 Ultimobranchial thyroid neoplasms in bulls. A syndrome resembling medullary thyroid carcinoma in man

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A syndrome of ultimobranchial thyroid neoplasms which shares many similarities with medullary thyroid carcinoma in man occurs frequently in populations of adult bulls. The results of this investigation demonstrated that ultimobranchial neoplasms were composed of poorly differentiated parafollicular (C−) cells with extensive aggregations of microfilaments, clusters of ribosomes, and prominent Golgi apparatuses. Secretion granules often were interspersed between microfilaments. Other more columnar neoplastic cells assumed a ductal pattern. The prominent stroma contained amyloid fibrils and collagen fibers. By comparison, cells comprising medullary thyroid carcinoma were more differentiated parafollicular cells with well developed cytoplasmic organelles and numerous membrane-limited secretion granules. Calcitonin activity was demonstrated by biologic assay in both ultimobranchial adenomas (466 ± 84 MRC mU/g) and carcinomas (409 ± 93 MRC mU/g) but serum calcium and phosphorus levels were within normal limits. Plasma calcitonin-like activity was increased significantly 1 hour after calcium infusion but rapidly returned to baseline values. Parathyroid glands from bulls with ultimobranchial neoplasms had ultrastructural evidence of atrophy and secretory inactivity. Numerous lipofuscin granules and cytosegresomes but few secretory granules were present in chief cells. Aggregations of amyloid fibrils surrounded chief cells and capillaries. Multiple endocrine tumors (pheochromocytomas and pituitary acidophil adenomas) and vertebral osteosclerosis with ankylosing spondylosis frequently were detected in bulls coincidentally with ultimobranchial thyroid neoplasms.
maintain the concentration of blood calcium within precise limits.

Pearse\textsuperscript{21} has demonstrated cytochemically that parafollicular cells belong to the APUD series of polypeptide-hormone secreting cells which are present in the pituitary, pancreas, adrenal and thyroid glands, intestinal tract, and carotid body. Present evidence suggests the APUD cells are of neural crest origin and migrate into the glands during early development.\textsuperscript{22,23} A common embryonic derivation of many polypeptide hormone-secreting cells would help explain the frequent coincidental occurrence of multiple neoplasms of different endocrine glands in the same patient. The objectives of this investigation were: a) to characterize the macroscopic, histologic, and ultrastructural lesions in bulls with ultimobranchial thyroid neoplasmas; b) to determine if ultimobranchial thyroid neoplasms contain calcitonin activity; and c) to investigate the release of calcitonin-like activity from ultimobranchial neoplasms in response to calcium infusion.

\section*{Materials and Methods}

\textit{Animals:} Thirteen bulls with ultimobranchial thyroid adenomas and two bulls with ultimobranchial carcinomas of the thyroid were studied in this investigation. Adenomas appeared as single or multiple nodules often near the hilus separated by a thin connective tissue capsule from adjacent normal tissue. Neoplasms were interpreted to be carcinomas when the capsule and normal thyroid parenchyma were invaded and secondary foci of growth were present in cervical lymph nodes and lung. Both dairy and beef breeds were represented in the group. The average age of the bulls was 11.5 $\pm$ 0.99 years. Twenty bulls with no histologic evidence of ultimobranchial neoplasia served as controls. The average age of control bulls was 7.61 $\pm$ 0.55 years. Serum calcium was determined by atomic absorption spectrophotometry (Perkin-Elmer 303) and phosphorus was determined by the method of Fiske and Subbarow\textsuperscript{8} at the time of euthanasia.

\textit{Calcium infusion:} Prior to euthanasia 6 bulls with ultimobranchial tumors were infused intravenously with 500 ml of a 5\% dextrose solution containing 8.42 gm of calcium (calcium borogluconate), 4.80 gm of phosphorus, and 1.88 gm of magnesium over a period of 30 minutes. Plasma and serum were collected prior to infusion and at 1, 2, 3, 5, and 8 hours post-infusion. Blood was collected in precooled heparinized centrifuge tubes (50 ml) and a 100 ml aliquot of plasma was frozen at $-20^\circ\text{C}$ within 20 minutes.

\textit{Assay of calcitonin-like activity in plasma:} Calcitonin-like activity was extracted from plasma samples by the oxycellulose extraction technique of Gudmundson et al.\textsuperscript{11} The extracts were lyophilized, sealed, and stored at $-20^\circ\text{C}$ prior to assay.

In studies prior to beginning the experiment, plasma extracts were reconstituted with 25 ml of 0.01 M sodium acetate trihydrate containing 20 mg of bovine serum albumen, adjusted to pH 4, and calibrated against a bovine standard. It appeared that some factor was interfering with the hypocalcemic activity of plasma extracts at the high dose level in this procedure. The mean calcium concentration of reconstituted extracts was 3.29 mg/100 ml. The hypercalcemic effects of a 3.29 mg/100 ml calcium solution were determined in assay rats injected at 2 dose levels with the high dose being 4 times the low dose. It was determined that 0.4\% w/v sodium oxalate would precipitate sufficient calcium to eliminate these hypercalcemic effects when injected into assay rats at 2 dose levels (Table 1). Diluent used to reconstitute lyophilized extracts in assays of plasma CT-like activity in this investigation was prepared as outlined previously but contained sodium oxalate (0.4\% w/v). The reconstituted extracts were centrifuged at 10,000 rpm for 10 minutes and the supernatants collected for assay. The mean calcium concentration of extracts prepared by this procedure was 1.04 $\pm$ 0.02 mg/100 ml.

\begin{table}
\centering
\caption{Effect of the Addition of Sodium Oxalate (0.4\% w/v) to Diluent in the Assay of Plasma Calcitonin-like Activity}
\begin{tabular}{|lllll|}
\hline
Group & Na oxalate & Diluent calcium & No. of rats & Serum calcium \\
      & (\%)        & (mg/100 ml)    &            & (mg/100 ml)    \\
\hline
Control & -          & -              & 30          & 9.7 $\pm$ 0.13 \\
Low dose (0.2 ml) & 0.4        & 3.29           & 30          & 9.8 $\pm$ 0.02 \\
High dose (0.8 ml) & 0.4        & 3.29           & 30          & 9.9 $\pm$ 0.04 \\
\hline
\end{tabular}
\end{table}
Twenty-one-day-old male Holtzman rats used for assay were placed on a low calcium diet 24 hours prior to injection. Four rats were used for each of 2 dose levels with the high dose being 4 times the low dose. The rats were injected intravenously via the tail vein and exsanguinated after 30 minutes. The reconstituted extracts were calibrated in a rat biologic assay system against a bovine calcitonin standard prepared from thyroid glands of mature dairy cows and calibrated against the Medical Research Council (MRC) Research Standard B for Thyroid Calcitonin in 3 comparative 6-point biologic assays. The logarithmic dose-response curve was calculated for each assay and relative potency ratios determined.

Light and electron microscopy: At the time of euthanasia the thyroid gland was collected from each bull and was examined for evidence of neoplasia. Representative sections of ultimobranchial tumors and normal thyroid tissue were fixed in 10% phosphate-buffered formalin for histopathologic examination. Thyroid tissue from 15 bulls with ultimobranchial neoplasms (13 adenomas, 2 carcinomas) and 20 bulls without tumors were prepared for electron microscopic evaluation. Blocks of tissue (1 mm cubes) were fixed in 3% glutaraldehyde with 0.1 M sodium cacodylate buffer at pH 7.4 and post-fixed in 1% osmium tetroxide with s-collidine buffer at pH 7.4. Subsequently, the tissue was dehydrated through ascending concentrations of ethanol, transferred to propylene oxide, and embedded in Epon (Shell Chemical Company, New York, New York). Thin sections were cut with a diamond knife on a Reichert OmU2 ultramicrotome, stained with uranyl acetate and lead citrate, and examined with either a Philips 200 or 300 electron microscope. A complete necropsy was performed on 3 bulls with ultimobranchial thyroid tumors. Thyroid glands from the remaining bulls were collected immediately after killing at an abattoir and only selected tissues were evaluated microscopically. Representative sections of parathyroid gland from 3 bulls were fixed in 3% glutaraldehyde and prepared for fine structural evaluation as described previously. Sections of thyroid, parathyroid, pituitary, adrenal, pancreas, spleen, liver, and intestine were collected in 10% phosphate-buffered formalin for light microscopic evaluations.

Thyroid bioassay for calcitonin: Ultimobranchial tumors were carefully dissected from normal thyroid tissue, frozen in liquid nitrogen (−190°C), and stored separately at −20°C for bioassay of calcitonin activity. Extracts of ultimobranchial neoplasms and thyroid glands from control bulls were prepared individually, lyophilized, and stored at −20°C prior to assay. The extracts were reconstituted with a diluent composed of 0.01 M sodium acetate trihydrate and 20 mg bovine serum albumin. The reconstituted extracts were adjusted to pH 4 and assayed in 35-day-old male Holtzman rats according to the method of Cooper et al. against a bovine thyrocalcitonin standard. The rats were exsanguinated from the abdominal aorta at 65 minutes after subcutaneous injection. In all of the 4-point assays the high dose was 4 times the low dose. Serum was collected and analyzed for calcium by atomic absorption spectrophotometry. The logarithmic dose-response was plotted for each assay and relative potency of extracts was determined.

Pathologic findings: Ultimobranchial adenomas (13 bulls) appeared as discrete, single or multiple, tan nodules of variable size in the hilar area of one or both lobes of the thyroid gland. A thin fibrous connective tissue capsule separated the adenomas from adjacent normal tissue (Fig. 1). Microscopically, the neoplastic cells were arranged into groups or nests of cells subdivided by a fibrous connective tissue stroma. Other cells formed small colloid-containing acini or were arranged into ductal structures lined by tall columnar cells. The cells comprising ultimobranchial adenomas had a lightly eosinophilic, poorly defined cytoplasm. The nucleus was centrally located with one or more nucleoli and evenly distributed chromatin (Fig. 2).

By comparison ultimobranchial carcinomas (2 bulls) completely incorporated the thyroid glands and metastasized to cervical lymph nodes (Fig. 3) and the lung. Metastases in lymph nodes were usually large with peripherally located areas of necrosis and hemorrhage obliterating the normal architecture of the lymphoid tissue (Fig. 4). Pulmonary metastases appeared as discrete tan nodules throughout the parenchyma. Ultimobranchial carcinomas were composed of solid nests of polyhedral to spindle-shaped cells. The cytoplasm was lightly eosinophilic, finely granular, and indistinctly outlined. The vesicular nuclei
FIG. 1 (left). Ultimobranchial adenoma (A) forming a discrete nodule in the hilar region of a thyroid lobe. A fine connective tissue capsule (arrowhead) separates the adenoma from the compressed thyroid parenchyma. The black bar at the bottom represents 2 cm.

FIG. 2 (right). Ultimobranchial adenoma. Neoplastic cells with light staining cytoplasm are subdivided into small groups or nests by a prominent fibrous connective tissue stroma (arrowhead). Other neoplastic cells form small colloid-containing follicles (F). A fibrous connective tissue capsule (C) separates the tumor from the thyroid parenchyma (×125).

were oval or elongate and contained a few mitotic figures. Neoplastic cells were subdivided into small nests or clusters by a fine connective tissue stroma (Fig. 5). Only occasional ducts and acini were present in ultimobranchial carcinomas. A similar histologic pattern also was present in the metastatic lesions in the cervical lymph nodes and lung.

Ultrastructure of ultimobranchial thyroid neoplasms: Ultimobranchial neoplasms evaluated from 15 bulls were composed of several types of cells with different ultrastructural features. The most characteristic cell type had large perinuclear aggregations of concentric or interwoven microfilaments often situated near the Golgi apparatus (Fig. 6). In some cells the nucleus was partially indented by the extensive clusters of microfilaments. Secretion granules were scattered between the networks of microfilaments and occasionally elsewhere in the cytoplasm. The secretory granules were membrane-limited, composed of fine dense particles and appeared similar to those in normal parafollicular (C—cells) of control bulls (Fig. 7). There were numerous aggregations of free ribosomes and dispersed profiles of endoplasmic reticulum in the cytoplasm.

The predominant type of neoplastic cell in
ultimobranchial tumors of bulls was polyhedral and appeared to be poorly differentiated. The relatively small cytoplasmic area contained clusters of free ribosomes, prominent Golgi apparatuses associated with small vesicles, scattered mitochondria but few mature secretion granules. These cells resembled primitive ultimobranchial cells reported in other species. Other neoplastic cells were more columnar and assumed a ductal or acinar pattern in arrangement (Fig. 8). Single or multiple layers of cells were arranged around a lumen containing finely granular material of moderate electron density. The plasma membranes of adjacent cells were intricately interdigitated and the apical cytoplasm contained numerous lipofuscin granules. Long microvilli and cytoplasmic projections extended into ductal lumens. Groups of mitochondria, clusters of ribosomes, and numerous vacuoles were present in the cytoplasm (Fig. 8).

Ultimobranchial tumors were firm and in some areas the stroma consisted of dense bands of fibrous connective tissue. In both ultimobranchial adenomas and carcinomas there were deposits of a homogenous eosinophilic material which stained positively with sirius red for amyloid. Ultrastructurally, large aggregations of fine amyloid fibrils frequently were observed between the bundles of collagen fibers, particularly in ultimobranchial adenomas (Fig. 9).

Cells comprising ultimobranchial thyroid neoplasms more closely resembled differentiated parafollicular (C-) cells than follicular cells in the thyroid glands of normal adult bulls. Differentiated parafollicular cells in control bulls were found wedged between follicular cells lining thyroid follicles. They had a prominent Golgi apparatus, lamellar arrays of endoplasmic reticulum, and large aggregations of membrane-limited secretion granules in those portions of the cytoplasm bordering interfollicular capillaries. The granules were of similar size and shape as those observed in cells of ultimobranchial thyroid tumors but
Fig. 6 (top). Cell from an ultimobranchial adenoma illustrating the distinctive large aggregations of concentric or interwoven microfilaments (arrow) which frequently indented the nucleus (N). Membrane-limited secretion granules (S) are scattered between the network of microfilaments and elsewhere in the cytoplasm. Large mitochondria (M), distended profiles of endoplasmic reticulum (E), clusters of ribosomes, and lipofuscin (L) granules are present (×20,500).

Fig. 7 (bottom). Membrane-limited secretory granules (S) composed of fine dense particles are scattered between microfilaments in a cell from an ultimobranchial adenoma (×42,300).
FIG. 8 (top). Ductal structure (D) in an ultimobranchial thyroid tumor lined by cells which extend long microvilli (V) and cytoplasmic projections (P) into a lumen containing finely granular material of moderate electron density. The cytoplasm contains groups of mitochondria (M), clusters of ribosomes, numerous vacuoles (arrowhead), and lipofuscin granules (L). The plasma membranes of adjacent cells are joined by prominent terminal bars (T) (~9,300).

FIG. 9 (bottom). Large aggregations of amyloid fibrils (A) in the stroma of an ultimobranchial thyroid tumor between bundles of collagen fibers (C) (~16,400).
were more numerous than in the less differentiated neoplastic cells.

The thyroxine-secreting follicular cells in the 20 control bulls directly lined the colloid-filled follicles and extended microvilli into the lumen. An occasional cytoplasmic pseudopodium partially surrounded a portion of the colloid. Large dense bodies and colloid droplets were present in the cytoplasm but small membrane-limited secretion granules were not observed. The endoplasmic reticulum appeared as an extensive tubular network containing material of moderate density and was not aggregated into lamellar arrays.

**Bioassay of thyroid neoplasms:** Bioassay of ultimobranchial thyroid adenomas (5 bulls) and carcinomas (2 bulls) demonstrated the tumors contained 466 ± 84 and 409 ± 93 MRC mU/g of calcitonin activity, respectively. Serum calcium (adenomas: 9.54 ± 0.2 mg/100 ml; carcinomas: 9.30 ± 0.6 mg/100 ml) and phosphorus (adenomas: 6.13 ± 0.3 mg/100 ml; carcinomas: 6.25 ± 0.8 mg/100 ml) were in the same range as in control bulls (calcium: 9.92 ± 0.2 mg/100 ml; phosphorus: 6.49 ± 0.5 mg/100 ml). The thyroid content of calcitonin in 8 control bulls was 663 ± 165 MRC mU/g and in 9 control cows was 617 ± 106 MRC mU/g. The slightly lower calcitonin content per gram of tissue in the large ultimobranchial neoplasms compared to normal thyroids was interpreted to be a reflection of the poorly differentiated nature of parafollicular cells comprising the tumors.

**Calcium Infusion:** The intravenous administration of 8.42 gm of calcium to 6 bulls with ultimobranchial thyroid tumors raised the serum concentration of calcium 2.51 mg/100 ml (from 10.13 ± 0.4 mg/100 ml to 12.64 ± 0.60 mg/100 ml) and produced a 207% increase in plasma calcitonin-like activity after 1 hour compared to preinfusion levels (Fig. 10). Two hours after calcium infusion plasma CT-like activity had returned to baseline levels and remained there to the conclusion of the experiment after 8 hours. Serum calcium gradually declined over this period to 10.56 ± 0.12 mg/100 ml at 8 hours post-infusion.

**Multiple endocrine adenomatosis:** The bulls available for complete necropsy evaluation had simultaneously-occurring ultimobranchial thyroid neoplasms, pheochromocytomas (Fig. 11), and pituitary acidophil adenomas. The pheochromocytomas in 2 bulls were bilateral and by their expansive growth had completely replaced the medulla and all

![Fig. 10. Plasma calcitonin (CT)-like activity (expressed as percent change from baseline levels) in 6 bulls with ultimobranchial thyroid neoplasms after intravenous infusion of 8.4 gm of calcium over a 30-minute period. Note the brisk increase in plasma CT-like activity 1 hour post-calcium and rapid return to baseline levels by 2 hours. Each point represents the mean value and the vertical line the standard error.](image)

![Fig. 11. Pheochromocytoma (P) in the adrenal medulla of a bull with an ultimobranchial adenoma. A narrow rim of compressed adrenal cortex (C) surrounds the pheochromocytoma. The scale at left represents 1 cm.](image)
but a thin rim of adrenal cortex. Acidophil adenomas compressed the pars distalis and pars nervosa in the pituitary glands of both bulls.

**Parathyroid glands:** Parathyroid glands were evaluated ultrastructurally from 3 bulls with ultimobranchial tumors. They all had ultrastructural evidence of secretory inactivity and atrophy of chief cells. Many chief cells were large and had a pale staining cytoplasm with prominent acidophilic granules. Other chief cells were small, irregular in shape, and appeared atrophic. Small groups or cords of chief cells were separated by dense bands of fibrous connective tissue (Fig. 12) and large homogenous deposits of amyloid (Fig. 13). Chief cells in parathyroids of control bulls were arranged in groups and broad cords separated by connective tissue septae without amyloid deposits (Fig. 14).

Ultrastructurally, chief cells were predominantly in the inactive stage of the secretory cycle. Cytoplasmic organelles were poorly developed and secretion granules were infrequent. The most striking feature was the accumulation of numerous lipofuscin granules and large cytosegresomes in the cytoplasm (Fig. 15). Rosettes of mineral granules were present within some mitochondria. These changes, suggestive of secretory inactivity, were interpreted to be related to the long-term feeding of high calcium diets to the adult bulls.

Large aggregations of amyloid fibrils were observed surrounding and apparently indenting the plasma membranes of inactive chief cells in the parathyroid glands of 1 bull. Cellular debris was trapped within the extensive network of amyloid fibrils adjacent to chief cells, and lipofuscin granules were present in the cytoplasm (Fig. 16).

**Skeleton:** Examination of the skeleton of bulls with calcitonin-secreting ultimobranchial tumors on which a complete necropsy was performed revealed the coincidental occurrence of severe ankylosing spondylitis deforming and osteosclerosis of vertebral bodies. An extensive proliferation of compact bone occurred along the ventral surfaces of

![Fig. 12 (left). Atrophic parathyroid gland from an adult bull with an ultimobranchial thyroid neoplasm. The chief cells are arranged in narrow cords (arrow) or small nests (arrowhead) separated by an abundant fibrous connective tissue stroma (C) (×125).](image1)

![Fig. 13 (right). Extensive deposition of amyloid in the parathyroid gland of a bull with an ultimobranchial thyroid neoplasm. Large deposits of a homogeneous acidophilic material (A) have compressed and displaced many chief cells (arrows) (×315).](image2)
FIG. 14. Parathyroid gland from a control bull of the same age-range as illustrated in Fig. 12 without ultimobranchial thyroid neoplasms. The predominantly inactive chief cells are arranged in groups and broad cords separated by a connective tissue septae without amyloid deposits (~125).

The lumbar vertebrae and compact bone replaced much of the trabecular bone in the marrow cavity (Fig. 17). Severe degenerative osteoarthrosis was observed in multiple joints of each bull.

DISCUSSION

The results of this investigation demonstrated that a frequently-occurring neoplasm in the thyroid glands of adult bulls was composed of cells with ultrastructural characteristics of primitive parafollicular (C-) cells. Biologic assay of ultimobranchial thyroid adenomas and carcinomas revealed the presence of calcitonin activity which could be released by intravenous infusion of calcium. Levels of plasma calcitonin-like activity increased rapidly (within 1 hour) after calcium infusion but returned to baseline values within 2 hours postinfusion.

Ultrastructurally, the predominant cell comprising the ultimobranchial thyroid tumors was a poorly differentiated parafollicular (C-) cell that contained few secretion granules. The neoplastic cell which most closely resembled differentiated parafollicular cells contained extensive aggregations of microfilaments and scattered secretion granules in the cytoplasm. Studies by Pearse and co-workers suggest that the production of fine protein microfilaments is one of the distinctive ultrastructural characteristics of C-cells and other polypeptide-hormone-secreting cells of the APUD series. By comparison cells comprising medullary thyroid carcinomas in man have been reported to be more differentiated parafollicular (C-) cells with well developed cytoplasmic organelles and numerous membrane-limited secretion granules. An increased concentration of calcitonin in neoplastic tissue and peripheral plasma appears to be a consistent finding in patients with medullary thyroid carcinoma. The higher levels of calcitonin activity reported in medullary carcinomas than observed in ultimobranchial thyroid tumors in bulls was interpreted to be a reflection of the degree of differentiation of neoplastic cells. Calcium infusion also has been reported to produce a prompt rise in serum calcitonin activity in patients with medullary thyroid carcinoma.

The oxycellulose technique reported by Gudmundsson et al. has been questioned as a method for extracting CT-like activity from plasma. It has been suggested that during the extraction procedure the oxycellulose would bind plasma calcium. When injected into assay rats the bound calcium could stimulate
the release of endogenous calcitonin and thereby produce an exaggerated decline in serum calcium. This would lead to the calculation of erroneously high calcitonin levels in the original plasma sample. Preliminary studies conducted in our investigation confirmed the presence of excessive calcium in the plasma extracts. The addition of sodium oxalate...
late (0.4% w/v) and centrifugation effectively reduced the calcium content of plasma extracts without adversely influencing the calcium concentration in assay rats. These modifications of the bioassay procedure have permitted the detection of CT-like activity in plasma of cattle under normocalcemic and hypocalcemic conditions.1

The high incidence of ultimobranchial thyroid tumors (approximately 30%) in bulls differs considerably from the infrequent occurrence of medullary thyroid carcinoma. Medullary carcinomas accounts for only 6–10% of all thyroid tumors in man and occurs only slightly more frequently in males than females.9,32 Thyroid neoplasms other than ultimobranchial adenomas and carcinomas are rare in bulls. A possible relationship has been suggested between the long-term dietary intake of excessive calcium and the high incidence of ultimobranchial hyperplasia and neoplasia in bulls.15,16 Krook et al.15 reported that adult bulls frequently ingest from 3.5–5.9 times the amount of calcium normally recommended for maintenance of bulls. The chronic stimulation of ultimobranchial derivatives in the thyroid by the continual high levels of calcium absorbed from the digestive tract may be related to the pathogenesis of these hyperplastic and neoplastic lesions. Cows do not appear to develop ultimobranchial lesions under similar dietary conditions possibly because of the physiologic requirements for calcium imposed by pregnancy and lactation. The recent demonstration that prolonged feeding of high calcium diets during pregnancy did produce ultimobranchial hyperplasia in the nonlactating cow suggests that lactation and not pregnancy is the mechanism which protects the cow from diet-induced proliferative lesions in ultimobranchial remnants of the thyroid.2

Ultimobranchial adenomas were encountered more frequently than carcinomas in bulls included in this investigation. They usually were small, well circumscribed, situated near the vasulostromal hilus of the thyroid, and caused little or no functional disturbance. However, ultimobranchial carcinomas were larger and metastasized widely to the regional lymph nodes and lungs. The aggressive behavior of the carcinomas was similar to the medullary thyroid carcinoma in man which either is multicentric in origin or frequently metastasizes to regional lymph nodes.32

Cushman7 and Manning et al.17 described parathyroid adenomas in some patients with medullary thyroid carcinoma and pheochromocytoma. In the present investigation 66% of bulls had bilateral pheochromocytomas in association with ultimobranchial thyroid neoplasms. Wilke and Krook30 also reported a significant correlation for the simultaneous occurrence of ultimobranchial thyroid tumors and pheochromocytomas in bulls. A similar incidence of bilateral pheochromocytomas in association with medullary thyroid carcinomas has been reported in man.5,17,25,27

Histologic and ultrastructural evaluation of chief cells in the parathyroid glands of bulls with ultimobranchial thyroid tumors and pheochromocytomas indicated that most cells were inactive or atrophic. Parathyroid hyperplasia and adenomas reported in patients with medullary thyroid carcinoma were not observed in bulls in this study. The fine structural changes in secretory activity of chief cells in parathyroids observed in bulls with ultimobranchial tumors probably reflect the effects

Fig. 17. Vertebrae from a bull with an ultimobranchial thyroid neoplasm with osteosclerosis (arrowheads) and severe ankylosing spondylitis. There is extensive new bone formation along ventral surfaces and fusion (F) of vertebral bodies. The black bar at the bottom represents 2 cm.
of long-term feeding of high calcium diets. Similar histologic and ultrastructural alterations were reported in the parathyroid glands of cows fed high levels of vitamin D or high calcium diets for long periods of time.\textsuperscript{2,5} Ultrastructurally, we could not confirm the presence of water-clear cells as described by Krook et al.,\textsuperscript{18} suggestive of long-term stimulation, in parathyroid glands of bulls with ultimobranchial thyroid neoplasms.

The amyloid observed in the parathyroid glands of a bull with an ultimobranchial thyroid tumor had ultrastructural features similar to amyloid reported in the parathyroid glands from a cow fed a high calcium diet.\textsuperscript{2} The amyloid fibrils appeared to penetrate deeply into and indent the cytoplasm of chief cells. Amyloid fibrils adjacent to chief cells in the bull parathyroid appeared to trap cellular debris in close proximity to the plasma membrane. It was not possible to determine if cell death resulted from the deep penetration of the cytoplasm by the amyloid fibrils or was due to a blockage of nutrients passing to the chief cells by the thick cuffs of amyloid around capillaries. The etiology of the localized amyloid deposition in parathyroid and thyroid glands was not determined; however, it did not appear to be associated with chronic supplicative lesions in other organs.

Severe vertebral osteosclerosis with ankylosis, spondylosis deformans and degenerative osteoarthrosis was demonstrated in bulls with ultimobranchial thyroid neoplasms. Skeletal lesions of this type have been reported to occur frequently in adult bulls but are rare in cows of the same age and breed.\textsuperscript{30} The relationship of excess calcitonin secretion by ultimobranchial hyperplasia or neoplasia to the pathogenesis of skeletal lesions in bulls currently is uncertain and requires additional investigation. Prominent bone lesions have not been reported in patients with medullary thyroid carcinoma despite the secretion of excessive amounts of calcitonin by the tumor.\textsuperscript{9,18,20}

25-27 This animal model offers a unique opportunity to investigate the long-term effects of excessive calcitonin secretion on bone metabolism and the influence of a chronic intake of excessive dietary calcium on the pathogenesis of hyperplastic and neoplastic lesions of ultimobranchial derivatives in the thyroid gland.

REFERENCES


