0·1 (5)	11·4 ± 0·2 (5)
	4·5	6·5 ± 0·7 (5)	90 ± 6 (5)	72 ± 11 (5)	3·5 ± 0·5 (5)	11·5 ± 0·3 (5)
21.viii.58	0	10·8 ± 0·7 (6)	99 ± 3 (6)	80 ± 4 (6)	4·6 ± 0·1 (6)	12·9 ± 0·8 (6)
	0·5	8·9 ± 0·9 (6)	112 ± 6 (6)	82 ± 5 (6)	4·5 ± 0·1 (6)	10·6 ± 0·3 (6)
	1·5	6·4 ± 0·4 (4)	127 ± 12 (4)	93 ± 6 (4)	4·4 ± 0·2 (4)	10·0 ± 0·6 (4)
	4·5	4·9 (1)	140 (1)	123 (1)	5·7 (1)	8·4 (1)

The shafts of the long bones were unmodelled; the appearance of the normal central diaphyseal constriction and the development of the contours characteristic of normally maturing bone were retarded. In addition the medullary cavities were poorly hollowed out (Plate 3) and the general trabeculation of the bone in the appendicular skeleton was coarse.

Another outstanding and constant feature observed was the presence of transverse bands of increased density found towards the ends of the diaphysis (Plate 3). Such a phenomenom has been described in new-born babies and children (Caffey 1945); however, this is not a characteristic feature of cretinism in young children. Harris (1933) claimed that maternal illness during pregnancy could induce the formation of transverse bands in the foetal skeleton. This would suggest that the phenomenon observed in the present study was not a specific feature of hypothyroidism but was more likely to be associated with the setback of the ewe caused by the administration of the drug.

The ages of the hypothyroid lambs as determined by using the regression formula based on osseous maturity and tibial length measurements (Lascelles 1959) are set out in Table 1. There is a significantly greater reduction ($P < 0 \cdot 001$) in age (maturity) than in age (length).

(c) *Protein-bound Iodine and Thyroid Iodine*

Although the PBI levels of the ewes of the control group were all lower than those of their lambs, this difference was not significant, probably due to the small number of specimens. The mean concentrations of PBI for the foetuses is similar to that for new-born calves found by Lewis and Ralston (1953) who also found higher values for animals 0–48 hr old than for adult animals. There was no significant difference between the concentrations of PBI in the control and treated groups of either ewes or lambs. In the lambs, however, there was a highly significant difference ($P < 0 \cdot 001$) between the concentrations in the pooled control and lowest dose groups and the pooled values of the highest dose groups.

(d) *Plasma Lipid Concentrations*

The concentration of phospholipid in the plasma of the ewes of the control group at birth was significantly higher ($P < 0 \cdot 01$) than that of the foetuses. Although each ewe of the control group had higher concentrations of cholesterol and total esterified fatty acids than their lambs these differences just failed to be significant, probably due to the small number of specimens.

There was a pronounced and significant rise in the levels of the lipid constituents of the lamb caused by the methyl thiouracil treatment. Although the same tendency was apparent in the ewes, the differences were not significant. A significant increase in the maternal plasma cholesterol concentration of the treated groups was found at the last bleeding during pregnancy (Table 2). The failure to show a significant increase in the maternal plasma cholesterol concentration at birth is probably due to the loss of two samples from the control group.

TABLE 3

BIOCHEMICAL ESTIMATIONS MADE ON PLASMA AND THYROID SAMPLES TAKEN AT PARTURITION FROM EWES AND LAMBS TREATED WITH METHYL THIOURACIL AND OF CONTROL GROUPS

Values given are means and standard deviations of the means. Numbers of animals in each group given in parenthesis

Dose Rate of Methyl Thiouracil (g/day)	PBI Estimations (mg/100 ml)		Total Thyroid Iodine (mg)		Thyroid Iodine (% dry wt.)		Plasma Concentration of: Phospholipids (mg/ml)		Cholesterol (mg/ml)		Total Esterified Fatty Acids (m-equiv/ml)		Calcium (mg/100 ml)	
	Ewe	Lamb	Ewe	Lamb	Ewe	Lamb	Ewe	Lamb	Ewe	Lamb	Ewe	Lamb	Ewe	Lamb
0	8·7 ±0·4 (4)	14·7 ±2·6 (5)	2·77 ±0·59 (6)	0·52 ±0·099 (7)	0·32 ±0·04 (7)	0·35 ±0·08 (7)	65·5 ±4·2 (4)	37·1 ±1·7 (5)	91·1 ±9·5 (4)	57·2 ±11·1 (5)	5·5 ±0·7 (4)	3·3 ±0·32 (4)	9·9 ±2·35 (4)	15·2 ±1·45 (5)
0·5	8·1 ±1·3 (6)	16·6 ±2·4 (8)	0·289 ±0·083 (6)	0·43 ±0·13 (7)	0·003 ±0·0004 (6)	0·007 ±0·0006 (7)	88·0 ±3·5 (6)	77·4 ±3·0 (8)	114 ±9·1 (6)	128 ±20 (7)	7·8 ±0·5 (6)	10·8 ±0·56 (8)	9·7 ±0·50 (6)	13·0 ±0·45 (8)
1·5	7·6 (1)	6·6 (1)	0·064 ±0·056 (2)	<0·01 (2)	0·001 ±0·001 (2)	<0·0001 (2)	80·5 ±8·5 (2)	102·5 ±18·5 (2)	100 ±8·0 (2)	156 ±9·0 (2)	6·3 ±1·75 (2)	10·3 ±0·85 (2)	6·4 ±0·65 (2)	4·4 ±0·65 (2)
4·5	4·1 (1)	6·7 ±0·1 (2)	0·060 (1)	<0·005 (2)	0·002 (1)	<0·0001 (2)	340 (1)	76·5 ±7·5 (2)	174 (1)	146 ±6·0 (2)	5·7 (1)	9·1 ±0·55 (2)	4·7 (1)	12·5 ±0·25 (2)

An increase in plasma cholesterol of ewes fed thiouracil has been reported by Barrick, Andrews, and Beeson (1950) and of other species treated with methyl thiouracil (Parodi and de Gregori 1948; Schettler 1950; Barr *et al.* 1955), although thiouracil did not affect the serum cholesterol concentration of rhesus monkeys (Aranow, Engle, and Sperry 1946).

There is a significant reduction ($P < 0 \cdot 001$) in the concentration of the thyroid iodine of both ewe and foetus in all treated groups. However, expressed as total thyroid iodine the difference between the control and lowest dose group is less in the ewes although still highly significant and there is no significant difference between the total thyroid iodine of the foetuses in the control and lowest dose group. The total thyroid iodine of the two highest dose groups is much less ($P < 0 \cdot 001$) than the control group for both ewe and foetus.

(*e*) *Plasma Calcium Concentration*

A decrease ($P < 0 \cdot 001$) in foetal plasma calcium concentration was found in the treated groups. A decrease ($P < 0 \cdot 01$) in maternal plasma calcium concentrations in the treated groups was shown at the last bleeding during pregnancy (Table 2) but the difference in the ewes at birth was not significant due to the loss of the two samples from the control group. The decreased plasma calcium concentration is in accord with the findings of Hall and Harvey (1952) but none of the sheep in the present work developed clinical hypocalcaemia. The biochemical results for ewe and foetus at parturition are summarized in Table 3.

IV. Discussion

Osseous development can conveniently be divided into growth and maturity. These data demonstrate clearly that growth and maturity are separable entities as hypothyroidism has delayed the process of maturity or differentiation of the bone to a significantly greater degree than it has delayed bone growth.

From the point of view of field diagnosis of hypothyroidism in lambs the most satisfactory and specific factor would seem to be a change in thyroid weight and iodine concentration (with the derived total thyroid iodine giving an indication of the severity of the condition). Of equal importance would be the changes in skeletal maturity which, as far as is known, are specific.

PBI seems to be of little value as it tends to be correlated with total thyroid iodine rather than thyroid concentration and consequently would be affected only in more severe cases. This is a little difficult to reconcile with the undoubted hypothyroid changes seen in skeletal development and lipid metabolism as PBI has been assumed to be a measure of circulatory thyroid hormone. However, this interpretation may be affected by the fact that the sheep in this experiment were drenched only once a day, blood samples being collected at the time of drenching. As Ely, Olsen, and Reineke (1948) showed that methyl thiouracil is eliminated within 24 hr from calves amd goats, it is possible that a diurnal variation of PBI concentration may be minimizing the extent of the changes seen. Unfortunately this point was not examined. At least of corroborative value are the lipid estimations and, although these are much less specific, changes in lipid concentration are considered by some authors as an inevitable accompaniment of hypothyroidism in man (Mason, Hunt, and Hurxthal 1930; Boyd and Connell 1936, 1937; Gildes, Man, and Peters 1939), in the dog (Entenman, Chaikoff, and Reichert 1942; Schmidt and Hughes 1938; Thompson and Lond 1941) and in the rhesus monkey (Fleischmann, Schumaker, and Strauss 1943).

It is probably, *in part*, a reflection of the mobilization of body fat reserves caused by increased thyrotropic hormone secretion induced by the hypothyroidism (Asboe-Hansen 1958). In addition, disturbance of hepatic lipid metabolism occurs. Both a decrease in synthesis (Lipsky 1955) and a decrease in excretion (Rosenman, Friedman, and Byres 1951) of hepatic cholesterol have been reported.

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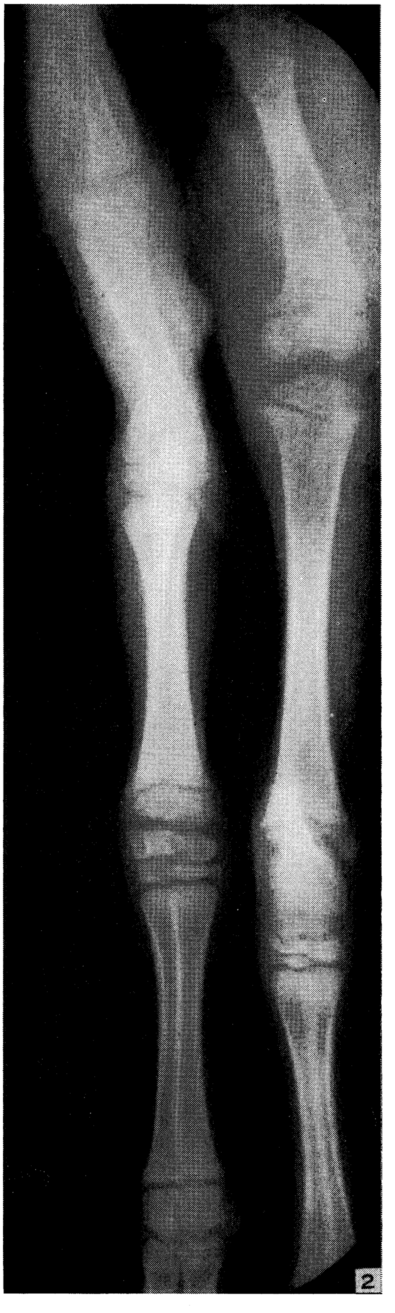
HYPOTHYROIDISM IN SHEEP



HYPOTHYROIDISM IN SHEEP

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Explanation of Plates 1–3

Plate 1

Radiographs, dorsal (Fig. 1) and lateral (Fig. 2) views, of the disarticulated fore and hind limb of the normal lamb demonstrating the extent of ossification at birth.

Plate 2

Radiographs, dorsal (Fig. 1) and lateral (Fig. 2) views, of disarticulated fore and hind limbs demonstrating grossly retarded ossification in a hypothyroid lamb at birth.

Plate 3

A lateral radiograph of the femero-tibial joint of a hypothyroid lamb showing transverse banding. In addition the narrowed medullary cavity and the unmodelled femoral diaphysis are obvious. No secondary centres of ossification have appeared in this region.