SPONTANEOUS GOITER AND CANCER OF THE THYROID IN ANIMALS[1]

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The role of trace elements in animal and plant nutrition is now under extensive investigation; however, it was over a century ago that Chatin (1850) presented evidence that the absence of iodine in the diet leads to goiter and cretinism. This foreshadowed many studies on the geographical distribution of iodine in foods, water, and soil, the results of which permitted McClendon (1939) to write, ". . . it seems possible that goiter maps and iodine maps, supposing they existed, would fit like the land fits the ocean, goiter incidence and iodine varying inversely."

These studies have been largely limited to the occurrence of goiter in man and a few domestic animals. The systematic investigation of feral animals living in so-called goiter areas has not been undertaken, and only a few reports of goiter and thyroid cancer in captive wild animals are available. It would seem that research on adaptive hyperplasia of the thyroid in response to insufficient iodine in the diet of native animals should be a cooperative effort of ecologists and pathologists.

FISHES

Among the cold-blooded vertebrates by far the most numerous studies of thyroid hyperplasia have been reported in fishes. Perhaps the first to call attention to goiter in fishes was Bonnet (1883), who described an epidemic of goiter that destroyed over 3,000 young lake trout, *Salmo lacustris*, in a German fish hatchery between February and June of 1883. The early literature has been reviewed elsewhere (Schlumberger and Lucké, 1948).

One of the most important studies of thyroid hyperplasia was reported in a series of papers by Marine and Lenhart detailing their observations on goiter among brook trout in a large Pennsylvania hatchery (1910 a, b; 1911). The development of the lesion was summarized by Marine (1914): "It was found that the thyroid hyperplasia began in the fry as soon as feeding was instituted, and advanced overgrowth was present at the fourth month of extra oval life; that the overgrowth progressively increased to the stage of clinical detectability, as ascertained by the reddening of the pharyngeal floor over the thyroid area about the tenth month in this hatchery; that visible goiters usually manifested themselves about the beginning of the second year . . . and progressively increased during the second and third years; that older fish were more resistant and tended toward spontaneous recovery." Iodine prevented the hyperplasia; in goiterous fish administration of iodine or removal from the hatchery ponds to an open brook effected a cure (1910b).

At a Wisconsin fish hatchery Hamre and Nichols (1926) observed the occurrence of unilateral or bilateral exophthalmos in trout-fry after resorption of the yolk sac. The thyroid was hyperplastic, the follicles were lined by columnar epithelium, and the lumina were devoid of stainable colloid. When 25,000 newly hatched fry were placed in water containing 100 parts of sodium iodide in a billion parts of water for 10 days, and were then kept in water containing 30 parts of sodium iodide per billion of water, exophthalmos and thyroid hyperplasia did not appear.

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The prevalence of goiter in trout and other *Salmonidae* may be due to their high oxygen requirement which is not met by the low oxygen tension of the water in hatchery tanks. Duerst (1941) stated that inactive fish such as carp require only 3–4 cc. of oxygen per liter of water, whereas trout need 7–8 cc. He believes that the functional demand upon the thyroid is in inverse proportion to the oxygen tension of the surrounding water. When the oxygen content of the water falls below 4 cc. per liter the young trout develop thyroid hyperplasia, at 1.5 cc. per liter they die of asphyxia; carp survive when there is only 0.5 cc. of oxygen per liter.

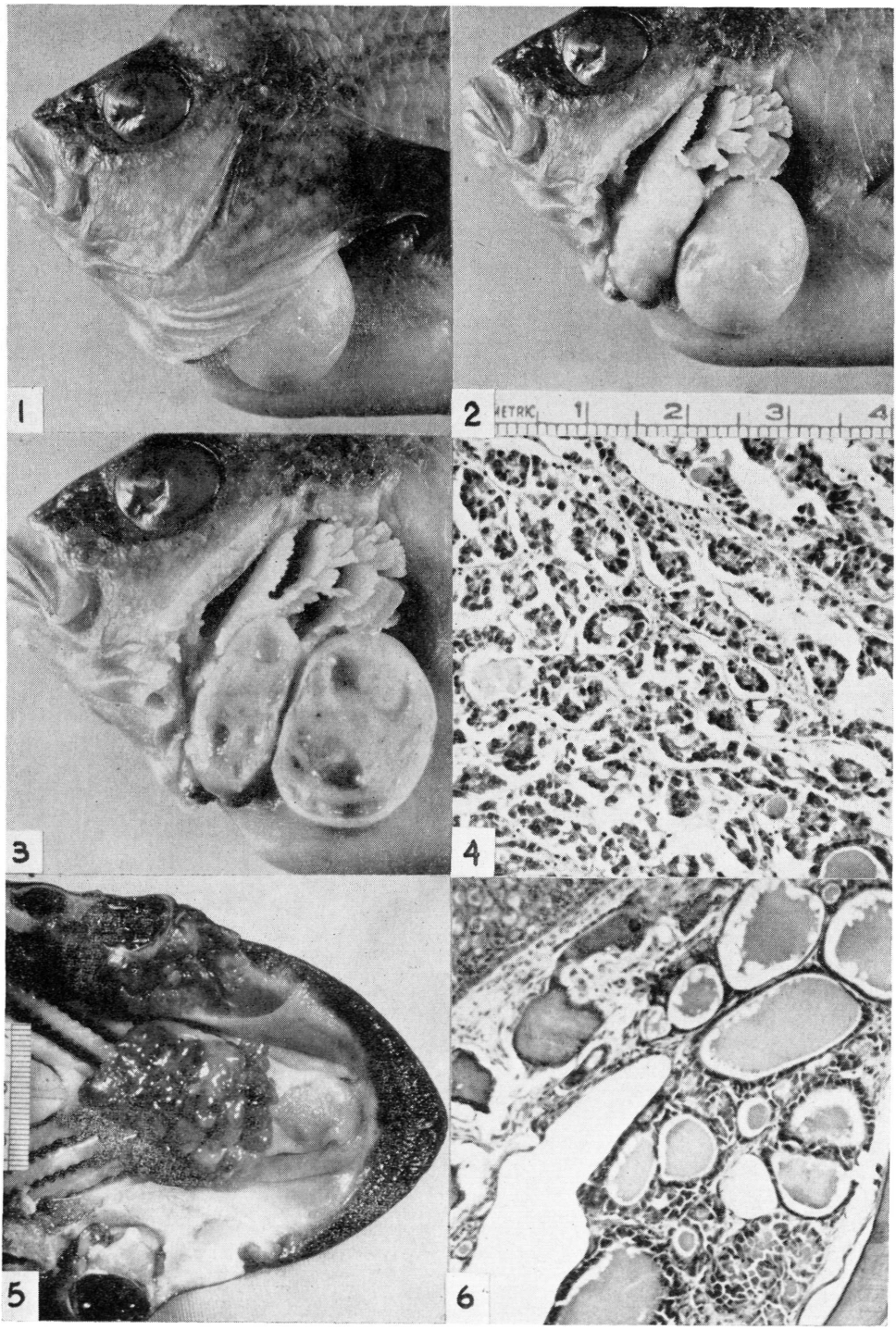
Isolated instances of goiter in other species of fresh water fishes have been reported (Schlumberger and Lucké, 1948). In the Scioto River of Ohio, with an iodine content of 0.21 μg. per kg. of water as compared with 0.83 μg. per kg. in the Mississippi River (McClendon, 1939), we have found several specimens of the long-eared sunfish, *Lepomis megalotis megalotis*, with goiter. In advanced cases the hyperplastic thryoid appears as a smooth spherical mass, often bilateral, that elevates the operculum and protrudes beyond its posterior margin (fig. 1 and 2). The cut surface may show the presence of cysts (fig. 3) similar to those occasionally found in human goiters. In histological sections colloid is seen in only a few large follicles; most of the follicles are small, have a lumen devoid of colloid, and are lined by tall columnar epithelial cells (fig. 4).

The occurrence of goiter in small tropical aquarium fishes has been reported several times (Schreitmüller, 1924; Müller, 1926; Smith, et al., 1936; Smith and Coates, 1937). Recent work by a group of investigators using a popular aquarium fish known as the "swordtail" is of particular interest. Gorbman and Gordon (1951) observed the occurrence of thyroid hyperplasia and neoplasia in an inbred stock of the swordtail *Xiphophorus montezumae*. The changes in the thyroid took place even though dried ocean shrimp with a high concentration of iodine made up a large part of the diet. Hyperplasia of the thyroid was not observed in the wild fish taken from their natural habitat in Mexico. A subsequent report by Berg, et al., (1953) indicated that when young fish were raised in iodized water, or adults with goiters were treated with potassium iodide, the treatment prevented the development of goiter in the former and occasioned regression in the latter. It was also discovered that highly inbred strains were more susceptible to the development of thyroid tumors and that these appeared at a much earlier age, suggesting a genetic factor leading to an exceptionally high iodine requirement of the fish. Using injections of a tracer dose of carrier-free I^{131} Berg and Gorbman (1954) showed that the thyroid tumors accumulated up to 60 percent of the injected isotope; uptake was rapid but turnover was slow. The radioautographs located most of the radioiodine in the apparently normal colloid-containing peripheral follicles and indicated the virtual absence of organic I^{131} in the more anaplastic parts of the growths.

The few reported cases of goiter in marine fishes have nearly all occurred in fish that were kept in aquaria for long periods (Cameron and Vincent, 1915;

EXPLANATION OF FIGURES IN PLATE I

1. Goiter in a long-eared sunfish, *Lepomis megalotis megalotis*, raising the operculum and protruding beyond its margin.
2. Same fish after removal of operculum showing compression and distortion of gills by the goiter.
3. Cut surface of goiter; a small hemorrhage and several cysts are seen.
4. Histologic appearance of goiter; large follicles with poorly stained colloid and small follicles devoid of colloid and lined by columnar epithelium. Mag. X 140.
5. Floor of mouth of pilot fish, *Echeneis naucrates*, showing a large goiter in the midline partly covering the anterior branchial arches.
6. Section of an arch showing surface epithelium and bone in approximation to "invading" thyroid tissue. Mag. X 100.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Marsh and Vonwiller, 1916; Nigrelli, 1952). Several years ago, in collaboration with Dr. Balduin Lucké (1948) the writer observed the occurrence of goiter in three pilot fish, *Echeneis naucrates*, exhibited at the Fairmont Park Aquarium in Philadelphia. Although fed on an iodine rich diet of fresh shrimp, oysters, clams, and chopped fish they all developed pink, translucent, coarsely lobulated tumors on the floor of the mouth (fig. 5). Microscopically the tumors proved to be thyroid, consisting in part of greatly dilated acini filled with marginally vacuolated colloid and lined by cuboidal or columnar epithelium. Alternating with the large colloid spaces were areas in which the acini were small; occasionally thyroid tissue was found between lamellae of bone (fig. 6). About a year later 13 pilot fish were received from another aquarium, none had gross evidence of goiter; however, within a year goiters 1–3 cm. in diameter were seen in all of them. On revisiting the aquarium 6 years later only a single survivor remained; it displayed a prominent 4 cm. goiter on the floor of the mouth. Analysis of the water in the tank showed an iodine content of only 7.8 μg. per kg., as compared with 37 μg. per kg. in ocean water collected on the following day.

Despite the low iodine content of the salt water in the Philadelphia aquarium no other species of marine fishes kept there showed gross evidence of goiter over a period of 12 years. It appears probable that the metabolic need for iodine is greater in this species than in others. A similar suggestion has been made by Berg, et al., (1953) in their study of the fresh water swordtail *X. montezumae*. This fish is only one of 7 species of Xiphophorin fishes that have been maintained by inbreeding for many generations under practically identical environmental conditions. In only 2 species, *X. montezumae* and *X. pygmaeus*, have the majority of a brood developed hyperplastic or neoplastic thyroids.

To distinguish between a hyperplastic or nodular goiter and a benign tumor is as difficult in fishes as it is in man. Furthermore, in fishes even the recognition of malignancy in the thyroid offers a serious problem. Many early investigators identified goiter in fishes as carcinoma because they interpreted the presence of thyroid follicles among adjacent muscle bundles and bone lamellae as evidence of invasion. However, as early as 1911 Gudernatsch had shown that the teleost thyroid is not encapsulated and that its follicles do not form a distinct organ but are scattered over a wide area. The following year Gaylord and Marsh (1912) published a much quoted monograph entitled "Carcinoma of the Thyroid in the Salmonoid Fishes," based on thyroid enlargements seen in several thousand trout at government fish hatcheries. Study of the histological descriptions and photomicrographs, however, suggests that most cases were examples of hyperplasia and colloid storage without evidence of malignant change. It cannot be denied that among these many thousand goiters there probably were instances of adenocarcinoma. In 2 cases metastases were recognized; one presented as a small mass in the wall of the rectum; the other, less clearly a metastasis, was a nodule on the tip of the mandible. Recently Baker, et al., (1954) reported extensive invasion of the head, pericardium, and myocardium of *Xiphophorus maculatus* by thyroid cells. Masses of unencapsulated cystic follicles were also found in the kidneys. Radioactive iodine injected into tumor-bearing fish yielded definitive radioautographs from cross sections through the kidney and thyroid regions.

AMPHIBIANS

Despite extensive work on amphibian thyroid physiology, including study of its role in tadpole metamorphosis, no report of goiter could be found in the literature. However, Professor J. M. Dodd (1954) at the Gatty Marine Laboratory of the University of St. Andrews in Scotland will shortly publish an account of spontaneous goiter in newts. In a personal communication Professor Dodd wrote that he had collected 5 goiterous newts in a small pond quite near the sea at Crail in Fife two years ago. Since then no additional goiterous animals were found. In

most cases the goiters were well marked and in photographs of the specimens a distinct ventral swelling is visible in the midline at the junction of head and trunk. The urodele was identified as *Triturus helveticus* and in all cases the goiters were associated with neoteny. The year before the goiterous newts were found, a crop of yellow turnips was grown in the field bordering the pond. Professor Dodd suggests that a possible explanation for the appearance of goiters in the newts may be the introduction of thiocyanates (brassica factor) by contamination of the pond with feces of rabbits feeding on the turnip tops.

An interesting ecological study on the frog thyroid has been carried out by Adler (1916). This investigator found that the histological appearance of the thyroid of tadpoles and frogs of the same species, *Rana temporaria*, varied with the environmental habitat of the animal. The cold-adapted alpine animals had large thyroids with many small follicles. The warm-adapted larvae from the shores of the Adriatic were distinguished by their relatively small thyroids composed of a few large follicles. The possible effect of differences in iodine content of the water was not examined.

In an excellent review on the thyroid gland and its functions in cold-blooded vertebrates Lynn and Wachowski (1951) record no instance of spontaneous hyperplasia of the thyroid in an amphibian, although they refer to numerous reports on experimental hyperplasia produced with thyroid antagonists and inhibitors. The frogs and toads (Anura) have been more frequently employed in these studies than have the newts and salamanders (Urodeles) probably because of the interest centering about the effect of the induced thyroid changes on metamorphosis in the anura.

In a study on the effects of thiourea administration upon thyroid histology in the frog, Joel, D'Angelo, and Charipper (1949) pointed out that the response of the amphibian thyroid to goitrogens is less marked than that of higher vertebrates. The qualitative and quantitative changes produced by these drugs are less pronounced than those which occur in the chick or mammal after similar treatment.

REPTILES

In a cursory search of the literature only 3 reports of goiter in reptiles were found; of these animals, 2 were turtles and 1 a lizard. All had been on exhibition in zoological gardens for several years suggesting a probable dietary deficiency of iodine.

A Brazilian fresh water turtle, *Platemys geoffroyana*, died at the Berlin Aquarium in 1903. The neck organs were examined by Pick and Poll (1903) who described a $6 \times 4 \times 2.5$ cm. egg-shaped mass on the ventral aspect of the specimen. Histologically the tumor was composed of tubular acini lined by tall columnar epithelial cells and separated by moderate amounts of connective tissue stroma. The second turtle, *Testudo nigrita*, died at the London Zoological Gardens and was autopsied by Hamerton (1930) who found one of the two laterally placed thyroids enlarged to the size of a golf ball—about 2 times normal size. The 2 thymus glands of this animal were also enlarged, each attaining the size of a coconut!

Müller (1926) described a goiter he found in a large lizard, *Zonurus giganteus*, that had been on exhibition at the Zoo in Frankfurt, Germany. One of the thyroids was greatly enlarged and measured $3 \times 3.5 \times 1$ cm. It compressed the trachea and esophagus; breathing was impaired and death was due to starvation.

Whereas thyroid physiology in amphibians has been thoroughly investigated, in reptiles it has been neglected. Lynn and Wachowski (1951) suggest that one of the chief factors hampering the study of thyroid function in reptiles is their low survival rate after operation. However, studies with thyroid inhibiting drugs are being undertaken. Adams and Craig (1951) found that in a lizard, *Anolis carolinensis*, thiourea or thiouracil administration produced gross enlargement of the thyroids; and histological sections showed marked hypertrophy of the follicular

epithelium with almost total loss of colloid. Response of the adult painted turtle, *Chrysemys picta*, was less striking (Adams and Craig, 1950), although in some animals there was an increase in height of the follicular epithelium as well as liquefaction and loss of colloid. The thyroid of reptiles, like that of amphibians, appears to be less responsive to these inhibitors than is the thyroid of birds and mammals.

BIRDS

Among the cold-blooded vertebrates the effect of the thyroid hormone in controlling the rate of body metabolism appears to be very slight or absent (Lynn and Wachowski, 1951). In birds and mammals, however, this regulatory action is an important function of the hormone. The metabolic rates of these groups when compared among animals of the same weight show striking differences. Benedict (1938) found that at 37° C a 20 g. fish would produce about 30 calories per kg., a 20 g. mouse 150 calories per kg., and a 20 g. canary 250 calories per kg. Among larger animals comparable differences are observed. The much higher metabolism of birds than of their mammalian weight equivalent may be reflected in the greater size of the avian thyroid in proportion to body weight. Cruickshank (1930) has found 3 times as much iodine in the thyroid of birds as in that of mammals.

In fowl as in most birds the thyroids are discrete bilateral glands at the base of the neck. Their size is susceptible to considerable variation depending on the age and sex of the bird as well as on the season of the year (Cruickshank, 1930). The reported cases of goiter in chickens are nearly all from regions known to be poor in iodine; however, there is some difference of opinion regarding its frequency of occurrence. Schwarte (1952) has stated that goiter among domesticated birds in the goiter belt states of the Northwest and Great Lakes regions is rare. Even before the general use of iodized salt Kernkamp (1925) found only 2 cases of goiter, both fowl hens from the same farm, among autopsies of 2,221 chickens, 141 turkeys, 42 geese, and 15 ducks. In this same area swine and sheep were often affected with goiter. On the other hand, Kalkus (1920) observed goiter frequently among the chickens of Washington, and Welch (1928) stated that in Montana goiter in poultry is very common. However, the thyroids, which may each be as large as a thumb, are entirely concealed by feathers; no ill effects on the bird were noted. Fritschi (1926) reported 2 cases of goiter in chickens from a mountain canton in Switzerland and cited 7 additional instances of goiter in fowl described by Backlehner at Munich.

Riddle (1929) has carried out extensive investigations on the metabolism of doves and pigeons. During these studies he observed that the thyroids of the birds undergo considerable enlargement in the winter and reduction in the summer. Similar seasonal changes were found by Haecker (1926) in the thyroids of crows, *Corvus corone*, caught in the Swiss and Austrian alps. Riddle further noted that the thyroids of pigeons and doves aged 30 to 90 months are in general distinctly larger than those of younger birds. Among 24 inbred races of ring doves he found 4 races in which the thyroids were characteristically large and 4 in which they were small.

Recently Hollander and Riddle (1946) reported the occurrence of goiter among pigeons from 2 non-goiterous areas, viz., Long Island and South Carolina. The goiters appeared with greatly varying frequency among birds on a fairly constant regimen without supplemental iodine. The birds were usually plump or even obese; the skin about the eyes was puffy. The large feathers were elongated and narrow; the small ones resembled hairs more than feathers. Feather regrowth was defective and in general the birds presented the appearance of myxedema. Their young showed pronounced weakness at the time of hatching, an abnormality not seen in the offspring of female thyroidectomized pigeons. Small amounts of

iodine added to the diet prevented the appearance of goiter in the adults and weakness of the newly hatched birds.

The Australian shell parrakeet or budgerigar, *Melopsittacus undulatus*, is widely bred in this country as a cage bird or pet and may be classed with the domesticated birds. Large numbers of parrakeets received from many different states have been studied in this laboratory because of the high tumor incidence that characterizes this species. Among birds received during 1953, enlarged thyroids were found in 23. The normal thyroid of the parrakeet is a paired organ, one gland lying on either side of the trachea at the base of the neck. Each gland is oval, measures up to 2 mm. in greatest diameter, and 2–5 mg. in weight. Some of the thyroids were only 2 to 3 times normal size; others were up to 12 times the usual diameter and weighed over a gram (fig. 7A). Many of the largest glands

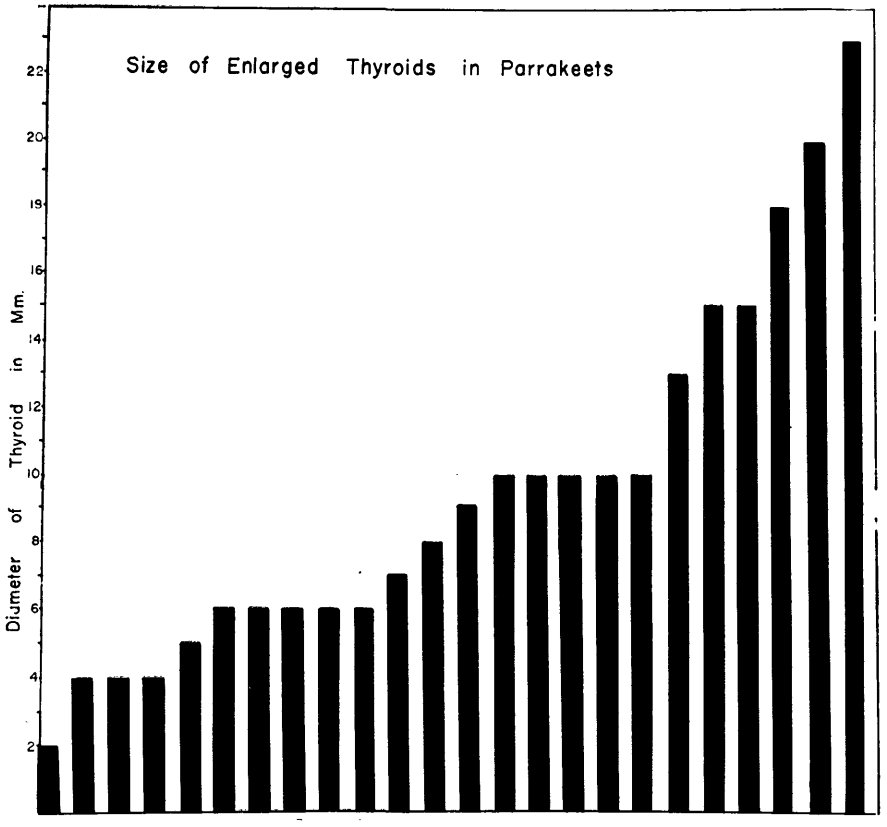


FIGURE 7A. The first bar represents the greatest diameter of the normal parrakeet thyroid gland. The remaining bars illustrate the different sizes reached by the enlarged glands.

were cystic and the cysts filled with a viscous amber fluid (fig. 7 to 9). Often one gland was much larger than the other, but even the smaller one was hyperplastic (fig. 8). Occasionally the goiters increased rapidly in size and were readily visible in the living bird. In such instances autopsy examination often showed that there had been extensive hemorrhage into the glands, greatly distending one or two large cysts. In one case the cyst had ruptured and the blood escaped into the body cavity.

Histologically the normal resting thyroid of the parrakeet has the usual follicular structure. The follicles are filled with well stained colloid devoid of vacuoles and

are lined by low cuboidal epithelium (fig. 10). In birds that are rearing young, the colloid stains less well and shows some peripheral vacuolization; the epithelium is taller. In the hyperplastic glands these changes are more pronounced; the lumina of the follicles are often small and irregular in shape, colloid is vacuolated and poorly stained or even absent. The epithelial cells are of increased height and frequently form papillary projections (fig. 11).

In two cases there was an associated pituitary adenoma; however, 92 parrakeets with pituitary tumors have been examined in this laboratory and no evidence of a distinct thyroid stimulating effect could be found (Schlumberger, 1954). Exophthalmos, which was first found only when the pituitary tumor had invaded the orbital space, has now been encountered several times when no such extension could be demonstrated. Whether the exopthalmos is a specific hormonal effect of the tumor is under investigation; however, in none of these birds was there evidence of thyroid hyperplasia.

TABLE 1

Geographic distribution of goiter in parrakeets

STATE	BIRDS WITH TUMOR+	BIRDS WITH GOITER	STATE	BIRDS WITH TUMOR+	BIRDS WITH GOITER
Massachusetts	4	0	Wisconsin	1	2
New York*	7	1	Minnesota	5	1
New Jersey	7	0	Nebraska	3	0
Florida	9	0	Arkansas	0	1
Kentucky	3	0	Texas	25	0
Pennsylvania**	15	1	Colorado	0	2
Ohio	31	8	Wyoming	1	0
Indiana	6	2	Washington	0	1
Illinois	7	4	California	7	0

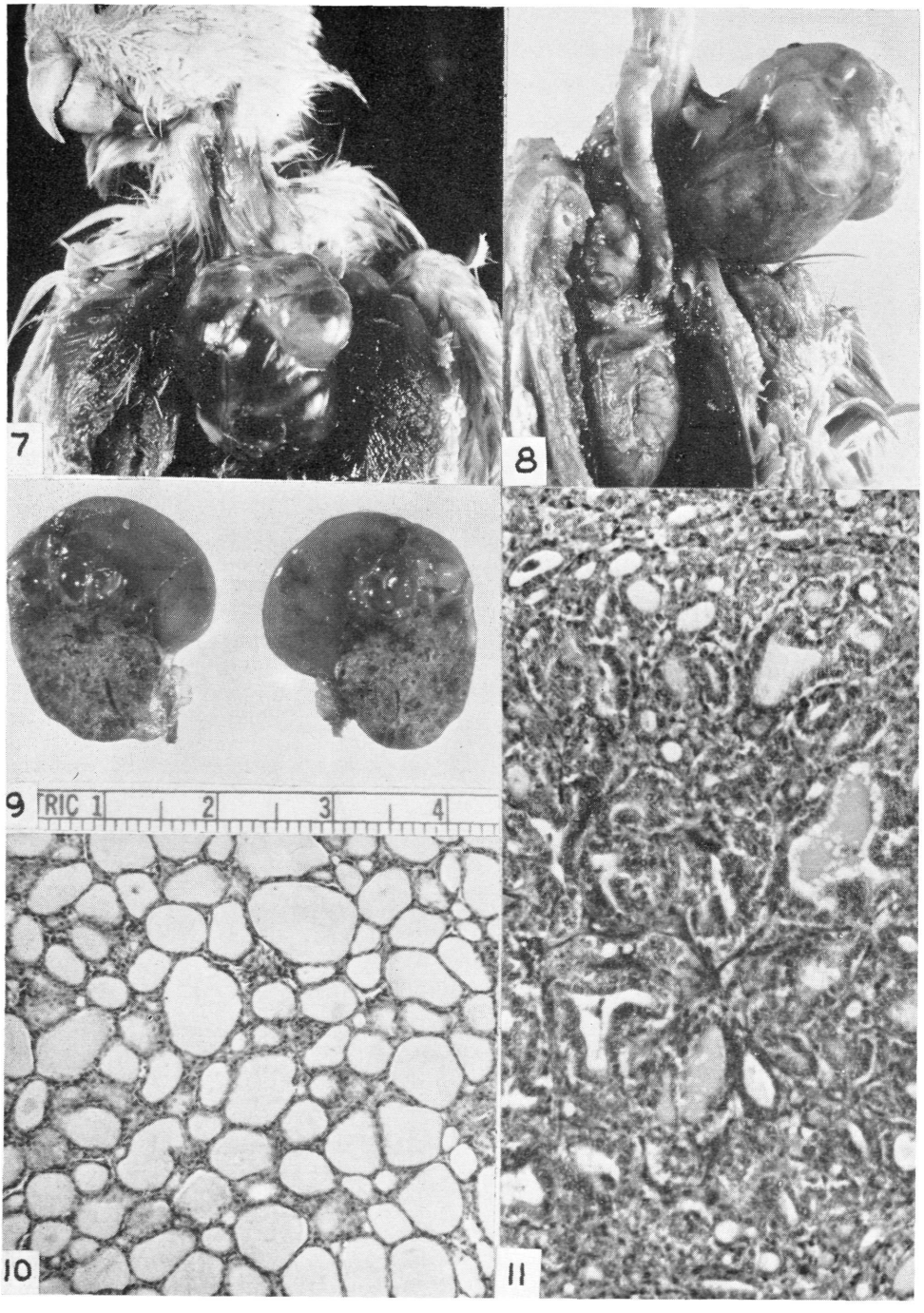
*Rochester, N. Y. **Erie, Pa. Both cities are in low iodine areas.
+Other than thyroid tumors, to show relative number of birds received.

The stress of breeding and caring for the young appears to be a factor in the development of these goiters; 18 of the 23 cases were received during April to July which is a period of great activity in these birds. It does not, however, coincide with the period of thyroid enlargement noted by Riddle (1929) in pigeons and by Haecker (1926) in crows. The probability that gonadal-pituitary activity is related to the thyroid hyperplasia is also suggested by the sex ratio—21 of the 23 birds were females. This high incidence in the female, though perhaps not as striking, has also been found in chickens, pigeons, mammals, and even man (Crotti, 1938).

Although parrakeets are received from all parts of the country, those that had goiters came from areas known as the goiter belt (table 1). This is well illustrated

EXPLANATION OF FIGURES IN PLATE II

7. Large cystic thyroid extending into the body cavity of a male parrakeet, *Melopsittacus undulatus*.
8. Bilateral goiter in a female parrakeet. One of the enlarged thyroids lies just above the heart, on the left; a much larger goiter occupies the base of the neck, to the right of the trachea.
9. Cut surface of large goiter shown in preceding figure. Note colloid-filled cyst at superior pole.
10. Section of normal thyroid; follicles are filled with colloid and lined by flattened epithelium. Mag. X 85.
11. Section of goiter seen in Fig. 7. The follicles are irregular, colloid is vacuolated or absent— the epithelium is cuboidal or low columnar. Mag. X 135.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by comparing two states from which a large number of birds was received. Among 39 birds from Ohio, 8 were goiterous; whereas of 25 parrakeets from Texas, none had enlarged thyroids. The diet of parrakeets is quite uniform throughout the country and consists chiefly of millet and canary seed with occasional addition of some oats and green foods. Rape seed, which is goiterogenic for chickens (Turner, 1946), is not used, nor is cabbage an item in the diet; carrot tops and spinach are the usual fresh foods offered. In the absence of a recognizable goiterogen in the food it seems probable that the geographical distribution of the goiterous birds is significant and may perhaps be linked with a low iodine content in the water. In some of these regions many breeders are aware of this and use a grit that has an iodine supplement.

No data is available on the occurrence of goiter among wild birds and only a few cases have been reported in captive birds. Those here described were autopsied at the London Zoological Gardens where most had been on exhibition for several years. A mandarin duck, *Axis galericulata*, had enlarged thyroids measuring an inch in diameter; death was attributed to pressure of the goiters on adjacent structures (Hamerton, 1933). An Eleanora's falcon, *Falcon eleanora*, died after 3 years in the Gardens. At autopsy an enormous cystic enlargement of the thyroids was found; each gland measured 8×15 cm. (Hamerton, 1935). The thyroids of a Houbara bustard, *Chlamydatis undulata*, were 2 cm. in diameter as compared with a normal of approximately 4 mm. In several areas the histological appearance resembled that of a papillary adenoma (Hamerton, 1936). A demoiselle crane, *Anthropoides virgo*, died from a hemorrhage into a large thyroid cyst that subsequently ruptured. The gland contained numerous other cysts and measured 2×0.5 cm. (Hamerton, 1937). A Chilean eagle, *Geranoaetus melanoleucus*, that had lived in the London Zoo for 27 years, was found to have enlarged thyroids, each measuring 5×3.3 cm. (Hamerton, 1942). In an Elliott's pheasant, *Calophasis elliott*, pressure was exerted on the major vessels of the neck by the enlarged thyroid glands and may have contributed to the death of the bird (Hamerton, 1943).

Cancer of the thyroid is rare in birds; Feldman and Olson (1952) do not list such a tumor in their recent extensive review on neoplasms of the chicken. Murray (1908) refers to a case of thyroid cancer in a macaw, *Ana macao*, and Fox (1923) describes a malignant tumor of the thyroid in a male shell parrakeet. The right thyroid was replaced by a 10×6×4 mm. mass; the left measured 5×3×2 mm. Each was well circumscribed, yellow-gray, and moderately firm. In histological sections thyroid tissue could be recognized at one edge; elsewhere the thyroid was replaced by poorly differentiated cells with scant cytoplasm and rather uniform spherical nuclei. Occasional cells were very large and had 2 or 3 nuclei. In a recent survey of neoplasms among captive wild birds at the Philadelphia Zoo, Ratcliffe (1954) found cancer of the thyroid in 2 psittacine birds and in one duck.

DOMESTIC MAMMALS

In regions where endemic goiter is common in man it is also prevalent among his domesticated animals. In the latter, however, it is chiefly significant as a disease of the newborn; when it appears in adult ruminants, swine, and horses the general health of the animal does not seem impaired (Madsen, 1942). Although both adult and congenital goiter occurs in the states bordering the Great Lakes (Andrews, et al., 1948), it is in the Northwest that the disease is of greatest economic importance. Before the introduction of iodized salt in the diet the mortality among newborn sheep, swine, and goats in Montana (Welch, 1928) and Washington (Kalkus, 1920) was so great that in some areas efforts to breed these animals were discontinued.

Kalkus (1920) reported that 30 to 50 percent of adult horses in Washington had

visibly enlarged thyroids; goiters became apparent within a year after the animals were brought into the area. About 75 to 90 percent of foals showed extreme weakness and died 3 to 4 days after birth; the thyroids were only slightly enlarged. Dimock, et al., (1944) studied 59 adult equine thyroids at Lexington, Kentucky, and found evidence of hyperplasia in 33.9 percent and a colloid goiter in 6.7 percent. In an aged mare the thyroid bore a circumscribed adenoma. Over a period of 3 years Venzke and Mannasmith (1940) studied the thyroids of 51 horses from central Iowa and found only a single case of colloid goiter. Sattler (1952) cites 4 cases of thyrotoxicosis in horses. The diagnosis was based on the presence of goiter, exophthalmos, nervousness, and tachycardia. Reports of single cases of carcinoma of the thyroid in horses are scattered throughout the literature; Sticker (1902) collected 8 cases and reported 2 more.

Adult cattle rarely show gross evidence of goiter, but this is due in part to the loose skin about the neck that would conceal any but very large thyroids. Among newborn calves in regions where goiter is endemic, up to 70 to 80 percent may be born with enlarged thyroids (Kalkus, 1920); the majority of these survive and become normal adults. A few are nearly hairless and myxedematous; these are either stillborn or soon die. Welch (1928) pointed out that the incidence of this condition in calves from the same locality may vary greatly from year to year. Matthew and Thomas (1935) have reported goiter in the calves of a pure bred herd of Afrikander cattle in the Middle Eastern Cape Province, Union of South Africa. Four cases of bovine goiter with exophthalmos were listed by Sattler (1952). Induced hyperthyroidism is now being observed following the use of the commercial type of thyroprotein to stimulate milk production (Andrews, 1950).

Cancer of the thyroid is rare in cattle. Sticker (1902) was unable to find a single case in his review of the early literature. However, in a personal communication Lt. Col. T. C. Jones (1954) reported that there are 5 cases of bovine adenocarcinoma of the thyroid on file at the Armed Forces Institute of Pathology. In addition, a case of thyroid adenocarcinoma in a sheep and one in a swine are listed. The rare occurrence of thyroid cancer in cattle, sheep, and swine as compared with horses and dogs may be sought in the youthfulness of these animals at the time of slaughter. Dogs and horses are permitted to reach a relatively advanced age, more favorable for malignant change in the thyroid.

Adult sheep when taken to iodine deficient regions will acquire hyperplastic thyroids which later develop the flattened epithelium and accumulated inactive colloid characteristic of goiter. The newborn lambs show changes similar to those of calves, but the mortality is higher. The lambs have scanty wool, are myxedematous, and may have huge goiters that interfere with parturition (Kalkus, 1920; Welch, 1928). In areas such as Indiana, where iodine deficiency is less marked, woolless lambs are uncommon. Nevertheless, in lambs from a flock fed a ration not supplemented with iodine. Andrews, et al., (1948) found the average thyroid weight was 5.7 g. and epithelial hyperplasia was observed in over 60 percent of the glands. In a second flock fed iodized salt, only 1 of 86 glands was hyperplastic and none weighed more than 1.8 g. The first outbreak of congenital goiter among lambs in Britain occurred in 1945 when the offspring of 40 ewes were affected. Jamieson and Harbour (1947) reported that many were stillborn, had little wool, and had enlarged thyroids that reached the size of an orange. The authors suggest that a rich pregnancy diet of oats, beans and linseed cake may have been a factor, a possibility also entertained by Welch (1928) when a large number of previously normal lambs developed goiter on a fattening diet.

The economic loss from the death of newborn pigs in iodine deficient areas was very great before supplemental iodine was fed the sows. The young pigs are hairless, myxedematous, and often stillborn; the thyroid may be 2 to 3 times normal size, but Kalkus (1920) states that a visible swelling is usually absent. When the iodine deficiency is less pronounced Andrews, et al., (1948) observed that

of 111 glands from newborn pigs 39 percent contained only a trace of iodine and over 30 percent were hyperplastic. When the diet of the sows included supplemental iodine, only 14 of 106 glands from the shoats contained less than 0.2 g. percent iodine and none was hyperplastic.

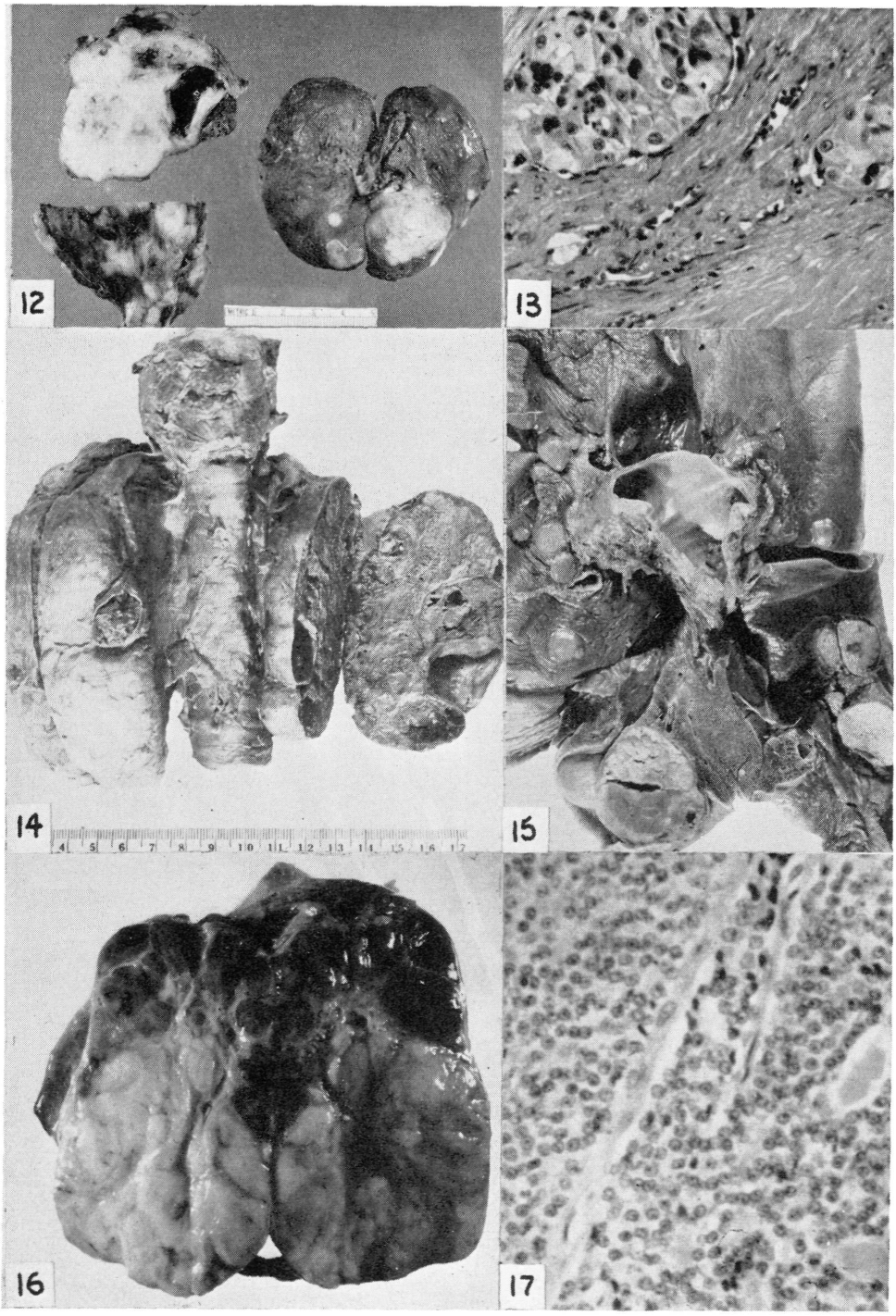
Goats are extremely susceptible to goiter. Kalkus (1920) observed that adults may have markedly enlarged glands but appear unaffected; the kids, however, are hairless and stillborn or die within a few hours. In the mountains of southern Germany half the goiterous kids die of suffocation due to pressure of the enlarged thyroid on the trachea (Koch, 1944). In a histological study of the thyroids of newborn hairless goats Baumann (1948) observed that the glands are larger than those of newborn pigs with myxedema and show considerable colloid storage.

Another domesticated ungulate, rarely seen outside zoos in this country, is the camel. In his treatise on the humped camel, Leese (1927) emphasizes the occurrence of congenital goiter among the young, born of dams during long sea voyages or when confined in zoological gardens. The thyroids may be enormously enlarged at birth, and death from suffocation may occur shortly after delivery. The animal may survive and the goiter persist throughout life, or even become larger. Kitt (1916) cites the case of a goiterous camel at the Dresdon Zoo; her young always had congenital goiter, whereas other camels and dromedaries housed in the same building were free of goiter and bore normal young. An instance of congenital goiter in a dromedary was encountered in the New York Zoological Gardens and described by Finkelstein (1939). The full term macerated fetus could not be delivered because of a large mass in its neck that necessitated embryotomy. Each lobe of the thyroid measured 25×15×8 cm.; death of the fetus may have been due to compression of the carotid arteries by the gland. The goiter was cystic and contained abundant colloid, unlike the hyperplastic thyroids found in congenital goiter of other species. Over a year later the dam died of an infection; at autopsy a moderately enlarged thyroid was found, the epithelium was hyperplastic.

Unlike the occurrence in ungulates, congenital goiter does not play a prominent role in thyroid dysplasia of the dog and cat—our domesticated carnivores. Nevertheless, Carlson (1914) recognized congenital thyroid hyperplasia in these animals when the mothers had hyperplasia thyroids. Before the introduction of prepared dog food and iodized salt, Marine and Lenhart (1909) found that goiter was very common among dogs reared in the so-called goiter belt of this country. Schlotthauer, et al., (1930) examined 234 thyroids from dogs of southern Minnesota. Among these they found 54 diffuse colloid goiters, 14 nodular colloid goiters, and 2 instances of carcinoma. The occurrence of exophthalmic goiter has been reported several times; 4 cases were collected from the literature by Sattler (1952). One of these was a male pointer that developed a goiter as large as a child's head in which pulsation and thrill was noted on palpation. The animal acquired a pronounced bilateral exophthalmos and marked muscle tremor.

EXPLANATION OF FIGURES IN PLATE III

12. Carcinoma of the thyroid in a dog. The tumor is seen in cross section to have partly encircled the trachea. Multiple metastases are present in the kidney.
13. Histological section showing poorly differentiated carcinoma invading connective tissue. Mag. X 140.
14. Carcinoma of the thyroid in a wolf, *Canis mexicanus*.
15. Multiple metastases to the lungs of the animal shown in Fig. 14. Philadelphia Zool. Soc. No. 7203.
16. Carcinoma of the thyroid in a leopard, *Felis pardus*. The tumor, which entirely replaced one lobe of the thyroid, measured 10 cm. in diameter.
17. Section of carcinoma showing poorly differentiated follicles and sheets of neoplastic epithelial cells. Mag. X 85. Philadelphia Zool. Soc. No. 14884.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There are many reports of carcinoma of the thyroid in dogs; several accounts record numerous cases and review the literature (Wondenberg, 1909; Ewald, 1915; Stunzi, 1947; Mulligan, 1949). In 8 cases of thyroid carcinoma Davis (1938) found metastases in both lungs and frequent invasion of the thyroid and pulmonary veins. The tumor is often firmly adherent to the trachea and partly encircles it (fig. 12). In one instance a polypoid structure in the right auricle proved to be metastatic thyroid carcinoma. The problem of so-called aberrant thyroid tissue which has been such a source of confusion in studies of human thyroid carcinomas has also troubled investigators of the canine neoplasms (Davis, 1938). The histology of the carcinoma is often that of a poorly differentiated adenocarcinoma. The cells frequently form solid sheets that infiltrate the adjacent tissues (fig. 13); venous invasion is common. The neoplastic epithelial cells occasionally become spindle-shaped and closely resemble a sarcoma (Slye, et al., 1926); this simulated carcinosarcoma is also found in human cases. Occasionally an unusual histological variant has been described; e.g., the mixed carcinoma and chondrosarcoma reported by Mason and Wells (1929).

Goiter is much less often reported in cats than in dogs. That this probably reflects a real difference in susceptibility between the two animals is indicated by reports of investigators like Carlson (1914) who examined hundreds of cats and dogs in his physiological studies and concluded that cats are much less subject to pathological changes of the thyroid than are dogs. Carlson found thyroid hyperplasia, but rarely colloid goiter in cats from the Chicago area. According to Crotti (1938) goiterous cats have also been seen along the banks of the Gunduk River in India. Huguenin (1927) found adenomas in the thyroid 3 times in 3,000 autopsies on cats. A single case of adenocarcinoma of the thyroid in a cat is in the collection of the Veterinary Pathology Section of the Institute of Pathology, Washington, D.C., as compared with 17 cases of thyroid carcinoma in dogs (Jones, 1954).

LABORATORY RODENTS

Interest in hyperplasia and neoplasia of the thyroid in laboratory rodents has increased during the past decade because of the ease with which these changes can be induced experimentally with thiocyantes and thiouracils. An extensive literature has arisen that will not be reviewed here. An early monograph on spontaneous goiter in albino rats was written by Langhans and Wegelin (1919); more recently McCarrison (1930) in India reported 148 cases of goiter among 2,168 albino rats on various vitamin deficient diets. Of these rats 56 were males, 92 females; goiters appeared most commonly at the time of maturity. Slye, et al., (1926) found 5 cases of sarcoma of the thyroid in rats reported in the literature and contributed one case of carcinoma. The latter developed in a wild female Norway rat caught when young and kept in the laboratory for 3 years and 4 months. Shortly before death symmetrical enlargements were seen in the neck. Histologically the tumor proved to be a papillary adenocarcinoma. Among nearly 3,000 rats Bullock and Curtis (1930) observed 521 primary spontaneous tumors; of these, only 2 occurred in the thyroid. One was a fibroadenoma, the other a carcinoma. The latter was a poorly differentiated adenocarcinoma that measured $9 \times 5 \times 5$ mm. and occupied the left lobe of the thyroid in a 948-day-old female. Despite this infrequency of spontaneous tumors of the thyroid in the rat it is interesting to note that hyperplasia and neoplasia occur readily following the use of drugs that inhibit formation of thyroid hormone.

Among 61,000 necropsies on mice with over 5,000 spontaneous malignant tumors, Slye (1927) found only 23 animals with thyroid enlargements. Of these, 4 were simple colloid goiters, 2 were papillary adenomas, and 17 were malignant growths. Of the latter, 11 occurred in a single strain of Japanese waltzing mice; no simple adenomas or goiters occurred in the strain, of which 8.2 percent of the

deaths were due to thyroid cancer. On microscopic appearance the tumors were identified as carcino-sarcomas. In 5 other strains of waltzers no thyroid tumors appeared. Besides the waltzers, malignant tumors of the thyroid were found in only 3 other strains of mice among hundreds of strains carried in the laboratory. The author concluded that in the waltzing mice the tumor appeared as a simple Mendelian recessive; resistance to thyroid malignancy was dominant.

Endemic goiter reported in a rabbit colony by Chesney, et al., (1928) subsequently proved to be due to cyanates in the fresh cabbage that had been a daily article of diet. Whereas the top normal weight of a rabbit thyroid was 2.0 g., the rabbits with goiter had glands that weighed up to 36 g.

CAPTIVE WILD MAMMALS

Most of the data for this discussion of thyroid lesions in captive wild mammals was obtained from autopsy reports of deaths at the London and Philadelphia Zoos. Dr. Herbert L. Ratcliffe, director of the Penrose Research Laboratory of the Philadelphia Zoological Gardens, was very generous with his time and material.

The distribution of goiter and thyroid carcinoma among the various orders of captive wild mammals shows a marked predominance of the carnivores (table 2).

TABLE 2

Distribution of thyroid lesions among mammalian orders

ANIMAL ORDER	GOITER			CARCINOMA		
	Lond.Z.Soc. 1926–1946*	Phil.Z.Soc. To 1923+	Phil.Z.Soc. 1923–1953§	Lond.Z.Soc. 1926–1946*	Phil.Z.Soc. To 1923+	Phil.Z.Soc. 1923–1953§
Carnivora	13	31	22	4	3	5
Rodentia	6	0	9	2	1	1
Marsupialia	1	7	0	0	0	0
Menotremata	1	0	0	0	0	0

*Cases reported in Proceedings of the London Zoological Society.
Cases reported in Fox's "Disease in Captive Wild Mammals and Birds."
§Personal communication, Dr. Herbert L. Ratcliffe.

This is particularly striking when contrasted with the absence of such lesions among the hoofed mammals, whereas in domestic animals the ungulates are most affected. Ratcliffe (1954) has suggested that this may in part be due to the ease of administering iodine in "salt licks" compared with the difficulty of including it in the diet of certain carnivores such as lions and tigers. The thyroid abnormalities are particularly common in old animals that can reach advanced age because of their protective custody in a zoo. Fox (1923) stated that the normal thyroid of carnivores is relatively larger than that of ungulates; carnivores have 0.55 g. of thyroid per kg. body weight, ungulates 0.18 g., and marsupials 0.44 g.

Among the carnivores the *Canidae*, relatives of the dog, such as the coyote, wolf, and fox, frequently exhibit goiter or thyroid carcinoma (tables 3 and 4). One of these was an 8-year-old female wolf, *Canis mexicanus*, born at the Philadelphia Zoo; she had always received supplementary iodine in her diet. At autopsy Ratcliffe (1954) found a massive carcinoma of the thyroid with extensive metastases to both lungs (fig. 14 and 15). Histologically the tumor was composed of sheets of poorly differentiated epithelial cells without evidence of follicle formation or colloid secretion.

Among the bears, *Ursidae*, goiter is not uncommon (table 3). Hackel (1954) found a nodular goiter in a male European Brown Bear, *Ursus arctos*, that was

sacrificed at the Cleveland Zoo because of old age. At the same institution he and co-workers (1953) found a carcinoma of the thyroid in a male Malayan Sun Bear, *Helarctos malayanus*, that was known to be over 20 years of age. The thyroid was greatly enlarged and nodular, but was not adherent to surrounding structures and did not obstruct the trachea. Microscopic examination disclosed a well differentiated adenocarcinoma that had metastasized to the regional lymph nodes.

The big cats, *Felidae*, e.g., lion, tiger, and leopard, appear prone to develop goiter (tables 3 and 4); among the older animals carcinoma of the thyroid is not

TABLE 3

Species distribution of thyroid lesions at the Philadelphia Zoo, 1923–53*

SPECIES	GOITER	CARCINOMA
Coypu, *Myocaster coypus*	9	1
Polar bear, *Thalarctos maritimus*	2	0
Black bear, *Ursus americanus*	2	0
Coyote, *Canis larus*	3	1
Grey wolf, *Canis mexicanus*	2	2
Red fox, *Canis vulpes*	3	0
Lion, *Felis leo*	5	0
Leopard, *Felis pardus*	2	1
Tiger, *Felis tigris*	3	1
	31	6

*Personal communication, Dr. Herbert L. Ratcliffe.
"Goiter" includes hyperplasia with enlargement.

TABLE 4

Species distribution of thyroid lesions at the London Zoo, 1926–46

SPECIES	GOITER	CARCINOMA
Coypu, *Myocastor coypus*	5	2
Fox, *Vulpes vulpes*	3	3
Racoon, *Procyon lotor*	2	4
Coati, *Nasua narica*	0	2
Lion, *Felis leo*	3	0
Kusimanse, *Crossarchus obscurus*	2	0
Others	6*	5**
	21	16

*Dingo, fossa, badger, mouse, wombat, echidna.
**Otter, hutea, wolf, cape dog, genet.

uncommon (table 3). A case of congenital goiter in a young leopard, *Felis pardus*, was reported by Sklower (1926). The animal lived only 10 days and had gradually increasing difficulty in swallowing; external examination showed enlargement of the neck in the region of the thyroid. At autopsy a large diffuse colloid goiter was found. In a male leopard, *Felis pardus*, exhibited for over 19 years at the Philadelphia Zoo a carcinoma was found to replace most of the thyroid gland (fig. 16). Metastases were present in the cervical lymph nodes and kidneys. Most of the tumor was composed of sheets of poorly differentiated epithelial cells, but in some areas follicle formation was still apparent (fig. 17). In an aged black

leopard at the Cleveland Zoo, Hackel (1954) found a 1 cm. firm gray nodule in each lobe of the thyroid. Microscopically these had the appearance of adenocarcinoma; metastases were present in the cervical lymph nodes. Although at both the London and Philadelphia Zoos nearly every lion, *Felis leo*, at autopsy showed thyroid hyperplasia with some enlargement and occasional adenoma formation, a malignant change was not seen. Three tigers, *Felis tigris*, at the Philadelphia Zoo showed hyperplasia and enlargement of the thyroid; 2 of these, both males, had been exhibited for 8 and 14 years, respectively; the third was a young female only 1½ years of age. In a male tiger over 17 years old a poorly differentiated carcinoma of the thyroid was found at autopsy; metastases were present in the kidneys (Ratcliffe, 1954).

A surprising incidence of goiter and thyroid carcinoma was found in the small carnivors of the family *Procyonidae* at the London Zoo. This includes the racoons, *Procyon*, of North America and the coatis, *Nasua*, of South America. Among these animals there were 6 cases of thyroid cancer (table 4). Metastases were present in the lungs of all 4 racoons and in the lungs of 1 of the 2 coatis (Scott, 1928; Hamerton, 1935, 1938, 1944). This animal, a ringtailed coati, *Nasua nasua*, had been on exhibition in the zoo for 9 years.

A few cases of thyroid carcinoma have also been found in the *Viverridae*, a family of small catlike carnivores like the civet. Scott (1928) described an adenocarcinoma of the thyroid in a pardine genet, Genetta pardina; and Purmann (1929) reported the case of a *Viverricula malaccensis* in which the primary carcinoma of the thyroid had metastasized to the lungs. The animal had been exhibited at the Vienna Zoo for 20 years.

Thyroid lesions are uncommon in captive ungulates; however, goiter is occasionally found; e.g., in camels (see above). Kitt (1916) cites the case of a newborn giraffe at the Dresden Zoo with a 3,600 g. goiter. The giraffe mother also had a fist-sized goiter and once before had been delivered of a goiterous calf. The sporadic character of endemic goiter is shown in the account by Seeberger (1923) of his experience with a colony of Alpine ibex, *Capra ibex*, in a park at St. Gallen, Switzerland. Of the 10 ewes 5 had goiterous young; the latter were stillborn or died in the neonatal period. Only 2 of these 5 ewes had grossly visible goiters; the rams showed no enlargement of the gland. The animals were kept in the same environment and given the same food and water—all Swiss water is poor in iodine, 0.2 to 1.5 μg./kg. (McClendon, 1939). After the adults were fed iodized salt none of the young were born with goiter. Kalkus (1920) has pointed out that wild deer in some regions of Washington, where goiter was common in sheep and cattle, were free of the disease. He attributed this to the observation that deer and other wild animals frequented so-called "licks" and ate the soil which had 0.032 percent iodine (no unit given) as compared with 0.0015 percent for that of the pastures. Finally, mention may be made of a goiterous antelope found in Siberia near the Chinese frontier and identified as a distinct species, "antelope gutturosa", by Radde. Crotti (1938), who cites the instance, points out that goiter is endemic in this region and that the enlarged thyroid is merely an adaptive response to the environment rather than a species characteristic.

Of the rodents autopsied at the London and Philadelphia Zoos the coypu, *Myocastor copyus*, had the highest incidence of goiter and thyroid carcinoma (tables 3 and 4). This is an animal that resembles the muskrat in appearance and behavior; it is a native of South America and the plucked fur is known in commerce as "nutria." In Philadelphia the average exhibition period of the animals showing thyroid hyperplasia was 2 years; most were killed by cage mates in the numerous fights that occurred. Although hyperplasia of the thyroid with slight enlargement was common, large goiters such as those found in the London Zoo (Hamerton, 1933) were not seen. In London the animals were older, up to 7½ years, and goiters the size of a tangerine were occasionally present. The

single example of cancer of the thyroid in a coypu at the Philadelphia Zoo occurred in an animal that was over 4 years old. Both cases of thyroid carcinoma seen at the London Zoo showed pulmonary metastases (Hamerton, 1936, 1939).

Fox (1923) reports 7 cases of nodular colloid goiter among marsupials in the Philadelphia Zoo. Four of these were in the carnivorous opossums, *Didelphys virginiana*, and Tasmanian devils, *Sarcophilus ursinus;* the remaining 3 occurred in herbiverous kangaroos. A Tasmanian wombat, *Phascolomys tasmaniensis*, one of the burrowing marsupials, died at the London Zoo. Autopsy by Hamerton (1935) disclosed an enlarged cystic thyroid the site of acute suppurative inflammation. Pettit (1900) described a carcinoma of the thyroid in an opossum, *D. virginiana*, exhibited at the zoological garden of the Museum of Natural History in Paris. Although the tumor did not metastasize it appeared to be malignant on histological examination. Solid sheets of neoplastic epithelial cells showing no evidence of follicle formation or colloid storage made up the bulk of the tumor.

The lowest order of mammals is represented by the egg-laying monotremes. The thyroids in these animals are paired, as they are in amphibians, most reptiles, and birds. Only a single report of thyroid enlargement was found in the literature (Hamerton, 1944). An echidna, *Zaglossus bruijnii*, had been exhibited in the London Zoo for 30 years when it died. At autopsy the left gland was a cystic nodular goiter approximately 3 cm. in diameter; the right thyroid measured about 8 mm. in length and was of normal size.

SUMMARY

Enlarged hyperplastic thyroids and colloid goiters have been found in fishes, reptiles, birds, and mammals. In nearly every instance the animals were in an unnatural environment; viz., fish in hatcheries or aquaria, reptiles in zoological gardens, birds and mammals under domestication or in captivity. Cancer of the thyroid occurs under the same conditions and in the same animal species as does thyroid hyperplasia and goiter; the animals affected with cancer are usually older than those with goiter. There is evidence that the cancers often arise in a previously hyperplastic or goiterous thyroid.

The fishes most commonly affected with goiter are the *Salmonidae*, particularly brook trout when reared in hatcheries. Salt water fish, though rarely affected, may show evidence of goiter if kept in poorly aerated or polluted water with a relatively low iodine content. The difference in species susceptibility to goiter is also apparent in these fishes, for the pilot fish, *Echeneis naucrates*, is particularly prone to develop the lesion.

The absence of reported instances of goiter among the amphibians is probably due in part to the small numbers of these animals that as adults are kept in captivity for long periods. The fact that their thyroid can respond to goiterogenic drugs would indicate that under conditions of iodine insufficiency thyroid hyperplasia and goiter formation would occur.

Only 3 cases of goiter in reptiles have been reported, but here again the factors discussed for amphibians mediate against the frequent occurrence of this lesion.

Among birds goiters have been observed in fowl and pigeons and in a small number of birds in zoological gardens. Shell parrakeets, *Melopsittacus undulatus*, have been received in this laboratory from many parts of the country. Twenty-three of the birds, all from low-iodine areas, had hyperplastic thyroids. Some of the glands were only 2 or 3 times normal size, but most were very large and cystic goiters. All but 2 of the birds were females. In the Philadelphia Zoo 3 cases of cancer of the thyroid were seen by Dr. Herbert Ratcliffe, 2 in psittacine birds and 1 in a duck.

Goiter in domestic animals presented serious problems in the Northwest, but these are now largely overcome by the use of iodized salt. Adult cattle, sheep, goats, and swine were not seriously affected; but the newborn were often

hairless, myxedematous, and stillborn or died shortly after birth. Large goiters in the fetus occasionally interfered with parturition. Dogs rarely are affected by congenital goiter, although enlarged thyroids and even carcinoma are not uncommon in the adult. Cats seldom have grossly enlarged thyroids.

In zoological gardens the carnivores are more often goiterous than any other mammals. Among these, lions, tigers, leopards, wolves, bears, and racoons are frequently affected. The coypu, a rodent, and some of the marsupials also show a high incidence of goiter. Cancer of the thyroid has been reported in all these animals. The ungulates and primates in zoos are remarkedly free of goiter.

There is a relatively high incidence, particularly among mammals, of thyroid cancer in species that frequently exhibit goiter or other evidence of thyroid hyperplasia. It would appear that in these animals the hyperplasia may be a precursor of cancer.

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ERRATA

In the article by August C. Mahr in the Ohio Journal of Science, 54: 1954, in line 27 on page 380, read, " . . . Harvard University Library," (for " . . . Howard University Library").